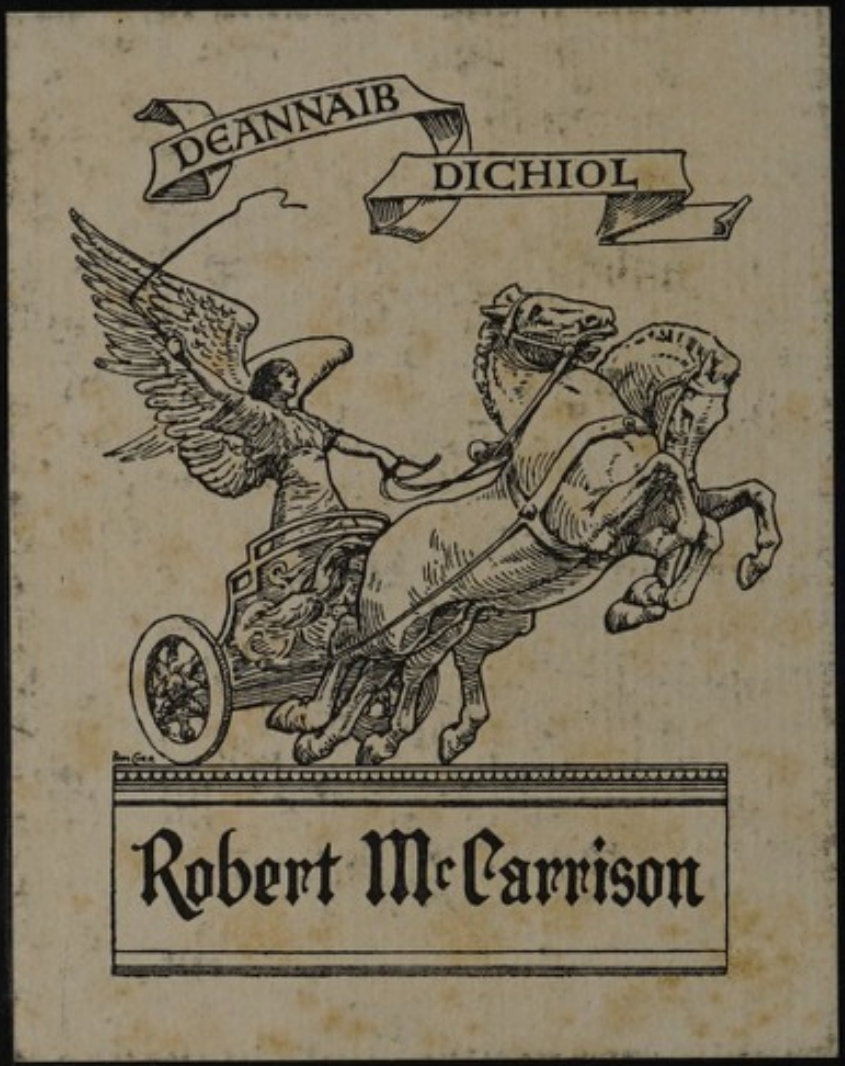

To Mr. Robert McCarrison

from -

S. H. Van Meter

The contributions from the following physicians have made the English translation of this volume possible: —

A. E. Hertzler, M. D., Halstead, Kans.
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Emil Goetsch, M. D., Brooklyn, N. Y.
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M. O. Shivers, M. D., Colorado Springs, Colo.
J. C. Moore, M. D., Seattle, Wash.
S. D. Van Meter, M. D., Denver, Colo.
André Crotti, M. D., Columbus, Ohio.
H. S. Plummer, M. D., Rochester, Minn.
R. L. Benjamin, M. D., St. Anne, Ill.
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J. R. Yung, M. D., Terre Haute, Ind.
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REPORT

of the

INTERNATIONAL CONFERENCE ON GOITER

IN BERNE

August 24 — 26, 1927.

Edited by the

Swiss Goiter Commission

HANS HUBER, EDITOR, BERNE

1929

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INTRODUCTION.

In issuing our Report on the International Goiter Conference — in session in Berne from August 24th to 26th, 1927 — we feel bound to apologize for the delay the publication has unintentionally suffered; the circumstance must be laid at the door of the voluminosity this book has gained in the course of its preparation and which far exceeded our anticipations. Having become conscious of the necessity to register these important initiatory deliberations not in a mere summary report, but to record the statements of the numerous orators, together with the respective commentatory discussions, in their verbatim tenor, we saw the modestly planned brochure grow into a ponderous book. We trust, however, to have won the approval of the participants, as well as of other parties interested in the goiter problem, who will be gratified in being able to trace in the volume everything said during those three days of sometimes very animated, yet courteous, discussions; for, are not these debates affording most useful edification on questions still ardently disputed?

For the sake of the perspicuity of our review, the chronological sequence of the debates has not been unconditionally adhered to, discussions on different topics having sometimes overlapped and taken a turn to complexity. We have therefore arranged our matter in strict conformance to the very chapters set down in the conference program. It is readily granted that our account had, in this manner, to forego some of the vividness it would have acquired in relating minutely the course of the proceedings with all their incidents; for being however less picturesque, the survey has, in our belief, gained in clearness — and this aim has been our principal concern.

We should have been glad, also, to do justice in a larger measure to the strain of polyglottism so greatly, and naturally enough, in evidence at the Conference. It is easily seen, however, that it was not feasible to include translations, even in succintness, of all

the statements evolved, without exposing our report to an unwarrantable risk of hypertrophy.

The idea of convoking an international assembly for the study and discussion of a strictly defined problem has found the general approval of the savants who honored us with their presence; our enterprise was welcomed as being distinctly practical and worthy of emulation, an encomium which could not but let us feel amply rewarded. And yet, it is due in greater part to Professor Aschoff, the original mover of the project of our Conference, and to the late regretted Professor Hotz. Tribute was also accorded to the organizers for having concurrently arranged an exposition, which, notwithstanding the shortness of time and the exiguity of means at our disposal in preparing it, yielded an important array of documents and highly valuable material, which found appreciation not only with members of the Conference, but aroused the lively interest of the public in general.

In resumption, we are hardly overstating the case in proclaiming our Conference a succes, inasmuch as it has fulfilled the purpose that inspired its movers and initiators, that, namely, of procuring an orientation as to the actual state of the goiter question; of establishing, moreover, a close contact among the scientists specializing in it and which contact was to lead to the much-needed consolidation and unification of research and working methods. The outcome of our undertaking fills us with elation, little credit as we may claim for ourselves in its achievement and conscious as we are of its being mainly owed to all those who, from the first, have tendered their precious collaboration with an eagerness we cannot too highly commend: we are referring here to the savants of every land who brought to us the fruit of their labors; to those, also, who contributed actively to the success of our exposition and several among whom have generously donated us portions of their exhibits in view of the constitution of an international goiter museum. It is, thus, with the reiterative expression of our thankfulness towards all those collaborators, that we now hand to the members of the First International Goiter Conference this volume as a souvenir of a first stage attained and which, itself, will be, as we hope, but the first of a series incorporating the records of conferences to be.

The Swiss Goiter Commission.

PROGRAMME OF THE CONFERENCE.

August 24:

9.00 A. M.: Opening of the Conference by the President.
Remarks on the general distribution of goiter.

9.30 A. M.: Reports on the subject: —
The Pathologic Anatomy of Endemic Struma.
1. Prof L. Aschoff, Freiburg i. Br.
2. Prof. C. Wegelin, Berne.
3. Dr. David Marine, New-York.

Discussion.

3.00 P. M.: Reports on the subject: —
The Pathologic Physiology of the Thyroid.
1. Dr. Plummer, Rochester, U. S. A.
2. Dr. B. Breitner, Vienna.
3. Prof. Dr. de Quervain, Berne.

Discussion.

8.30 P. M.: Assembly in the Kursaal Schänzli. Welcome by the Officials of the Canton and City of Berne.

August 25:

9.00 A. M.: Reports on the subject: —
Aetiology and Epidemiology of Endemic Struma.
1. Prof. Bérard, Lyons.
2. Dr. McCarrison, Cooroon, India.
3. Prof. Galli-Valerio, Lausanne.
4. Dr. E. Bircher, Aarau.

Discussion.

3.00 P. M.: Continuation of the discussion concerning the Aetiology and Epidemiology of Endemic Struma.
Inspection of the Exhibit concerning the Pathology of the Thyroid, University Building, Rooms 44—49.

August 26:

9.00 A. M.: Reports on the subject: —
Prophylaxis of Endemic Struma.
1. Prof. Wagner von Jauregg, Vienna.
2. Dr. Muggia, Sondrio, Italy.
3. Prof. Silberschmidt, Zürich.

Discussion.

3.00 P. M.: Continuation of the Discussion.
4.00 P. M.: Conclusion.

* * *

August 27:

As it was not possible during the three days of the Conference to discuss the question of the surgical treatment of goiter, Professor de Quervain has kindly consented to give demonstrations of operations on goiter. These will take place on Saturday, August 27th, in his clinic in the Insel Hospital. Previous to these operations, in order to complement the discussion on cretinism, a film on this affection will be shown. In the afternoon a visit to the poor-farm at Riggisberg will offer the opportunity to inspect the institution and study the cretins, who are housed there.

Program for August 27:

8.30 A. M.: Presentation of a film on goiter and cretinism at the Insel Hospital.

10 A. M. to 12 M.: Goiter operations:.

2.00 P. M.: Excursion to the poor-farm at Riggisberg. Leave by autobus promptly at 2 o'clock from Hotel Schweizerhof. The members of the Conference, who desire to take part in this excursion, are requested to register their names at the secretariat of the Conference (University auditorium No. 43), not later than Thursday evening.

List of Participants.

Switzerland:

Swiss Goiter Commission.

President: Dr. H. Carrière, Chief of the Federal Department of Public Hygiene.

Dr. Bayard, Physician, St. Niklaus.

Dr. E. Bircher, Chief Physician of the Cantonal Hospital at Aarau.

Dr. Eggenberger, Chief Physician of the Herisau Hospital.

Dr. B. Galli-Valerio, Professor of Hygiene at Lausanne.

Col. Hauser, Chief Military Surgeon, Berne.

Prof. Dr. Hunziker, President of the Board of Health, Basle.

Dr. Hunziker, Physician, Walchwil.

Dr. F. Messerli, Department of Hygiene of the City of Lausanne.

Dr. Oswald, Professor of Internal Medicine, Zurich.

Dr. F. de Quervain, Professor of Surgery, Berne.

Dr. César Roux, Professor of Surgery, Lausanne.

Dr. W. Silberschmidt, Professor of Hygiene, Zurich.

Dr. Steinlin, School Medical Officer, St. Gall.

Dr. Otto Stiner, Federal Health Department, Berne.

Dr. K. Wegelin, Professor of Pathological Anatomy, Berne.

* * *

Aarau: Dr. H. Vetter, Pathological Institute.

Basle: Dr. A. Gigon, Professor of Internal Medicine.

Dr. Henschen, Professor of Surgery.

Dr. Luxenburger, Scientific Assistant at the Psychiatric Clinic.

Dr. Merke, Assistant Physician at the Surgical University Clinic.

Dr. R. Roessle, Professor of Pathological Anatomy.

Dr. Ruedin, Professor of Psychiatry and Manager of the Genealogical Department of the German Research Institute for Psychiatry in Munich.

Dr. F. Staehelin, Professor of Internal Medicine.

Dr. E. Veillon.
Dr. E. Wehrle.

Berne:

Dr. J. Abelin, University Instructor for Biochemistry.
Dr. L. Asher, Professor of Physiology.
Dr. E. Bürgi, Professor of Pharmacology.
Prof. Dr. Bürgi, Head of the Federal Veterinary Department.
Dr. Dardel, University Instructor for Surgery.
Dr. J. U. Duerst, Professor of Zootechnics.
Dr. F. L. Dumont, University Instructor for Surgery.
Dr. R. von Fellenberg, University Instructor for Gynaecology.
Dr. Th. von Fellenberg, Chemist at the Federal Health Department.
Dr. Flückiger, Veterinary Expert.
Dr. H. Guggisberg, Professor of Gynaecology.
Dr. Hauswirth, Municipal Medical Officer.
Dr. B. Huguenin, Prof. of Pathological Anatomy.
Dr. R. Isenschmid, University Instructor for Internal Medicine.
Dr. Alb. Kocher, University Instructor for Surgery.
Dr. K. Kottmann, Professor of Internal Medicine.
Dr. H. Matti, Professor of Surgery.
Dr. Lauener, Municipal School Medical Officer.
Dr. H. Sahli, Professor of Internal Medicine.
Dr. G. Sobernheim, Professor of Hygiene and Bacteriology.
Dr. Fr. Steinmann, Professor of Surgery.
Dr. K. Stiner.
Dr. M. Stoos, Professor of Paediatrics.
Dr. H. Wildbolz, Professor for Urological Surgical Diagnostics.

Fribourg:

Dr. G. Clément.

Geneva:

Dr. M. Askanazy, Professor of Pathological Anatomy.
Dr. H. Christiani, Professor of Hygiene.
Dr. E. Kummer, Professor of Surgery.
Dr. Maurice Roch, Professor of Medical Clinics.
Dr. Tomanek, League of Nations.

Glarus:	Dr. Fritzsche, Head Physician at the Cantonal Hospital.
Langnau i/E.:	Dr. A. Fonio, University Instructor, Head Physician of the District Hospital.
Lausanne:	Dr. G. Châtenay, Physician.
	Dr. L. Michaud, Professor of Internal Medicine.
	Dr. Renaud, Physician.
Lucerne:	Dr. Dœpfner, Municipal Medical Officer.
Neuchâtel:	Dr. Pettavel.
Porrentruy:	Dr. Juillard.
St. Gall:	Dr. Brunner, Head Physician of the Surgical Department of the Cantonal Hospital.
	Prof. Dr. K. Helly, Prosector, Cantonal Hospital.
Winterthur:	Dr. E. Looser, Head Physician of the Surgical Department of the Cantonal Hospital.
Zürich:	Dr. Conrad Brunner.
	Dr. P. Clairmont, Professor of Surgery.
	Dr. H. von Meyenburg, Professor of Pathological Anatomy.
	Dr. Ed. Monnier.
	Dr. F. Nager, Professor of Otiatrics.
	Dr. Wydler, University Instructor for Surgery.

Argentine:

Buenos-Aires:	Dr. Zampini.

Austria:

Graz:	Dr. von Haberer, Professor of Surgery.
	Dr. V. Orator, University Instructor.
Innsbruck:	Dr. Starlinger.
Semmering:	Prof. Dr. Wiesel.
Vienna:	Dr. B. Breitner, University Instructor.
	Dr. von Eiselsberg, Professor of Surgery.
	Prof. Dr. Kraus.
	Dr. Wagner von Jauregg, Professor of Psychiatry.

Belgium:

Brussels:	Dr. L. Mayer, Fellow of the University.
Liège:	Dr. A. Hallet, Surgeon of the Hospitals.

Brazil:

Dom Pedrito: (Rio Grande do Sul)	Dr. Mercio Xavier Alvorino.

Sào Gabriel: Dr. Arlêo Petrarca Torquato.
(Rio Grande do Sul)

Czechoslovakia:

Prague: Prof. Dr. Biedl, Professor of Experimental Pathology.
Dr. Reiss.
Tatranska-Polianka: Dr. Guhr.

Dantzig:

Dr. Feldmann, Assistant Physician at the Municipal Hospital.
Dr. Klose, Professor of Surgery.
Dr. Fr. Lülsdorf, Assistant in the Surgical Department of the Municipal Hospital.

France:

Lyons: Prof. Dr. L. Bérard.
Prof. Dr. Dunet, Fellow of the University.
Mulhouse: Dr. Kleinknecht.
Paris: Dr. Béclère.
Dr. Coulaud.
Dr. Folley.
Prof. Dr. Lemaître.
Dr. Roussy, Professor of Pathological Anatomy.
Strasbourg: Dr. Freyss.
Dr. Rhein, Institute of Hygiene.

Germany:

Bamberg: Dr. W. Lobenhoffer, Professor of Surgery.
Berlin: Dr. Frey, Director in the General Board of Health.
Dr. His, Professor of Internal Medicine.
Dr. W. Jaensch, University Instructor.
Dr. Krohne, Chief of department ministerial.
Dr. Lubarsch, Professor of Pathological Anatomy.
Dr. Marmann, Governmental and Medical Counsellor.
Bonn: Dr. Garré, Professor of Surgery.
Cassel: Dr. Th. Hœpfner.
Dr. O. Mennicke, Governmental and Medical Counsellor.

Constance:	Prof. Dr. Meisel.
	Dr. E. Weisschedel, Municipal School Medical Officer.
Frankfort-on-the-Main:	Prof. Dr. Blum, Dir. of the Biological Institute.
	Prof. Dr. Kolle, State Institute for Experimental Therapeutics.
	Dr. W. Kübler, Assistant Physician.
	Dr. Schmieden, Professor of Surgery.
Freiburg i/Br.:	Dr. Aschoff, Professor of Pathological Anatomy.
	Dr. Büchner, Medical Assistant in the Pathological Institute.
	Dr. Bürkle-de la Camp.
	Dr. Lexer, Professor of Surgery.
	Dr. H. Pflüger, Municipal Medical Officer.
Halle:	Mr. Klaus, LL. D.
Heidelberg:	Dr. Enderlen, Professor of Surgery.
Jena:	Dr. A. Sturm, Medical Clinic of the University.
	Dr. W. H. Veil, Professor of Internal Medicine.
Leipsic:	Dr. Payr, Professor of Surgery.
Marburg:	Dr. von Engelhardt, Physician.
Munich:	Prof. Dr. Dieudonné, Ministry of the Interior.
	Dr. Lang, Assistant Medical Officer at the Genealogical Department of the German Experimental Institute for Psychiatry.
	Dr. Schulz, Assistant Medical Officer at the Genealogical Department of the German Experimental Institute for Psychiatry.
	Dr. F. von Müller, Professor of Internal Medicine.
	Dr. Sauerbruch, Professor of Surgery.
Treysa:	Dr. Wittneben, Head of the Hephata Institutes.
Weihenstephan near Munich:	K. Scharrer, Ph. D.
	Alfred Strobel, Counsellor of Agriculture.
Würzburg:	Dr. M. B. Schmidt, Professor of Pathological Anatomy.

Great Britain:

Bucksburn, Aberdeen:	Dr. Isabella Leitch, M. A., D. Sc., Rowett Research Institute.
	Gladys Lee Stuart, Rowett Research Insitute.
London:	Sir James Berry, F. R. C. S.
	T. P. Dunhill, C. M. G., M. D.

Dr. Innes H. Pearse, St. Bartolomew's Hospital, Medical Research Council.
Dr. Hugo Rast.
Dr. George Scott-Williamson, Royal College of Surgeons.

Manchester: Dr. G. J. Langley, M. R. C. P.
Prof. Dr. George R. Murray.

Hungary:

Budapest: Dr. Nicolas Novák, Fellow of the Medical Faculty of the University.
Dr. T. de Vérébély, Professor of Surgery.

Italy:

Armeno: Dr. Achille Marchesa Monneret.
Rome: Dr. V. Ambrosi, General Medical Inspector, Ministry of the Interior.
S. Lazzaro: Prof. Pighini, Psychiatric Institute.
Sondrio: Dr. G. Muggia, Director of the Psychiatric Hospital.

Japan:

Kyoto: Dr. Riuso Torikata, Professor of Surgery at the Imperial University; at present in Berlin.
Dr. Kojimee, at present: University of Berne.

Netherlands:

Utrecht: Dr. de Josselin de Jong, Professor of Pathological Anatomy.
H. J. Laméris, Professor of Surgery.

Norway:

Oslo: Dr. Johan Holst, University Instructor, Surgical Clinic of the University.
Dr. Gulbrand Lunde, Ph. D.
Dr. J. Nicolaysen, Professor of Surgery.

Serbs, Croats and Slovenes (Kingdom of the):

Zajecar: Dr. Mileta Branovacky.

Spain:

Madrid: Dr. Gr. Marañon, Professor at the Royal Academy of Medicine of Spain.

United States of America:

Bloomington, Ill.:	Dr. E. P. Sloan, The Sloan Clinic.
Boston:	Dr. Robert L. Mason.
Charleston, W. Va.	Dr. R. K. Buford.
Cleveland, Ohio:	Dr. Allen H. Graham, Lakeside Hospital.
Colorado Springs:	Dr. M. O. Shivers.
Columbus, Ohio:	Dr. André Crotti.
Dayton, Ohio:	Dr. E. R. Arn, Fidelity Medical Building.
Denver, Col.:	S. D. Van Meter, M. D.
Fairmont:	Dr. H. S. Keister.
Grand Rapids:	Dr. Ehner W. Schnoor, Butterworth Hospital.
Flint, Mich.:	Dr. George Curey, Hurley Hospital.
	Dr. J. T. McGregor.
Indianapolis, Ind.:	Dr. F. E. Gifford.
	Dr. Edgar J. Kiser.
	Dr. J. D. Moschelle.
New-York:	Dr. Charles L. Gibson.
	Dr. W. Hutchinson.
	Dr. F. Kammerer.
Oklahoma City, Okl.:	Dr. R. M. Howard.
Oswego, N. Y.:	Dr. Shennan M. Burne.
St. Anne, Ill.:	Dr. R. L. Benjamin.
Seattle, Wash.:	Dr. J. C. Moore.
South Bend, Ind.:	Dr. J. L. Wilson.
Terre Haute:	Dr. Yung.
Troy, N. Y.:	Dr. W. T. Diver.
Wichita, Kansas:	Dr. C. A. Hellwig, Director of Laboratories, St. Francis Hospital.

GENERAL ACCOUNT.

The opening session of the International Goiter Conference in Berne took place on the 24th of August 1927 at 9 a. m. in the aula of the University (kindly placed at the disposal of the organizers by the Cantonal Department of Public Instruction) and the following

Inaugural Address

was pronounced by Dr. Carrière, President of the Swiss Goiter Commission, before a very numerous auditory (see initial pages for list of participants in the conference; the medical community of the city of Berne having also been largely represented):

« Ladies and Gentlemen! — The highly gratifying task being confided to me to open, on behalf of the Swiss Goiter Commission, this first International Goiter Conference, I venture at once upon the most agreable part of my duty in extending a cordial welcome to all the savants who have answered our call. I do so, firstly, in the name of the Federal Government and, more especially, in that of the Home Departement, whose chief, Federal Councillor Chuard, has asked me to convey to you his great interest in your labors and his regret at being prevented, through unavoidable absence from Berne, from presiding personally at the opening of your conference. I have also to welcome you, Ladies and Gentlemen, in the name of the authorities of the Canton and City of Berne, whose representatives are present at this inaugural meeting and to whom — as well as to the Federal Government — I am certain you will join in expressing our respectful homage. And, finally, I am here to welcome you on behalf of the Swiss Goiter Commission and to say with how great a feeling of joy and pride they are seeing assembled upon their invitation such a numerous gathering of eminent savants come, as they have, from so many different countries in order to study a nosological problem which is not only one of the most arresting, but also one of the most obscure engaging the ingenuity of investigators.

The honor of welcoming you having fallen to me much more owing to my functions than in regard to scientific merits, it is not for me to entertain you at great length on the subject of goiter. The problems we propose dealing with having long ago been taken up by everyone here present, you must, in a fuller sense than I, be conscious of the pathological and sociological importance of the goiter endemic and of the gravity of its influence as an agent of degeneration among the populations affected, where it creates so great an amount of social waste and renders so many young men unfit for their country's defence. If, therefore, I am venturing upon your ground, it is mainly in considering the obvious anomaly of having to open a goiter conference without saying a few words on the subject of its deliberations.

The goiter affection and its satellite, cretinism, were until recent times regarded as a speciality, if I may say, of certain countries, and, particularly, of my own. Scientific inquiry having, however, gained in precision and become more circumstantial, this affection was found to be spread over a far wider area, than was originally imagined; many countries who formerly believed, may be with a feeling of vanity, in their own indemnity, have had to acknowledge contamination within their own borders.

If a goiter map of the world were before us, few regions indeed would it contain that did not show smaller or larger patches of endemic, or where affected centers could not be numbered to any extent. It has appeared, moreover, that if in some regions the endemic be unmistakably losing in depth and, consequently, some of its gravity, it is gaining in extension, which amounts to saying that its domain, as it becomes better explored, seems gradually to enlarge.

It might be fancied that the cause of an affection similarly diffused and known since long, would not have escaped discovery up to now. And yet, as you are aware, such is the case.

Among the nosological problems which at present solicit our efforts, the etiology of goiter is, along with that of cancer, the one around which the greatest obscurity persists. If the etiologic agent of goiter is yet unknown to us, it is not, however, for want of endeavours in tracing it. Numerous, if not innumerable, are the causes that have been invoked in turn. Saint-Lager, whose « Etudes sur les causes du crétinisme et du goître endémique » are even to-day a precious source of information, makes mention of about forty supposed agents of hydric, tellurical, atmospherical, ethnological or other nature. Among the theories that have emerged

subsequently, the one based on infection — and which hardly could have been propounded in 1865, the year in which Saint-Lager published his work — has been taken up and is represented today, even among us, by eminent adherers. It competes in fact in this etiological disarray for primacy against the theories of hydric causes, of iodic deficiency, of attributing goitrous endemic to unhygienic conditions supposed to prevail among the affected populations. But, is there an exclusive goiter agent? May we not admit the existence of goiters of different origin and that thyroid troubles may spring from variable causes? that goiters to which a physiological character might be ascribed, such as arise in puberty or during pregnancy, are essentially and pathologically differing from those met with at other periods of life? that goiter in mountainous regions is not identical with that found in maritime districts? or, finally, that some of the variously incriminated agents may combine in provoking goiter? To all these questions, a precise answer cannot be given at this moment. Goiter, although having afforded to surgery one of its triumphs, has remained a mystery to epidemiologists. None of the more or less plausible hypotheses prevailing in that connection has yet succeeded to obtain unanimity. Our sphinx persists in withholding the solution of her riddle and the problem abides in its entirety.

But of all this, I repeat, you are better aware than myself and I dare not abuse of your time by insisting further on facts too well known. I should wish instead, finding ourselves in Switzerland, which has long enjoyed the doubtful privilege of being mentioned in the first rank among the countries particularly visited with goitrous endemic and whose scientists have been forcibly brought to deal intensively with the subject — it may suffice here to call to mind, among many others, the names of Reverdin, Bircher, Kocher and, to go further back, those of Coindet, a Genevese, who, in 1820, was the first to apply iodine (discovered by Courtois) in goiter treatment, and of his compatriot Prévost, who, already in 1849, attributed goiter to a deficiency of iodine and brome, being thus a precursor both of Chatin and the modern iodists — I should wish to enumerate in few words what attempts we have so far undertaken in Switzerland with a view to ridding ourselves of goiter. It may be taken, if you agree, as a short introduction to the several relations on our thesis you will afterwards listen to:

Goiter in Switzerland is very unequally distributed, some regions showing a far greater prevalence of the disease than others,

and we have not succeeded so far to explain the causes of the disparity. Few, at any rate, are the districts which goitrous endemic could be said to be entirely absent from. I have neither the time nor the intention to enlarge on this subject on which one of your colleagues will entertain you to-morrow; merely allow me to point to two facts as resulting from the only reliable documents we have at our disposal in surveying the extent of the affection, viz. the school-statistics and the medical reports of our recruitment commissions. According to the former, thyroid hypertrophy shows great diffusion already in the pre-scholastic age, a fact calling for the institution of prophylactic measures at the first stages of life. On the other hand, recruiting-returns reveal an ever decreasing proportion of deferments or total exemptions from service on account of goiters: from 10 %, as it was in 1885, it fell successively to 2,9 % (1909) and to about 1,3 % in 1924/1925; since, however, on the suggestion of the Swiss Goiter Commission, the investigation of thyroid hypertrophy became an object of especial care on the part of the military authorities, the number of recruits presenting hypertrophy to any degree has remained considerably high. We may, thus, repeat in relation to Switzerland, what I remarked a little while ago concerning the general extension of goiter in the world, namely, that goitrous endemic seems to have gained at the surface, in the shape of simple thyroid hypertrophy in one degree or other, what it may have lost in depth, i. e. in gravity; goitrous enormities and difformities, which formerly would strike an observer at first glance, have, in fact, almost disappeared.

The above state of things having attracted the attention of the Federal authorities, some twenty years ago, a commission was then charged with the task of investigating the causes of the endemic and to determine, if possible, its prophylaxis. The labors of the said commission were mainly directed along the lines of the hydric theory and it included among its members several scientists here present; the commission, however, found itself impeded by the war and the results of its work have remained unpublished. On the return of peace, the thought of a resumption gained ground; a new Swiss Goiter Commission was constituted, and on its behalf I have now the honor to address you.

This commission has notably enlarged the program of its predecessor; to the problems of the etiology and of the prevention of goiter, those arising out of its anatomy and physiology have been added — naturally and logically enough — seeing that all these problems are closely connected and interdependent and that none

of them can be investigated without concurrently viewing the others.

The problem, however, which has from the first obtained our utmost attention is that of prophylaxis. It might seem like putting the plough before the horse and surprise might be felt at the attempt of establishing prophylaxis in regard to an affection the cause of which is still as deeply surrounded with mystery. But, here, precedents are not wanting. Have we not applied prophylaxis against smallpox, now for over a century, without the agent of the disease being discovered? Did not anti-malarian and anti-syphilitic prophylaxis exist before the disclosure of Laveran's haematozoon and Schaudin's spirochaeta pallida? Thus, our commission has contemplated the possibility of an anti-goitrous prophylaxy on the basis of a few precise facts, as a first step towards a practical and definite solution of the problem, and in this direction we have worked from the outset.

The employment of iodine for goiter prevention is not a novel idea. It had already arisen in France after the publication of Chatin's work and was applied in some departments, that first attempt not being however followed up. Since then the idea has asserted itself anew. In Austria it found a propounder in Professor Wagner von Jauregg; Italy has seen certain trials undertaken in regard to which Dr. Muggia will speak. In Switzerland itself, and before the Goiter Commission adhered to the idea, it had been preconized and defended by Bayard, Eggenberger, Hunziker, Roux, Klinger, Messerli, Steinlin and others. In adopting it, however, — and this point must be insisted upon — the Swiss Goiter Commission did not mean to commit itself to the theory according to which thyroid hypertrophy is attributable to iodine deficiency. We have started from a merely empiric point of view, the one, namely, that had been admitted by the first adepts in iodine prophylaxis and from which it is argued that a body, whose curative action on goiter be ascertained, might with some reason be viewed also as a possible agent of prevention and this without prejudicating either the essence or the mechanism, direct or indirect, specific or non-specific, of that action.

I shall no longer dwell on this thesis, which will later on be evolved before you. May it suffice to recall that we apply prophylaxis by means of iodine in two spheres: in schools and among the population. Scholar prophylaxis is realized in arranging the periodical absorption by pupils of a tabloid enclosing a small quantity of iodide; this method, however, being rather of a curative

than of preventive character, cannot be expected to give other than incomplete results, since we are aware that thyroid hypertrophy prevails largely at the pre-scholastic age and that goiter, on the other hand, may develop long after the schooling period. Anti-goitrous prophylaxis, therefore, to achieve efficacity, must reach the population generally, and, for this purpose, the admixture of a certain amount of a iodic salt in a victual consumed by one and all from infancy, viz. in our kitchen salt, has been resorted to, an idea which, again, is not a novel one. This, at any rate, is the prophylaxis which the Swiss Goiter Commission has championed towards our authorities and which is now carried out according to methods about which you will hear more in detail during your debates, and on which, therefore, I need not here comment further. One point must be called to mind at this juncture, as of essential importance: it is that of the possible drawbacks, which the administration of iodine to a whole population may bring in its train. The method has been taxed with bringing about the multiplication of accidents of iodism and with provoking the generation of Basedow goiter, or, if you prefer, with the basedowification of the goiter. We must, however, discriminate: the fact is fully admitted, and our statistics prove it, that an excessive and uncontrolled consumption of iodine preparations may have undesirable consequences; but a remedy is at hand and not difficult in its application: it consists merely in a rigorous control of the sale and dispensation of these preparations. For this purpose, our new pharmacopea provides the inclusion of iodine and iodic salts among the separanda.

An infinitely more complex and delicate character inheres to the question of the Basedow in connection with the consumption of iodized salt: it seems, at all events, to have been demonstrated that with some subjects, predisposed no doubt by a specific idiosyncrasy, the ingestion of a certain quantity of iodine, be it even in as minute a proportion as that contained in our iodized salt (5 milligrams per kilogram) may provoke the emergence of a symptomatic complex analogous to the symptoms accompanying Basedow goiter. These facts have not escaped the attention of our commission, but are actually forming the subject of a very close inquiry, the definite results of which will shortly be made public. We have been able to base this inquiry upon the materials of a provisory investigation by which the Federal Office of Hygiene had endeavoured to bring home to the cantonal authorities the dangers of the unrestricted sale of iodine and its preparations.

Our own inquiry will no doubt enable us to appreciate the ascertained facts as to their real significance and to draw a balance between the gravity of the accidents in question and the advantages of iodine prophylaxis as instituted by ourselves. As regards actual results of the said prophylay, we may not expect them to become palpable before the lapse of a few years. By then, we shall perhaps have succeeded in lifting the veil which still cloaks the original cause of goiter endemic. We also may augurate that goiter conferences of the future find before themselves a greater amount of positive facts than is given to us to deal with to-day and that defeat of the enemy may thus come within sight! Before leaving this subject, I have to allude to a few of the tasks among those undertaken by our commission, such as are: local inquiries, the publication of instructions for the examination of school-pupils and recruits and which, if properly followed, will allow us to establish accurate statistics. As regards especially our investigations on thyroid hypertrophy among recruits, we have met with the most efficacious support on the part of the sanitary service of our army and of its director, Colonel Hauser; those investigations are now carried out with a precision that will impart real value to the materials collected. Lastly, I have to mention the researches undertaken by Dr. von Fellenberg on behalf of the commission and bearing on the presence of iodine in physical surroundings and in foodstuffs and the results of which researches are, to my belief, known to many among you.

And now, to approach conclusion, let us revert to our conference:

The notion of organizing an international conference of the savants specialising in researches connected with the problem of goiter, a malady of almost universal character, was certainly an obvious one and surprise might be felt at its not having arisen earlier. A suggestion to that amount was addressed few years ago to our commission by the eminent pathologist, Professor Aschoff of Fribourg in Breisgau (Baden), who thus became the spiritual father of our conference; the idea was moreover strongly supported by our regretted colleague Prof. Hotz of Basel. I hardly need to emphasize our elation — yet excluding vanity — at our having been thought of as organizers. That this realisation has taken some time to come about is due to reasons of opportunity on which I have not to insist. What really matters, is the fact of the idea having taken shape and that we are now here assembled to form this first International Goiter Conference. From a certain

reserve we felt as befitting those embarking on a new venture, we resolved on a closed conference to be constituted upon direct invitations, i. e. without the intervention of governments. We might, perhaps, be exonerated in regard to some unavoidable omissions that may have occurred in sending out those invitations. We crave the pardon of those whom we may have forgotten and beg them to consider that this conference has been a first start and that the organizers of successive ones will certainly make good the omissions we have involuntarily commited. I have little doubt, moreover, that future conferences will be organized upon a different basis and that the interest of governments will be enlisted. We extend very sincere thanks to the savants who so benevolently accepted our invitation, and have arrived, respectively, from the Argentine, Austria, Belgium, Brazil, Czecho-Slovakia, France, Great-Britain, Hungary, Italy, Japan, the Netherlands, Spain, the United States of America and Yougo-Slavia in order to take part in these first sessions on the goiter; they will perhaps allow me to express particular thanks, also, to the physicians of my own country who have, on their part, so readily concurred. Our conference will be a laborious one. We have before us a very heavy program, comprising a whole series of important questions, statements on which will be submitted to you by savants whose names spell authority and whose collaboration we appreciate as of highest value. I am certainly at one with all of you in the earnest wish, that your labours may prove useful and abound in results. This personal contact among scientists specialising in problems of capital importance, this disinterested confrontation of their respective views, these three days' discussion and conversation now before us — all this, certainly, cannot remain without its outcome. If our conference will not — nor will you assume that it shall — carry full light at once into a domain where so much obscurity obtains, we may nevertheless look forward to one primal result: The unification, namely, of the working methods adopted by those striving for the solution of the problems involving the goiter. I could hardly allow myself to insist on this neccessity, so obvious to me, of the unification of the methods of investigation and of nomenclatures. It would constitute a very important step if this conference could, if not carry through integrally, at least motion its realization and thus prepare the ground for its successors who are to complete its work.

Having formulated this desire, I now proceed, Ladies and

Gentlemen, to declare the first International Goiter Conference to be open ! »

M. Carrière dwells, further, on a few matters of an administrative order. He draws the attention of membres of the conference to the exhibition installed in some of the University rooms and the organization of which — excellently directed by Professors de Quervain and Wegelin and Dr. Stiner — has been made possible through the favour of a great number of savants whose preparations and documents have been put at our disposal.

It is also pointed out that members' statements, as far as they came to hand in time, have appeared in print and will be distributed to all participants. On that score, the conference will no doubt regret that Mr. Plummer was unable to prepare his relation on the Pathological physiology of goiter, as requested, and his being prevented from coming to Berne. The absence will be further regretted of Messrs. Marine and McCarrison, but their statements will be read and commented on, Mr. Marine's, namely, (on the Pathological anatomy of the goiter) by Mr. Graham and Mr. McCarrison's (Etiology and epidemiology) by Sir James Berry.

The Conference thereupon decides on the nomination of a certain number of honorary presidents, who are in turn to conduct debates, the following gentlemen being appointed by acclamation: Professor von Eiselsberg (Austria), Professor Biedl (Czecho-Slovakia), Professor Bérard (France), Professor F. von Müller (Germany), Sir James Berry (Great-Britain), Professor de Verébély (Hungary), Dr. Muggia (Italy), Professor Josselin de Jong (Netherlands), Professor Nicolaysen (Norway), Professor Marañon (Spain), Dr. Van Meter (United States of America), Professor C. Roux (Switzerland).

On the proposal of Professor Roux, a message of sympathy is despatched to Professor Jacques Reverdin, one of the earliest pioneers in goiter research and whose age had not permitted his participation in our conference. A reply expressing his emotion and gratification was communicated to the assembly during a subsequent sitting.

The conference, now under the presidency of Professor von Eiselsberg, proceeds at once to the discussion of the first item of its order of the day, viz. the question of the pathological anatomy of goiter, and which is introduced by a statement from Professor Aschoff of Fribourg in Baden.

The conference came officially to an end on the 26th of August, at 6 p. m. The texts of its three days, deliberations, recorded further on, are there in attest of their full importance. In a short résumé, Dr. Carrière, president of the Swiss Goiter Commission, dwelt on the general results of the work accomplished by the Conference and expressed gratification on account of its having fulfilled the expectations of its initiators. — If, as could be foreseen, it has brought to light a good deal of divergency of opinion on many points, notably on the subject of goiter etiology, it has, on the other hand, incontestably cleared the ground to a notable extent. Though not having as yet landed on the exact definition of goiter, opinions seem nevertheless to have appreciably concentrated and the day not to be very far, when the different theories, now still confronting each other, will have achieved concordance. To have arrived at this stage, appears to me of good augury as a first result emanating from this meeting of savants devoted to the solution of these grave problems. — But there is more on which to rejoice, seeing that on some points the conference has been able to record results of a positive character and to which it has testified by two resolutions reflecting clearly the spirit that animated its debates:

The first of those resolutions viewed the unification of anatomo-pathological nomenclatures, the necessity of which I abstain from underlining anew, the conference debates having moreover shown that it would not be of very difficult realisation. A small committee, composed of Messrs. Aschof-Fribourg i. B., Graham-New-York, de Josselin-de Jong-Utrecht, Roussy-Paris, M. B. Schmidt-Würzburg and Wegelin-Berne, who had started preparatory work already during the conference, has been charged with the task of formulating precise proposals, based in a general way on the Bernese nomenclature, and with enlisting, according to need, the collaboration of other persons.

The second resolution was also in the way of a unification, namely, of statistics and of the methods of investigation, through which alone the cluster of facts and hypotheses can be disentangled and the final solution of the problem be brought nearer. The task of studying this question is to be entrusted to a comittee of personalities from the different countries and to be designated by their respective governments; the Swiss Goiter Commission has been assigned by the Conference to advise on the ways and means by which the said committee is to be constituted. To the latter will also incumb the mission of arranging further

conferences, it having been unanimously recognized that Berne was only to be considered as a first stage on the way towards conclusive results.

The Conference has appeared to be unanimous on a further point and not by any means the least important — viz. the necessity of pursuing experiments of anti-goitrous prophylaxis by the dispensation of iodized salt and iodic preparations specially destined for scolastic prophylaxis, as is already in practice in different countries, notably in Switzerland. With this purpose in view, the following resolution had in fact been prepared by the Italian members of the Conference, and its principle would certainly have been formally sanctioned, had time permitted its discussion:

« The members of the First International Goiter Conference, « convinced of the expedience of extending iodic prophylaxis « in a general manner by the means of iodized kitchensalt, con- « currently with general hygienic provisions, to all regions pre- « senting endemic in any degree of gravity; being further convinced « of the indispensability of a preliminary ascertainment of the « aspect, extension and gravity of the endemic in any given district, « express the desire of uniform criteria of discernment « being adopted, such as could be easily applied even where the « endemic be less persistent, and that systematic investiga- « tions be undertaken for the purpose of determining in every « region the physico-chemical, hydrographic and cultivatory con- « ditions of environment, together with the habits of life of the in- « habitants (personal and domestic hygiene, alimentation, occupa- « tion etc.), investigations which might afford an inference as to « whether, or not, the same conditions must in every case be held « responsible for the creation and maintenance of a center of « affection. »

Thus, the work of this conference has not been superfluous, since the achieved results afford a good presage in regard to a following one and for which the Swiss Goiter Commission has been charged to prepare the way. M. Carrière expresses the gratification of the Commission in accepting the mission confided to it by the Conference through the resolution afore-recorded and which it gladly undertakes to fulfil with the utmost endeavor.

M. Carrière desired once more to convey the thankfulness of the S. G. C. to all who have taken a share in assuring the success of the Conference of Berne, viz. the Federal, cantonal and municipal authorities, whose moral and material support has proved so precious to the organizers; the cantonal Department of Public

Instruction, who has put at our disposal the aula and other rooms of their handsome University building; to the exhibitors, whose ready compliance surpassed every expectation; and, finally, to the members of the Conference themselves who have concurred to form this large assembly and whose reports and relations have lent to this primal meeting the significance of a veritable scientific event. Mention is also made of the preponderant part taken in the organization of the Conference by Professors de Quervain and Wegelin; Dr. Carrière is certain of being the interpreter of a general sentiment in addressing to the gentlemen named a specially cordial vote of thanks on behalf of the assembly. He concludes in giving renewed expression to the hope that future conferences will accomplish the ultimate realization of the work initiated by the one now ending.

Following on M. Carrière, a discourse was pronounced by Dr. Hauswirth, representing the Municipal authorities of Berne, and the tenor of which is recorded below:

« The City Council of Berne has imparted to the municipal physician the task of representing it at the International Goiter Conference and to convey to this distinguished assembly their best wishes for the success of its labors. I am conscious of speaking in unison with the authorities, as much as on behalf of the entire population of this town, in expressing our thankfulness for the honor of Berne having been made the abode of your Conference.

Though it be customary for us to welcome eminent guests only under fine weather conditions, we have to regret that the marvellous view upon our eternally snow-clad mountains, which at other times can be enjoyed from this place, has been, during the three days of your conference, concealed behind a grey wall of rainy clouds. Our authorities, however, who, in consequence of the devastating hurricanes and thunderstorms of this summer, have to struggle with tasks almost as difficult to solve as the goiter problem of this illustratious assembly, are confident that you will not hold them responsible for the truly deprecable meteorological state of things in your Conference town.

I live in the best of hopes that to-morrow, when motor-cars will convey you through our beautiful Bernerland, towards Riggisberg, there to admire the convexities and prominences adhering to the necks of our unlucky compatriots, you may have the chance, also, of admiring thence in a clear view those gigantic eminencies of our country's surface, the Bernese Alps !

Your labors and researches being of such singular importance to our people, we hold their authors, who have come here from all parts of the world, as highly deserving of all the recreation that a few sunlit days in Switzerland can afford !

And it is under this reflection also that I conclude in begging the members of the International Goiter Conference, to accept on behalf of the City of Berne our heartfelt thanks ! »

Professor von Müller, in his turn, spoke in the following terms:

« At the conclusion of our session, it is our common desire to present our most sincere recognition to those gentlemen by whom this Conference was convoked and organized in a fashion so exemplary, Messrs. Dr. Carrière, Professor de Quervain and Dr. Stiner having been the leaders, and also to the other gentlemen of the Swiss Goiter Commission. —

« The positive solution of the problems discussed may not be expected to result from one conference. Its task may rather be looked for in the settlement of an understanding among the physicians and investigators in the different countries and territories of research and the preparation of new ways towards the solution of the problems. This aim has unmistakably been brought nearer by the Berne Conference, in departing from which every participant will carry away a great many new conceptions and experiences. A study of the exhibits has afforded us an idea as to the great diversity in which the goitrous affection occurs in the respective countries: The thyroid gland of the newly born, already, as shown in Wegelin's preparations, presents a disposition different from that of the Munich one. In the former case, as, moreover, in congenital goiter in Switzerland, solid cellular columns are predominating, whereas in Southern Germany, the new-born thyroid gland shows, almost exclusively, the vesicular form. Juvenile goiter in Switzerland offers, together with that of Vienna, the aspect of parenchymatous proliferation, while colloid goiter is the rule in Germany. In the goitrous preparations from Holland and Norway, colloid abounds to still a greater extent than in Southern Germany. An extraordinary regionary diversity seems to prevail, also, in respect to goiter toxicity. We have gathered entirely new facts concerning the diffusion of endemic goiter in France, Holland, in the Himalaya and, especially, in Switzerland and learnt above all that endemic districts are not by any means maintaining permanent conditions, but are undergoing decided changes in the course of decennaries.

It is urgently desirable for us to become much more precisely acquainted with the diffusion and character of endemic goiter in the different countries of the world and we appeal to their governments with the request that they may arrange for statistics on goiter prevalence being drawn up. Our debates have left us with the impression that goiter is by no means an affection of uniform character. According to McCarrison's report, it seems to offer a different complexion in the Himalaya from the one it shows, for instance, in central Switzerland or in the northern countries, the Chagas disease being left entirely out of consideration. Epidemic goiter ought evidently to be well distinguished from the endemic variety, as should be done also with the genuine Basedow disease, in spite of all the transitions leading from goiter endemic to cretinism. A great difference seems, on the other hand, to prevail in the respective countries as regards effect and dangers of iodine dispensation.

It is thanks to Swiss hospitality that the workers in our branch have been able to meet as fellows from all the parts of the earth in common deliberation on an important problem, for the accomplishment, that is to say, of a real work of peace! After well ponderated preparation, only such men were called in to debate on a closely circumscribed question as were known to have undertaken these problems in a thorough manner. The way had thus been paved for the participants in the conference to come to a ready understanding, and a fruitful debate has been the outcome. The time of great international congresses, at which medical men met in their thousands, appears to me as having past; they segregate into a series of special congresses, holding their sessions apart from each other, without an inner cohesion, and whose participants hardly become acquainted to one another. Few of the metropoles, moreover, would still find it possible to arrange for the lodgings and to muster the enormous financial means required in connection with a universal congress. Besides, the great official apparatus which is usually put into function involves not only great sacrifices of time, but also occasions impediments of a political character, which, in our period, are not yet quite easily to be overcome. Here, then, in Berne, a new type of international conferences has been originated, that deserves of imitation and, before all, of our thanks.»

Upon which, M. Carrière declared the First International Goiter Conference to be closed, inviting its participants to attend, equally, at the next conference.

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The official program of the Conference was therewith concluded, but the latter not yet definitely broken up, as, on the following day, its members met upon the invitation of Professor de Quervain at his clinic in the Isle Hospital, where he had assembled a few caracteristic types of cretins and where he demonstrated to his guests his surgical methods in performing before the assistance a few typical goiter operations. During an interval, an open air lunch, graciously offered by the hospital authorities, was partaken in the hospital grounds.

Still under the direction of Professor de Quervain, a charming excursion through the Bernese country was undertaken in the afternoon and connected with the purpose of a visit to the Riggisberg Asylum. This establishment, lodged in a former patrician mansion, gives refuge amidst a population of indigents to a number of cretins of all types, sorry examples of human waste, whose number is however undergoing a steady reduction, consequent with the advance of social progress. We may hope, and the Berne Conference has confirmed us in this anticipation, that they will before long have entirely disappeared.

The return journey was effected under the tardy rays of the sun, the same having after all deigned to show itself. With the arrival in town, the moment of bidding good-bye and a hearty « au-revoir ! » on all sides, had also come. —

Mention should yet be made of the auspicious reception which took place on the opening day of the Conference (August 24th) in the rooms of the Schweizerhof at Berne and at which the Swiss Goiter Commission had assembled its guests in a congenial meeting; acquaintances where then formed and conversations entered into, resulting thus in an exchange of ideas, such as is often more fecund, even, than the debates of an assembly. —

Pathological Anatomy of Endemic Struma.

On the Anatomy of Goiter.

By Ludwig Aschoff, Freiburg, Baden, Germany.

Honored Presidents! Honored Colleagues!

The duty has been imposed upon me to take the lead in addressing this meeting. It therefore becomes my agreeable task to express appreciation and gratitude, in the name of the lecturers, to the Organizers of this First International Goiter Conference and to the Chairman and Members of the Swiss Goiter Commission for all their efforts and the time, which they have sacrificed in making all the preparations for the conference. In this connection I specially desire to mention the name of one man, to whom we are no longer able to return thanks since he has meanwhile departed from us, namely Colleague Hotz, who understood so well how to surmount with a determination and an energy, that were so characteristic of him, and with all his personal relations, the manifold difficulties which naturally obstructed the way for such a gathering, the first after the war. We shall also miss the great wealth of experience and the chain of reasoning due to his accurate observations.

This conference is for me the symbol of that periodicity, which has become manifest in all the fields of medical research. After a problem has been investigated most zealously, there always follows a time of certain exhaustion. That we have also had such culminating points along the line of goiter research, we all of us know. It may suffice to mention the names of Virchow, Chatin, Baumann and Kocher for the sake of referring to the productive labors of the past century in this field of enquiry. This period bequeathed to us the realization of the vital significancy of the so-called thyroid apparatus. It is now about 20 years, that we are living in a period of goiter research. The era of glands with internal secretion compels all special departments to take up also the careful study of

everything that pertains to the thyroid gland. This period was introduced and the preliminaries for it were made through the studies along the lines of pathological anatomy and histology, which originated in Berne and it is really in this sense, that I also consider myself called upon to address you as first speaker.

* * *

We are convened here to-day in this city of great historical importance to discuss the goiter problem. The special obligation is imposed upon me of placing a laurel wreath of gratitude before the portrait of that man, to whom we owe the most important acquirements of kowledge in the domain of the anatomy and histology of goiter. Without Langhans and his disciples we should not be to-day where we are. I look upon it almost as a piece of presumption on my part to make an address before you upon a subject, to which only a short time ago the present incumbent of the Langhans University Chair, my honored colleague Wegelin, has given a conclusive monographical foundation. If I nevertheless venture to do so, this is due above all to the desire to make clear to you the far-reaching consistency in the pathological-anatomical conception of the nature and distribution of goiter, not only in Europe but throughout the entire world. I can make this address in the name of the most noted goiter histologists, viz: Wegelin, Askanazy, vonJauregg, Bircher, Holst, Josselin de Jong, Lanz, Marine, Lenhart, Boothby, MacCarty, Wilson, Crile, Masson.

If we proceed from the usually accepted definition of Endemic Goiter or Struma as a swelling of the thyroid gland occasioned through the specific increase in tissue, then we shall recognize without any further thought that we have here a question of development, which must be treated both from the formal as from the causal point of view.

How do the different processes of development, known as Struma, originate and in what manner are they incited? These are the two questions which must occupy our attention. Inasmuch as every pathological development copies the physiological — at all events finds there its origin — there follows for us also a simple arrangement of the material into a) the physiological development of the thyroid gland, b) the pathological non-malignant development of the same, i. e. the so-called non-malignant strumas, c) the pathological ma-

lignant development of the same, i. e. the so-called malignant strumas, and, finally into d) the pathological development, with simultaneous functional interruption, of the non-proliferated glandular tissue, the so-called cretinous struma. Wegelin and I have divided this work between us. Whereas I shall speak on the physiological and non-malignant development, colleague Wegelin will address you on the malignant and cretinistic strumas.

I shall begin with the physiological development curve of the thyroid gland of man. We are aware that the thyroid gland, as all the other glands that secrete internally, acts primarily as a development gland. We shall learn more particulars about this question in the physiological discourse. All the more comprehensible does it become, that with the periodicities of life there stand in close relationship periodicities in the development of the thyroid glands. After the first indication of the thyroid gland as a solid epithelial bud between the first and second branchial ventricles, there follows a more rapid development of the gland substance incited by the ductus thyreoglossus in the form of closely connected epithelial laminae, which become separated into solid cords through more strongly penetrating mesenchyme. In these latter there appear already the first vesicles (follicles) in the second month of pregnancy through a peculiar transformation of the epithelia. While the change in the form of vesicles is going on from the periphery to the centre, there is a separation of the entire complex taking place into individual laminae. Each lamina continues thereupon to develop through the epithelial germination of the separate vesicles directed outwardly and the segmentation of the shoots, whereby through penetrating connective tissue the separation into a further number of laminae is brought about. Shortly before birth the chief work in the development is accomplished. Naturally there must be material on hand which is capable of proliferating, otherwise there could certainly be no extra-uterine development. This is to be found in every individual follicle. But it seems, however, quite certain to me, that there are differences along the line of growth in every follicle as well as in every lamina. Those parts of the laminae, which are first of all completely transformed into vesicles, are the peripheral ones, whereas in the center there are one or more residual canaliculi remaining, which are distinguished through their rather long and much indentated form from the fully developed follicles, as also through an epithelium, that can be mostly stained of a deeper

curve of growth

intra-uterine growth

lobules?

lobules?

Extra-uterine growth

color. To these central caniculi Langhans and his disciple Miss Zielinska have already called attention. I should like to consider them as the least differentiated material of the thyroid gland structure out of which in later years new thyroid tissue is most readily formed under the influence of special development stimuli. We shall however come back to this question. We could designate them as residual caniculi or as central caniculi. This is not intended to mean, that the extra-uterine development of the thyroid gland laminae takes place only from the central caniculi. Here, however, it is also the fully developed follicles that are active. But here too the growth seems to be governed by absolutely definite laws. Although these laws can not be shown definitely in the passive or the slowly developing thyroid gland, they appear much more definitely in increased growth. As we shall see later on it is the one pole in each follicle that achieves preference and that may be termed the vegetative pole. It is from here, primarily, that the new structure of the epithelium and the formation of new follicles takes place. We should like to state as a sort of law governing development, that in every follicle there is one pole preferred as the vegetative pole and that in each lamina the growth-giving energy is preserved and longest in the so-called central caniculi. It is an established fact that the thyroid gland begins to form its specific secretion, the colloid, even during the foetal existence. The quantities are, however, insignificant and very variable. This secretion is most frequently found in the peripheral follicles of the laminae and more rarely in the central caniculi.

At the time of birth the thyroid gland has attained not only clearly defined differentiation but also great weight, considered relatively. For countries free from goiter the weight is about 1 : 1500 of that of the body. An attempt has been made to explain this relatively high weight, which falls quickly 1 : 4000, as a special hyperaemia of birth and as an oedema of the parts of the throat caused through the act of birth. Such a change at birth doubtlessly exists. An attempt has been made to attribute to it also a condition particularly frequently found in the thyroid glands of the new-born, i. e. epithelial desquamation. According to the view of some investigations this scaling off of the epithelium is a physiological process and contributes towards the creation of the thyroid secretion; according to the views of others it represents a pathological process of degeneration prejudicial to child-life. We may say that at the present time, neither of these assumptions can be

regarded as true. It has been successful to reject all of these desquamation structures through the hardening of the thyroid glands of new-born children that had been handled as little as possible, performed very soon after death and executed carefully. In this manner it is shown very clearly, that it is only a question of a post-mortem maceration — of a cadaverous change which is favored by the bruising of the organ at its removal from the cadaver; a new indication for the necessity of critical investigation of possible changes produced everywhere artificially. Among such productions of art there belong also the strong agglomerations of cells found in the newly born thyroid gland, which have played such a great rôle in medical works as foetal adenomas of Wölfler. We are now in the position to state, that, as a rule, it is a question here of nothing more than especially strong contusion-products occasioned by small forceps etc. We can also prove the existence of the same structures of very dense agglomerations in the case of ectomized tonsils, of exstirpated vermiform processus etc., at the surgical places of contusion.

If we leave out of account these artificial changes there will remain of the birth hyperaemias, not taking into account the oedema, nothing that is specially characteristic of the newly-born thyroid gland.

Nevertheless the absolute fall in weight, which occurs in the course of the first month of life, is not to be considered as being brought about only by a compensation of the circulation but also actually by a diminution of the glandular tissue. This is certainly not in the sense of a degeneration of cells, as through the desquamation already mentioned but rather in the sense of the disappearance of oedema and secretion. Only very gradually does the formation of a secretion set in again. The increase in weight in the childhood years of the glands, which follows with the development of the body, can however be really attributed to a proper development of the glands. Nevertheless growth and formation of colloid keep within moderate limits until the second dentition period.

Not until then, in the boy and girl age, does a greater increase in weight begin, which continues until the beginning of puberty and even occasionally until its end. In the countries free from goiter this brings about a more or less noticeable increase in the circumference of the neck. In as much as this does not as a rule cause any inconvenience or disfigurement, we speak of a pre-puberty or puberty swelling, but not of a goiter. It is generally known,

that the swelling usually subsides after the time of puberty and the normal structure of the adult thyroid gland is seen.

With the puberty swelling it is sometimes a question of a greater filling of the follicles with colloids and at other times of the proper formation of thyroid tissue. Considered as a whole, these take place usually through a slow process of germination and segmentation of new follicles on the part of old follicles and the central caniculi. We can not speak of the development processes as in any way becoming visible. The usual type of growth remains preserved.

On the other hand the decrease which sets in after puberty is not based on a breaking down of tissue, but on a reabsorption and inspissation of the secretion of the follicle, whereas the change in the fullness of the blood can play a certain rôle. The thyroid gland of the pubescent woman experiences similar variations in size, but of course to a far less extent, at each menstrual period and at the time of each pregnancy.

The weight of the thyroid gland of an adult diminishes during life at first very slowly and at old age somewhat more quickly. The histological structure remains the same until about the sixth year. The lobules of the thyroid gland consist of medium-sized and small follicles containing colloid and rarely being empty. The central caniculi are very few in number or are even not at all present. The colloid is inspissated, tough and intensely capable of being stained. The explanation of the different capabilities of the colloids (basophile and acidophile colloid) of becoming stained meets with difficulties. I, myself, am inclined to recognize in the varying behavior towards the different coloring matters, in agreement with Wegelin, no indications of chemical differences, but only different grades of dispersity. In the colloid some crystals make their appearance. The epithelia show fatty degeneration, occurring in small drops, and pigment deposits. The structure of the thyroid gland, its lobular and follicular divisions, remains in perfect preservation.

In old age, in the seventies and eighties, there can be no talk of any real degeneration of the thyroid gland. To be sure there is to be seen a decrease and complete disappearance of the colloid, an increasing atrophy of the follicular epithelia with a peculiar transformation of some epithelia into structures containing enormous nuclei, so-called atrophic nucleus proliferation; a stronger degree of pigmentation and an increase of the paraplastic substances through a trickling together may also be seen. Accordingly

we can speak of a senile sclerosis, but not of any fibrous, hyaline, calcareous or other degeneration, such as is so characteristic of the nodular strumas which will be spoken of later. These are not to be found in the usual thyroid lobules even in very old age. The rather strong appearance of small lobules of adipose tissue must, however, be specially mentioned.

I shall not speak here of the nervous and vascular systems of the normal thyroid gland, and shall also barely touch upon the question of colloid formation and colloid reabsorption, since this will be treated of in the physiological address. In so far as it has any significance for the strumas, we shall revert to the subject.

From this short sketch of the developmental course of the normal thyroid gland in countries that are free from goiter, we have obtained an insight into the rough anatomical and histological foundations of a comparative study with regard to those processes of growth, which we observe in the so-called goiter-lands at the thyroid gland. Here also we can make a development curve and with this before us discuss the so-called struma question. For, in anticipation of this, we may say that the chief difference between the thyroid glands in countries having little goiter and those having much goiter lies in the fact that in the latter the weight of the thyroid glands during the entire life from birth till death shows the higher figures. The curve of the thyroid gland in goitrous countries runs upon higher level, if judged according to weight. For this reason all of the variations appear much more plainly in it. This can be already seen in the case of the thyroid glands of (1) the newly born. The comparative investigations, which have been carried out in Berne as well as in Freiburg on the newly born of the North German lowlands on the one hand and on the newly born of the Central European mountain regions on the other hand, have shown that the weights of the thyroid glands in the latter regions average from 5 to 6 grams more than in the former. Often astonishing figures, e. g. as high as 102 grs., are found. The difference is seen to best advantage in the comparative preparations. The newly born infant in the goiter countries is in many cases born with a perfect goiter-neck. If we expose the thyroid gland, we can see that it has developed not only laterally but also towards the back of the neck, around the trachea and the oesophagus. It represents a veritable obstruction to the respiration and the taking of food. It happens frequently that children with such goitrous thyroid glands die from suffocation. Whether the goiter is alone

morphological proof that "r"-curve in goitrous unc. same as non "r"-curve on a higher level. See our goitr. ancestors? animals.

congenital go

this seen in rats.

the cause of this, through the difficulty in being shifted or through its evident influence on the circulation, is still a matter of doubt. In the course of the last 10 years we have seen at Freiburg some 20 cases of suffocation in newly-born goitrous children from a total of 186 autopsies performed on newly-born children. No other causes of death could be ascertained in these cases. Especially did a status thymico-lymphyticus play no part in the deaths.

The histological structure of the newly born goiter is that of genuine hyperplasia. We therefore speak of this goiter as Struma Parenchymatosa Neonatorum. Whether more lobules are developed or only larger lobules are found, is difficult to determine in isolated cases. In any case the separate follicles are not enlarged. The thyroid gland resembles on an average that of a newly born one of the goiter-free countries. Naturally here also the so-called desquamation is observed, of the post mortem character of which we have already spoken. From the plethora of the newly born goiter, which is frequently very considerable, the sensitiveness of the epithelia can well be understood. The excessive fulness of the capillaries has also occasioned mention of a Teleangiectatic or Vascular Goiter. Nevertheless nothing can be said about this.

It would be most important to know, at what time this goitrous hyperplasia is developed in foetal life. Does there exist from the very beginning too great a predisposition or is it a fact that the thyroid gland does not develop to this special size until the later months of pregnancy? The question of the foetal goiter — Struma foetalis — has not yet received satisfactory investigation.

The decrease in the weight of the thyroid gland after birth takes place in a manner similar to that in the thyroid glands of the North German low lands. On an average the absolute weight decreases certainly by 1 gramme. All that I have said on this question when speaking of the normal thyroid glands, applies here also.

(2) Just as it was found amongst the newly born, so in boys and girls after the beginning of the second dentition is found a strikingly strong development of the thyroid gland as compared with that of goiter-free countries. This is the School Goiter, especially known from the North American and Swiss conditions. Inasmuch as it develops progressively into the time of puberty and occasionally even beyond that time (or at any rate it can be so developed before a retrogressive metamorphosis sets in), it is also designated as Puberty Goiter (Adolescent Goiter, goitre dit scolaire). Its dimensions can become very great. Such figures of

ing point is that "pre-puberty" or "puberty swellings" are often included in surveys of "School Goitre."

weight as 170 grammes are nothing extraordinary. Here we find also differences between the sexes. In the female sex there appears besides the puberty swelling also a menstrual, or, as the case may be, a pregnancy swelling, which will naturally also be apparent in the later years of life. For this reason the average weight of the female thyroid gland exceeds that of the male gland also in the goiter countries. The inspissation of the neck is in this form of goiter a variable one, since all the children are not affected to the same degree. Therefore we have distinguished between several grades of swelling, so as to have a definite scale for measurements in schools. The proposal, of Klinger, which was made by the Swiss Goiter Commission, has also been accepted in the remaining European countries. I refer to the clinical address.

As a rule we find anatomically a diffuse swelling of the thyroid gland. Of exceptions we shall hear more later. The contours remain smooth, and therefore we speak of a Diffuse Goiter. The extension in this type is limited to the region of the neck. It has a strong touch upon the respiratory and digestive passages, which leads to important disturbances. Occasionally even in tender years of life, in the second decade, a compression of the trachea giving a flattened sword-like appearance, is found. Unquestionably it is not only the corporal defect, which gives the impulse for an operation, but also the disturbed physical condition. The reaction upon the heart is a known fact. It will be spoken of later. We may mention here the greater filling of the vessels, especially in the capsule of the thyroid gland. The goiter in itself which occasions a charge of the overlying soft parts, is not known to me. For eventual hardening of the capsule the previous therapeutic measures taken, such as iodine treatment and irradiation, must be held responsible.

Of especial interest is the macroscopic and microscopic development of this School or Puberty Goiter. So far as I have found from my examination of the literature on the subject, we find in all goiter lands, as the United States, Switzerland, South Germany, Austria, the same structure. Any deviations require a special explanation. This structure consists of a peculiar type of growth. It is not only a question of a new formation of follicles, but also one of a considerable enlargement of the follicles themselves. In this the follicle becomes also more intensely filled with colloid, so that the entire incised surface of the enlarged thyroid gland becomes transparent. As a usual thing we are able even to recognize the enlarged follicle, which has become expanded into small cysts, with the naked eye. Such a form of goiter is called, on

account of its conspicuous distinctive characteristic, a Struma Diffusa Colloides (a diffuse Colloid Goiter, or goitre colloïde diffus), and on account of the large follicles Struma Diffusa Colloides Macrofollicularis.

Considered microscopically the structure is still more remarkable and that through the nature of the thyroid growth. We see in the enlarged follicles numerous small cushionlike projections, which are covered by a specially high and rather strongly colorable epithelium, whereas the remaining sections of the follicle bear only a low flat-pressed garland of cells. The cushionlike curvatures correspond as a whole to the vegetative pole of the follicle which is well filled with colloid. They contain numerous very small follicles that have been newly formed by segmentation. Under gradual magnification, these are seen to extend outwards into the interstitial spaces and thus contribute their share towards the general enlargement of the thyroid tissue. In this the general development of the thyroid gland is in the beginning not changed. The structure of the lobules is preserved throughout, only each lobule has increased many times in size. Because of the strong, readily visible proliferation this form of goiter is called the Struma Diffusa Colloides Macrofollicularis Proliferans.

If we consider what this kind of thyroid gland growth signifies, then we can call it a specially precipitated but otherwise absolutely physiological growth. The segmentation of new follicles from the old, which can only with difficulty be followed in the quiet, slow growth of the normal thyroid gland, becomes perceptible here. Through the relatively rapid new formation at the vegetative pole this becomes now readily recognizable. Notwithstanding the precipitate new formation the young follicles gradually follow into the structure as a whole. Accordingly, and this I say with emphasis, the nature of the thyroid gland growth has undergone no change with the formation of the Puberty Goiter. It is simply the quantity of the formation of colloid and the rate at which the follicular new formation continues, that has been changed.

If we considered as characteristic the form of Puberty Goiter that has just been described, then we must add that this does not apply to all goiter districts. In some countries we find in place of the Colloid Goiter the so-called Parenchymatous Goiter (the Diffuse Hypertrophy of the thyroid, goitre parenchymateux = Struma diffusa parenchymatosa). Here the incised surface of the enlarged thyroid gland nevertheless shows us a very changed structure. The vitreous luster of the colloid has vanished and a more

fleshy, often liverlike appearance predominates, which calls to mind the thyroid gland in Basedow's disease. From verbal information this kind of Puberty Goiter seems to occur more frequently in Switzerland as regards percentages, than, say, in Baden, in the Palatinate or in the Oden Forest. However, the colloid goiter predominates also in Switzerland during the age of puberty. On the other hand Orator could observe in Vienna almost only Parenchymatous Goiter. This difference, which seems to apply also to the United States, according to Marine and Lenhardt, reminds us of definite influence, found in the world about us, which cause a regional, different appearance in the Puberty Goiter. It is very strange, that the nature of the Viennese Puberty Goiter, as colleague Bürkle-de la Camp has informed me, has been changed during the past year, and also independently of iodine prophylaxis. In the place of the Parenchymatous Goiter we really have at present the Colloid Goiter.

what are environmental influences accounting for difference

Notwithstanding the lessening of, or only temporary outbreaking of the Parenchymatous Puberty Goiter, we must occupy ourselves very particularly with it. In the histological view we recognize a general enlargement of the lobules in consequence of an increase of the parenchyma. It is a question of a new formation of follicles, which we can not however follow so readily as in the Colloid Goiter, because the individual follicles contain very little colloid or none at all. This lack of colloid leads us to understand how it is that the periphery of the Parenchymatous Goiter never equals that of the Colloid Goiter. In the latter case there occurs, besides the increase of the real parenchyma, an increase of the periphery through the aggregated colloid.

i.e. circumference

Here also we have an accelerated but throughout physiological development. Through the epithelial germination from the walls of the follicles and central caniculi and the segmentation, that quickly follows, the new follicles take their origin. We should like to conclude from that fact, that in the structure of the Puberty Goiter, and this would likewise apply to the simple puberty swelling of the thyroid gland seen in non-goitrous countries, it is no pathological, but only an increased physiological stimulus, which concerns the tissue. Why this stimulus should in the one case lead only to the increase of parenchyma and in the other case simultaneously to an increased formation of colloid, must be founded on secondary conditions. We shall speak of this later.

this also is physiological

and therefore

due to a physiological stimulus

but why? the different effect

This Puberty Goiter diminishes slowly from the middle of the third decade of life, as does the simple puberty swelling. With the

the medi mean 'epoch': first, infancy
second, puberty
third, adolescence: between childhood & manhood

recognized strong individual difference in relation to age and force in the outbreaking of the Puberty Goiter, we are not astonished if the manner of diminishing takes very different courses. The slower this takes place, the larger does the goiter, which the person affected carries with him into the later decades of life, remain. But also in those individuals, where the decrease is more evident, the weight of the goitrous thyroid gland remains noticeably higher than that obtaining in non-goitrous countries. In so far as in Europe this goiter of adults is chiefly met with in the mountainous regions, it has received the name of Mountain Goiter. The appearance of this Mountain Goiter or the Goiter of adults is a more or less characteristic one in those cases in which no complications have set in through the development of nodules, the so-called Adenomas. On the surface of incision it has a very evident transparent appearance, from which we can at once conclude the presence of a rather large colloid content. This is confirmed by the microscopic section. Nevertheless the colloid shows a greater capability of being stained, it has become more viscous and apparently inspissated. To a great extent the diminution of the circumference, which we were able to determine not only in the thyroid glands of the inhabitants of goitrous countries, but also in those of non-goitrous countries at the transition from the age of puberty to the age of manhood, is certainly due to this fact. With the inspissation of the colloid there is also an accompanying diminution of the follicle. But before this sets in, the further development of the thyroid gland has stopped, as was characteristic of the Puberty Goiter. We see no more vegetation buds, in so far as it is a question of the colloid goiter. The polster formations in the follicles have disappeared, the epithelium has become similary decreased again throughout the entire circumference. But the follicles are still large and contain abundant colloid of a thinner consistency. We then speak of a Struma diffusa colloides macrofollicularis non proliferans. As soon as the thyroid gland comes to rest, however, the inspissation of the colloid and the diminution of the follicle also set in. With this, the condition of the mountain goiter, the struma diffusa colloides microfollicularis has been reached.

Now the decrease in size of the mountain goiter keeps pace very slowly with increasing age in a manner that corresponds entirely with the age-decrease of the non-goitrous thyroid gland, and this is evident from the weight, but in the more advanced years of life the curve shows a stronger downward tendency. We could de-

signate this Old Age goiter as Struma diffusa atrophicans. It likewise shows remarkable peculiarities. The gland which has decreased in size and is, as regards weight, the adult thyroid gland of non-goitrous countries, but nevertheless a still conspicuous one, is astonishingly tough, its cut surface has lost some of the transparency and the color is approximately brown. In the histological structure we notice immediately the great decrease of the individual follicles, the high degree of inspissation and strong capability of being stained or even the disappearance of the colloid. The cells also show the same changes as in the ordinary senile thyroid gland. Some of them become strikingly large, their nuclei are increased in size and occasionally there are several of them contained in one cell. The structure resembles indeed that of the ordinary senile thyroid gland, only that the amount of colloid and the total circumference of the parenchyma are greater than in the latter. To this rule, that the goitrous thyroid gland degenerates down to the same life atrophy as the non-goitrous one, there are certainly exceptions. Not so rarely do we see that it is in aged individuals of the sixties, seventies and eighties that the thyroid gland again increases in weight. The great transparency of the incised surface again shows the increased colloid contents and the microscopic structure resembles exactly the puberty form of goiter. We could speak of a Recurring Colloid Goiter. We actually have before us a rejuvenation process, a relapse into childhood and puberty age. To what extent in this relapse the two sexes are concerned, it is not possible for me to say. Up to the present time I have the impression that it is especially the male sex that is affected. This procedure in the atrophic thyroid gland brings to mind recurrence of blood-forming bone-marrow in the long medullated bones and the abundant formation of lymphatic nodules in the marrow.

With this we have gained a survey of the life-curve of the goitrous thyroid gland. We see that it runs parallel more or less with that of the non-goitrous thyroid gland and only collectively, on the basis of the weight observations, does it run into a higher position.

The attempt has recently been made to construct a curve of the life of the thyroid gland for comparative purposes of study, not only according to the weight (Klöppel) or the vigor of growth, in so far as it is to be recognized from the histological view (Bürkle-de la Camp, Büchner), but also according to the average size of the follicles (Schaer). The thyroid glands with the greatest average dimensions of the follicles were looked upon as the ones

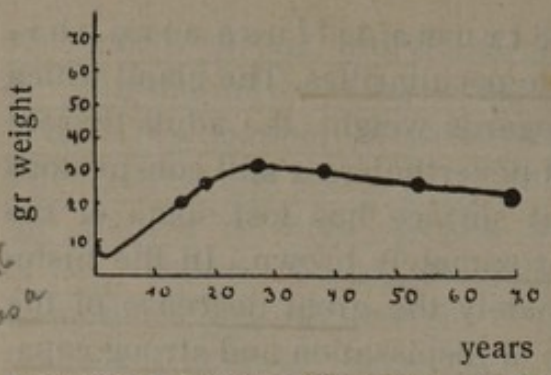


Diagram 1. Curve of growth of the thyroid gland and its nodules in a "non-goitrous" district.

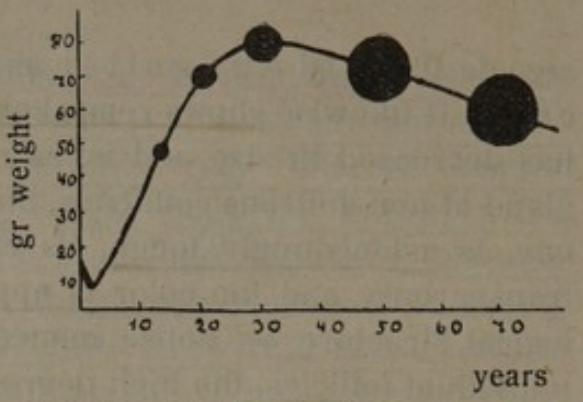
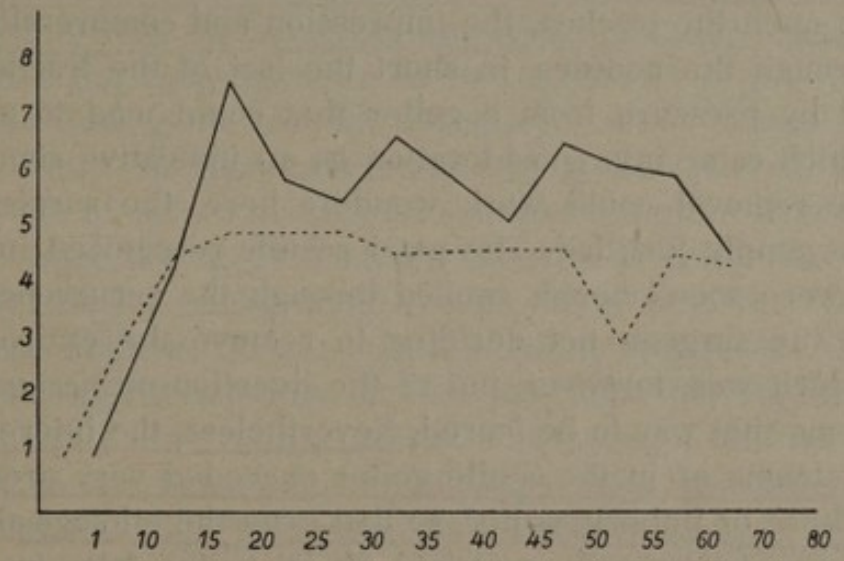


Diagram 2. Curve of growth of the thyroid gland and its nodules in a "goitrous" district.

that had the most vigorous development. In this effort the remarkable fact was revealed that the life curve of the mountain district thyroid gland rose much more slowly than that of the lowland thyroid gland. Besides in the case of the mountain district thyroid glands the average dimensions of the follicles lie continually below those of the thyroid glands of the lowlands, the maximum being about 200 micra. This is a contradiction of the above representation of the curve of growth of the thyroid gland in mountainous countries. On the other hand Büchner and May, with a rather large amount of material on hand both of goitrous and non-goitrous countries, have again figured out curves of life in accordance with the vigor of growth of the gland, as they are seen in the histological structure in its entirety, with special consideration of the proliferation processes. In this the plain parenchymatous thyroid gland was chosen as the starting point and the macro-follicular proliferating form as the maximal figure. As we see, it was not alone the dimensions of the follicles, but the decisive factor was the indications of proliferation, whether present or not present. If the proliferation buds in the enlarged follicles are being very strongly developed, then not only will the cavities of the follicles be concentrated through this fact, but also the average dimensions of the follicles would have to fall upon a medial size or even below that because of the abundant development of small new follicles within the proliferation bud. The average size of the follicles alone, such as Schaer has taken as a basis, is no real criterion for the judgment of the tendency of growth of the thyroid gland. If we however, at the same time, take into consideration the proliferation processes, then we find a far-reaching agreement with the previously described course of the life curve, which had been figured out in accordance with the weight and the histological structure as a whole by Bürkle-de la Camp on the one hand

and Büchner on the other. The most developed proliferation was found to be at the time of puberty, both in the thyroid glands of the lowlands and in those of the mountain regions. All of this proves, especially with the consideration of the curve of weight, that the growth of the thyroid gland in the period of puberty takes place quicker in the so-called mountain district thyroid glands than in the lowland thyroids, and that accordingly the development curve is not more level in the former but rises more sharply than in the latter. On the other hand the assumption of Schaer, that the maximal point of development in the thyroid glands of the mountain regions is not attained until the 30th year has been reached, can very well apply, inasmuch as the increased tendency of growth of the age of puberty is able to continue in effect until this time.



——— Thyroid glands of the mountain regions ♀ 58
..... Thyroid glands of the lowland districts ♀ 52
} not including the thyroid glands of pregnant women.

This relatively regular life curve of the thyroid gland, both of the non-goitrous and of the goitrous, undergoes an interruption through the development of nodules within the thyroid tissue. These nodules in the goitrous thyroid gland are found usually to be developed very markedly and give the characteristics to the entire goiter trouble in old age, hence this form of old age goiter has been called the Nodular Goiter or Struma nodosa, the Adenomatous Goiter or goitre nodulaire, in contradiction to the Struma diffusa. If I am speaking here of a special form of senile goiter, I do not wish to be understood as saying that these nodules can never appear at the time of youth. This certainly

does happen. I have even seen nodular goiters in children at the time when second dentition was beginning. But these are exceptions and such nodules belong to the category of varieties if they make their appearance before the second dentition or even in the new-born child. As a rule they do not become perceptible and visible very much until at, or after puberty.

Some 30 to 40 years ago this nodular goiter of adults was playing the chief rôle in our theories of goiter. Surgery, medicine and prophylaxis were busying themselves only with that. This was the brightest period of operative surgery and goiter became entirely a surgical problem. That can be readily understood, because the nodular strumas even if they were of moderate size occasioned very readily all manner of disorders, especially of respiration but also with regard to the action of the heart. Above all, it was the pressure upon the trachea, the impression and compression of the same through the nodules, in short the fact of the trachea being flattened by pressure from a goiter that could lead to a sudden death which came into consideration as an indicative sign. As the operative removal could work wonders here, the surgical treatment was amply justified. The good results recognized in the beginning were soon enough spoiled through the recurrence in the event of the surgeon not deciding to remove the entire thyroid gland, which was, however, out of the question on account of the myxoedema that was to be feared. Nevertheless, the interest in the nodular struma or in the senile goiter exceeded very greatly that in the diffuse or puberty goiter, so that even the etiological investigations were temporarily switched off on to the false tracks. For with the explanation of the genesis of the nodular struma, it was believed that the explanation of the diffuse struma had also been found. So it happened that we, at least in Europe, did not at all draw any more definite lines between the diffuse and the nodular struma. One spoke in general of hypertrophy and as a matter of fact of diffuse and of nodular hypertrophy, that is to say both processes were considered equal as regards their nature. We even transferred especially to goiter the phenomena of involution, which will be described later, and finally came to the idea of subdividing goiter in general in accordance with the results of involution. A distinction was made between the parenchymatous and the fibrous, between the colloid and the haemorrhagic, and cystic ones, etc. Not until the exact histological investigations of the nodules, which had been initiated by the disciples of L a n g h a n s and encouraged by the pathological institutes of the chief goitrous countries, had

been made, naturally of course only by the pathologists, did we come to the conclusion that we ought to make a more definite distinction between the diffuse and the nodular goiter; and that the formation of nodes was only a matter of a secondary nature — a something that has supervened, and which could advantageously develop on the soil of a degenerated thyroid gland but could not constitute the real essence of goiter. We brought this into connection again with former views, where the nodules had already been considered in their true nature as genuine tumors and called adenomas (Virchow et al.).

As it is now well known that swellings come under different developmental laws from physiological tissue, so it was to be assumed, from the beginning, that it would not be proper to draw any direct conclusion regarding the cause of the goitrous growth of the thyroid gland from the investigations on the nodular tumor formations. Since the investigations on the causes of goiter that have been made during the last few decades, received a new impetus and apparently one that was attended by greater success than formerly, it can therefore be understood, that the interest in the nodules and especially in the nodular varieties of goiter has receded somewhat into the background. As, however, from the standpoint of practical medicine these as usual continue to constitute the chief branch of surgical activities in this line and also maintain their special interest from the theoretical standpoint of the pathology of swellings, we are hence obliged to occupy ourselves more particularly with them, notwithstanding their unimportant significancy for the etiological researches.

The so-called goitrous nodules occur in all sizes from those that are hardly visible to the naked eye to those of the size of a fist or of the head of a small child. They are generally globular in shape and rarely of an oval form. The greater the size the more defined do they appear on section contrasted with the remaining thyroid parenchyma. Their incised surface shows the most varied structures, which have so often been described that it would be extremely tiresome showing if we gave the description over again. Only the most fundamental matters will be stated here. The histological development of the nodules, that have not suffered any further changes, indicates to us that it is a question of genuine tumors, i. e. of real adenomas and not of a circumscribed hypertrophy of the thyroid tissue. How can we know that? In contrast with the normal or the enlarged thyroid tissue, which always shows a typical lobular division, the Adenoma shows nothing of this

adenomas

nature. They exhibit a more or less radiate structure, that is essentially homogenous, in which we can find one or more centers as starting points of the tumor formation. We can speak here, according to the idea of Ribbert, of one or occasionally of several conglomerated development centers. A second important characteristic of adenomas is their histological constitution. In the typical cases the newer nodules show at least a so-called parenchymatous structure. But this parenchyma is no ordinary thyroid gland parenchyma, such as we find in a youthful thyroid gland, i. e. one that is made up of nothing but the smallest follicles which are often still solid or containing scarcely any colloid. Here predominates an entirely different typical growth. The glandular tube-like caniculi, or solid trabeculae, which can be observed only occasionally, are something quite ordinary. The segmentation into follicles and the filling of these with colloid is noticeably suffering delay or is entirely wanting. The epithelial trabeculae disintegrate into epithelial remnants, which in no way resemble the follicles of the thyroid gland any longer, especially as the epithelium is much higher and broader than in the normal. Naturally there are all transitions to the proper follicle structure, that contain colloid. In such cases we can absolutely not determine from a small field of vision, whether ordinary, say hypertrophic, thyroid tissue or an adenoma lies before us. The survey over the
(3) whole, the absence of the lobular division, the eventual juxtaposition of normal and abnormal types of development allow us to decide. We could speak of adenomas of different degrees of maturity. There are continuous transitions of rapidly maturing adenomas, following the normal type of growth, to those maturing too late or remaining unchanged in an incomplete state of maturity.

A third distinctive mark is the special vascular system
(3) of the adenomas. Their vascular network is not inserted physiologically into the general vascular network of the thyroid gland, but depends, as it were, on a few trunks of vessels which alternately here and there enter and leave the same through the capsule. Within the adenoma there is also another kind of vascular division in conformity with the different structure, as a deviation from the normal course of the vascular network is certainly characteristic for all swellings. From this we can explain the tendency towards disturbances in the circulation in the nodules, which will be described later. The case is similar regarding the lymph vessels, so that conveyance of the tissue lymph is easily arrested. As a visible

indication of this we find in the adenomas an aggregation of colloidal substances in the interstitial tissue between the follicles, a phenomenon which is only seldom, if ever, demonstrable in the normal thyroid gland.

With this inadequate vascular supply and with this lymph stasis, the fourth characteristic indication of the adenoma is at least, in part, connected, i. e., its great tendency towards degeneration. This is not intended to signify that the factor, which was emphasized by Ribbert, namely, the spontaneous involution of all developing tumors in their oldest, i. e. central-sections, does not rightly exist. On the contrary it is in the adenomas of the thyroid gland that the premature degeneration of the parenchyme cells and their substitution through the diffusing connective tissue, saturated with hyaline, is best demonstrable. In this way central fibrosis or cirrhosis conditions come about. If it is a question of the so-called nodular colloid goiter, i. e. an adenoma of a more mature character, then the colloid retention in the connective tissue-like meshes also comes into account. As a matter of fact it is in this variety of goiter, that we see the disintegration of the follicle through the breaking down of its walls and also plainly taking place the direct extravasation of the colloid into the surrounding tissues. Here we can learn that the desintegration spot of the follicle lies opposite the vegetative pole with its somewhat higher epithelium.

Through this fibrous and hyaline thickening of the paraplastic substance, which proceeds at first centrally and then gradually peripherally, with the simultaneous disappearance of the parenchyma, there arises the fibrous nodule out of the originally parenchymatous nodule or, in the case of more mature varieties, out of the colloid nodule; this we designate as Struma nodosa fibrosa. Through secondary calcareous deposits an increasing sclerosis can set in, which, with a possible later — if very rarely occurring — substitution for the tissue of bone, may end finally in perfect ossification.

Not always does the involution in the development center take place so smoothly and uniformly. It is especially with the goiters abounding with colloids, that rather marked disturbances of the circulation with haemorrhages and sanguineous softening are not rare occurrences. The haemorrhages are favored by all kinds of degeneration processes, the vessels often being greatly enlarged, and simulating an angiomatous or cavernous condition of the tumors. If the haemorrhages and necrosis have once begun, then other

haemorrhages into the softening tissue can take place, which will lead to sudden considerable increase of pressure within the nodules. The blood can, when coagulating, separate by weight, but finally can also be further liquified. Through marked thickening of the connective tissue at the limits of the haemorrhagic softening, the well known cyst formation takes place, the walls of which can be infiltrated with cholesterin, while in the cystic fluid the cholesterin itself is precipitated in glittering pieces. Through secondary calcification in the cystic wall, an atherosclerotic hardening of the same is brought about. Through the fact, that some of the nodules may take on a fibrous, hyaline-softening change, others a calcification one and still others a haemorrhagic-cystic softening one, the originally more homogeneous structure of the parenchymatous or colloidal nodular struma becomes very much altered. Unquestionably it becomes evident from this whole description that we are familiar with only one non-malignant form of goiter, and that is the Adenoma. We therefore speak of Struma nodosa s. adenomatosa. All other designations, which formerly played such a great part in the classification of the strumas, such as Str. fibrosa, Str. calcificans, Str. haemorrhagica, Str. cystica, are only varieties of involution of one and the same non-malignant form of tumors. No special value can be attached to these adjectives. It is just as unimportant if the Struma nodosa takes on a more immature parenchymatous or a more mature colloid character. We regard it only as a sign of a special condition of irritation to which the nodule has been subjected, if the nodule itself shows the structure of a proliferating, macrofollicular struma colloides, such as we are accustomed to find in the real thyroid tissue as an indication of the irritation of puberty. The fact that such nodules can show such transformations quite isolated while the surrounding glandular tissue shows an unaltered structure, is more evidence of the definite independence and special capability of reaction on the part of these adenomas. Whether this stimulation comes to the nodules through the blood or through the nerves is a question which has yet to be considered when we are discussing the genesis of goiter. Then we must also consider if the nodules have any hormonal influence on the rest of the body and if any, of what nature is this influence.

Before we take up that question, the formal origin of the nodules must still be touched upon. Where and how do the adenomas originate? First of all, there is the question, whether they occur only in the goitrously enlarged thyroid glands,

that is to say, in the goitrous countries. This must surely be answered in the negative. The more carefully we examine the thyroid glands of non-goitrous and goitrous countries, the more certain may we be, at least in the histological investigation, that we shall find very small adenomas, so-called adenoma nuclei. We may feel justified in saying, that the tendency to form adenomas is a general characteristic of the thyroid gland, just as is the case with the mamma, the prostate and also to a moderate degree with the pituitary body. We can therefore study the development of the adenomas just as well and perhaps even better in the thyroid glands that have not undergone any goitrous changes than in goitrously enlarged ones. For in the former they develop very slowly and remain small, so that their earliest stages of development can be better followed. Then it can be seen very plainly, that the majority of the adenomas, at least of the so-called parenchymatous ones, take their origin from the so-called central caniculi. It is a question of the better formation of germs at several spots of the central caniculi, the epithelium of which has thereby taken on an especially strong capability of being stained. As we see, the character of the epithelium is changed from the beginning. First of all these cannulae, which are dark colored with nuclear staining, simply lie like a foreign mass in the particular lobule without distorting it. Gradually with the continued development, the displacement of the contiguous follicles becomes noticeable, and later on the adjoining lobule, and the structure of the goiter proper becomes more distinct. With still larger nodules atrophy due to pressure of the surrounding thyroid tissue becomes very pronounced.

While the development of the small parenchymatous nodules can very readily be followed, it is more difficult to meet with success in the case of the so-called colloid-containing nodules, which tend to develop just in diffuse strumas which contain considerable colloid. In the beginning we can not say here whether the specially strong cushion formation in a rather large follicle, which corresponds to a transformed central caniculus, will lead only to the formation of an adenoma filled with colloid. The adenomatous character will not become more distinct until with the further development, if the new formation is not adapted to the structure of the lobule, but raises this through displacement, and if the neighboring lobules are likewise affected by the pressure. In this way it can be explained that it is in the colloid-rich diffuse strumas that the demarcation towards the developing adenomas is much more difficult to define macroscopically as well as microscopically, than

in the parenchymatous nodules in the ordinary thyroid gland. Under no circumstances do we want to be understood here as declaring that in the ordinary glands it always happens that only parenchymatous nodules originate and in colloid-rich thyroid glands only colloid nodules, but it is really the case that one finds a certain regularity. The difficult of distinguishing hyperplasia from adenoma in diffuse strumas, rich in colloid, must be emphatically mentioned here. In those cases, where the new formation of the nodules takes place in simultaneously developing parenchymatous strumas so diffusely, that a proper demarcation of them does not at all occur, we also speak of adenomatosis.

If now, as has been already said, the adenomaformation is observed in thyroid glands of non-goitrous regions as well as in those of goitrous regions, we are justified in asking, whether a difference and what difference between the two exists. To this question the reply may be made that the essential difference is only the difference in size. Whereas the adenomas of the thyroid glands that are not goitrous remain usually relatively small and only rarely make a surgical operation an urgent matter, the adenoma development in the goitrous thyroid gland generally increases to a definitely nodular structure way, which is great and endangers life. The intensity and the extensity of development are accordingly the factors which distinguish the nodules of the goitrous thyroid gland. Compared with these quantitative differences the qualitative differences fade into the background. Taking everything into consideration, the adenomas are naturally the same in both kinds of thyroid glands. But we understand that the more rapidly and markedly developing adenomas of the goitrous thyroid gland have also a stronger inclination to undergo processes of involution and degeneration, i. e., in them there are fibrous, hyaline, calcareous, haemorrhagic and cystic transformations to be found in greater abundance and to a greater extent than in the adenomas of the otherwise unchanged thyroid gland.

If it becomes a question of making more especially quantitative distinctions, then we may be inclined to think that the nodules develop so strongly in the goitrous thyroid gland, only for the reason that they have been perhaps planted in a fertile field. Inasmuch as these nodules do not make their appearance until the time of puberty and after that time, we can also say that the stronger the puberty swelling, the stronger and more enduring is the development of the adenomas that

exist in the thyroid gland. The marked nodular structure is accordingly no direct but an indirect consequence of the goitrous noxa. The next consequence of the same is the goitrously increased development of the thyroid gland as a whole, especially at the age of puberty. Only on the basis of this goitrous stimulation of the total thyroid gland, does there follow later on an increased development of the adenoma. But of course in the above nothing has been said about the causes of adenoma formation.

Before we turn to this question and to that of the causation of goiter, we must still make brief mention of a form of struma, which really does not belong to our subject, namely to the Endemic Goiter. This is the so-called Basedow Goiter. Grave's disease, or Exophthalmic Goiter, makes it appearance everywhere in the world. It takes its origin independently of goiter noxa. The transformations, which a Basedow thyroid gland makes manifest to us, are well enough known. It is here far less a question of a proliferation process of the thyroid tissue, as we see in the puberty swelling or even in the puberty struma, but of alterations of the follicular epithelium within the follicle. The epithelium becomes greatly enlarged, becomes almost high-cylindrical, presses forward papillary-like into the cavity of the follicle and then takes the place of the more or less disappearing colloid. In this manner the individual follicles take on the appearance of central caniculi with abnormally high epithelium. How far in the ordinary Basedow thyroid gland there is also a proper new formation of thyroid follicles going on, must remain open in the individual case. However this does not play so important a part. We also get here the impression that there is something wanting as regards maturity, but more in the functional than in the morphological sense. The nature of the development reminds us of the parenchymatous strumas of the period of puberty, but is distinguished from it through the special prominence of the epithelial hypertrophy. Thus it happens that we can observe transition structures between the Basedow thyroid gland and the Struma parenchymatosa, although both differ greatly from each other in their outspoken forms.

We have thus far spoken only of Basedow thyroid gland. Here it is a question of a transformation of a thyroid gland with colloid-containing follicles, that had thus far been normal, into one with epithelial hypertrophy within the individual follicles. The increase in dimensions of the real thyroid tissue does not come into account here. Now there are certainly also some Basedow

cases with greatly enlarged glands, i. e. strumous thyroid glands. These are in fact goitrously changed thyroid glands, which subsequently are subject to a Basedow change. We accordingly meet with them only in goiter countries. To the best advantage we find these changes appearing in the diffuse colloid strumas here and there. We then speak of a Basedowificized Goiter, a Struma diffusa colloides basedowificata. Such cases are not at all rare ones. Into this group comes also the so-called Iodine-Basedow in the goiter countries. Far more rarely it is observed that a Basedowification takes place in a nodular struma and that both in the thyroid gland and the nodules at the same time or if possible only in the nodules. This is then the Struma nodosa basedowificata. These cases are instructive for the reason that it is probably due to them that the Basedow toxin is transmitted to the thyroid gland not by way of the blood but by way of the nerves. Otherwise such an isolated affection of a nodule would be scarcely imaginable. To be sure, we can also picture a possible special sensitiveness of the nodular tissue, which reacts more easily to haematogenously conveyed toxin. Therefore we take it that that Basedow change occurring in the ordinary strumas progresses quite irregularly, often only here and there to be seen and at times scattered regularly over the entire thyroid gland.

Now, what was to be said on the formal genesis of the goiters has been essentially stated. If I now turn my attention to the causal genesis I shall speak very briefly in view of the addresses which will follow. Morphology must necessarily emphasize this one thing in the discussion of this question, that we have to make a strong distinction between the origin of the diffuse goiter, i. e. the real one, and that of the nodules. It follows from my previous remarks that the predisposition to the formation of nodules is found in all thyroid glands and that it is only their especially strong development in goitrous-enlarged thyroid glands which is anything remarkable and indeed only probably the result of the generally increased metabolism in the goitrous thyroid gland is outstanding. Accordingly for the morphologist the question simply is: How does the diffuse goiter originate? Here also he is obliged to limit himself to the knowledge gained from the comparative histological findings and from the chemical investigations and experimentation. The first mentioned prove that a goiter ailment necessitates a general increase in weight of the thyroid gland, even in those individuals, who on mere sight do not appear to be goitrous. Hence there must be a toxin on hand that has gener-

al influence and which occasions a weaker or stronger reaction according to the individual disposition. It is the belief to-day that the explanation of the enlargement of the thyroid gland in goitrous countries is to be found in the theory regarding lack of iodine. There can be no doubt, that the lack of iodine in the world about us plays a certain part. Comparative chemical investigations make clear to us that the percentage of iodine contained in the thyroid gland in non-goitrous and in goitrous countries shows great differences. It appears very plainly in regions poor in goiter. But the total contents of iodine in the thyroid gland in countries that have little and those that have much goiter remains about the same. We could accordingly consider that the goitrous enlargement of the thyroid gland represents an adjustment procedure in those districts that are poor in iodine-content (M a r i n e). In favor of this idea we know as a fact that after the removal of the greater part of the thyroid gland we can suppress the regeneration of the remaining part by giving abundant iodine and reversed we can accelerate it by a diet lacking in iodine. But there is still an explanation wanting for the facts, that the diffuse puberty goiter is at times a more parenchymatous one, at other times a more colloid one. Here an individual disposition towards development of the parenchymatous goiter, e. g., a weakness of the constitution has been thought of. But the previously stated facts that for a while there had occurred in Vienna almost only cases of Parenchymatous Goiter and later more particularly goiter rich in colloid, cause us to believe that special exogenous factors also play a part here. It may be a question of differences in the degrees of the lack of iodine. It has been found frequently by experience that we can favor the increase of colloid in Parenchymatous Goiter cases by the giving of iodine, by so doing we can pacify — as it were — the thyroid gland. It can accordingly be imagined that the change in the goiter types has been a result of the iodine prophylaxis, which has meanwhile been introduced. This idea is, however, contested. If it is not the iodine alone, then we shall have to think of disturbances in the equilibrium between the iodine and other substances. For a long time lime has been in the picture here. The peculiar relations between parathyroid glands and the thyroid gland (B l u m) cause us to think all the more along this line. Experiments have fully demonstrated this relationship. It is possible to cause the thyroid gland in rats to proliferate if not only through a lack of iodine but reversed through an abundance of lime in the food. The more unfavorable the balance of the iodine-lime contents becomes, the more markedly do we see the formation

of goiter, which we can favorably influence through the giving of iodine or the withdrawal of lime. To what extent such bases as magnesium and strontium which are closely related to calcium, are concerned, I must, as a pathological anatomist, leave undiscussed as also the question whether unilateral nourishment with albumen, fat or carbohydrates can really generate goiter, as certain authors assert. One remark may still be allowed, namely, that the quantity and quality of sunlight exposure has an influence upon the development of the thyroid gland and must be taken into account when considering goiter genesis. From this we might be able to cite avitaminosis as a cause. But now, the pathologist — for his part — must lay stress upon the fact that local infectious-toxic stimulation, a sort of infectious illness, shall we say, does not come into consideration according to the histological determinations as a cause of endemic goiter. Chagas' Goiter has nothing in common with Endemic Goiter. Nevertheless we must remark here, that in our domestic animals occur goiter swellings in the goitrous countries very similar to those found in man. This, however, does not apply to the Nodular Goiter, even it does in some degree to the Diffuse Goiter (sheep, pigs, cattle, horses, goats). The disposition towards the formation of adenomas appears to be very different in the different animals.

Entirely distinct from the question concerning the origin of Endemic Goiter, which we must attribute to an exogenous factor, is that concerning the origin of its special varieties, which appear before us as goiter of the newly born, as Puberty Goiter, as Pregnancy Goiter and as Senile Goiter. In so far as we know that very similar, even if very much smaller, swellings are observed in non-goitrous thyroid glands which correspond to these varieties of goiter, it follows at once that for these some endogenous factors must come into question. Regarding the swellings of the newly-born — or let us say — the goiter of the newly-born, the final cause must be sought for in the special metabolic balance between mother and child. We might speak of a physiological insufficiency of the entire metabolism of the pregnant woman, which is made manifest in the pregnancy swelling of the maternal thyroid gland and in the swelling of the child thyroid gland in the newly-born. Whether any disturbances of iodine and lime metabolism play any part here, or perhaps something else, is unknown to us. That we are able in goitrous countries to effect very well the keeping down of the development of the swellings of the newly-born through the iodine treat-

ment of the pregnant women appears from the published observations to be the case. On the other hand it has successfully brought about that a goitrous enlargement of the thyroid gland in the young of pregnant animals has been produced by the removal of large parts of the thyroid gland from the mother and at the same time that this, however, may be prevented by the giving simultaniously of iodine.

With reference to the swelling of puberty and the Puberty Goiter, we shall have to seek for the decisive factor in the characteristically increased metabolism of these years. But here also there appears to me to exist a physiological incompetency on the part of the thyroid gland, even if only a temporary one. In the goitrous countries the physiological process of adaption on the part of the goiter noxa increases correspondingly to a special height. We again do not know, whether it is also a question here of a fundamental disturbance of the iodine-lime metabolism. Only this one fact is certain, viz: that we can exert a favorable influence upon the School and Puberty Goiter through the careful administration of iodine. Here it might be investigated to see if we could with iodine check also the simple puberty swelling of the non-goitrous thyroid gland, or whether here there are other factors playing a part, which have to do with corporal development. Then the relative lack of iodine in the goitrous countries would still supervene in such a way as to advance and further the swelling of puberty.

Whether finally the lighting again of the swelling of the goitrous thyroid gland in old age, for which we have determined no counterpart in non-goitrous countries, and perhaps because we have not sought for it, can be attributed also to endogenous factors, (probably peculiar metabolic changes of this age of life) must remain undecided.

The assumption brought out in the foregoing remarks that endogenously necessitated metabolic changes are to be held responsible for the physiological fluctuations in the weight of the thyroid gland in the different periods of life appears to be verified by chemical investigations, this is also true for the special age swellings of the goitrous gland. These show us, that in all swellings of the thyroid gland, the relative percentage of iodine in the thyroid tissue falls. We could draw the conclusion from this, that exogenously occasioned disturbances of the iodine metabolism or of the iodine-basic compensation result in the goitrous swelling of the thyroid gland in the main, whereas endogenously occasioned swellings of this kind result in the special swelling in pregnancy and in the

newly-born, in puberty and in old age. As a support for this view we could state that, by the actual diminution of the functioning tissue of the thyroid glands (giving at the same time food poor in iodine), we can call forth in the remainder of the thyroid gland a diffuse enlargement in the sense of a Parenchymatous Struma; this, however, fails to appear, and there appears instead the structure of an ordinary colloid-containing thyroid gland, which becomes only slowly enlarged, if at the same time an abundance of iodine is administered.

There would still remain the question of the origin of the Nodular Goiter. Above it was reasonably fully explained that the germs of, or the predisposition for, the adenomas can be proved as existing in all rather old thyroid glands even if in varying quantities. The pronounced development of them in the goitrously degenerated thyroid glands is attributable to the increased development tendency, to marked hyperaemia in the parent tissue, indeed in this goitrous thyroid gland. The question remains entirely untouched as to how the development of the adenoma could come about. With this question we would touch upon the chapter of the theory of swellings. It is out of question that we open that chapter here. The ultimate causes of the genuine structure of the swellings are still unknown to us. We simply know from experiment so much, that continually repeated and quickened regeneration growth can lead to the formation of swellings. For this reason we are justified in thinking that in the thyroid gland also an increased and finally a tumor-like regeneration will set in as a consequence of repeated onslaughts, e. g. through infectious diseases or through progressive arterio-sclerosis. That these should proceed just from the central caniculi does not astonish us after what was said at the beginning. Several authors therefore look upon the adenomas of the thyroid gland as compensatory or regenerative proliferations, like those of the prostate gland. Nevertheless we must emphasize that the necessary condition for such an assumption, viz., the proof of the definite morphological injuries to the thyroid tissue, from which the adenomas begin to form has not been produced. That the pressure of the developing adenoma injures the surrounding thyroid tissue is self-evident.

The origin of the Basedow thyroid gland or the Basedow-change in the already goitrous thyroid gland remains likewise without any explanation. Endemic or exogenous factors do not come into consideration here, for the reason that the appearance of this is too irregular and it is found spread over the entire world. Endog-

enous physiological factors do not play any part here, since there is indeed a certain preference for middle age and an outspoken preference for the female sex, but no connection with definite development phases of the body, as is the case with the swelling in the newly-born and in puberty. Here there must accordingly be special pathological transformations, probably in the sympathetic nervous system. The pathological anatomist has thus far not been able to produce any morphological equivalents for these nervous transformations. At any rate all histological determinations on the Sympathicus are still subject to discussion. In any case this one thing is certain, viz., that the initial point in this disease must not be sought for in the thyroid gland but in the nervous system. This is especially proved by the simultaneous changes in the thymus gland, in the suprarenal capsule and especially in the lymphatic system. The Status thymico-lymphaticus is just as characteristic of Basedow, at least in the younger years, as is the swelling of the thyroid gland. To this belongs mention of that fact that numerous and in part genuine lymph nodules have been defined in the Basedow thyroid gland. In the thymus we can recognize exactly the same as in the thyroid gland a sort of epithelial hypertrophy in the form of increased reticulum cells and the new formation of the smallest Hassall's corpuscles. We also find there indeed a very marked augmentation of the lymphatic tissue and here I shall leave the question open as to whether this originates from thymolymphocytes or from genuine lymphocytes. In the suprarenals, as Wegelin has emphasised a hypoplasia of the medulla can be found. Nothing definite is known about any characteristic changes in the pituitary body. In contrast with the ordinary goiter heart we find in the Basedow heart all kinds of changes, e. g. as very small necrotic areas, areas of lymphocytic infiltration. In addition there is often a dilatation, and according to Wegelin also definite hypertrophy.

Whether we have here to deal with a direct influence of the nervous system tissues and organs or whether indirect effects are present, due to changed metabolism and toxins originating from this, must remain at present unanswered.

Thus, with regard to causation from the standpoint of the pathological anatomist, we arrive at the conclusion that for the Endemic Goiter in the main in all probability an exogenous conditioned disturbance of the iodine-basic equilibrium may be held responsible, for the special varieties of this form, e. g., the pregnancy goiter, that of the newly-born, the puberty and senile goiter endogenously conditioned physio-

logical metabolic changes, perhaps also changes in the iodine-basic equilibrium, may be regarded as responsible: for the Basedow thyroid gland endogenously conditioned pathological influences, which attack the nervous system, and also influences acting directly or indirectly through the changed metabolism, are to blame.

There is still a final question to be briefly touched upon: What can the pathological anatomist say about the effects of goiter upon the remaining organism? I shall disregard here the so-called hypothyreotic or thyreotoxic symptoms. They are not comprehensible to pathological anatomists. To be sure, however we can say something about them e. g. in which varieties of goiter hyper-thyreotic and with which hyper-thyreotic symptoms are found. I shall also leave here the Basedow thyroid gland and the Basedow-changed struma untouched on. It is a well known fact, that we have here an outspoken hypothyreoidism, at least to the extent that here the augmentation of the fundamental metabolism (which we can also produce with pure hormon of the thyroid gland: Thyroxin), is strongly marked and in a characteristic manner. That all of the indications of Basedow's disease can not be produced by the thyroxin, especially not the eye-symptoms, has been especially emphasised by the American authors. We take it therefore from this, that Basedow's disease is no real thyroxin poisoning, that is to say, no ordinary hyperthyreoidism.

This is, however, here a matter of the Endemic Goiter. As a rule, with the most common variety of goiter, the so-called Mountain Goiter of adults, there is no hyperthyroidism but usually an euthyreoidism, and more rarely a hypothyreoidism. The diffuse hyperplasia of the thyroid gland is, according to our view, only the consequence of an increased demand on the function of the thyroid gland. For this reason the hormonal influencing of the rest of the body can lie chiefly close to the normal level but not above the état normal. Still less are the adenomas able to gain an augmented influence over the body, since they mostly contain immature tissue or, if they have developed into colloid-containing tissue, the colloid remains within them for the greater part. With stronger development of the nodules the remaining thyroid gland tissue becomes more and more atrophic and the nodules themselves pass through a marked involution process and then the consequence will necessarily be that in the end a condition of

diminished hormon structure, i. e., a hypothyreoidism will appear (adenomatous goiter without hyperthyreoidism).

Only exceptionally do we see in the genuine Endemic Goiter, without any demonstrable subsequent Basedow-change, indications of a genuine hyperthyreoidism, recognizable from the acceleration of the pulse, greater excitability, and varying basal-metabolism rate. These cases form to a part the so-called Puberty Goiter and the so-called Toxic Adenoma. With puberty goiters it is a question apparently of thyroid glands in which the proliferation tendency stimulated through puberty does not come to a standstill quickly enough, so that an augmented function of the gland persists into the post-puberty period, although the organism in itself does not require it any longer. Nevertheless the causes of the nervous symptom-complex lie also in special changes of the state of the nervous system, found coincidentally at the same time, so that these cases would have to be counted with the «formes frustes» of Basedow's disease, always provided that the basal-metabolism is also perceptibly increased. If this symptom is wanting, or if it is simply intimated, then it is questionable whether the nervous manifestations on the whole have any connection whatsoever with the enlarged thyroid gland.

In those cases, in which we might feel inclined to attribute the symptoms to the thyroid gland, i. e. in which we could speak of a hyperthyreoidism, we find histologically nothing other than the structure of the proliferating colloid struma. As regards the toxic Adenoma (Adenomatous Goiter with Hyperthyreoidism), we, European pathologists, are able to say but little, since it occurs but rarely amongst us as a distinct entity. As a rule we tend to put such cases into the partially Basedow-changed gland group. We hope that in the address of Colleague M a r i n e we shall hear more details of them.

Besides the diminished or increased hormonal effect of the goitrous gland upon the body as a whole, we should have to touch upon the question briefly, whether particular organs have been changed into a diseased condition in the morphological sense, dependent upon the goitrous degeneration of the thyroid gland. I shall leave out of consideration the changes in the thymus and other glands with internal secretion, which have already been mentioned by Basedow. They do not come into question in the matter of Endemic Goiter, apart from the doubtful enlargement of the thymus gland. Likewise I shall pass over the corporal changes in the cretinoid or cretinistic degeneration, of which

Colleague Wegelin will speak in detail. I am speaking only of the simple goiter. The purely mechanical factors I have already made mention of. The topographical relations of goiter (Struma retrovisceralis, intrathoracica, intralaryngotrachealis) are of special interest to the surgeon.

We must still keep in mind the cardio-vascular symptoms. It has been believed that in consequence of a cellular infiltration of the muscle of the heart a special kind of myocarditis or of cardiopathy could be determined, in accordance with which the light failure of the cardiovascular symptoms could be explained. I have not been able to convince myself of such changes, though I had at my disposal the abundant Freiburg material. I believe that the eventual cardiac weakness is attributable to the specially strong strain upon the right ventricle through the difficult breathing. I have been just as unable to find any trace histologically of a thyreotoxic affection of the heart muscle, although this has been definitely spoken of quite often.

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Conclusion :

1. In order to understand the morphological and etiological genesis of goiter it is necessary to grasp the fact that the biological curve of the goitrous thyroid is parallel to that of the non-goitrous thyroid gland. The curve of the non-goitrous thyroid is, however, more elevated than the other. From the morphological point of view goiter is a real hyperplasia of the thyroid.

2. In these curves of age incidence there are several corresponding sharp rises to be noted, viz. the swelling or goiter of infancy, puberty and advanced age. In point of origin they are to be distinguished as follows :

a) In the case of the goiter of infancy there is in addition to increased new formation a simultaneously increased moisture of the whole parenchyma.

b) The swelling or goiter of puberty is of chief importance since upon its degree essentially depends the intensity of the later developed adenoma.

c) In advanced age a retrogression of the proliferating goiter of puberty may come to pass.

3. The biological curve of the thyroid, goitrous or otherwise, is deformed by the development of the so-called adenomata. The germ of them occurs in all thyroids. In districts where goiter

seldom occurs they develop slowly and only to a certain size, in goitrous countries much faster, and on occasion up to the size of a child's head or even larger. This intensified development of the tumors, the so-called struma nodosa, depends especially upon the enhanced metabolism of the goitrous thyroids.

In point of histological origin the adenomata present either an unphysiological growth with immature (struma nodosa parenchymatosa) or riper stages (struma nodosa colloides). According to the type of involution to which these tumors generally tend, the names of struma nodosa fibrosa, calcificans, haemorrhagica, cystica etc. are given. Struma nodosa originates commonly at or after puberty.

4. The question of causation must be considered with that of the source of origin of the diffuse goitrous increase in size, in other words, of the general increase in weight of the thyroid in goitrous countries. Comparative histology supports the view that here an exogenous noxa met with in the surroundings is at fault, which leads to enhanced physiological growth. According to chemical analysis of goitrous and non-goitrous thyroids, it must be assumed that the thyroid as a whole is continually striving for certain iodine content. Where the supply is deficient, the absorbent surface of the thyroid increases through further growth of the parenchyma. Conformably thereto the percentage of iodine content is similar in the goitrous thyroid. Experiment indicates that it is not simply iodine deficiency which comes into play, but disturbed equilibrium between iodine and other substances.

5. The question of the periodical swelling or increase in size of the thyroid (that of pregnancy, infancy, puberty, advanced age and their respective forms of goiter) is quite independent from that of the goitrous swelling. Here factors at once endogenous and physiological, among them perhaps an insufficiency of iodine metabolism or disturbances of iodine equilibrium connected with growth, have to be reckoned with.

6. A sharp distinction must be drawn between endemic goiter and the thyroid of Grave's disease. In this case the onus lies on an endogenous cause, but in contrast to the swelling mentioned in section 5, pathological. Simultaneous affection of the thymus, adrenals and lymphatic system warrants the conclusion that this cause attacks the nervous system and not the thyroid. Grave's thyroid is characterized by a special hyperplasia in the interior of the individual follicles. Intermediate stages occur between the hyperplasia in Grave's disease and in parenchymatous goiter.

7. In contrast to the thyroid of Grave's disease which shows marked symptoms of hyperthyroidism, in the case of the goitrous thyroid it is rather the picture of hypothyroidism with all stages down to complete cretinism. Only in a few cases does goiter exhibit hyperthyroidism. Such are usually late forms of the goiter of puberty or so-called toxic adenoma.

8. Provided that no signs of cretinism occur, endemic goiter displays no secondary influence on other systems. Goitrous heart, implying that the heart muscle is damaged by thyroidal toxins or bacterial toxins, is, according to morphological evidence, non-existent.

This is a splendid and most enlightening paper. In many respects our work on the life-line of the thyroid gland (Munsen, 1922) confirms it. Bahr-Ashoff and many others, when speaking of goitre-causation assumes that the thyroid is always physiologically efficient and able to satisfy all demands upon it. Increased demand

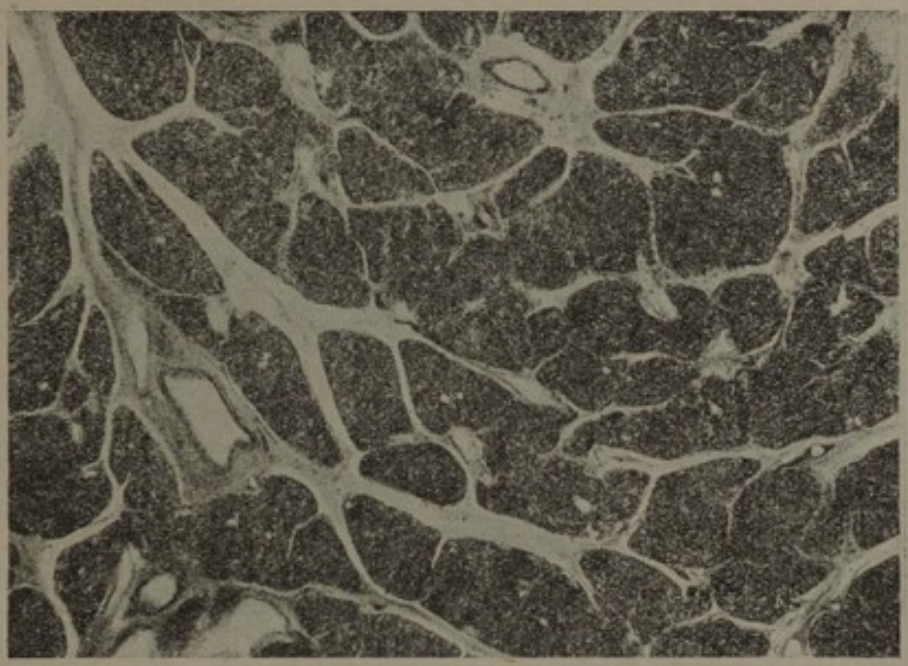
Incipient development of nodules in a parenchymatous thyroid gland.

from whatever cause arising is undoubtedly a but not the only cause of thyroid-enlargement. Physiological inefficiency of the organ is another cause that must be considered and the causes of it are also goitrogenic. These causes are usually multifactorial. The causes of goitre may be classified as follows:

(1) Anything which increases the demand for thyroid-growth and for thyroid products.

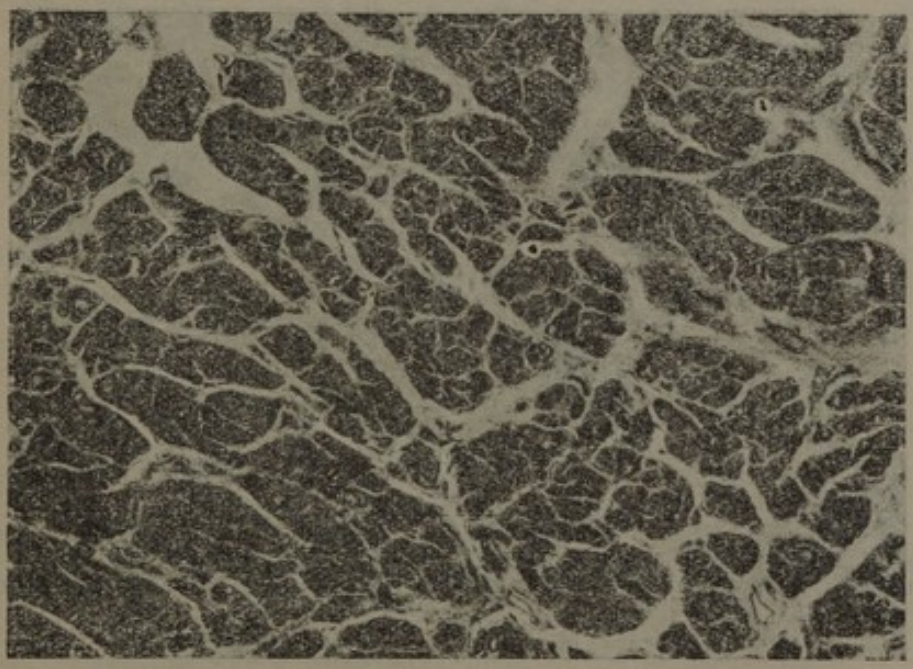
(2) Anything which interferes with the normal functional activity of the thyroid epithelium.

Fig 1.



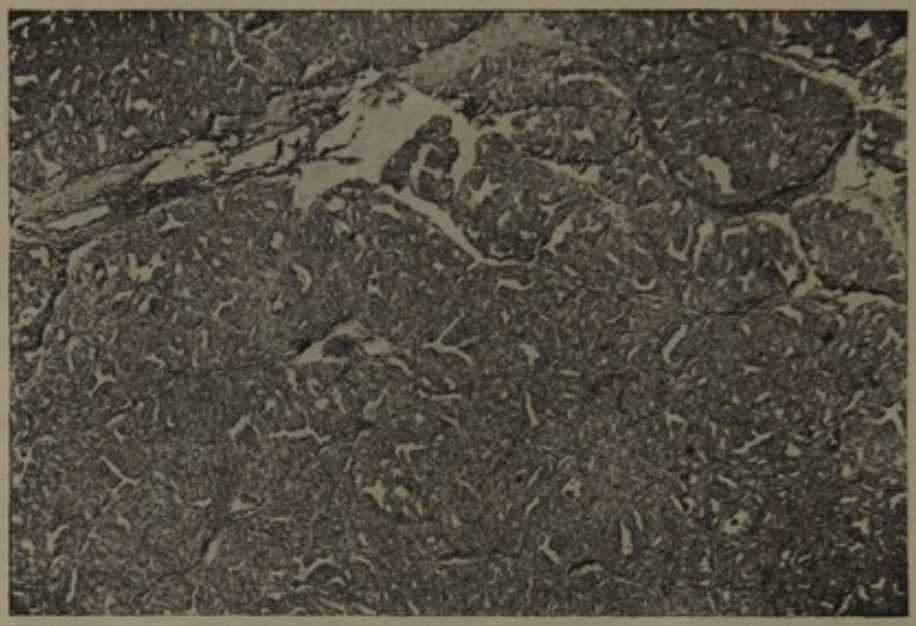
Normal parenchymatous newly-born thyroid gland
from non-goitrous region.

Fig. 2.



Struma diffusa parenchymatosa neonatorum from a goitrous region.

Fig. 3.



Struma diffusa parenchymatosa adolescentium.

Fig. 4.

Struma diffusa colloides macrofollicularis proliferans.

Fig. 5.

Struma diffusa colloides microfollicularis.

Fig. 6.

Re-appearance of proliferations in the struma diffusa colloides of a 59 year old man.

Figures 1—6 were taken in the same magnification.

The Pathological Anatomy of Struma Maligna and the Cretin Thyroid Gland.

By C. Wegelin, Berne.

My comments are intended mainly to supplement the address of Professor Aschoff in two ways; namely, to consider the pathological anatomy of the malignant tumors and the thyroid gland of the cretin in their relationship to the goiter problem.

I.

The propriety, to discuss malignant tumors of the thyroid gland at this time is pertinent for two reasons. In the first place there are many varieties of malignant tumor, which originate almost entirely from the non-malignant endemic goiter; secondly, from a pathological standpoint the dividing line between non-malignant and malignant tumors can probably nowhere be drawn with greater difficulty than just here.

It has long been known, that in regions where goiter is endemic the malignant tumor is a great deal more prevalent than in countries that are free from goiter. The experience in the clinics as well as post-mortem statistics give sufficient proof of this fact. From the latter we learn the following facts:

Berne	15 250	necropsies	159	malignant	tumors	1.04 % = 1 : 96
Vienna	18 147	»	50	»	»	0.27 % = 1 : 363
Prague	7 700	»	17	»	»	0.22 % = 1 : 453
Berlin	13 426	»	13	»	»	0.09 % = 1 : 1033
U. S. A.	40 847	»	44	»	»	0.107 % = 1 : 928

The more frequent occurrence of malignancy in the thyroid at Berne, as shown here, which city can be looked upon as the center of the European goiter endemic, is very evident. The clinical statistics give us the same results. According to Bérard and Dunet, to whom we owe an excellent work on thyroid cancer, there occur in regions that are free from goiter 4 to 5 malignant tumors of the thyroid in each thousand malignant growths, whereas in the goiter regions this incidence is increased for malignancy of the thyroid to 25 to 40 per thousand new growths. Furthermore it can be determined anamnestically that 81 % of those suffering from a ma-

lignant tumor had previously suffered from goiter. Other statistics present figures varying between 61 and 90 %. This also indicates the significance of pre-existing goiter and hence it is not to be wondered, that Bérard and Dunet, as also the Americans Coller and Barker, speak of the adenoma, that appear endemically, as a pre-cancerous lesion. The word «pre-cancerous» is used, to be sure, only in the sense, that a malignant degeneration of the adenoma sets in frequently, relatively considered; perhaps in 1 % of all patients who suffer from goiter, at Berne. However this relative occurrence does not necessarily follow.

We also learn from pathological anatomy, that the great majority of the malignant tumors originate in the struma nodosa. This naturally applies primarily to the epithelial tumors, but those originating from connective tissue and from the blood vessels also occur with predilection in the nodules of adenomas. Among the epithelial tumors however there is to be found a variety, which is oftentimes malignant and which has little or nothing in common whith endemic goiter, but is found to occur at least just as frequently in the regions that are free from goiter. This is the Cystadenoma papilliferum or Langhans' Papilloma, which now and then is met with in the neck, taking origin occasionally outside the thyroid gland, and probably in most such instances is of branchiogenous origin. Hence I shall not discuss this particular tumor in any greater detail here, but wish only to remark that it usually metastasizes by the lymphatic rather than by the blood stream, differing in this respect from other tumors of the thyroid gland.

The epithelial forms of the malignant strumas we can simply designate, from the biological point of view, as Carcinomas (Cancer), notwithstanding that they also manifest, biologically considered, a number of special characteristics when compared with forms of cancer of other organs. But if looked at from the histological standpoint to be sure not all of these tumors are carcinomas in the ordinary sense of the word, i. e. alveolar tumors growing in an irregular fashion in the stroma of the connective tissue. It is rather the case that the tumor tissue occasionally reaches such a state of perfection in differentiation, surpassing even non-malignant adenomas in this respect, such that at first glance there would appear to be nothing present that would betray the malignancy of the tumor.

The highest grade of differentiation is to be found in metastasizing adenoma, the epithélioma adénomorphe of

Bérard and Dunet. Since the time of the famous case of Cohnheim there have been a great many observations of this kind reported. The primary tumor, rarely solitary but on the contrary frequently associated with other adenomatous nodules in the thyroid gland may be very small and may present macroscopically the appearance of a very ordinary adenoma, more or less abounding in colloid and may even, as in Cohnheim's case, have a gelatinous appearance. In other cases the metastasizing nodule betrays itself, to be sure, through a more whitish color and relatively slight transparency. Histologically such tumors are as also their metastases to be distinguished through the predominance of small to larger sized colloid-containing vesicles, the epithelium of which is cubical or columnar. Mitoses are as a rule very rare and the «monstruosités cellulaires» emphasized by Bérard and Dunet, may be absent altogether. I agree entirely with Graham, when he says, that neither the character of the cells nor the mitoses, nor the colloid, nor the structure of the vesicles admit of any definite conclusion as regards non-malignancy or malignancy. Decisive alone, as Graham also emphasizes, is the bursting of the capsule and above all the penetration of the tumor tissues into the blood vessels, which exceptionally may even be seen macroscopically but usually must patiently be looked for in a consecutive series of sections.

The metastases of such tumors takes place primarily by way of the blood and only rarely through the lymph passages. The metastases occur most frequently and are usually found first in the osseous system and later are likely to appear in the lungs. A very particular characteristic is the occurrence of solitary bone metastases, the removal of which surgically has oftentimes been successful. These solitary metastases are distinguished further through their exceedingly slow development. To what extent the functional differentiation of such metastases may be developed, occasionally is apparent from the amount of iodine contained and from the efficacy of the employment of such tissue in tadpole experimentation (Ch. Abelin).

The best illustration of the functional value of such tumors is the celebrated case of v. Eiselsberg, in which the bone metastases fully replaced the completely exstirpated thyroid gland. The secretory functions of tumors of this type accordingly stand in the foreground, while the growth of the tumor is retardet. This is also apparent in the behavior of the primary tumor, which is oftentimes completely overlooked or is considered perfectly harm-

less because of its continued small size. Nevertheless the primary tumor is always to be found in a careful anatomical examination. The metastases of the «normal thyroid gland tissue», such as has been assumed by several authors, do not occur.

The next step in the lack of differentiation but with an increasing malignancy is the variety of tumor designated by Langhans as proliferating adenoma, which we find was formerly generally described under the name of adeno-carcinoma or of medullary carcinoma. Here also the nodular form is still preserved and the encapsulation from the surrounding gland tissue is oftentimes strikingly sharp, but the colloid content is so small that macroscopically the tumor tissue appears mostly whitish or marrow-like. Very characteristic in fairly large nodules is the hyaline-connective tissue nucleus lying in the center, the cicatrix of Langhans, from which septa radiate toward the periphery. From the microscopic structure we can draw the conclusion that we have here a stronger epithelial growth than in the ordinary adenoma, for broader radiating cords, corresponding to large polyhedral fields in transversal section, are the primary form of the histological structure. In addition the stroma is extremely scarce at the periphery, and sinusoidal capillaries, which are only rarely accompanied by collagenous fibrils, separate the epithelial cords and fields. In the latter, we find a sieve-like appearance of round lumina in the edge of the adenoma extending inward, in which there is a moderate accumulation of colloid. This proceeds generally from the periphery of the nodule inwardly. Penetrating stroma isolates the newly formed vesicles, so that the oldest parts of the tumor correspond to the micro-follicular adenoma. That the development is not an especially rapid one is evident from the small number or the actual lack of mitoses. On the other hand, the secretory process may continue to such an extent that an iodine containing substance may be secreted which at times produces a typical action, even though weak on tadpoles (Branovacky-Pelech, Ch. Abelin).

For malignancy, the proof of which is the formation of metastases, the behavior of the tumor tissue with respect to the blood vessels is here also conclusive. A penetration into the capsular veins is often observed, such that the latter may be completely filled with tumor tissue for long stretches. The result is a metastasis through the blood stream especially, in the osseous system, but not infrequently there is also an extension by way of the lymphatics. Here also, there is sometimes a very striking lack of proportion

between the miniature of the primary tumor and the frequently great volume of the bone metastases.

If the cell anaplasia of the tumor tissue still continues and if the latter loses more and more its similarity to normal thyroid tissue, then we shall finally have the ordinary carcinoma. Macroscopically this tumor may indeed also appear in nodular form or at least one rather large nodule may be recognizable, the adjoining thyroid tissue is here however more frequently markedly infiltrated by a whitish, largely marrow-like tissue. Microscopically, solid and quite irregularly arranged and mostly small-celled cords predominate, although here and there we find a tendency to lumen formation and accumulation of colloid. Even secretion containing iodine may also be formed (Meyer-Hürlimann and Oswald). The usual alveolar structure of the carcinoma owes this arrangement to the connective tissue septa, still, the stroma occasionally is decreased to such an extent that the tumor tissue becomes pseudo-sarcomatous. The mucous and precollagenous deposits, which arise in cancerous tumors through the special activities of the epithelial cells, are very peculiar. The deposits of precollagen, which were first described by Zipkin, are attributed by P. Masson to an inverted polarity of the gland cells, that have become cancerous, and which now secrete precollagen instead of colloid at their basal poles. Furthermore the carcinoma cells are able to store up fat and glycogen, wherein here and there we find a great similarity with the structure of the parathyroids and their tumors as well as of the hypernephromas (Kolodny). Moreover, this is also observed in the proliferating adenoma and the occurrence of glycogen is accordingly in no wise a proof for the origin of a tumor in the parathyroids.

The development of metastases occurs primarily by way of the lymph passages, inasmuch as an accumulation of the tumor cells seldom is lacking in the cervical lymph nodes, but nevertheless, haematogenous metastases in the lungs, bones and other organs are no rarity. Even the brain is not spared (Overhamm). Here also the primary tumor may remain fully obscure until the autopsy on account of their small size. This occurrence prompted Carrel to speak of such tumors as latent cancer (e. g. cases of Huguenin, Derischanoff).

The three epithelial tumors, thus far spoken of, viz. the metastasizing adenoma, the proliferating adenoma and the solid carcinoma (simplex), are in fact related through transitional forms, which can only be allotted to the one or the other group with difficulty. They

are, however, very closely connected genetically, for all three of them in all probability owe their very first orgin to a proliferation of the glandular epithelium in the form of the adenoma-„anlage" of Hitzig-Michaud. At any rate, there is not the least ground for assuming an origin from embryonic glandular cells, for which reason I consider the designation «foetal» adenoma as wrong. An ordinary adenoma may first originate, in which at some later time new proliferating centers are formed, from which a proliferating adenoma or a carcinoma comes forth; or the two latter forms can be developed between somewhat old adenomatous nodules independently from the beginning. Which of the two possibilities is the more frequent, I do not venture to decide, since the initial stages of such tumors naturally come only very rarely under observation. That, however, the ordinary struma nodosa stands in very close connection with the formation of malignant epithelial tumors can be learned not only from the previously mentioned clinical data but also from the fact that a cancer formation in an otherwise normal thyroid gland is a very rare exception. The struma nodosa, the simple adenoma. is accordingly either a prior stage or an accompanying occurrence of the malignant epithelial struma. At least it indicates a rather strong local inclination of the glandular epithelium towards proliferation.

As concerns the rare forms of cancer, the columnar-cell carcinoma and the squamous-cell epithelioma, they may also have their initial start in adenomas. The columnar-cell carcinoma represents the non-typical proliferating metamorphosis of the tubular adenoma. The squamous-cell epithelioma, which to be sure in many cases can probably be derived from partially dislocated epithelia of the branchial canals or the epidermis, can also arise from metaplastically metamorphosed glandular epithelium of adenomas, for I have occasionally found within the adenomas small cords of many-layered pavement epithelium, which could only have originated through metaplasia from the proliferated glandular epithelium.

Another point is worthy of mention. I refer to the factor of age. As frequently the rapidly growing adenomas develop from the trabecular or micro-follicular type as early as the second decade of life, just as rarely do we come across metastases notwithstanding the strong proliferating ability of the epithelium. Quensel has recently reported a case of this nature, which pertained to a 16 year old boy. The Langhans proliferating adenoma is similar, I have many times seen structures in youthfoul individuals, at least

here and there in parenchymatous nodules, which corresponded entirely to the proliferating adenoma cords, in which, however, no malignancy was to be seen either anatomically or in the further clinical course. Very recently E. Bircher has reported on more than 35 cases of proliferating adenoma of which not fewer than 14 were between the ages of 6 and 20 years and were clinically non-malignant, only that they manifested a tendency to recurrences. If, however, E. Bircher draws the conclusion from this, that the proliferating struma is clinically non-malignant, then he goes in this particular altogether too far, for the metastases, which are so pronounced in my material, nevertheless give very clear evidence for frequent clinical malignancy. Otherwise it is striking that frequently in his material only matters of agreement with the proliferating adenoma are mentioned, for which reason I must consider a great many of his cases as trabecular and microfollicular adenomas.

In my opinion it is no special matter of chance, that the formation of metastases i. e. the pronounced malignancy of the adenomas and the proliferating struma, do not become known until the higher ages of life have been reached i. e. especially the fifties and the sixties exactly as is the case with the ordinary cancer. The cause of this is not alone to be sought in the peculiarities of the tumor cells, but also in the resistance of the organism, since misplaced tumor cells can not take root in the youthful organism and are destroyed. In a similar manner the differences between the malignancy inferred from the histological structure and the clinical course, that is oftentimes quite non-malignant (Flörcken and Mues), can in part be explained.

This completes the discussion of the epithelial tumors. Let us now pass over to the malignant tumors of connective tissue origin and those arising from the vessels. Here there are two varieties, which are specially worthy of note, namely, the sarcoma and the haemangioendothelioma. The sarcoma consists of gray-white or gray-red tissue, which diffusely infiltrates the thyroid gland and its adenomatous nodules and quite frequently, even macroscopically, fills out the lumina of the veins. Polymorphous-cell sarcomas are, according to my experience, the most frequent, then follow the spindle-cell sarcomas and the giant-cell sarcomas. In the latter different types of giant-cells may be found (Schulz). Much less frequent are the round-celled sarcomas, which in accordance with the more recent observations are to classed under the lymphosarcomas. Among the sarcomas with intercellular substance the

osteo-chondro-sarcomas, besides the fibro-sarcomas and myxo-sarcomas, are for this reason especially to be mentioned, because here the sarcoma tissue, similar to that of many epithelial tumors, manifests the ability of far-reaching differentiation and maturity. In almost all sarcomas there can be observed an infiltration of the walls of the blood-vessels with the formation of an intima-sarcomatosis (Hedinger). Haematogenous metastases occur very frequently; in addition to the lungs, liver and kidneys the heart and the gastro-intestinal tract are especially frequently involved. In my experience however metastases are absent in the osseous system, in sarcoma in this regard a sharp contrast with the carcinomas is present.

In the consideration of the origin of the sarcoma, misplaced germinal rests are still less to be considered than in the epithelial tumors. In the majority of the cases, to be sure, the place of their origin can no longer be definitely ascertained, but in certain cases there is absolutely no doubt that the starting point of the tumor is quite definitely in an adenomatous nodule. More than once, I have observed in the stroma of such nodules a not sharply defined proliferation of large fibroblast-like cells, which no longer bore any great distinction from a sarcoma. Inflammations and haemorrhages especially appear to incite such a proliferation of stroma cells; there have also been some clinical observations of sarcoma developing after strumitis, which agree with this. The regeneration of the stroma cells would here pass over into sarcomatous development under the influence of factors that are still unknown.

Related to the sarcoma is the Haemangioendothelioma, which in Berne is a form of tumor rather frequently met with. Its macroscopic appearance which in many cases is very characteristic has quite recently been stressed by de Quervain. Nodules with a cavity, which are filled with blood or with hyalin elastic substance and whose walls consist of a grayish red or a grayish white tissue, permeated with haemorrhages and necroses, must necessarily always give rise to suspicions of endothelioma. Sometimes the tumor tissue is so limited that it is easy to believe that we have before us a simple haemorrhagic cyst. Histologically there can be no mistake about the proliferation of the endothelium of blood vessels, since many a spot in the tumor is purely angiomatous, in which cavernous vessels may predominate. The proliferation of the endothelium leads on the one hand to the filling out of the lumina of the vessels, such that structures similar to carcinomas arise, but remind on the other hand, because of the infiltration of the stroma,

of sarcoma. As concerns metastases, the lymphogenous and the haematogenous routes are about equally frequent and in the latter the osseous system is also involved.

In contrast to Hedinger, I have gained the impression, that the haemangioendothelioma arises very frequently in old adenoma nodules and, as a matter of fact, in the nodules, whose parenchyma has been destroyed for the greater part through haemorrhages and has been replaced through hyalin elastic substance. In such nodules we frequently come across cavernous blood spaces, which have developed from capillaries and whose endothelium here and there has become strikingly swollen. In my opinion such is the starting point of the majority of the endotheliomas. Further growth leads then to extension through the adenoma capsule and to the infiltration of the adjoining thyroid tissue.

The same age incidence prevails here for the sarcomas and also for the haemangioendotheliomas as for the malignant epithelial tumors i. e. they occur particularly during the later years of life. This goes also to prove the significance of the preliminary adenomatous condition, which prepares the ground for the stroma proliferation.

Finally we must also mention the carcino-sarcoma, which appears either as a tumor of collision through the encounter of carcinoma and sarcoma that have originated independently or as a composition tumor (R. Meyer). In the latter case the sarcoma structure proceeds from the stroma of the carcinoma and we have in principle similar conditions as with the origin of the sarcoma in an adenoma. It oftentimes happens here also that with continued growth and with the formation of metastases, that the epithelial part becomes choked, in accordance with the experiences with certain transplantable tumors in mice.

The mixed tumors and teratomas, which exceptionally occur also in the thyroid gland as malignant tumors, I shall not discuss, because they have nothing to do with endemic goiter, but originate on the bases of some early disturbance in development.

If we again cast a glance over the series of thyroid tumors, we shall recognize from this anatomical-histogenetic consideration, that the great majority of these tumors do not take origin in the normal thyroid, but that the endemie non-malignant goiter, and to be sure especially the struma nodosa, represent the connecting link between both. The abnormal processes of growth, which become manifest in endemic goiter, prepare the ground for the malignant

growth. To be sure up to the present day, it is entirely unknown, whether the metamorphoses into the malignant tumor cell are set in action through chemical, parasitic or endogenous factors e. g. heredity. At all events we may hope to diminish also very considerably the number of malignant thyroid tumors through the systematic control of endemic goiter, so that with goiter prophylaxis we also promote cancer prophylaxis.

II.

If I now take up the discussion of the cretinous thyroid gland in its morphological peculiarities, I probably need scarcely to emphasize before you, that endemic goiter and endemic cretinism are most closely related to one another. We may assure the symptom-complex of cretinism to have originated in one way or another, we may look upon it as a consequence or as an accompanying manifestation of goiter, at least so much is certain: endemic cretinism appears only in the endemic territory of goiter. This fact had already received recognition from Fodéré, Virchow, Nièpce, St. Lager, Baillarger and Allara, just to mention the names of a few of the meritorious investigators of the past century. And if in recent times Finkbeiner again denies the connection between goiter and cretinism and makes an appeal to the fact that with goiter the female sex is more strongly affected and on the other hand the male sex suffers more from critinism, then this plea is easily refuted with the fact that in the early childhood years goiter afflicts boys at least just as frequently as or even more so than girls. It must certainly be stated emphatically that endemic goiter and endemic cretinism do not entirely correspond with one another regionally, but that cretinism occurs endemically to a much more limited extent than goiter and really only in those regions, in which the endemic goiter reaches a high frequency, does it make its appearance. Many a goiter region, as that of the United States of North America, seems to be completely spared from cretinism.

correct-at. in rats.

Epidemiologically and from a pathologico-anatomical standpoint the concurrence of frequent struma nodosa and cretinism is unmistakable. Even if, as Professor Aschoff has declared, the adenomatous nodules are not restricted in any way to the territories of endemic goiter, their premature and frequent occurrence and marked development are nevertheless indications of intensive endemicity. Many cretins and still more frequently cretinoids are

also afflicted with a struma nodosa. Here we certainly seem to face a contradiction, for it is just those cretins, who portray to us the classical picture of cretinism in their dwarfed stature and their intellectual obtuseness, that do not as a rule have a palpable goiter, but an atrophic thyroid gland. This apparent contradiction is explained, when we learn that in the first place the atrophic thyroid gland of the cretin contains small adenomatous nodules, and that secondly, the atrophic thyroid tissue of the dwarfed cretins and the glandular tissue or « interstitial tissue » of the goitrous full or half cretins manifests sympathetic changes. For that reason the autochthonous thyroid tissue preeminently deserves our attention. As it is especially the case with endemic goiter, so it is also with the thyroid gland of the cretin, that the diffuse changes appear, as regards time, before the nodular structure, in addition they also lay claim to greater importance from the functional point of view.

If we direct our attention first of all to the various facts, that we have at hand, we find that the atrophied thyroid gland of the older dwarf cretin, according to the co-inciding reports of Hanau, de Coulon, Getzowa, and in full agreement with my own observations, is a very degenerate organ, in which the original glandular tissue manifests all of the different stages of slow degeneration. The epithelium of the atrophic vesicles, which are often empty and completely obliterated, have undergone marked fatty degeneration; frequently they are also full of pigments of a lipoid nature, with sometimes shrunken nuclei occasionally enormously enlarged, hyper- or hypochromatic, with cell walls often obliterated. The scanty colloid has become inspissated and largely basophilic; the indications of fresh secretion are wanting and the very rare lymph vessels also contain no substances resembling colloid. In addition there is marked sclerosis, which is dependent on the increase of the intra- and the inter-lobular connective tissue of which surely a part may be transformed into adipose tissue.

Exactly the very same changes are also to be found in the gland-lobules of the goitrous enlarged thyroid gland of the cretin as is proved from the individual older cases of de Coulon and particularly from the recent extensive material of Wydler. The largely very scanty « interstitial tissue », which has been retained between the nodules, has likewise passed over into a state of degeneration and sclerosis. Wydler also points to the quite frequent occurrence of lymphocytic infiltration, the appearance of which stands probably in intimate relation with the degeneration of the glandular tissue.

We certainly almost regularly meet with regenerative epithelial proliferations also in the thyroid gland of the cretin. It is here a question in part of small groups of vesicles and in part of ramified canals, which bring to mind the central canal of the thyroid gland of a child, the epithelium of which is distinguished through the abundance of chromatine in the nuclei, and through the basophilic protoplasm. Inasmuch as such epithelium is almost always free from fat and thus stands in sharp contrast with the degenerated epithelium, that has undergone fatty degeneration, we can probably conclude that it is young. As a matter of fact such spots correspond to the initial stages of the adenoma nodules, as described by Hitzig and Michaud, and we see among them all transitional stages up to the sharply defined independently growing adenomatous nodules. Furthermore a more vigorous secretory action can begin in some newly formed vesicles or in small groups of such, which produce an accumulation of colloid, for which there is evidently no possibility of resorption. In this way small cysts containing colloid can originate.

As concerns the adenomatous nodules, present in the thyroid gland of the cretin, we learn from the compilation of Wydler, which comprises almost 100 cases, that the goitrous nodules exhibit the parenchymatous type to an overwhelming degree. These are chiefly micro-follicular, more rarely trabecular and tubular adenomas, which frequently occur side by side in great numbers and finally may stifle the interjacent thyroid tissue. It scarcely ever happens in such cases that there is an accumulation of colloid in the adenomas in any quantity worth mentioning; unquestionably the macro-follicular adenomas are an exception and according to Wydler occur in only about 9 % of these cases. De Coulon, as well as Wydler, emphasizes that degenerative metamorphoses of the nuclei, such as occur in the thyroid tissue, are also met with very frequently in the adenoma nodules. Wydler lays weight also on the oftentimes marked epithelial fatty degeneration, as well as the proliferation of the stroma with secondary hyalin degeneration and calcification. I have also observed the very frequent degenerative changes in the adenomas, among which we may also mention the obstruction with mucus; however it is not specific for the cretin goiter, for it appears also in other nodular types of goiter.

Through the occurrence of the nodules the structure of the cretin goiter becomes very varied and oftentimes manifests great similarity to the nodular goiter types of non-cretins. We can tho-

roughly agree with E. Bircher, when he rejects the conception of a specific cretin goiter, for qualitatively similar metamorphoses of the glandular tissue occur also in ordinary nodular goiters of adult individuals and even in senile atrophic glands. As regards the glands of idiots, which have been described by Getzowa, I would conjecture in their derivation from the endemic territory, that it was here a question in part of cretins without any strongly marked physical characteristics. Two of these idiots were, moreover, of such an age, viz. 69 and 70 years, that senile involution alone would suffice to explain the histological changes; in the case of a younger individual the small stature had been expressly stated in the post-mortem report.

If we accordingly can likewise not consider the alteration of the cretin thyroid glands as qualitatively specific, they do nevertheless exhibit, as compared with the ordinary nodular goiters, a certain peculiarity in the quantitatively greater and more premature developing degeneration of the original glandular tissue. The impression could be gained, that the latter is prematurely degenerating to senile atrophy and suffers a « senilitas praecox ». I, however, do not in any way desire to assert that with such a conception the question as to the pathogenesis of the cretinous thyroid gland changes has been cleared up. Above all it will be necessary to determine to a certain extent at what point of time the degeneration sets in, and whether there have not been alterations taking place previously. Unfortunately we have only very scanty material at our command for the solution of this question, inasmuch as investigations of cretin thyroid glands of early childhood have thus far been almost entirely wanting. The case of Schlagenhaufer and Wagner von Jauregg, which pertained to a four year old child, is of special importance. The normally large thyroid gland even here showed histologically the degeneration of the epithelium with peculiar changes in the nucleus, which is a constant finding in the older dwarf cretins. In the case of another child, whose age was not mentioned, McCarrison found a sclerosis and an atrophy of the glandular tissue and I, myself, saw likewise an increase of connective tissue in addition to very outspoken epithelial degeneration in the case of two deaf-and-dumb dwarf cretins of 7 and 10 years respectively, whose thyroid glands were atrophic on palpation. In both glands there was an increase in connective tissue and quite distinct epithelial degeneration. In somewhat older children between 10 and 15 years of age, where only light symptoms of cretinism are manifest, a diffuse parenchymatous goiter

years!

(adolescent goiter) or struma nodosa may appear; most of these exhibit marked nuclear degeneration that remind us of the changes in the above mentioned cases (Wydler, own observations). To be sure, the epithelial proliferations are here sometimes very great, as they also were in the cases described by Hotz.

The cases, spoken of in the foregoing, nevertheless appear to me to prove, that in pronounced cases of endemic cretinism the thyroid gland gives evidence, as early as within the first decade of life, of epithelial degeneration that may even progress to atrophy with sclerosis. It seems probable to me, that the epithelial changes may set in even as early as prior to the time of birth, for in many freshly fixed cases of congenital goiter we may meet with the same monstrous and knotted nuclei, as in the atrophic cretin thyroid gland. According to the clinical investigations of Diviak and Wagner von Jauregg we may assume that the thyroid gland of the cretin may be goitrous after birth and in the very first years of life, at least in some of the cases. The atrophy would therefore follow secondarily upon a diffuse parenchymatous goiter, whereas in the lighter stages of cretinism atrophy under no circumstances is to be found. Here the congenital goiter passes directly over into the adolescent goiter, which perhaps in its turn may also atrophy. Unquestionably, however, the regenerative epithelial proliferations and nodular structures make it clear that the process of development is in no wise checked through the appearance of premature atrophy.

Certainly! I'm in my experience to so.

If I may be permitted to draw a conclusion from the standpoint of pathological anatomy regarding the function, it would with all caution be to the effect, that the cretin thyroid gland is an organ of inferior value. It is impossible that the greater or lesser injury of the original glandular tissue can be without significance for the secretory function; on the contrary it must lead to a diminution of the function in a quantitative and probably also in a qualitative relation. With this, the functional tests of the cretin goiter which the collaborators of de Quervain have made and which I do not need to discuss, the objection may be raised from a morphological point of view, that it is still possible for many cretin goiters in isolated spots to form a colloid, which microscopically can not be distinguished from the colloid of a perfectly normal gland. In the first place we know however that histologically homogeneous colloid may when tested functionally exhibit different degrees of activity and secondly we must remember that with the sclerosis of the interstitial tissue the lymph vessels are destroyed

and for that reason the resorption of the colloid is at least made difficult. Furthermore it appears to be excluded, that the adenomatous nodules may take over the function of the damaged interstitial tissue in full compass, for they are, as we know, quite predominatingly parenchymatous-microfollicular and hence adapted for epithelial proliferation and not for secretion. Nevertheless I believe it is just the regenerative epithelial proliferations and the development of the adenomas, that can bring about certain improvements in the functional ability of the gland. As Wagner von Jauregg has at all times emphasized, endemic cretinism is certainly not an immutable condition, but there may appear in the course of its development variations, exacerbations as well as improvements, which do not admit of any difficult explanation from the histological behavior of the thyroid gland.

If we concede the thyroid gland of the cretin to be of inferior value, then to be logical, we should also admit that the remaining organism is under the influence of hypothyroidism. What has long been recognized to belong to sporadic cretinism may also truly be accepted for endemic cretinism. For the sporadic cretinism, dependent on congenital thyroaplasia is as a rule certainly not complete aplasia but a hypothyroidism, inasmuch as almost all cases still possess more or less thyroid tissue at the base of the tongue. It is accordingly not justifiable to make a strict distinction functionally between athyreosis and endemic cretinism. As a matter of fact both of these diseases have the most far reaching similarity and in many points they are in complete agreement. It would lead us altogether too far afield if we were to enter into all of these matters within the scope of a short report that pertains to the thyroid gland. Elsewhere I have brought together the reasons, which speak for the fundamental significance of hypothyroidism in the case of the physical and intellectual derangements of endemic cretinism. Here I shall only direct attention to the character of the skeleton with the delayed disappearance or the complete persistence of the cartilaginous epiphysial discs and to the late appearance of the osseous nuclei, to the late dentition, to the enlargement of the hypophysis with increase of the chief cells, to the hypoplasia of the sexual organs, to the myxoedema of the skin, to the insufficient activities of the blood-forming organs, and finally to the retardation of intellectual development, all of these being common to endemic cretinism as well as to congenital athyreosis. Although the cretin manifests many more gradations and even though often a certain dissociation of the symptoms may be present and even though the disease

may appear in many more forms than in the more uniform picture of athyreosis, this is probably in no small part dependent upon the fact that in the cretin the thyroid gland function is not always the same at different times during the age of development, but can be subject to definite variations. According as the depression of the thyroid gland function falls into the time of the critical differentiation of this or that system of organs, the later derangement in the individual systems of organs will be lacking in varying degree, which is especially to be taken into account with the psychic changes. The dissociation of the symptoms can in this manner be explained without any too great difficulty. Nevertheless I am perfectly willing to admit that many of these derangements have not been investigated sufficiently.

What the nature of the injury is, which causes the thyroid of the cretin to degenerate, can not be said at the present time. It appears not unlikely to me, that in the majority of the cases an intra-uterine injury of the thyroid gland has already occurred. Pfaundler assumes in addition to a predisposition brought about by an inherited (idiotypical) or exogenous (paraphorized) injury of the germinal layers an insufficiency of the maternal organism as well as the effect of an exogenous-provincial injury which probably still comes into account in an increased degree for the time following birth. Whether this deficiency is exclusively due to a lack of iodine, whereby the thyroid gland would degenerate into a state of atrophy in consequence of the omission of a secretory stimulus, is not known as a positive fact at the present time and that can probably not be understood until some time when an entire generation has been provided with sufficient quantities of iodine. At all events a toxic injury does not appear to me to be excluded.

To follow up Finkbeiner's anthropological explanation of endemic cretinism is probably not necessary after critical discussions of his theory by Wagner von Jauregg and de Quervain. The idea that cretinism is an atavism, a reversion back to the type of primitive human races, namely neolithic pigmies and certain polar tribes, will be awaiting acceptance so long as it is not proved that the remaining population of the endemic territory is really distinguished from the cretins through the shape of the bones and other anthropologial distinctive indications. The pathological anatomy of cretinism at all events does not point merely to a reversion in the anthropological sense but to diseased interruptions in the development. The primitive distinctive features of the cretin

skeleton which have been subscribed to by Finkbeiner in such a meritorious manner are really more readily to be looked upon as accompanying manifestations of this interruption in development. For, as Finkbeiner himself even calls attention to, such distinctive characteristics are the marks of the foetal skeleton and of the skeleton of thyroid aplasia. Cretinism is a disease, as de Quervain has maintained, and not a racial peculiarity. In proof of this there are not only the clinical observations but also in the same degree the anatomical make-up of the cretin body.

* * *

Conclusion :

A. *The malignant tumors.*

1. The malignant tumors of the thyroid gland are far more frequent in countries where goiter is endemic than in countries which are free from goiter.
2. The epithelial forms of the malignant struma may be designated as carcinoma (cancer) from a biological point of view. Their malignancy is chiefly shown in the formation of metastases.
3. Histologically these tumors are often not ordinary cancers, but more differentiated and typically formed tumors, which almost always appear in form of nodules. The highest degree of differentiation is reached by the metastasizing adenoma, a lesser by the Langhans' proliferating adenoma and the least by the simple carcinoma. There are transitions which unite all these forms. They only metastasize after invasion of the blood-vessels especially of the capsular veins. The age of the patient must be considered as another important factor.
4. The malignant epithelial tumors, as well as the sarcoma and the haemangioendothelioma often originate in the nodules of old adenomas.
5. The study of the histogenesis thus shows a definite relationship between the malignant tumors and the usual endemic nodular goiter. An efficacious prophylaxis of goiter will therefore be able to diminish the number of malignant goiters.

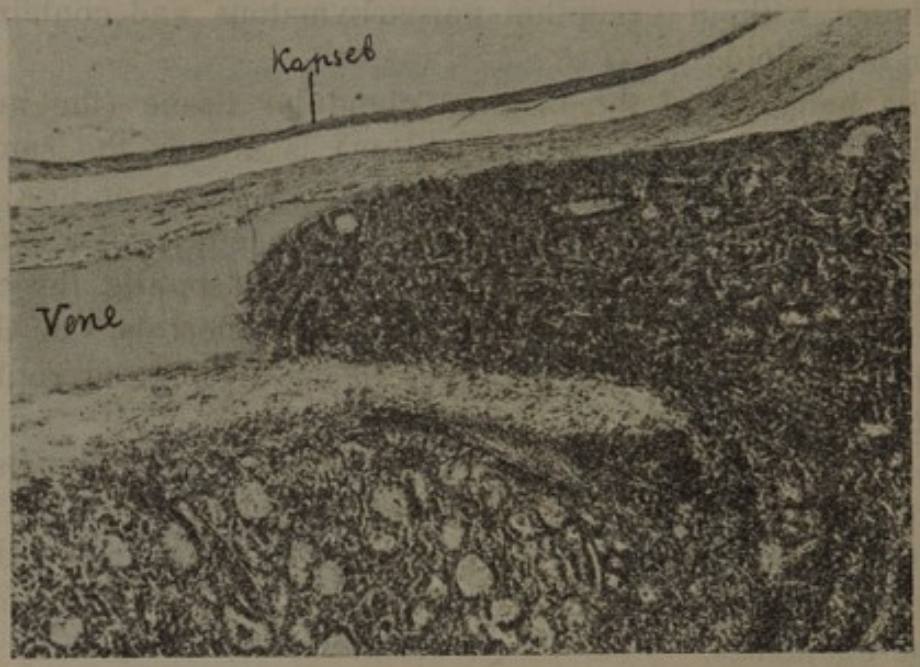
B. *The thyroid gland of the cretin.*

1. Endemic cretinism is only to be found in districts where goiter is endemic, on a geographically narrower range, however, than goiter and only where the endemic has reached a high degree.

2. The thyroid gland of the cretin almost always contains adenomatous nodules which however vary greatly in size. They are almost without exception parenchymatous and contain little or no colloid.
3. The behavior of the original glandular tissue (the intermediate tissue of the struma nodosa) is always the same, the epithelial cells of the gland undergo a more or less severe degenerative change regarding nucleus and protoplasm. The colloid of the vesicles is scanty, chiefly basophile, the connective tissue increased to a high degree of sclerosis. The changes are found in the highest degree in the atrophic thyroid gland of dwarf cretins.
4. An early beginning of degeneration of the epithelial tissue of the gland is characteristic for the cretin thyroid.
5. The cretin thyroid gland is, as regards function, an inferior organ, although a part of its functions may be taken over by the adenomas.
6. The whole organism of cretins is influenced by a hypothyroidism of different degree. The changes in the other organs show considerable resemblance or conformity with the state found in congenital or acquired athyreosis.
7. In the etiology of endemic cretinism external injuries of the thyroid gland must be taken into account as well as hereditary factors (inbreeding). The nature of the external factors is not yet known with certainty. The supposition that cretinism is a recurrence to the type of the primitive human races is not sufficiently proved.

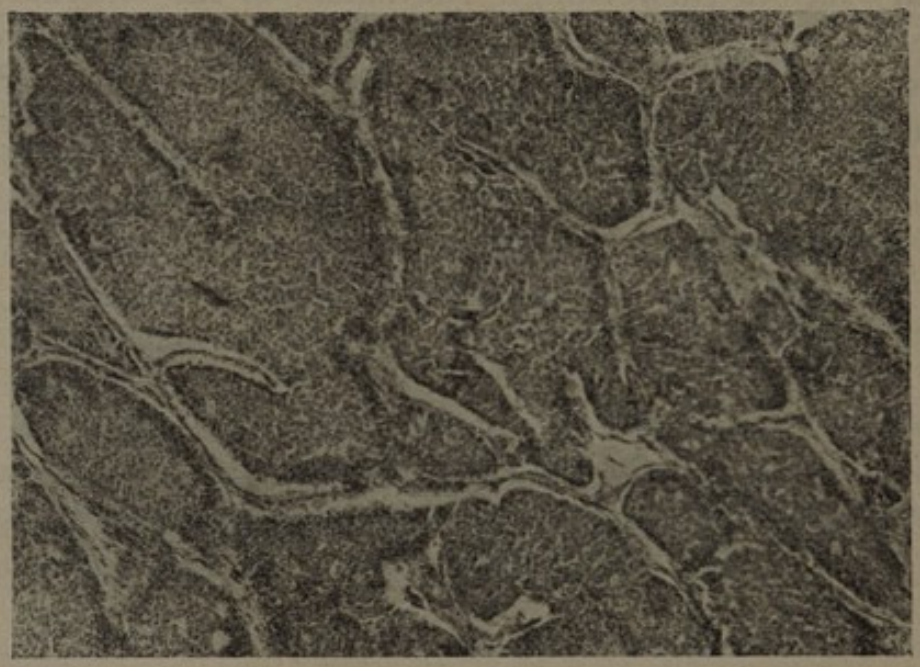
* * *

Fig. 1.



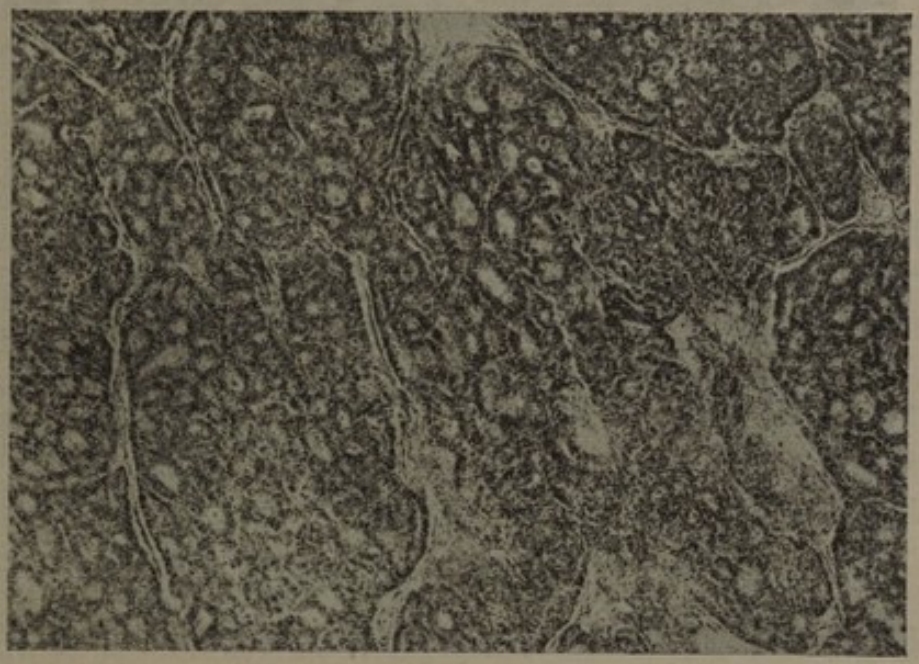
Metastasizing adenoma of the thyroid. Penetration of the tumor tissue into a vein of the capsule. Magnification 60×.

Fig. 2.



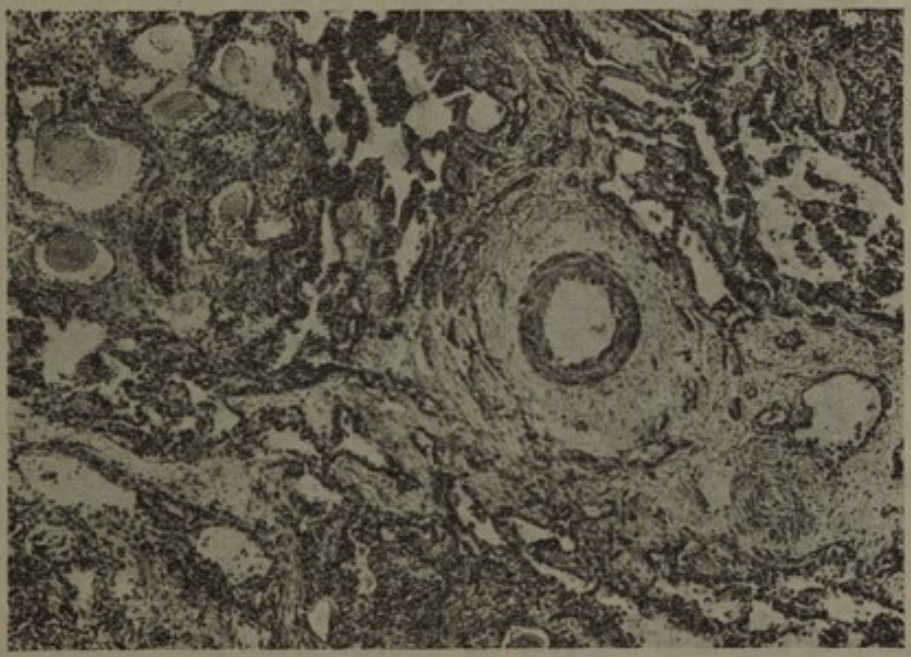
Proliferating adenoma of Langhans. Solid epithelial cords, separated by sinusoidal capillaries. Magnification 60×.

Fig. 3.



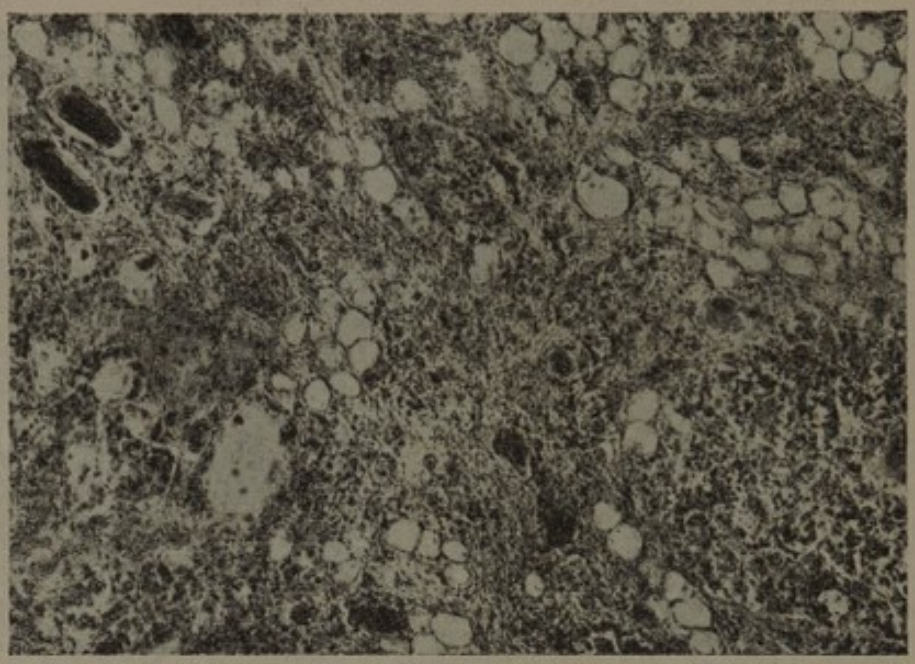
Proliferating adenoma of Langhans. Formation of noumerous small lumina in the epithelial cords. Magnification 80×.

Fig. 4.



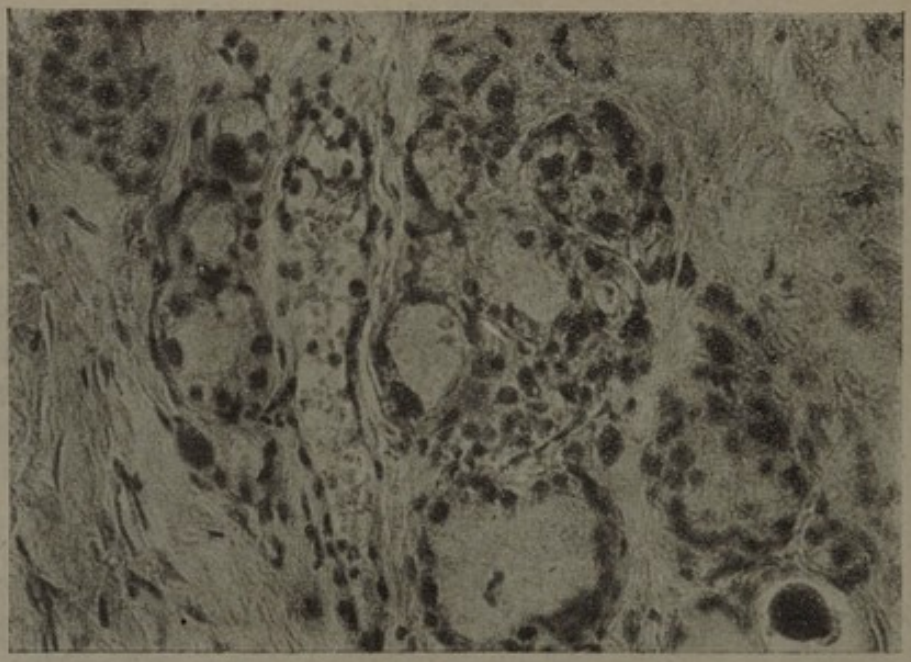
Haemangioendothelioma of the thyroid. Infiltration of the tumor tissue between the follicles of the thyroid. Magnification 80×.

Fig. 5.



Atrophic thyroid of a 57 year old dwarf-cretin.
Partial replacement of the glandular tissue by fat.
Magnification 80×.

Fig. 6.



Atrophic thyroid of a 7 year old dwarfed cretin girl (105 cm high).
Atrophy of the follicles with hyperchromatic nuclei. Increase of connective tissue.
Magnification 260×.

Certain Features of the Morphologic Pathology of Endemic Goiter.

By David Marine, New-York.

The foundations of our present conceptions of the morphologic pathology of goiter are based largely on the chemical investigations of Baumann and his pupils and of Oswald. The discovery of iodine as a normal, and the proof that it was a necessary, constituent of the thyroid are as certainly the source from which most of the recent advances in pathology have sprung as they are the source of the recent brilliant achievement of Harington in working out the structure and synthetic production of thyroxine.

As pathologists we perhaps have underestimated the debt we owe to those pioneers. Prior to their discoveries pathology of the thyroid was largely an aimless cataloging of the various morphological features encountered. Unfortunately thyroid pathology is still encumbered with descriptive morphological details of terminal metamorphoses, sequellae and complications to such an extent that the essential changes and their sequence are often obscured.

It has been the combined studies of morphological changes in relation to variations in the iodine store, both naturally occurring and experimentally controlled, on large series of thyroids from the lower animals that have given us a schema of the sequence and relative importance of the major morphological features of the thyroid cell cycle.

After attempting in vain to use human thyroids (both surgical and autopsy material) as a starting point, the writer turned to the simpler and more controllable material of comparative pathology in the hope that a combined study of the iodine store in relation to morphology in large series of goiterous and nongoiterous thyroids of fish, birds, rabbits, sheep, cattle, pigs and dogs might give us a means for more intelligently classifying and grouping the morphological changes encountered in human goiter. Out of all these studies there has evolved a fairly simple schema of the sequence of the major features both morphological and chemical as regards the developmental stages of goiter in all animals and to a lesser extent for the involutionary or regressive changes. This schema embodies our view of the thyroid clycle and if I am

correctly informed, it does not differ essentially from the views of Prof. Wegelin.

If I am able to contribute anything to the subject of the pathology of goiter it is in this field where I have had a large experience during the past 20 years and it is from this material largely that I have drawn the following summary.

In the first place we may dispense with the idea (sometimes advanced) that the essential features of the thyroid cell cycle are different in different parts of the world even in the same animal.

The following outline of the principal types of pathological changes encountered in the thyroid indicates in the briefest way the results of our combined physiological, chemical and morphological studies:

I. *Normal thyroid.*

II. *Active hypertrophy and hyperplasia* (regeneration):
   1. Developing from the normal gland;
   2. Developing from the colloid gland (goiter).

III. *Colloid goiter.*

IV. *Atrophies:*
   1. Exhaustion atrophy (of cretinism and myxedema);
   2. Starvation;
   3. Senile.

V. *Degenerations:*
   1. Parenchymatous;
   2. Hyaline;
   3. Calcareous;
   4. Fatty, glycogenic;
   5. Amyloid disease.

VI. *Inflamations:*
   1. Acute { non-suppurative, suppurative;
   2. Chronic (tuberculosis, syphilis).

VII. *Tumors:*
   1. Benign:
      a) Adenomas (Struma nodosa).
   2. Malignant:
      a) Carcinoma: 1. Arising from adenomatous tissue
                 2. Arising from nonadenomatous tissue
                 3. Papilloma.
      b) Sarcoma;

c) Epithelioma;
d) Endothelioma.

VIII. *Complications:*
1. Hemorrhage;
2. Cyst formation;
   a) from hemorrhage;
   b) from adenomas.

The thyroid has the same basic pathological lesions common to all other body tissues. The apparent differences depend largely on its remarkable capacity for growth and involution together with its peculiar architecture so characteristic of a storage gland.

NORMAL.

Differences of opinion still exist in regard to many of the essential features of the normal human gland. In our experience the average weight of the normal adult thyroid (seacoast type) is around 25 gms. or 0,3 to 0,35 gms. per kg. and a similar relation to body weight holds for the dog and cat.

We find no essential difference in the thyroid unit — the follicle — throughout the vertebrates. This unit consists of a rounded closed space of highly variable size, but averaging from $^1/_4$ to $^1/_2$ mm. in diameter. The condition of the lining epithelium and colloid is of greater importance. The thyroid gland cell is so labile that a definition of the normal limits is difficult. We believe, however, that the normal cell is flat cuboidal and never taller than cuboidal with a small vesicular nucleus and granular mitochondria. The colloid completely fills the follicular space save for occasional vacuoles. Oswald first pointed out, and we have confirmed the fact, that the iodine store and the stainable colloid are in general parallel, but since iodine determinations are more accurate than any estimations of the colloid morphologically, we urge that in addition to morphologic standards of normal, the iodine store should be determined and this must be at least 0.1 % of the dried weight.

HYPERTROPHY AND HYPERPLASIA
(Struma diffusa parenchymatosa).

We believe that all thyroid enlargements begin as active work hypertrophies and hyperplasias and, in their early or developmental stages, are essentially the same in all animals.

The proper physiological and sequential relations of these

morphological changes may be represented in the following scheme:

Normal → Hypertrophy → Hyperplasia → Exhaustion atrophy / Involution (Colloid goiter)

Colloid goiter → Hypertrophy → Hyperplasia → Exhaustion atrophy / Involution (Colloid goiter)

Colloid goiter → Hyperplasia → Hypertrophy

Whenever the iodine store of the thyroid falls below the normal minimum (with our methods 0,1 % per gm. of dried gland) the gland undergoes changes characterized by a general increase in its blood supply, a general decrease in the stainable colloid and a change in the epithelium from a low cuboidal to cuboidal to columnar. There are all degrees of gland cell growth from the slightest departure from normal (hypertrophy) to the most marked proliferation (hyperplasia). This series of changes is strikingly constant in all animals from fish to man and bears no necessary relationship to the clinical condition with which it is associated.

When the epithelial proliferation has reached its maximum, the blood supply has also reached its maximum. The colloid has decreased to a small amount of granular albuminous material and the iodine content has fallen to an inestimable trace.

Considerable confusion has arisen because pathologists have not always borne in mind the fact that progressive and regressive changes may succeed each other in rapid sequence and that these progressive and regressive changes are variable in degree. Thus most goiter undergo active hyperplasia and involution for one reason or another several times during their life history and each of these cycles entails certain morphologic differences in degree but not in quality, which may easily be misleading when too great stress is laid on any particular detail. Thus variations in the stroma, variations in the size of the follicles due to the presence of newly formed follicles or the passive dilatation of follicles from the deposition of colloid or pressure atrophy and rupture of the follicular walls are examples of details which may be overemphasized. Also such changes bring about variations in the blood supply in different parts of the gland and these in turn markedly influence involution or secondary regeneration as first pointed out

by Ribbert in his studies on thyroid regeneration. Hemorrhage also modifies the appearance of goiters in a great variety of ways. There are numerous other factors which influence the morphologic appearance, but the few mentioned will serve to illustrate the point.

For convenience and emphasis one may divide active hypertrophy and hyperplasia into (1) primary, that is, arising from the normal thyroid and (2) secondary, that is arising from glands which have previously undergone hyperplasia and involution one or more times (colloid goiters).

The histological and cytological changes in the regeneration which follows partial removal are indistinguishable from the changes seen in the spontaneously developing or experimentally produced goiters.

INVOLUTION (COLLOID GOITER).
(Struma diffusa colloides)

Involutionary or restitutional changes may begin at any stage of the active hypertrophy or hyperplasia. These changes occur spontaneously or may be artificially or rapidly induced by the administration of iodine. The end stage in either event is colloid goiter. Colloid goiter is the nearest condition to normal, physiologically, chemically and anatomically, that a thyroid which has once been hyperplastic can again assume. The process of involution may be arrested at any stage and active hyperplasia begin again. All stages of involution from the marked active hyperplasia back to the colloid gland exist just as all stages of hyperplasia exist and the morphological appearance of a given gland merely represents the stage of this cell cycle at the time of examination. The anatomical changes are the reverse of those seen during hypertrophy and hyperplasia. The gland as a whole becomes firmer. The color changes from the grayish red and opaque appearance of the hyperplastic stage to a translucent amber red color when involution is complete. The blood supply diminishes. The alveoli become highly variable in size (from 0,1 mm to 1 cm). The colloid becomes dense and viscid. Paralleling the accumulation of colloid is a rise in the iodine store, often to the normal or above if involution has been artificially induced. The high columnar epithelium slowly or rapidly returns from columnar, to cuboidal and finally to flat cuboidal if the involution is complete. The stroma becomes less prominent either from compression, decreased vascularity or absorption.

The involution of thyroid hyperplasia in animals is usually accompanied by a decrease in the size of the gland. This is not essential because even in animals and frequently in man not only is the decrease in size lacking but actual enlargement may occur, particularly when iodine is given suddenly in large doses.

The development of a colloid goiter (struma colloides) from a normal gland by pressure distention of the follicles with colloid we consider impossible. Our experience shows that the thyroid enlargement is always initiated as an active hypertrophy and hyperplasia. Pressure distention of the follicles with colloid clearly is an important factor causing further enlargement in the later stages of active hyperplasias when the rate of cell growth and proliferation is declining as seen in the stage of involution described as *struma diffusa colloides proliferans*. Such glands, as is well known, have an abundance of iodine poor colloid, whereas in the fully arrested or involuted stage (struma diffusa colloides) the iodine store is much greater.

EXHAUSTION ATROPHY

While involution or recovery is the usual mode of termination of compensatory hyperplasia, it occasionally happens that the maximum degree of hyerplasia reached fails to bring about functional compensation and sooner or later a state of thyroid exhaustion supervenes. This outcome is most frequently seen in goiterous cretins, both in man and animals, and it is occasionally observed in the late stage of cases of exophthalmic goiter going over to myxedema. The morphological changes observed we believe are the result of a long continued hyperactivity of the cells without sufficient physiological rest. The most characteristic morphologic changes are seen in the epithelium and stroma. There are all stages of the process from the typical, uniform, active hyperplasia to high grade scirrhous atrophy. In the first stages the epithelial cells are high columnar in type with here and there an atypical cell mass. As atrophy and cell death progress the epithelial cells become more variable in size, shape and staining reactions. Later the cells lose their uniform arrangement in the follicle, desquamation and disintegration may be seen in the same follicle with mitotic figures. All the cells of a given follicle are not uniformly affected. Nuclei of the affected cells show great irregularity, sometimes enlarged and hyperchromatic, sometimes small and picnotic, but always variable in size, shape and staining intensity. The colloid is greatly reduced or absent, though occasio-

nally large dense masses of colloid may be embedded in the stroma (retention cysts) with little remaining evidence of the original follicle. As the atrophic process continues the follicles become greatly reduced in size by cell death and advancing sclerosis until those remaining appear as compressed nests of irregular cells. The stroma is always relatively increased and in some instances seems to be absolutely increased. Instances of exhaustion atrophy have been mistaken microscopically for carcinoma.

STRUMA NODOSA (ADENOMAS).

One of the secondary morphologic features of goiter in man requires special notice, namely, the development of nodules of glandular tissue, the so-called adenomas. I have always grouped them under the general heading of benign tumors. This, however, is not satisfactory, and the designation «struma nodosa» or «nodular goiter» is much safer with our present limited knowledge.

The fact that this type of growth is restricted almost entirely to human goiter makes it exceedingly difficult to test experimentally any hypothesis regarding its origin or nature. As Wegelin has shown, goiter in the white rat resembles slightly the nodular goiter found in man, but even here the resemblance is only slight. The suggestion of Woeffler that these nodules arise from fetal thyroid rests, and the introduction by Billroth of the term «fetal adenoma» have served unduly to emphasize the hypothesis of their fetal origin. While a few may arise in this way, there is general acceptance of the view that the great majority must arise from differentiated thyroid tissue usually beginning in goiter of adolescence. We do not believe that there is any fundamental difference between struma diffusa and struma nodosa since all nodular goiters were in the beginning diffuse goiters, and one sees all gradations between the two types. The clear distinction between struma diffusa and struma nodosa which Aschoff supports we are unable to accept. As to their mode of origin from previously differentiated thyroid there are still differences of opinion as to detail. Our studies indicate that the nodular hyperplasia is an integral part of simple or diffuse goiter and is due to the same stimulus which causes the gland as a whole to hypertrophy. The nodules arise during the late stages of the compensatory hypertrophy because of different rates of growth. These different rates of growth depend on many factors — first, differences in blood supply (for example they rarely start in the subcapsular zone) depending on pressure effects from stroma bands, colloid retention cysts, etc.

does not agree with Aschoff. See page 1

If one studies experimentally the secondary regeneration of the thyroid in a long standing goiter, one sees, as is well known, that the hyperplasia occurs in islands surrounded by areas of follicles densely packed and distended with colloid. In man this patchy hyperplasia is most frequently seen in long standing goiters that have passed through numerous cycles of hyperplasia and involution, partial or complete. Clinically this condition is seen most frequently in the connection with recurring pregnancies and the development of secondary Graves' disease. Some pathologists have sought to explain the Graves' disease as being due to the activity of these islands of hyperplasia. The unicentric and concentric growth of these areas are universally accepted. If the rate of growth is rapid these areas acquire a false capsule by stretching and pressure atrophy of the adjacent thyroid tissue. The various degenerations and sequelae which may occur in them are the results of their outgrowing their blood supply.

Since in their origin they are integral parts of the late hyperplastic stage of goiter it is easy to understand why they so closely resemble nonadenomatous hyperplasia in their physiological behavior. Thus, they have a growning or hyperplastic and a recovery or involutionary (colloid) stage, just as ordinary thyroid tissue. They react with iodine. The more differentiated often react identically with the nonadenomatous thyroid while the less differentiated react more slowly. Therefore if these adenomata are tumors in any physiological sense they are only partial tumors since they retain to a greater or less degree this outstanding physiological attribute of thyroid tissue which in our experience is absent in cases of malignant epithelial tumors of the thyroid despite the much quoted incomplete and single observation of von Eiselsberg.

On the other hand that these adenomata are potential tumors is indicated by the facts that they may continue to grow after the rest of the thyroid has ceased to grow and that a large percentage of the malignant epithelial tumors of the thyroid arise from them.

Certain observers in America (Goetsch and Plummer in particular) have ascribed a more specific pathological and clinical significance to adenomata as is implied in the terms « toxic adenomata » and « adenomatous goiter with hyperthyroidism ». The basis for this separation from Graves' disease is purely clinical but even on a clinical basis such a separation is without adequate foundation. Virchow and all subsequent writers have pointed out that adenomata were one of many morphological states that might occur in the thyroid in Graves' disease and their presence offers

no basis for assuming that Graves' disease and « toxic adenoma » are different in any essential feature.

I have attempted to describe the three principal stages of the thyroid cycle concerned in goiter and have intentionally omitted mentioning any of the multitude of secondary changes except the nodules or adenomas of struma nodosa. Students are in general agreement as regards the major facts of thyroid morphology. Existing differences depend largely upon whether we limit ourselves to a strict morphological or insist on a combined morphological and physiological interpretation of these facts.

In my own country as the experience of the various workers has increased we have come into closer agreement. So also we find ourselves in close agreement with the morphological features so excellently outlined and illustrated by Prof. Wegelin in his recent monograph.

EXPLANATION OF ILLUSTRATIONS.

The six illustrations depict the two terminal or end stages which may result from a parenchymatous (actively hyperplastic) goiter.

Figure 1 is the ordinary appearance of hyperplastic endemic goiter in man and is indistinguishable from similar goiters in animals.

Figures 2, 3, 4 and 5 illustrate stages in the involution or physiological recovery of active hyperplasias. This is the usual mode of termination of all hyperplastic goiters.

Figure 6 illustrates the second or rare terminal stage of parenchymatous (actively hyperplastic) goiter in which the maximum degree of hyperplasia fails to compensate and exhaustion atrophy supervenes.

* * *

Conclusion :

The cycle of morphological changes in the thyroid is essentially the same in all animals and consists of hypertrophy and hyperplasia followed either by exhaustion atrophy (cretinism and myxedema) or by involution to the colloid or resting stage (recovery). Exhaustion atrophy occurs only in the severest grades of uncompensatory hyperplasia, while involution to colloid goitre is the usual termination of active hyperplasia.

Of the numerous secondary changes that occur in goitre, the development of adenomatous nodules is most prominent in human

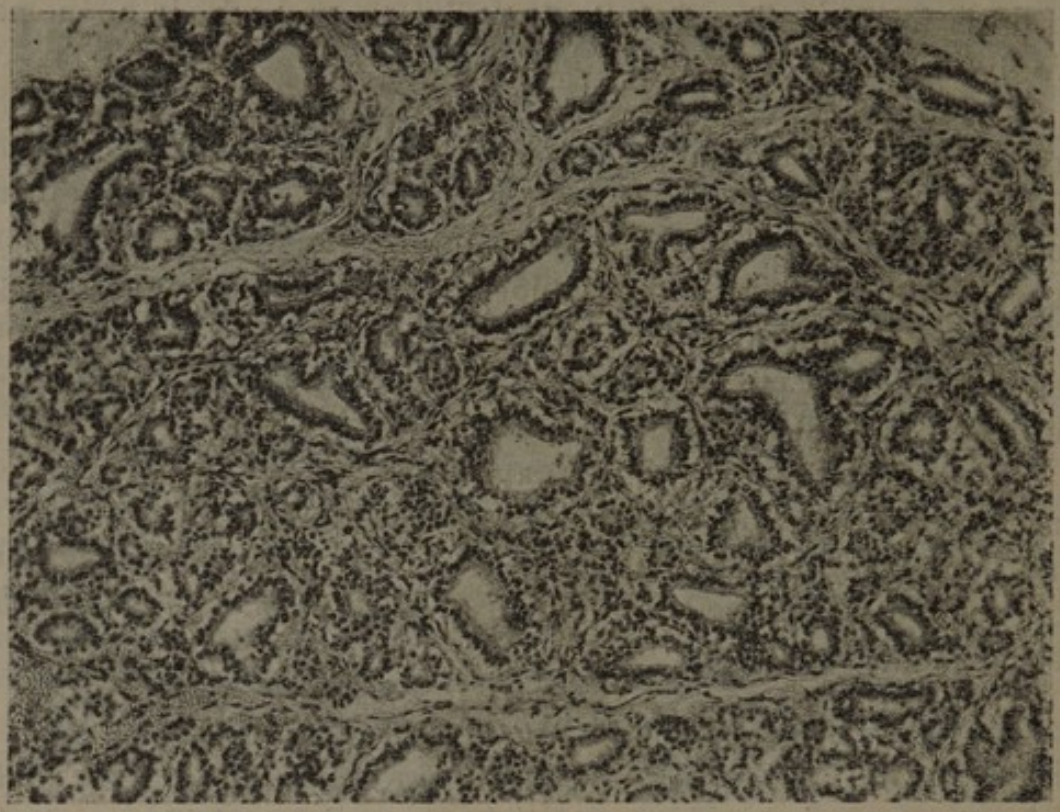


Fig. 1. Struma diffusa parenchymatosa.
(Simple or endemic congenital goiter).

Fig. 2. Struma diffusa parenchymatosa et colloides.
(Simple or endemic goiter of adolescence.)

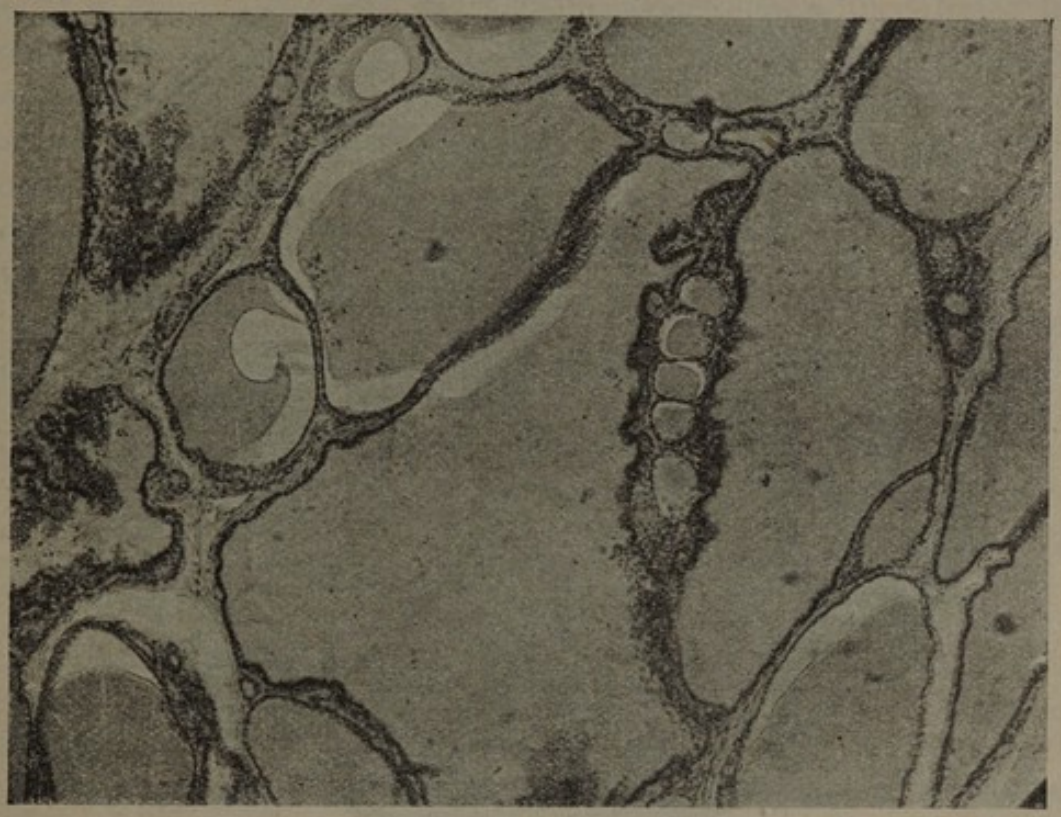


Fig. 3. Struma diffusa colloides proliferans.
(Simple or endemic goiter of adolescence.)

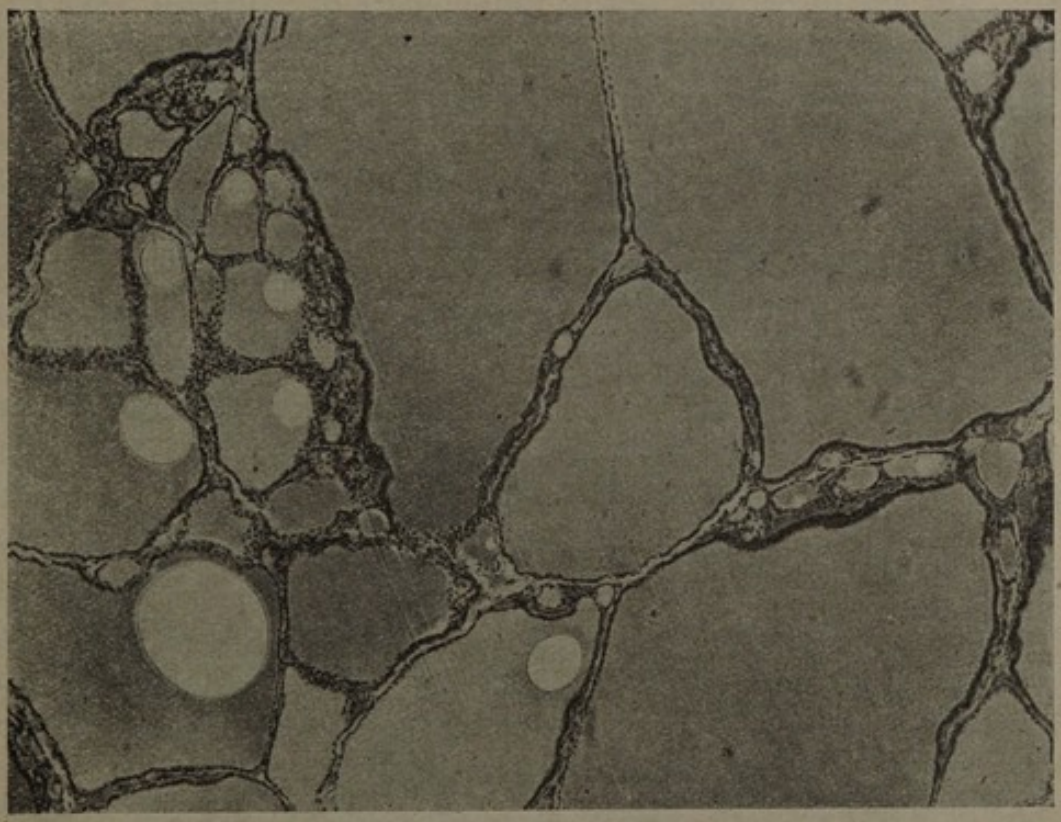


Fig. 4. Struma diffusa colloides proliferans.
(Simple or endemic goiter of adolescence.)

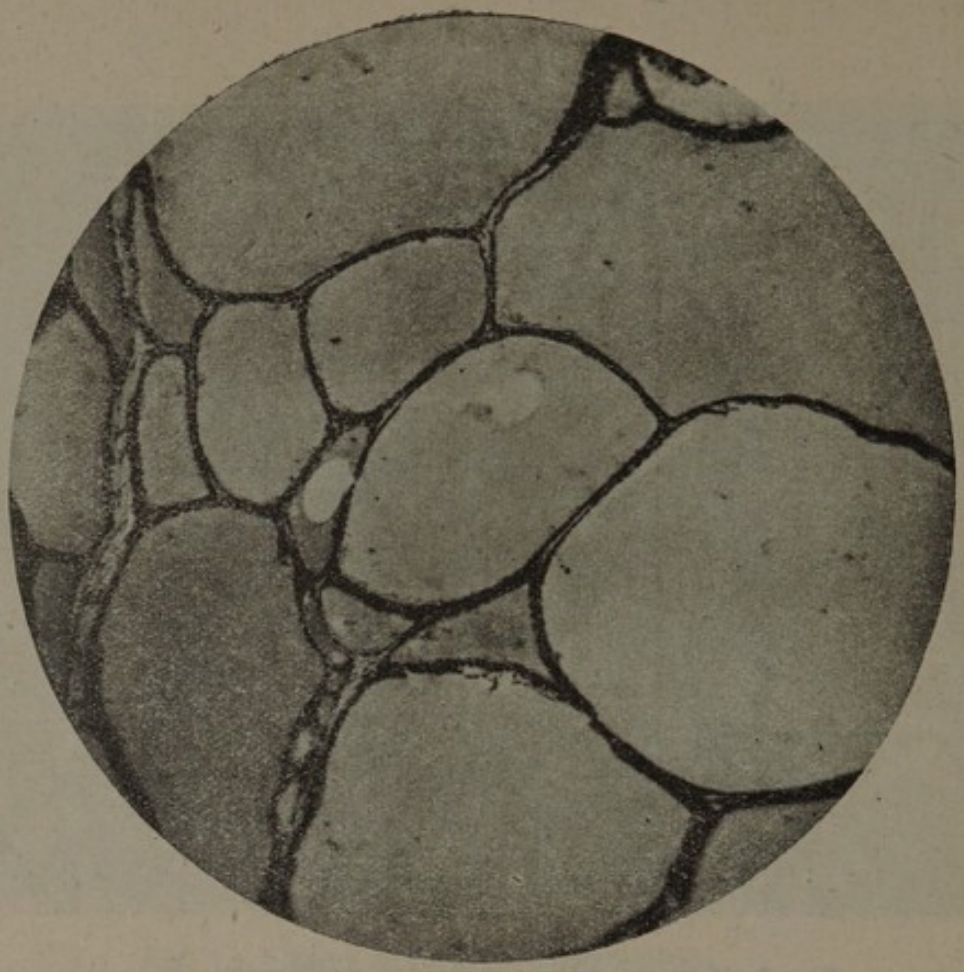


Fig. 5. Struma diffusa colloides, resting stage.
(Simple or endemic goiter of adolescence.)

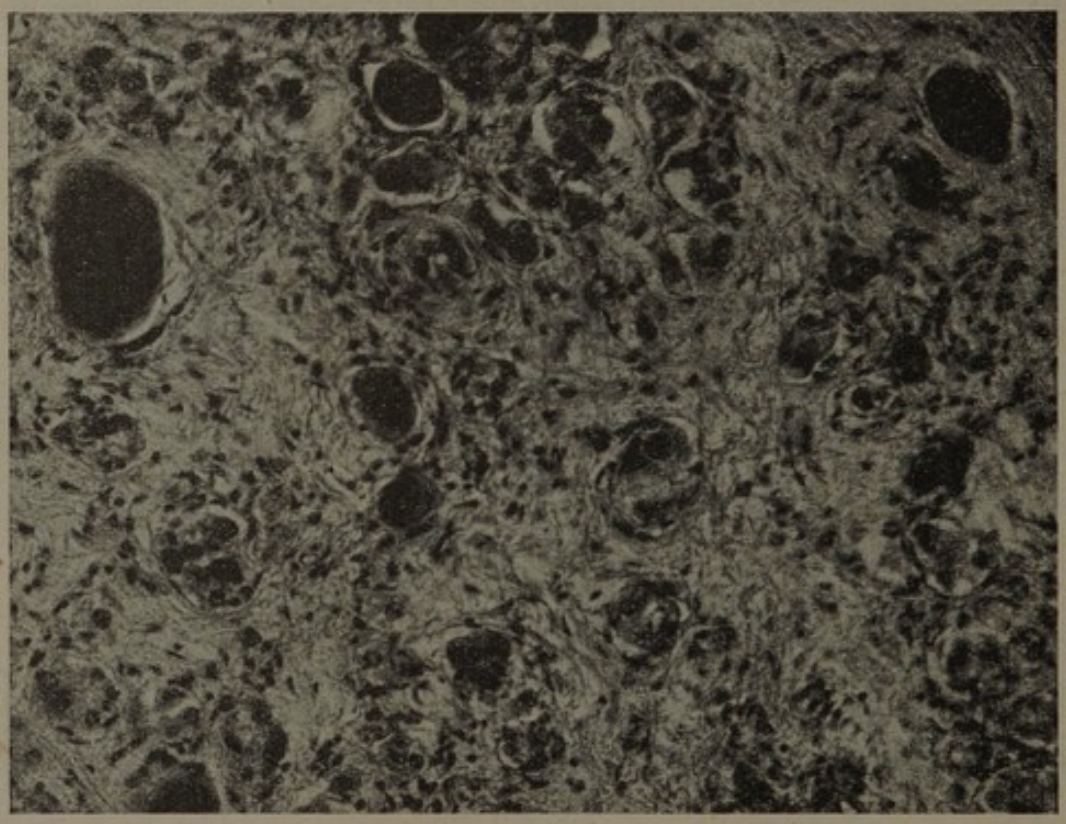


Fig. 6. Struma diffusa atrophica.
(Exhaustion atrophy of simple or endemic goiter.)

goitre. Struma nodosa is very rarely seen in the lower animals. The belief is expressed that these nodules arise from differentiated thyroid tissue during the late stages of compensatory hypertrophy because of different rates of growth. These nodules tend to repeat the same morphological cycle as non-adenomatous tissue although somewhat modified. There is abundant evidence that these adenomatous growths can produce thyroxine. There is no evidence that true tumors can produce this substance.

Thyroid hyperplasia (goitre) is a compensatory process dependent upon a relative or absolute deficiency of iodine.

Discussion and Remarks,

Goiter in Animals.

By Prof. H. Huguenin of the Veterinary-pathological Institute, Berne

I take pleasure in responding to the request of the organizers of this conference and shall briefly address you on the researches, which have been made in the veterinary-pathological institute on the occurrence of goiter in animals. As the time that stands at my disposal is rather limited I am obliged to confine myself on the one hand to explain the stereopticon views, which will be shown to you, and on the other hand the preparations, which are on exhibition at this conference.

From the investigations made on the thyroid glands of healthy, full-grown animals taken from different districts I hold to the view that the normal structure of the organs is characterized through small vesicles somewhat round in shape, which are formed at the middle of the section, i. e. the equator, in the circumference of about 20 cells and exhibit a small quantity of colloid. In these thyroid glands the connective tissue is but poorly represented, and contains numerous blood vessels. The aspect, as described above, which was obtained from a section of a thyroid gland of a full-grown female hart, that had died of an acute enteritis shortly after its arrival in Berne, is not to be recognized in the following projections: 1. Goiter of a stag with irregular vesicles, almost

without any colloid, with cylindrical epithelium, which forms more or less high papillae. 2. Goiter of a roebuck, which was shot in the southern part of the Canton of Aargau, where goiter endemic is very strongly developed. The majority of the vesicles are filled with colloid and the wall of the same is filled out with flattened epithelium. In the middle of the diffuse swelling there is an adenoma of about ¼ millimeter or $^1/_{100}$ inch in diameter with vesicles without colloid, the epithelium of which is made almost only from the nuclei.

The following slide shows a goiter (of a 6 year old cow) having twice the weight of a normal thyroid gland. The aspect of this case typifies that, which is most frequently met with among the animals in Berne. I have observed this variety not only among the herbivorous animals, as cattle, sheep, goats and horses, but also among the carnivorous as dogs and cats. Even among the birds this type has been found, viz: domestic fowl, ducks, swans, peacocks and pigeons. The vesicles are large and filled in the middle with colloid which has generally throughout its entire extent a uniform pink color. The colloid occasionally is of a uniform blue color, when colored by haemotoxylin. In some special cases the center is blue while the peripheral parts have a pink color given by eosin. Between the colloid and the connecting tissue there is a bed of several layers of cubical polyhedral or flat epithelial cells. The vessels are not very numerous.

Besides this form, which is by far the most frequent, we find vesicles which are entirely filled with cells and in which no colloid is to be seen — and, in contrast to these, we find those with much colloid and with a single layer of cylindrical, cubical or flat cells. An intermediary form may still be mentioned, which is particularly characterized in that a large number of isolated cells are found in the colloid. Since these cells show various degrees of necrobiosis either of the protoplasm or of the nucleus or both together, the cell can scarcely be seen in very advanced stages and usually merely a shadow is visible.

The congenital goiter is likewise to be found in animals: I have observed it in dogs, cats, deer and sheep. It was always a question of a parenchymatous goiter type without any strong formation of cells and the vesicles were of medium size without colloid or with merely a trace of it. As an example I shall mention the goiter of a cow-foetus sent me from the slaughterhouse, which foetus was still in the mother's body. The mother was in the seventh month of pregnancy; the thyroid gland of the foetus weighed 80 grammes.

Histologically it was found that there were vesicles without colloid, entirely filled with cells.

In the case of pigs I have never seen congenital goiter, but, on the other hand, I have often observed inherited goiter in sucking pigs and one of my students, Mr. Marti, has done work on this point. The formations which we find here are very singular. The epithelium is always cubical, it lines very irregular hollows, in which there are finely granulated masses or small quantities of colloid colored pink by eosin. The irregularity is brought about by the capillaries being extended to the maximum; these are so greatly dilated that they press back the epithelia into the inner part of the vesicle. The aspects in older pigs, nevertheless such that are still young from the biological point of view since the epiphysis lines are still there, show great differentiations as contrasted with those of quite young animals.

We find, at times, thyroid glands having a weight of several hundred grammes, containing much colloid and with medium vascularization. Between these two extremes we meet with a great number of intermediary steps, or transformations with folded and more or less papillomatous epithelia.

I have had the thyroid glands of horses coming from Rome, Paris, Lausanne and Berne studied. The average weight increased, according to the origin, in the same succession as the cities are mentioned. These investigations, which were carried on by Balsiger, were confirmed by Geiger for the thyroid glands of goats; those from Malaga had the lowest weight and those from the Bernese « Oberland » (Highlands of the Canton of Berne) the highest. In a number of investigations of the same kind, which were made by Gschwend, we found the thyroid glands of goats from Styria having the greatest weight and those having the least weight were from Northern Germany. Dolder has found the same differences in weight in thyroid glands of cattle from Paris, Lausanne and Berne.

We pass on now to the study of goiter in dogs. When investigated microscopically, a metamorphosed thyroid gland is always found in the dogs of Berne. The swelling may be recognized even at birth and it sometimes happens that the thyroid gland takes up the whole space between the os-hyoideum and the sternum. With young dogs this swelling is very often connected with a dilatation of the heart and here it is not a question of any reaction of a mechanical nature, for it is only exceptionally that the trachea is compressed and then only for a short time after the birth. I have

never found the compression of the trachea in the case of animals over 3 months in age.

With old dogs the thyroid gland is often smaller than the normal; this senile grade of involution is characterized by a badly conserved epithelium with little or no colloid, by an increase of the connective tissue, by diffuse calcification or such that is even visible to the naked eye as a concretion and by the deposition of cholesterin. The calcification of the thyroid gland begins with the dog even during the first year of life. I am in possession of a preparation in which the calcification already existed in a dog of three months of age. It had begun in the epithelial cells, which filled out the enlarged vesicles and which had already gone over into necrosis. Nozcnic has designated as Strumoid the senile involution of the thyroid gland of a dog, which had previously been affected by goiter.

The goiter of the dog is particularly interesting owing to its reactions upon the dispersed thyroid gland germs. It sometimes happens that even these thyroid glands found in the pericardium reach very considerable dimensions even to the size of walnuts. The accessory thyroid glands are very frequent, more than 50 % of the dogs have such and in one and the same animal there may be found even as many as 15 of this kind of formations. I may say that I have found them practically everywhere from the hyoid bone to the pericardium where they are lying on the pericardium parietale, on the pericardium of the large vessels and even in the interior of the heart to the height of the conus pulmonaris. The microscopic aspect is the same in the real thyroid gland and in the accessory thyroid glands.

Special attention must be given to the question of the adenomas. They are not as frequent in animals as in human beings. In the case of 500 thyroid glands of pigs I have not one single time met with them, in necropsies on 3000 cats only three times, and of 200 thyroid glands of cattle only one showed an adenoma. With dogs the ratio is higher, 1 : 100; with horses it is the highest: 30 % of the animals over 8 years of age show adenomas of the thyroid gland.

The prevalence of carcinomas is very varied with the different kinds of animals. In 200 dissections of horses I found only one case of cancer and it is probable that we have here to do with a characteristic of the breed. However, it ought not to be lost sight of that the horses, or at least the greater part of them, are either imported from foreign countries or come from the Bernese Jura

mountains, a locality, which has very little goiter, as is well known. I have never been able to observe cancer in cattle, sheep and goats.

There are two animals which live in close proximity to mankind, viz. the dog and the cat; both animals are carnivorous and mankind has trained them to be omnivorous. Of 3000 examinations of cats there was found to be only one that had a carcinoma. The matter was quite different as regards the dog. Of the last 750 dissections on dogs, in 6 % of the cases I found carcinomas of the thyroid gland and this percentage increased to 26 % in the case of dogs over 7 years of age. These conditions can not be compared with those ascertained regarding human beings, for it must be taken into consideration that the majority of the animals, which were dissected, did not die of any disease but were sacrificed for reasons which had nothing to do with their state of health. For more than one half of our material a comparison could not be made with the total number of those treated in hospitals but rather only with those dying through intercurrent diseases or by accident, where by chance a cancer would be found.

I have previously made mention of the great frequency of thyroid gland cancer in dogs and have drawn attention to the fact that I consider the goiter in the animal as being a precancerous condition, (1918, «Gesellschaft zur Krebs-Bekämpfung» — [Swiss Society for the Cure of Cancer]). I said this by beginning with the great differences in the frequency of cancer of the thyroid glands with persons from Geneva and Berne and at the same time drew attention to the different frequency of goiter in Geneva and Berne and I made mention of the differences in the intensity of goiter, the dog being afflicted with much harder forms of goiter than the other domestic animals. I also drew attention to the differences in the frequency of thyroid gland carcinomas in the different kinds of animals. Likewise here the dog very often shows malignant tumors, whereas the other animals, especially the cat is almost entirely spared from neoplasms in the thyroid glands. The different elucidations make it perfectly clear to us that the factor «genus» plays a most important rôle.

"genus" not cancer.

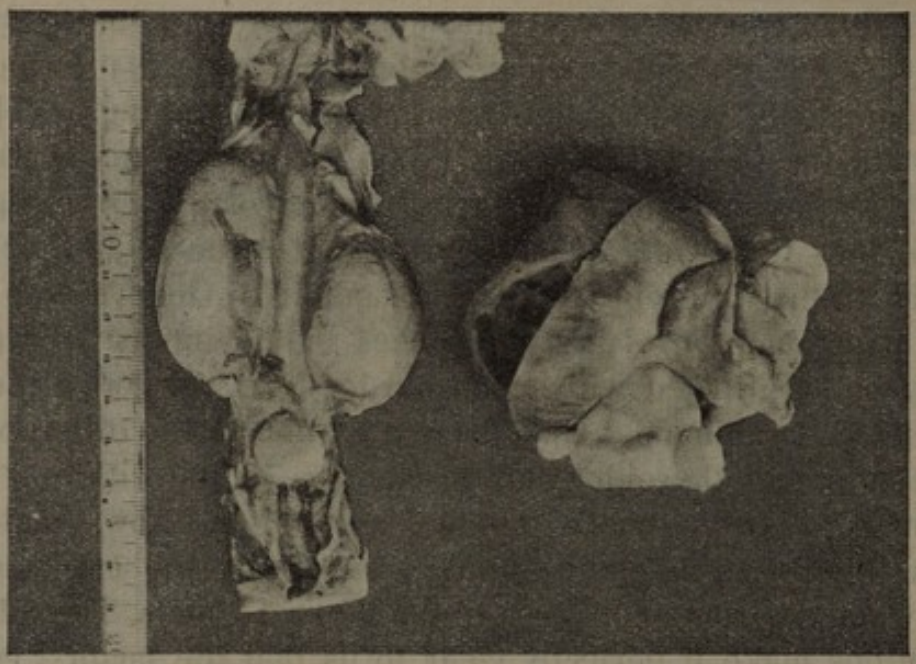
The carcinoma of the thyroid gland of the dog makes evident some peculiarities, both as regards frequency and development, to which I desire particularly to call attention. Above all, it is striking that the malignity of the carcinoma is simply limited in a relatively great number of the cases: the tumor penetrates only into the lumen of the blood vessels or, to speak more exactly, into the veins, without forming metastases. No metastases are ever

met with in the skeleton, but they frequently are developed in the other thyroid lobe or in the accessory thyroid glands.

I should like to bring my statements to a close with an observation, which relates to the influence of the vitamines upon the origin of goiter: the goiter appeared upon white rats after an alimentation for a period of about 25 days with foods that were free from vitamines and disappeared after feeding with the kitchen leavings of green vegetables. The food containing no vitamines consisted of a thick porridge of oat flakes, that had been boiled a long time, and some rye bread. In another series of experiments the goiter appeared as a result of feeding exclusively with white bread.

? How can he say that?

Fig. 1.

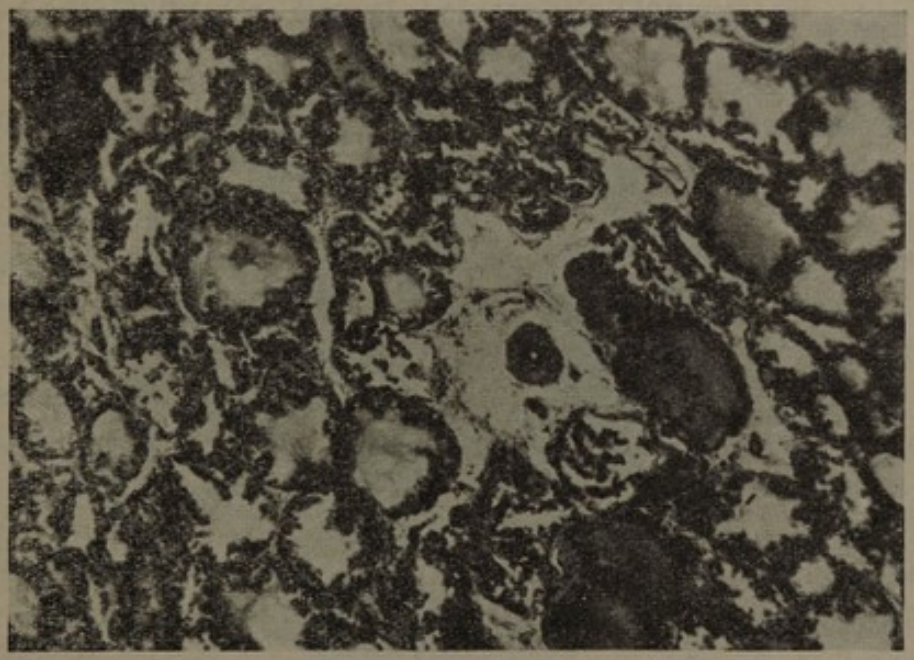


Goiter of a 5 month old fox terrier. Struma diffusa on both sides, struma aberrans at the level of the hyoid bone, several aberrant strumas near the *pars intrapericardialis* of the aorta.

Fig. 2.

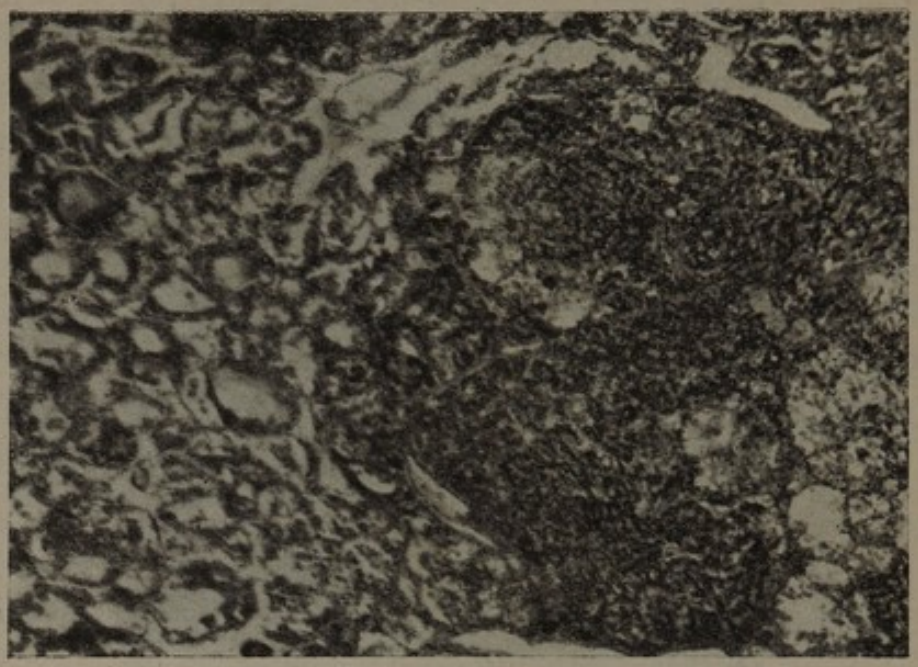
Above at the left: the normal thyroid gland of the cat. Below and at the right: goiters of cat, in part split.

Fig. 3.

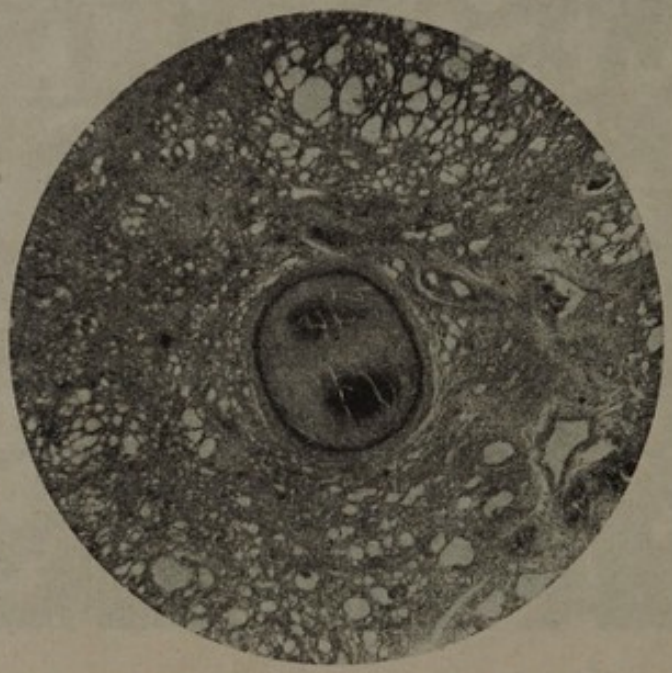


Goiter of cattle: Epithelium in several layers, colloid. Magnified 80 ×.

Fig. 4.

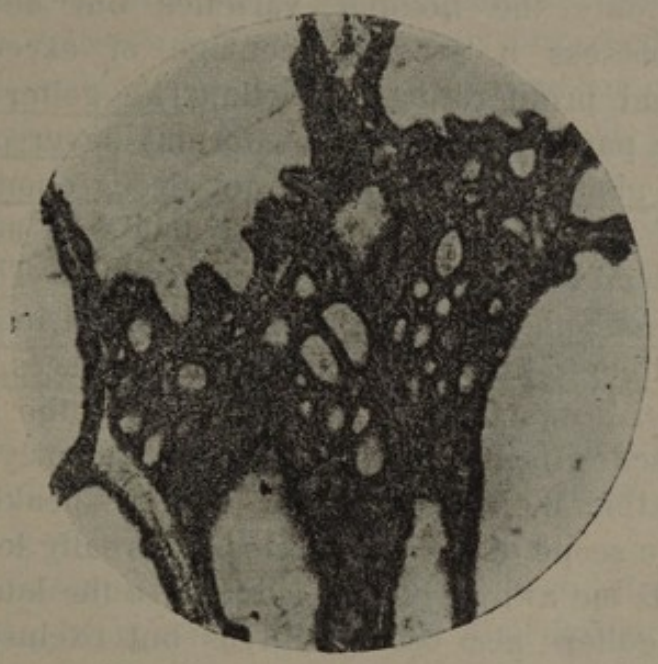


Goiter of roebuck with solid adenoma.
Magnified 80×.



Goiter of dog with senile degeneration and calcification.
Magnified 50×.

Fig. 6.



Goiter of cow with large and small vesicles and papillae.
Magnified 100×.

Endemic Goiter in the North German Lowlands.

By Dr. Ernest Feldmann, Danzig.

Professor Aschoff showed us in his address the life curve of goiter and at the same time described the dependency of the morphology upon the age and the different individual stages of development. I should like at this place to supplement his declarations with a comment on another dependent relation. I desire to add a general, local-geographical qualification to the individual one. The differences in the morphology and the physiology of endemic goiter, that are occasioned in a geographical sense, constitute an extremely important chapter, to which but little attention has thus far been given.

Within the time-limit, that is allowed a speaker, to comment on any address, I shall give you my contribution on this subject by describing the regional peculiarities of the endemic goiter of the low plains of Northern Germany, which is by no means of rare occurrence with us in Danzig, the morphological and physiological deviations of which from the goiter of Switzerland, for example, are very apparent to the eye.

Our goiters in Danzig are without exception extremely rich in colloid, not only the nodular varieties but also the diffuse ones, and possess a great percentage of exceedingly active cylindrical and proliferating epithelia. The goiter of the newly born (struma parenchymatosa neonatorum) never occurs with us; to bring that about our endemic is not strong enough. The goiter of the age of puberty is the diffuse struma with active epithelial proliferations and is extremely rich in colloid. The parenchymatous variety of puberty goiter, which appeared in a predominant degree from time to time in Vienna and other places, does not at all occur with us. Now and then we can observe the struma diffusa colloides Basedowificata originating spontaneously or in consequence of iodine therapy. But this, strictly speaking, no longer belongs in the scope of endemic goiter, but really to morbus Basedow and leads me away from my subject. In the later years of life the nodular goiters also occur with us but exclusively matured, often proliferating colloid nodules and their forms of degeneration. Parenchymatous nodules are found extremely seldom.

The very conspicuous frequency of the hyperthyreoses in the genuine endemic goiter, with the exception of the time of puberty in which we never observe any hyperthyreotic strumas, and also the complete lack of any cases of cretinism are further regional peculiarities of our North German goiters, that are likewise in close connection with the morphological peculiarity.

Professor Aschoff has declared in his printed report that genuine hyperthyreoidism is an exception in the case of genuine endemic goiter. I feel that I must contradict this statement as far as our local conditions are concerned and recognize in this also a contribution bearing on the regionally varying character of goiter endemics.

A further characteristic of our North German goiters is their susceptibility to iodine, and this is likewise exceedingly closely connected with their morphology. We very frequently find with adults the occurrence of genuine morbus Basedow *e therapia iodi* after iodine medication, so that for our district we are most strongly disinclined towards iodine treatment in the case of adults.

The theory as to the lack of iodine can not explain the frequent occurrence of endemic goiter to us, who live in the vicinity of the sea in surroundings rich in iodine with an amount of iodine, that according to von Fellenberg is high. An increased supply of lime can also not be held accountable, for we possess drinking water that is throughout of a medium degree of hardness.

In order that my statements will not be misunderstood, I should not like to bring my allusion to the geographical peculiarity of the North German endemic goiter as specially observed in Danzig to a close without laying stress upon the fact, that our endemic goiter also follows throughout the generally accepted curve of life, notwithstanding any and all regional peculiarities. The fact that the type of endemic goiter varies geographically, is a significant indication of the great influence which local exogenous factors have upon the origin and the conformation of goiter.

I shall now also show you several photos:

1. Here we see the type of puberty goiter that occurs exclusively with us. Large follicles turgescent of colloid having a diameter of 1 to 2 millimeters.

2. The microscopic aspect of such a puberty struma shows us vegetation buds, everywhere in uniform distribution, with cushion formations and abundant new formations of daughter follicles.

3. This picture, which is that of the diffuse struma of a 26 year old girl, with hyperthyreosis, shows us how active the proliferation of the epithelium can be even after the completion of puberty. I state emphatically, that this with us in Danzig is of frequent occurrence and that a certain degree of hyperthyroidism belongs to the typical qualities of our endemic goiter and has nothing in common with Basedowification and Morbus Basedow.

4. In contrast with this fact and for the purpose of bringing out more strongly the differences, I shall now show you a really Basedowificized diffuse colloid struma, such as we meet with now and then spontaneously or after iodine medication. The parts, that still contain some colloid, are bright, whereas the centers, which are already Basedowificized, are dark.

5. The histological aspect, pertaining to this, shows the same: spots of Basedow tissue, free from colloid, in a macro-follicular colloid struma.

6. Here we see a typical nodular colloid-goiter. We can observe even in the nodules that activity of the epithelia very frequently, appearing in form of cylindrical cells and strong proliferations, combined with the clinical symptons of increased thyroid function.

7. Another nodular goiter. Our nodules, even those of rather large dimensions, have always only a very tender capsule. This circumstance favours the functional action in the sense of hyperfunction.

8. A colloid nodule with cystically dilated follicles and intrafollicular papillary proliferations, that are visible even macroscopically.

9. Here we see the corresponding microscopic section. A struma nodosa colloides papillaris, according to the nomenclature of Prof. Wegelin.

10. This is a colloid nodule in the stage of degeneration with a large cyst formed by colliquation of tissue. The fluid contents have run out.

I shall now bring my remarks to a close and should like to emphasize as a collective characteristic, that there is great activity within our goiters. We have active production of colloid with extensive infarction and at the same time abundant supply to the organism. This functional activity is accompanied by active cell proliferations of the follicular epithelia. The nodular goiters behave in this particular exactly like the diffuse strumas.

Comments

on Pathological Anatomy of Endemic Goiters with special Consideration of the Norwegian Endemics. [1])

By Johan Holst, Oslo (Norway).

From the various reports made at this conference and especially from medical literature we get the impression that endemic goiter in correspondence with its nature appears to be the same throughout the entire world. But it seems, nevertheless, as if more or less characterizing peculiarities of the endemics and of goiters might be developed through special external conditions in the respective countries, such that specially characterized them.

This fact attracted my notice above all when instituting comparisons between the Norwegian goiters and the mountain goiters of Central Europe. Regarding the external conditions, which come into question, we find that Norway contrasts with the Central European countries especially in the following particulars:

1. Although in Norway. the coast line likewise can be looked upon as being free from goiter, our endemic diseases lie nevertheless much nearer to the sea and our population uses for its food more of the sea-fish, that are rich in iodine, than the population of the Central European countries.

2. Our endemic diseases in great part are found in the level country.

Those characteristics of our endemics, which we can properly accept as being dependent upon the above-mentioned external conditions, consist in the intensity of the endemic diseases, in the function and the anatomical structure of the goiters.

1. Our endemics are far less intensive than those of Central Europe. Compared to those of Switzerland they can be designated in some places as being rudimentary. The thought seems quite natural that the reason for this mild course, which our endemics take, lies in the fact that the alimentation of our people is so rich in iodine, when taken into comparison with that of the Central European people. This assumption is also confirmed through the research work of Nicolaysen and Lunde, according to which there is also, to be sure, a certain lack of iodine in the investigated endemics, yet by far not so great a lack as in the Swiss endemics.

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[1]) Several endemiological and functional conditions are also discussed here, which are necessary for the better understanding of special characteristics of the pathological anatomy of our strumas.

2. In the majority of the cases there are no disturbances of function with our goiters. If there are any functional changes observed, it is a question in most of these cases of a hyperfunction, which makes itself conspicuous in some regions in a well-developed way. For example, there were 45 of the 489 goiters, that were operated upon in the municipal hospital at Drammen, which manifested clinical thyrotoxicosis symptoms. To this I may add that I have proved during the past 5 years through investigations in basic metabolism, that in Norway there frequently exists a latent thyrotoxicosis of the goitrous. (On latent thyrotoxicosis see the chapter on «Pathological Physiology of Struma» in this report.)

There is absolutely no cretinism occurring in Norway in the well-developed manner, that we, e. g., can find in Switzerland (Full cretins on «Pflanzenstadium»). To be sure, we do occasionally see lighter forms of cretinism, but really only very rarely. The hypothyroidal strumas likewise occur with us very rarely. Very isolated cases of inherited «athyreosis», which were influenced by thyroidine treatment, have been observed in several of our goitrous regions.

Some years ago I expressed the thought (Schweiz. medizinische Wochenschrift, 1923, No. 6), that the cases of clinical and latent thyrotoxicosis in our endemic diseases were due to the fact that the afflicted persons had been supplied with too much iodine.

Whether this idea is correct or not, can not as yet be said positively. The fact, brought out by Lunde, that some individuals can be found in goitrous regions who have very strong excretion of iodine through the kidneys and who have always been great consumers of fish, could perhaps be interpreted in the same way. On the other hand I have myself observed 6 cases of hyperthyrotic, endemic nodular strumas (toxic adenomas), the thyrotoxic symptoms of which were improved with a stronger dispensation of iodine. In these cases we could scarcely assume, that the thyrotoxic symptoms had originally been brought about through iodine.

All cases of secondary thyrotoxicosis (secondary Basedow) can, as it seems, scarcely be explained through the intake of iodine.

3. Anatomically we can come across all of the usual varieties of goiter in the Norwegian endemic diseases, but among these some are, however, especially predominant. Among the diffuse strumas we find the diffuse colloid goiters of more frequent occurrence than the diffuse parenchymatous ones and among the nodular varieties the colloid nodules preponderate. Colloidal

nodular strumas constitute anyway the most frequent varieties of goiter among the adult population of Norway. Struma afflicting newly born infants we see rarely with us and it has never become known to me that in Norway a case of death was brought about through struma in a newly born infant.

goitre in new born rare.

As far as I can understand it, this abundance of colloid on the part of our strumas calls up in our minds very vividly the Danzig strumas, which have just been described by Feldmann. It seems quite natural to me to refer this wealth in colloid also to the less pronounced lack of iodine of our endemic regions. We, of course, are aware that a parenchymatous goiter can become richer in colloid through the supply of iodine. This fact we know from the primary toxic strumas, «genuine Basedow strumas», that have been treated with iodine pre-operatively (according to Plummer).

wealth colloid to less pronounced lack iodine.

During a stay in Freiburg, Baden, Germany, Professor Aschoff in an exceedingly kind manner placed at my disposition the research work on the formation of nodules in strumas, which had been made by him and his student doctors. Later on I took up the investigation of this formation of nodules in the Norwegian diffuse colloidal strumas, taking as a basis this instruction, which was most inspiring to me. I thereby ascertained that the colloidal nodules can develop step by step from the indentations in the alveoli of the proliferating colloidal goiter.

The following microphotographs show the process of development that takes place here:

Figure I shows us the section of a diffuse proliferating colloidal goiter of a 20 year old invalid of a goitrous region.

Figure II is the general microscopic view of the same goiter. In the somewhat enlarged alveoli we can see at several places hemispherically shaped indentations. Directly out of these indentations nodules can develop according to the plan shown below in figure III.

The indentations are continually increasing in size. From being hemispherical at first (Figure III a, b) they become spherical (Figure III c) and at last completely fill the alveoli. Thereupon the superficies of the indentation fuses together with the alveoli (Figure III d) and the first, perfected, microscopic nodule takes its origin. The course of development simply continues to proceed, as we see in the microphotographs of figure IV to IX.

It must now be looked upon as having been demonstrated, and that especially so according to the investigations of the Aschoff

School, that the adenoma nodules are genuine tumors. On the other hand, no one looks upon the diffuse colloidal strumas as tumors. It is a matter of interest, that we are able to follow step by step, in the preparations which are represented here, the development into a tumor of a tissue, which has not the character of a tumor. This circumstance is entitled to still greater interest from the fact, which Wegelin has laid stress on in his address, namely, that carcinomas develop much more frequently in goiter nodules than in diffuse goiter tissue or in normal thyroid tissue.

As has been stated, there are quite frequently secondary toxic symptoms, secondary «Basedow symptoms», accompanying our endemic goiters. In the great majority of the cases it is the nodules, the adenoma nodules, to which the phenomena are due. These cases of so-called «Basedowificized» endemic goiter accordingly do not with us stand for anything else than what the Americans call with a more suitable expression «toxic adenomas». I have not been able to distinguish in our toxic adenomas or, if it is preferred, our «Basedowificized» adenoma nodules, any uniform histological aspect. We can find there colloidal nodules as well as parenchymatous ones. To be sure, in these cases papillae with cylinder epithelium are to be found there. Our toxic nodules are not seldom cystic and some of them show positively the structure of a Cystadenoma papilliferans.

The toxic symptoms in the «Basedowificized» nodular goiters of our endemic occur in a very fluctuating manner, from the very lightest to the most severe ones. I have seen an augmentation of basic metabolism up to 190 % of the normal and the clinical aspect of a «perfect Basedow», also with exophthalmus. The expression «toxic non exophthalmic goitre» accordingly does not apply for our toxic adenomas.

That the products, which cause the toxic symptoms, the «Basedow symptoms», are produced in these cases by the adenoma nodules, will become perfectly clear to us from the following example:

In the case of one patient, Miss M. H., 18 years of age, who came from a goitrous region, Hamar, with semi-dangerous secondary thyrotoxicosis, the basic metabolism being 155 % of the normal or an increase of 55 %, two sharply defined adenoma nodules of the size of English walnuts were enucleated. Only these two adenoma nodules were removed, but nothing else of the thyroid tissue.

The action of the operation becomes best evident to us in the basic metabolic curve, Figure X. The basic metabolism fell in the course of 11 days down to 13 % below the normal value and the symptoms disappeared from the patient. After this it gradually rose and during the course of a year it reached normalcy again. The desiccated parenchyma of the removed adenoma nodules proved in the tadpole experiment to be especially effective.

It appears to me to be a matter of significant and fundamental interest that the products in these cases, which the thyrotoxicoses occasion, are furnished by adenoma nodules, that is by tumors: tumors are distinguished as excesses of development of autonomic character. The function of a toxic adenoma can be designated as a functional excess of autonomic character. For no proof can be given for any requirement of the hyperfunction on the part of the organism. The hyperfunction is no physiological reaction and is in no sense of the term compensatory. As long as the invalid has the hyperfunctionating adenoma nodules, she is ill. With the removal of these nodules, she becomes well. If it were to be a question of a compensatory hyperfunction, it would necessarily be the reverse.

In my opinion there seems to be much in favor of the thought that the irregular hyperfunction of the toxic adenoma nodules is a peculiarity, which these structures possess as tumors.

Figure I.

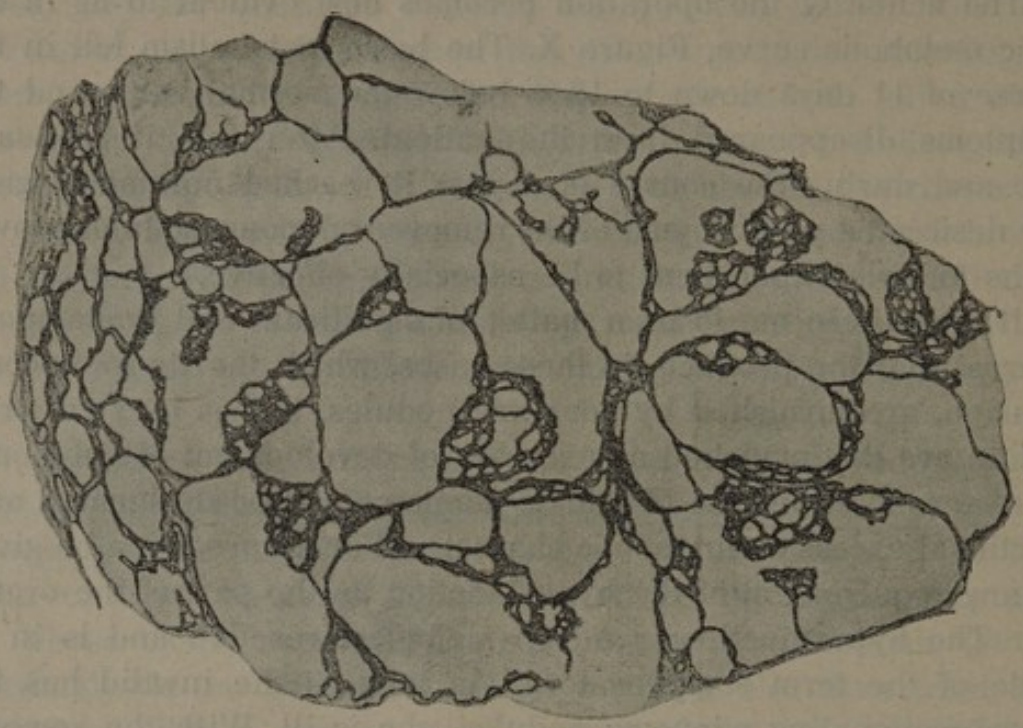


Figure II.

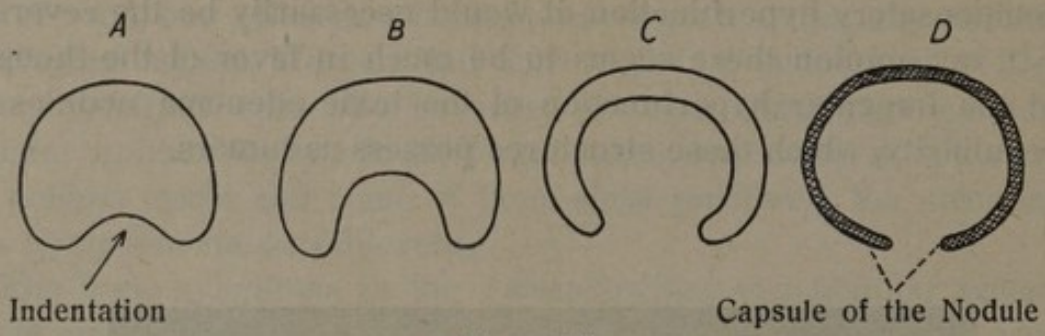


Figure III.

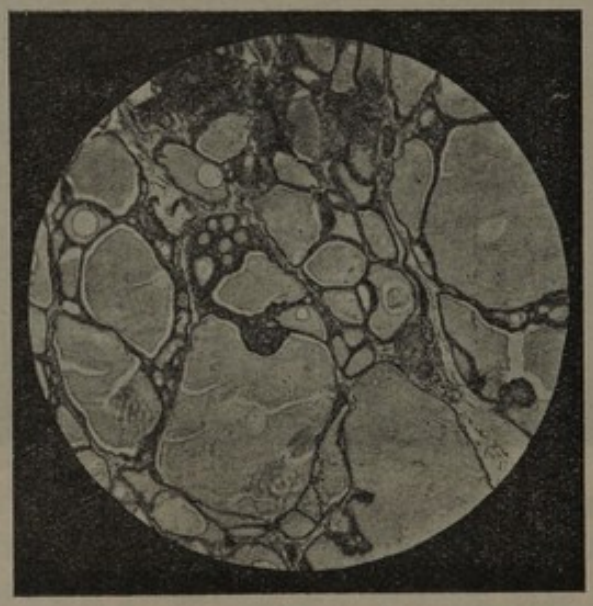


Figure IV.

Figure V.

Figure VI.

Figure VII.

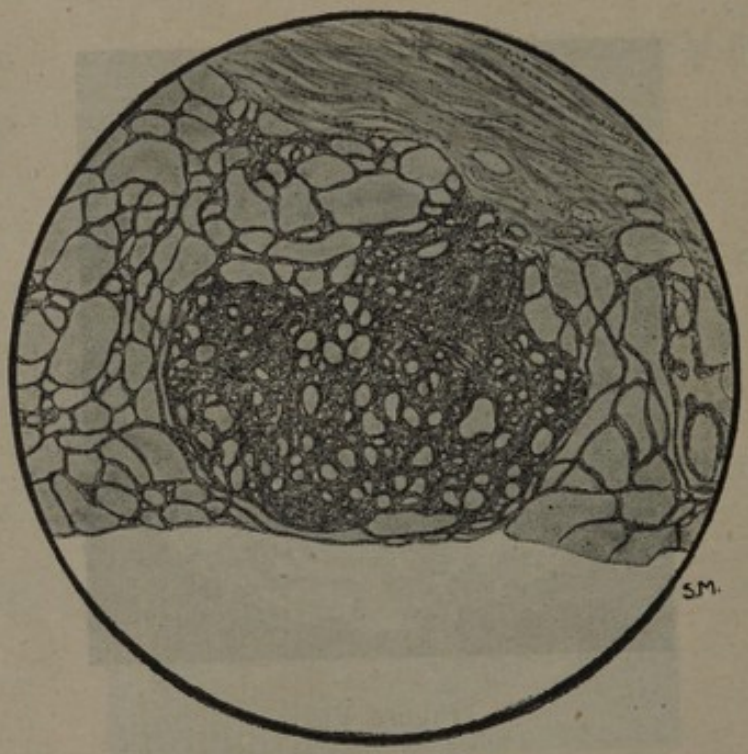


Figure VIII.

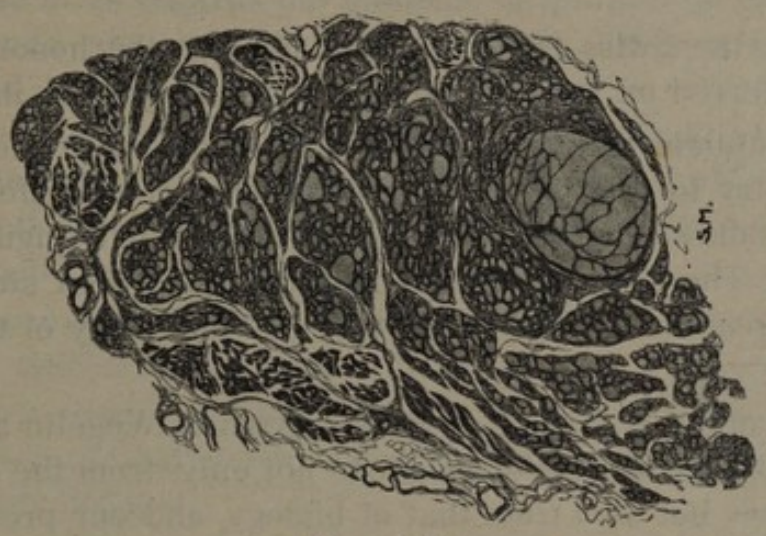
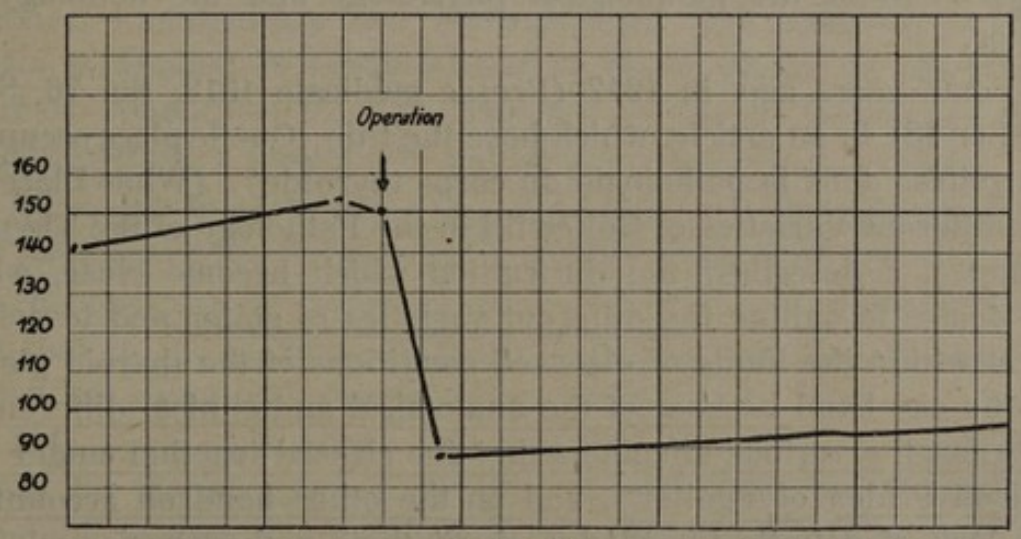


Figure IX.



Fignre X.

This paper is exceedingly badly translated. The original must be consulted.

Comments
on the Addresses on Pathological Anatomy.

By Professor M. G. Roussy of the Medical Faculty of Paris (France).

I thank the Swiss Goiter Commission for the honor it has so kindly conferred on me by inviting me to take part in its labors.

I congratulate the Commission for having taken the initiative in its country to this «First International Goiter Conference», in which the noteworthy observations of Jacques and Auguste Reverdin and of Theodore Kocher constituted the initial steps for all modern researches on the physiology and pathology of the thyroid gland.

The excellent addresses of Messrs. Aschoff, Wegelin and Marine have approached the goiter problem not only from the anatomical point of view but also from that of biology, and our president, Mr. Carrière, emphasized especially in his opening remarks the necessity of investigating the problem from the general biological standpoint.

In my declarations I shall endeavor, while confining myself to the realm of morphology, to undertake several incursions into the department of the pathological physiology and the aetiology of goiter.

Some years ago, in 1912 (Presse médicale 1912, No. 76, September 18), in an article, which bore the title «Quelle place occupent les goitres dans la pathologie du corps thyroïde?» (What Place do the different Varieties of Goiter fill in the Pathology of the Thyroid Gland?), I described the difficulties which become clear, when we desire to outline the different varieties of goiter and to define them within the limits of diseased conditions of the thyroid gland; on the one hand because of the anatomical and clinical differences between the various affections that are classed together under the collective idea of «goiter», and on the other hand on account of the lack of definite knowledge about their pathogenesis.

The several addresses, which have been held at this conference, have made it clear that since the date mentioned considerable progress has been made. All authors are agreed at the present day that there are several main types of goiter which bear special characteristics and are distinctly differentiated, the one from the other.

But there are still certain divergencies of opinion between the investigators, who are giving special attention to this question. These are not occasioned by the fact that the real causes of the majority of the goiters are still beyond the scope of our knowledge, but they are also due to the difference in the nomenclature, which is made use of as regards the ailments of the thyroid gland by the clinicians and anatomo-pathologists of the different countries of Europe and America.

I therefore believe that the conference, which is having its sessions here to-day, would accomplish useful work, if it would make the effort to get the nomenclature for the different categories of goiter made uniform as far as possible.

The expression goiter or struma (goitre, gozzo etc.) is used to indicate a special lesion, which is peculiar to the thyroid gland; having been made sanctified through custom, this expression deserves to be retained with the proviso that its real signification be accurately defined.

The expression is understood to mean a lesion of the thyroid gland, of chronic development, of the nature of a hypoplasia, which in that way is distinguished from inflammatory lesions of the organs, from acute and chronic, banal or specific thyroidites. It is a question in the main of a hypoplasia and not of a simple hypertrophy. Since the days of Virchow and Recklinghausen, Lancereaux, Cornil and Ranvier, Chantemesse and Podwyssotsky, the expression hyperplasia is applied to modifications of tissue where the numerical increase constitutes the basic character, whereas the term hypertrophy embraces essentially the idea of increase in volume.

As we see hypertrophies can occur with or without hyperplasia, but with goiter the latter is the true and dominating lesion.

The question of goiter is moreover complicated through the fact that in the goitrous thyroid gland neoplasms are present, to which the name adenoma has been given.

This expression gives rise immediately to the thought of a tumor, for the adenoma is the type of non-malignant tumor of the glandular system for the authoritative pathologist. To be sure the views and doctrines of the biologists and morphologists diverge here and it is a difficult matter for them to agree on the limits of the field of benignant tumors.

Whereas some of them are undoubtedly found in connection with congenital malformations, others, on the contrary, such as condylomas, papillomas, the adenomas of liver cirrhoses are closely

related to inflammatory reactions, from which they have originated either directly or indirectly.

Still others are from the beginning malignant tumors, carcinomas in a latent state. So, e. g., certain so-called non-malignant tumors of the mammary gland or certain varieties of stomach tumors.

Besides, we can observe transition stages in the glands as, e. g., in the liver, hypophyse or thyroidea, among tumor-like neoplasms of the type of adenomas and the inflammatory reactions of the type of hyperplasias, which can be designated as nodular hyperplasias or adenomatous hyperplasias. The investigation between the different stages is often impossible both with the naked eye and with the microscope.

As we know, it is just this way with the different types of goiter, which are looked upon as benignant tumors by some authorities and as hyperplastic reactions by others. It will simply suffice to study over the authoritative treatises, which have appeared on this subject in the different countries to be fully convinced regarding this variety of ideas and doctrines.

I believe that it is an easy matter to agree upon some fundamental distinction, if we were to consider the question from a truly general point of view by looking upon the goiter as the expression of a hyperplasia of the thyroid gland, which is sometimes diffuse and sometimes nodular, whereby the latter form may be uni-nodular or multi-nodular. It is possible that this distinction of the morphological appearance is determined by the nature of the reaction of the interstitial tissue and stands in connection with the mode of operation of the cause of the goiter. The parenchymatous or diffuse form corresponds perhaps to the sudden and extensive injury, the nodular circumscribed variety to a light but long injury.

There are the differences regarding appearance, which are met with in the different varieties of goiter: 1) in the simple endemic and sporadic goiters, with or without cretinism, of a colloid or parenchymatous type or 2) in the Basedow strumas, in typical Basedow and in the struma Basedowificata.

* * *

I approach now the question of the malignant strumas or the thyroid cancers, on which Mr. Wegelin has addressed you. I have few comments to make on his address.

Here also I should like to say something on the question of nomenclature, for, not only with the tumors of the thyroid gland and other organs but still more so for the simple goiters, the sense

of the descriptive names is different in the various countries and languages.

Above all let me point out that the term carcinoma, as it is being applied by our colleagues of the German language, is used with us to indicate a variety of epithelial tumors, viz: the infiltrated or non-typical epitheliomas.

Accordingly, the classification, which I should recommend for thyroid cancers, is somewhat different from that of Mr. Wegelin. It is, namely:

a) Epithelial cancers or epitheliomas; alveolar type; trabecular type with bright or dark cells; infiltrated type, the carcinoma; Malpighian type (Herrenschmidt).

b) Connective tissue cancers or sarcomas, among which are to be understood all mesenchymatous tumors, especially those proceeding from the endothelio-vascular system, which Messrs. Wegelin and de Quervain have described as endotheliomas.

I must acknowledge that I am very skeptical as to the occurrence of endotheliomas as tumors, which proceed from the endothelium of the vessels. I have never myself come across any tumors of this type and my opinion regarding these is, moreover, shared by the majority of my French colleagues, especially by Masson of Strassburg.

But I do not wish to start here any discussion, which, moreover, could only be pursued with the microscope at hand and would tend to take us away from our real subject.

* * *

Causes ?

In conclusion, I shall have a word to say on the question of the origin and nature of endemic goiter, which has already been referred to by several of the speakers and is to be more thoroughly considered at to-morrow's session.

iodine nil

Even if it seems more and more certain that the origin of goiter is due to impure drinking water and that the part that iodine plays is ever gaining in importance, nevertheless I do not believe that the latter rules supreme over the entire pathogeny of endemic goiter. Moreover, the statements made by some of the speakers, as those of Mr. Galli-Valerio, make a deep impression in this respect.

We can not look upon endemic goiter as an illness due to the lack of iodine. There are numerous observations, which speak against this conception. I need only mention the occurrence of goiter in regions bordering on the sea.

* This sentence reads as follows in the original text: "If the "hydrique" (water) origin of endemic goiter appears to be more and more evident, and the role of iodine more and more insignificant [illegible] summarizes the entire pathogenesis of endemic

There are other observations of an experimental character, which deserve to receive mention at this place. These are the investigations of Répin of the Pasteur Institute in Paris, who died in the course of the war, in which research work I myself participated in the years 1910 and 1911.

Répin gave rats some goitrous water from the Maurienne to drink. All of those rats, which drank the water when fresh, contracted goiter. Others received water, which had been heated for a few minutes at 212° Fahrenheit. With these there was also the appearance of goiter but less extensively than with the animals that had received unboiled water to drink. A third series of rats received in Paris water, the ingestion of which would cause goiter, that had come from Savoy but which had been kept for several hours under diminished pressure in order to extract every trace of gas from it and to call forth an abundant precipitation of calcium salts through the removal of the air. These animals remained free from goiter. The same happened with animals which drank water, in which the precipitation of the lime salts was occasioned through the addition of a solution of caustic soda and which had been afterwards neutralized with hydrochloric acid. It must be observed that the water could not be rendered harmless through boiling. According to Répin this was due to the fact that the very active water contained at the titration 120° hydrotymetrical and free carbonic acid gas. Under these circumstances only a part of the dissolved salts was precipitated. Répin had requested me to undertake the histological examination of these experimental goiters and I was able to determine as a fact that the microscopic lesions corresponded with those of goiter, especially those which were called forth through the water that was not heated. With water which had been heated to 212° Fahrenheit the changes are less distinct but they are nevertheless to be recognized. On the sections we can notice the irregularity of the acini, of which the most are seen to be enlarged and in part show on the parietes an excessive development.

The vessels are somewhat expanded and the scarcely visible stroma of the glands consists of young connective tissue, which is very poor in collagenous fibers. It must be observed that there is only a small quantity of colloid in these goiters. Many vesicles are empty, others contain colloid in small globules or homogeneous flakes, or also in the shape of an amorphous granular mass, which can be stained with difficulty, an aspect which is certainly due to some error in the fixation.

* The sentence reads in the original: "Hat kochendes Wasser nicht ausgereicht, das Wasser unschädlich zu machen."

The experiments make it clear that the substance, which causes goiter, can resist a temperature of 212° Fahrenheit and disappears only to that extent that the precipitation of the salts, that are dissolved in the water, is brought about through any particular process. If we assume with Répin, that this substance must be looked for elsewhere than among the carbonates and sulphates of calcium and of magnesium, then it is possible to explain the non-activation of the water through the removal of a compound, which acts similar to a colloid substance or through the occlusion of a gas.

Whatever may be our idea concerning the physical-chemical or colloidal theory of goiters, which I for my part am also glad to accept, there can be no doubt that the experiments, which I have carried out, contradict the theory of goiter as being a « maladie par carence ». The physical-chemical changes, which were undertaken with the different kinds of water that originate goiter, without having their iodine contents affected thereby, lead to different results with the animals experimented upon.

As ultimate results, according to my opinion, it follows from the addresses made at our conference, that the goiters, which are polymorphous in conformity with their morphological manifestations, strictly speaking, do not originate through one single cause but through a multiplicity of causes. The effects of different goiter noxas, of physical, chemical and perhaps even of animated nature, produce parenchymatous and interstitial homogeneous changes, which ultimately lead to hyperplasia of the thyroid gland, namely, to goiter.

Pathology of the transplanted thyroid gland.

By H. Cristiani and Mme. A. Cristiani
Institute of Hygiene, University of Geneva.

A considerable number of experiments performed by us ever since 1892 on the grafting of thyroid tissue, have allowed us to conclude that it is possible by grafting to obtain permanent thyroid organs whose structure is identical, in all respects, with that of the normal gland. The neothyroid glands thus obtained took part in the changes of the organism into which they were transplanted; they could retain the original volume of the grafting, or undergo

hypertrophy or atrophy, according to the needs of the organism of which they now formed a part.

These new organisms were permanent, i. e. they could persist during all the normal life of the host. Besides this possibility of revivification was not only a prerogative of the autograft, but extended also to the homograft: when, for instance, in the case of white rats, grafts were made between brothers, there was no difference, or hardly any difference, from the result of autografting.

As we now had continued further along the lines of this research we have extended it to the pathology of grafting.

We thought that the International Goiter-Conference would be interested in listening to a summary of the work done in dealing with the diseases of the neothyroid glands, and especially in ascertaining the outcome of autografts and homografts in the case of goiter of the giver or of the taker.

The experiments under consideration consisted in exchanging bits of thyroid gland between animals of the same species, as a rule between brothers, it being understood that the animals retained throughout a part, usually half, of the gland in it's place.

The following possibilities required consideration:

1. Grafting taken from an animal, normal as to thyroid, upon another animal in the same condition.
2. Grafting done between two animals, both goitrous, but possibly presenting goiters of different structure.
3. Grafting from a goitrous animal upon a normal one and vice versa.
4. Grafting done between two animals, one of which, the giver or taker, had become goitrous later on.

The experimental endemics of goiter among our animals (white rats and white and black rats) gave us the opportunity to push our research. The material which we have thus gathered is abundant, but we have not yet been able to work it out in it's entirety. In order to get further reaching and more conclusive results not only a large number of animals is necessary, but it is also imperative to extend the histologic control. We began to cut all our pieces in series, not only for the graftage, but also for the gland which had remained in place; but later, as the experiments became very numerous, we had to limit the scope of our work. The pieces which we will show you, will complement, at least partially, the conciseness of our text.

The summary of our observations is the following:

1. Bits of thyroid gland grafted between apparently normal rats produce as a rule completely normal neothyroids. These graftages done after our method, on transparent organs (ears of the white rat) permit a continuous control of the macroscopic evolution of the grafted tissue (which can be studied also with the magnifying glass). It is notably possible, during life, to watch the degree of vascularisation of the graftage, judging by the state of progressive hypertrophy of the earvessels, which are very visible even in normal conditions.

2. Thyroid grafting between goitrous rats tends to the formation of new glands, at once of goitrous structure. These graftings have a great tendency to hypertrophy. According to the stage of reconstitution of these graftings, there can be observed some differences in the detail of their structure (as is observed in the goiters themselves) but generally are obtained in this way graftings of a structure analogous, if not always identical, with the tissues grafted.

3. Grafting of a goitrous thyroid upon a healthy animal or vice-versa.

a) Grafting of healthy thyroid tissue upon a goitrous animal. The grafting in this case has at first a tendency to reconstitution, as the graftings between normal animals, but, as a rule, one soon observes a transformation, generally of hypertrophic character, with gradual disappearance of colloid substance and evolution towards the parenchymatous goiter.

b) Goitrous tissue (of different types) upon a healthy animal. In these cases the histological constatations are not always identical and may be very different in different parts of the grafting. The degree of goitrous transformation of the gland of the giver is not always the same. The evolution of the tissues of the grafting tends sometimes towards health, and, more seldom, to manifestations of atypical hypertrophy.

(This point is actually the object of a study which is not yet finished.)

4. Finally, and this seems to be most interesting part of our work, the exchange of thyroid tissue between two normal animals one of which becomes goitrous later on (sometimes very much later) produces at first normal grafts between the two animals, but the homografts of the animal which becomes goitrous finally present the same modifications as their host's gland, while those of the animal whose thyroid remained sane show no traces of illness.

The observed facts give us these conclusions (which we shall complete later on).

1. Thyroid homograftings upon the rat adapt their life to that of their new host and behave about in the same manner as the autograftings.

2. The thyroid homograftings in rats having a normal thyroid do not present any goitrous transformation at any period of their evolution.

3. The goitrous transformation of the graftings of an animal which becomes goitrous after transplantation is accompanied by the development of goiter of the taker: it is therefore of central origin.

4. One must not consider as normal a thyroid gland judging it's dimensions only, for the goitrous transformation is not necessarily hypertrophic and then histologic examination alone permits precise diagnosis.

Fig. 1.
Small thyroid-parathyroid homograft in the ear of a rat. Graft aged three months normal, the giver and the taker presenting thyroid glands without goitrous modifications.

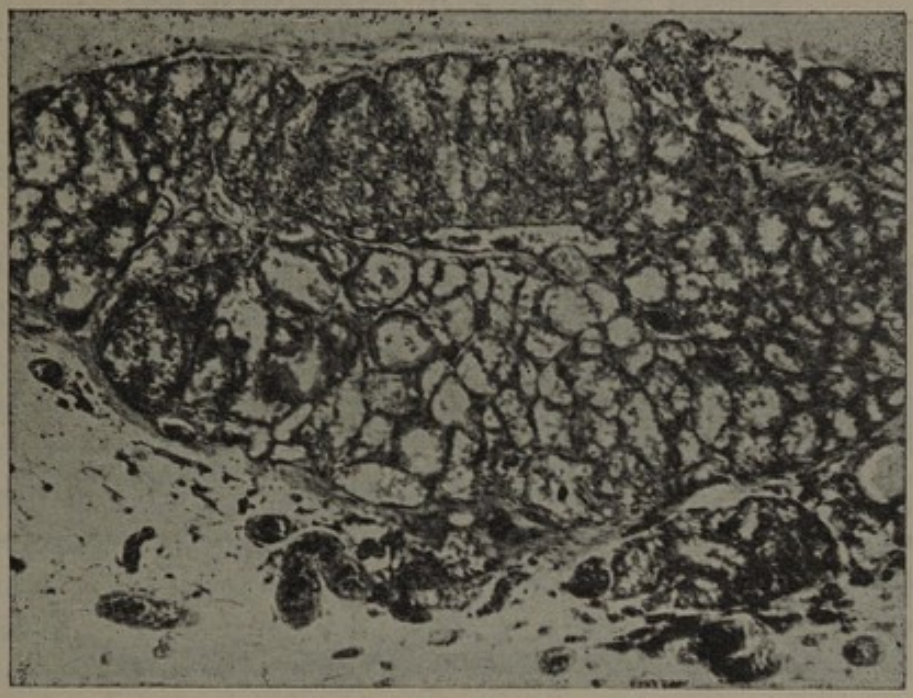


Fig. 2.
Thyroid homograft of a rat (under the skin of the abdominal wall); the thyroid tissue was normal, when transplanted. The photo represents a slice of a grafting aged five months and shows a goitrous transformation of parenchymatous type. The taker of the grafting is afflicted with a goiter a slice of which is reproduced in the fig. 3.

Fig. 3.
Goiter of the rat N. 2.

Fig. 4.

Homograft of a rat extirpated three weeks after. Reorganisation of the tissue with about normal aspect (in the middle there is an artery with it's muscular strate). This degree of reorganisation is observed in the beginning, even in animals presenting goitrous modifications.

Fig. 5.

Graft of 17 months presentiug late modifications in the structure of the gland evoluated towards the formation of a real parenchymatous goiter of te graft.

The Iron-hard Strumitis of Riedel.

By Professor E. Payr, Leipzig.

I want to ask the opinion of the pathologists with regard to the iron-hard strumitis of Riedel.

It is a very curious illness. I have seen it five times. In medical literature there are about 100 cases reported.

He who has not seen manifestations of this disease does not believe in it. To distinguish between it and malignant tumors is very difficult. The goiter tumor grasps the trachea like an iron fist. It does not adhere to the skin and the great vessels, but to the long flat cervical muscles. It does not make swell of the glands and metastasis. The missing of symptoms of the sympathicus is also remarkable. The adhesion is as a rule very strong, therefore total removal would seem nearly impossible. One has the impression of a «wooden phlegmon». A considerable leukocytosis is lacking as well as other symptoms of inflamed blood formation. The reactions of Wassermann and tuberculin are negative. Ichor is not found, even when the thyroid lobes are deeply punctured.

Usually this disease gives the impression — sometimes before and sometimes during the operation — of a malignant tumor of the thyroid gland. Sometimes the question of tracheotomy is considered, because one has nearly always been forced to discontinue the operation. Having already operated on several cases of this disease however one is of a different opinion. It is sufficient to make an incision in the very strong weals of the thyroid lobes or still better to cut out wedge-shaped pieces. Bleeding is as a rule not very great. It is sufficient to close the wound with sutures. Healing is nearly always satisfaction. The remainder of the tumor decreases after some weeks in most cases. The compression of the trachea vanishs after a short time by itself. X-ray treatment quickens the diminution as do the local use of heat and light massage. One has to be very careful with the Prognosis. When there is any doubt about the pathological-histological condition the probability of ironhard strumitis is very strong.

Patients operated on in this palliative manner are healthy and will remain so. I have seen cases with a time of confirmation of 16—20 years.

What form of disease have we here, seen from the pathological-anatomical point of view? We have very different diagnoses from

excellent and experienced pathologists: scirrus, sarcoma, chronic inflammation, more seldom lues. Sometimes the examining specialist changes his opinion about the method of cure. Very often there is a great divergence of opinion between surgeons and pathologists. I think it very important for the decision to know that we always find the whole gland affected, sometimes both side-lobes and a great middle-lobe. Sarcomas of the thyroid gland begin only in one lobe.

The histological appearance is very difficult to explain. There is fibrous tissue, in some places atrophy of the glandular tissue, as well as wild epithelium. These conditions change very often. It seems to be a very peculiar form of chronical goiter and we do not know enough about the cause and bacillus. A pathologist with as much experience as Marchand has emphasized many times that it is impossible to form a pathological-anatomical diagnosis without the exact knowledge of the clinical conditions and progress.

The following are the characteristics of an hardening goiter: in spite of the tight grasping of trachea and oesophagus which is not to be influenced by the operation, there are no compact adhesions with the great vascular bundle, no swelling of the lymphatic glands, no paralysis of recurrens and sympathicus. An inflamed blood formation is wanting, the sinking of the blood corpuscles is not quickened, all parts of the thyroid gland are affected. A simple excision causes the involution of the tumor and therewith of the compression. After many years we hear of no relapse, in spite of the small success that an operation seems to bring in the beginning. Sometimes it will be goitre which has been treated some time ago with large doses of iodine.

Explanatory Comments

by Prof. Dr. Helly, St. Gall.

The experiences made by me on self collected examinations during 20 years at Vienna, Prague, Wuerzburg and St. Gall showed me the variety of the anatomical types of goiter in these districts. The structure declared characteristic for the Basedowic goiter was for example at Vienna very distinct, while it is left in the lurch at St. Gall sometimes so that in spite of clinical declarations of Basedow-disease it is not at all possible to find out a structure

corresponding to this type. On the other part the Lower-Franconian goiters contain considerable cysts of colloid, which may be seen also in the preparations exposed from Frankfort and Wuerzburg, while at St. Gall indeed the macrofollicular goiters enriched with colloid are not seldom; but such large cysts of colloid are seldom, not cysts by emollition or liquefaction, which are frequent. On the other hand the goiters of St. Gall are marked out through their tendancy for hemorrhages and through the fact, that the schematically pure types do not at all appear regularly. Very often we find by predominancy of the nodular conglomeratic form in one and the same goiter side by side all the four principal forms: the diffuse and nodular, colloid and parenchymatous goiter, especially together with the form very excellently called by Wegelin the nodose hyperplastic form, and therefore a purely schematical distinction between different types is not always possible at all. Also the reports of Messrs. Feldmann, Holst, Bircher, let us recognize the geographical differences of the goiters and it would perhaps be possible to promote the labor of future goiter conferences, if especially certain questions would be the theme of adresses considering the individual and geographical differences of goiter forms; on the other side it would be desirable, that the clinicist always would state the most remarkable point as to any goiter declared for examination. In this way it would be possible to get material giving the possibility not only based on personal experiences, but also on those from geographically more distant regions to judge the anatomical form in this manner, so that the questions demanded by the clinicist could be answered satisfactory; it would correspond to the effort now being made by pathologists and clinicists to understand one another. Only with the schematical classification it is not possible to do so, I think.

To the pathological anatomy and physiology of the endemie goiter.

By Prof. Meisel M. D., Constance (Germany).

The fact based on experience that treatment with iodine has influence only on the fundamental tissue of the thyroid gland and not on the goiter nodules, caused me to make comparative quan-

titative investigations of both kinds of tissue in one and the same thyroid gland. The results won by my assistents Dr. Wehrle and Dr. Eisenlohr, Director of the civic office of probing must yet be issued completely. I shall give here only the total impression. From 18 cases there was in three nodules no iodine at all to be found. In the other 15 cases the content of iodine was lower than that of the original tissue, with a single exception of very high content of iodine; there had been injected iodine directly into the nodule and as proof of it, there was in yet the broken neadle. It is of great importance, when making comparative investigations to pay attention to the capsule: the capsule always contains iodine. Thus a calcified capsule contained 1 : 8,4 mill. gr. with an fundamental index of the tissue of 1 : 21,7 mill. gr. Let us put the case that a capsule is grown together with the fundamental substance, then we expose ourselves to the danger to examine instead of the substance of the nodules quite other tissues. If we have regard to the source of mistakes, we have yet to deduct something of the already very low ciphers of iodine with regard to the nodules. Te fact of the want of iodine in the goiter nodules ascertained is a farther support for our conception, that the nodules are real tumors. As complete or partial metaplastical formations of cells they have lost the faculty of assimilation of iodine according to the degree of harm. Now the question is thrown up: Are these real tumors in the sense of Aschoff to put on a level with the adenomas of other organs or are they in the sense of Hitzig and Michaud a form of the endemic struma?

In my apprehension of the origin of the Tumors the want of iodine of the goiter nodules has also a signification for our conception of the origin of the endemic goiter. The poison has to be looked for in the thyroid gland. Because it is there that it displays its sinister effects. The thyroid most touched is the cretinistic one, in the intermediate tissues of which, poor in iodine, the adenomas take up enormous forms: the same poison which nearly entirely destroyed the thyroid gland has in it brought near to death some clumps of cells and the adenomas have formed themselves of these damaged metaplastical cells. As to my conception, the problem of the goiter is at the same time a problem of tumor.

As to the prophylaxis, the adenomas surely take a peculiar position, then the formed adenoma is surely no more influenced by iodine. Therefore there is not to be wondered at, that in countries rich in iodine content and small thyroid glands, adenomas

develop themselves; but strange it is that they do not get so big. For that reason I have given right in a personal discussion to Hunziker and Eggenberger that the early form of the adenomas may probably be influenced by a general prophylaxis. But more than what mother Nature grants to people of so-called countries free from goiter, we also may not expect from the prophylaxis.

I look upon the small thyroid gland, sometimes with a formation of nodules in the low countries, as a gland also touched by the goiter noxa which however constantly stood under the influence of food containing iodine.

If we are able to develop in our local territory by means of prophylaxis such high-grown healthy bearers of goiter without the slightest cretinic signs, we may consider it as a great gain for the whole of our people. And for that reason I believe a severe legal prophylaxis to be an aim worthy to be strived for.

Comment on Professor Aschoff's Lecture.

By Professor Dr. Biedl, Prague.

The classification of goiter in accordance with criteria of morphological nature, as given in the statements of Professor Aschoff, signifies unquestionably very satisfactory and genuine progress. A great deal is certainly gained, if goiter in any particular case can be classed according to its morphology in one of those groups, which the pathological anatomist was in the position of making as a result of his researches. We are all aware that up to the present time there has been in this field such a state of confusion, that progress was positively retarded and this was due to the fact that goiters, which differed morphologically and accordingly also genetically, were given similar names on the basis of their macroscopic and occasionally their microscopic behavior. It is, however, a matter of greater importance still, that with the morphological diagnosis of any variety of goiter there were also combined judgings on the functional valence and importance of goiter, whether consciously or unconsciously, whereas it is nevertheless clear that the morphologist has insufficient essential facts for the judging of function. Just because I hold to the view that morphology must constitute the firm basis for the judging of function, I can not refrain from emphasizing the fact

that for the latter there are still many other deciding factors, such as the behavior of the clinical symptoms, their capability of being influenced through therapeutic measures, our knowledge of the normal secretory process and the course it takes, the consideration of the chemical reactions of the gland and many other matters.

For this reason I reserve for myself the privilege to speak again on goiter in its functional significancy when the question of the physiology of the thyroid gland is under discussion. Here I shall only briefly remark that the possibility of the secondary malignity of a primary thyroid adenoma, which was emphasized by Wegelin, possesses also a certain importance clinically. In a case of my own observation a thyroid adenoma, with which an individual had been afflicted for many years without experiencing any special symptoms, suddenly manifested a state of malignancy in encroaching upon neighboring organs, so that a total thyroidectomy had to be carried out as a life-saving operation. Notwithstanding the complete lack of thyroid tissue there were nevertheless the indications of athyreosis wanting almost entirely, for, as the necropsy showed, the metastases contained thyroid tissue of such a constituency and quantity, that it could act as a substitute of the missing organ.

Goiter in The Netherlands.

Discussion on the pathological Anatomy of Goiter.

By Prof. Dr. R. de Josselin de Jong, Utrecht, (Holland).

Since we have gathered together here at the international goiter conference, above all else, to mutually exchange opinions and experiences regarding goiter in the various countries of the old and new world, I, on my part, should like to make a few remarks about goiter in the Netherlands.

Firstly, because this country forms a contrast in a way to Switzerland, viz., lowland-highland.

Secondly, because thereby attention is drawn to the fact, how important it would be to know more details about goiter in the territory of the Rhine, that river, which has its source in a goiter country, then passes through territory in Germany where goiter is

often found and finally ends in lowland. The Netherlands form, in part, the delta of the Rhine.

Thirdly, although the country is not large, nevertheless we have two districts, which, however, in climate, soil and water conditions, etc., show very considerable differences, viz., the coast and the eastern and southern diluvial regions, so that the Netherlands constitute a suitable region for the question of the significance of these factors.

Hence it is well worth while to see how matters stand with us concerning goiter. Formerly, for example, in the previous century, Holland was considered to be free from goiter. However, in the art galleries of Northern and Southern Netherlands we may see that as early as the 15th, 16th and 17th centuries in these countries goiter was not of rare occurrence, for van Eyck, Lucas van Leyden, Rubens, Riemenschneider and others often painted women with goiter in portraits, madonnas, etc. Goiter of slight degree was even considered to be more or less a mark of beauty.

As regards present conditions, I desire to ask first: what do we understand by goiter? The more I hear at this conference all the harder does it become for me to form a sharply defined idea.

Again and again it has been emphasized, that goiter is not always and everywhere the same.

Likewise attention has been called to the fact that it is only a symptom of a general change or disturbance of metabolism.

Be that as it may, in many instances it is a symptom which goes on without important other disturbances, so-called eutrophic struma; in other cases it comes so into the foreground, that it necessarily draws the main interest to itself; in some countries it makes its appearance as endemic, connected with cretinism or deaf-mutism or with both, etc. Therefore it is clear, as has already been said, goiter does not mean always and everywhere the same thing.

A good definition of goiter, satisfactory to all, can scarcely be given. The best one to be recommended is this, viz. — that by goiter is to be understood a continuous enlargement of the thyroid gland, which is caused neither through inflammation, nor from bleeding, nor by the development of a tumor. This definition is not beautiful but I know of no better one, nor have I been able to find a better one given by other authors.

As long as we are not better informed about the nature of goiter, it is practicable to take the anatomical-histological indications as guides of action toward a classification of goiter and I shall therefore in connection with the addresses of Professors Aschoff, Wegelin and Marine, speak briefly regarding the structure, frequency, etc. of goiter in the Netherlands.

1. The attention of many has been drawn to the fact, that, during the last 20 to 25 years, goiter or perhaps, to be more accurate, enlargement of the thyroid gland, has been observed to increase in several parts of the Netherlands, e. g., in the central part (Utrecht), in the east and in some places of the south (Brabant).

This has led to an investigation among school-children in places having little goiter and others having relatively many cases of goiter; my own home-city (Utrecht) serves as a particular example of the latter.*) Here it was found that in the case of girls from 12 to 18 years the enlargement of the thyroid glands increases with age, so that at the age of 18 years some 82 % of the girls show this enlargement (that is, goiter). In the case of the boys the number having goiter increases up to 15 years of age: it is then 64 %. Then the number again diminishes.

Is this enlargement of the thyroid gland to be considered as goiter?

The number of adults having goiter is certainly not in proportion to these high figures of 64 % and 82 %. Although goiter is now being more observed by us and is being operated upon more than formerly, nevertheless the number of cases with us is not to be compared with those of Switzerland. My colleague, Mr. Wegelin, has told me that of those persons upon whom he performed necropsies, 75 % had a slight or well developed goiter, whereas among the 350 necropsies, which I have to perform annually there were scarcely 8 to 10 cases with goiter.

It is possible that a certain percentage of the enlargements of the thyroid glands in the case of boys and girls will develop later into goiter, that is, that with a number of children this temporary school-goiter forms the basis for a future goiter. Hereby there is, at least, the correspondence, that, as is found from the investigations of Dr. Brand**) upon 46,976 military recruits in the years 1916

*) Compare R. de Josselin de Jong: Ueber Kropf in den Niederlanden. Zieglers Beitr. Bd. 73, 1925.

**) Vergrooting der schildklier in Nederland. Dr. Brand. Im Auftrage des Centr. Ges. Rates. 1916—1917.

and 1917 and as likewise our experience in Utrecht on the operated cases and the cases investigated histologically shows, goiter is particularly noticeable with adults in those districts of the country where there is the greatest frequency of school-goiter among the boys and girls. Likewise the ratio as regards sex gives support to the theory given, for the number of women having goiter is 3,5 to 4 times that of men. (See accompanying survey-card.)

What, then, is the significance of this school-goiter, which, in most instances, is of a temporary nature? Is it to be looked upon as being due to lack of iodine in the drinking water as some maintain? Or is it here chiefly a matter of conditions of growth? How is this school-goiter constituted? Is it a purely parenchymatous swelling, or is it an accumulation of colloid in enlarged vesicles? We do not know.

see Aschoff

I desire to accept the conclusion of Professor Aschoff, that it is greatly to be desired that the conditions of growth of the normal thyroid glands of the two sexes in the different countries be studied in detail.

and in environs.

With regard to the relationship of a lack of iodine in drinking water on the one hand and goiter on the other, I may say that now for two years attempts have been made to investigate the drinking water from various sources, viz. — near the surface, deep water and water from the dunes etc. as to iodine and to compare results with the frequency of goiter in accordance with the statistics of Dr. Brand (± 47,000 military recruits in 1916—1917). These investigations are still in progress. Up to the present time, with one exception, a correspondence has been noted of a low degree of iodine in water, and higher number of goiters. A final judgment can not be given before the water investigations have come to an end and the frequency of school-goiter and goiter in adults for both sexes throughout the entire country has become known and then all compared and worked out along statistical lines.

iodine

2. With regard to the macroscopic and microscopic structure of goiter in the Netherlands, I may say that we see there all of the forms, which have been found and described everywhere in other countries. (See the work of Wegelin in the manual by Henke-Lubarsch, 1926.) The preparations, diapositives and sections shown by me at the exhibition of the congress prove this very distinctly

General Map

regarding frequency of goiter in the Netherlands.

Distribution of goiter according to investigations by Dr. Brand c. s. made upon 46,976 military recruits in 1916—1917.

●●●●●●●●● Struma — Women
○○○○○○○○ Struma — Men

Goiter-material by Prof. de Josselin de Jong (Utrecht), in all 450 cases.

In the case of men there is more struma diffusa: of women somewhat more struma nodosa; at least, according to the material which I have worked over, viz. — more than 450 cases!

The so-called toxic adenoma occurs scarcely or very seldom with us.

3. The co-existence of goiter and cretinism occurs likewise with us very, very seldom and during 10 years I have only been able to observe three cases of cretinism: of these three cases, one was without goiter; the other two had large goiters.

little or no cretinism

4. The nodular goiter (struma nodosa) is exactly the type as described by Aschoff and I also consider the nodules as tumors, viz. — fibro-adenomata. They are recognized by:

a) independent growth;
b) continuous growth;
c) deviating structure;
d) inferior function;
e) inclination toward degeneration;
f) sharp differentiation.

These are all qualities, which, all taken together, entirely correspond to the idea of «tumor».

These are tumors, the great majority of which have and retain a mild kind of character and it is only a small portion which go over to a malignant growth. The struma nodosa begins to develop in the thyroid glands after the 20th year of the person concerned: and we find them up to the age of 70 years.

If we consider the struma nodosa to be a tumor-structure, then this form of thyroid-gland-enlargement is eliminated from the real goiter problem: it may be that possibly this tumor structure is furthered through goitrous swelling and degeneration of the thyroid glands, and as such it does not form any integral part of the question as to the causes and the distribution of endemic goiter in certain countries and localities of the earth. We must certainly keep our minds clear as regards this.

The question of tumor-structure in the thyroid glands is another one than that of the endemic goiter.

Cancer of the thyroid glands I have found only in the case of old persons, over 50 year of age.

With regard to the development of the nodules: according to my experience, this is not alone to be traced from the so-called central canals; the growth-centers also, which are to be found in many strumas and which, according to Aschoff, are to be found on the growth-poles of the follicles, come into consideration in this.

5. According to my opinion the question of the Basedow struma has no relation to the real goiter problem, that is, primary Graves-Basedow disease occurs in the Netherlands and, as far as I know, also in the other countries of Europe, independent of endemic goiter (Switzerland), of school-goiter (Netherlands) and of the occurrence of goiter in the case of adults in countries where goiter is rare, viz. — Netherlands and the other lowlands of Europe.

The goiter of the primary Basedow disease is recognized by:

a) slight enlargement (usually not over 130 grams);

b) firm structure: grey-yellow color; macroscopic similarity to pancreatic tissue;

c) high, flake-like epithelium, colloid, small in quantity, thin liquid, rich in vacuoles, and colored slightly by Eosin;

d) in nearly all cases more or less lymphoidal tissue.

6. The development of a Basedow disease upon the foundation of a non-Basedowic, diffuse or knotty goiter, the so-called secondary Basedowification, is seen much more rarely in the Netherlands than in Switzerland. Likewise, in the Netherlands it corresponds more to a hyperthyreosis of slighter or greater degree than to the fully developed symptomic complex of the Basedow disease.

A difference from the goiter in Switzerland is also the fact that this hyperthyreosis develops more in the case of diffuse goiters than with nodular goiters.

7. I am surprised at the statements of Prof. Aschoff as regards thyroid gland enlargement in the case of persons of great age as a sign of youthfulness. Nothing is known to me of this matter through personal experience. It seems to me desirable that we, especially as a basis for the question of the growing conditions of the thyroid gland, should in future give our attention to this point.

8. There is one point upon which I can not agree with Prof. Aschoff, at least according to my experiences, viz. — as to what he has said as to the significance of proliferations in goiters. If I understand correctly Aschoff considers these as a sign of increased function, that is, as the morphological basis of higher effectiveness in secretion.

My experience has been otherwise. Very often I have found and, above all, in diffuse, colloidal goiters of young persons, viz. — 18 to 25 yrs. of age, strong symptoms of proliferation (Sanderson's

cushions, papillary and microfollicular growths in the follicles, etc.), without any sign of hyper-function, that is, without any trace of hyperthyreosis. I, for my part, look upon these proliferations, therefore, as a sign of a stronger growth, and not as an indication of increased function. It may be that closer study would make it possible to find histological indications for purely growth-proliferation and for the signs of increased secretory function. According to my experience the papillary cauliflower-like follicular and other developments, which have been written about so much, are growth-proliferations. With this thought in mind I ask you to kindly inspect the macroscopic and microscopic preparations and diapositives which I have placed on exhibit.

9. I most heartily support the proposal of Prof. Aschoff with regard to the attempt to arrive at an understanding as to the question of nomenclature.

When we bring to mind the blackboard with the eight rows of divisions of goiter, which were shown to us yesterday, it is not necessary that I speak further as to the desirability of uniformity in this question. In two of the lists I found the word « lymphadenoïd goiter » (McCarrison, Williamson). This form of struma is unknown to me. Is the iron-struma meant thereby? The iron struma of Riedel, however, is a chronic inflammation, that is, an enlargement of the thyroid gland of a very peculiar variety, which does not come under the chapter of goiter.

This and other questions of nomenclature ought to be more closely considered and solution found.

Uniformity and an understanding in the question of nomenclature might possibly serve as an introduction to an understanding as to ideas and theories and this all in itself would be a most beautiful result of this conference.

In conclusion, I wish to present in the following summary a survey as to the differences between goiter in Switzerland and in the Netherlands.

The Netherlands:	Switzerland:
1. Thyroid glands of Neonatus, small (1,5 to 3 grams). Inherited struma rare.	1. Thyroid glands of Neonatus large (6 grams and more). Inherited struma frequent.

2. With school-children struma not frequent. In some parts of country thyroid gland enlargement (struma?) frequent with pupils. (Breda and Utrecht).	2. Struma frequent with school-children.
3. In certain localities of the country (Rhine, Maas, Yssel districts, also Brabant and Overijssel) struma rather frequent.	3. Struma frequent in large territories of Switzerland.
4. Very seldom is coincidence of struma and cretinism.	4. Cretinism and struma endemic.
5. Secondary Basedowification of a struma not frequent.	5. Secondary Basedowification of a struma frequent.
6. Secondary M. Basedowi has the type of a light, incomplete M. Basedow, respectively a hyperthyreosis.	6. Secondary M. Basedow usually of heavier degree, up to complete M. Basedow.
7. Struma nodosa more in case of women, diffuse struma more with men.	7. With both sexes, chiefly struma nodosa.
8. Struma diffusa colloides as a rule, macrofollicular.	8. Struma diffusa colloides, as a rule microfollicular.

Comments

on the Declarations of Prof. Helly and Prof. Biedel.

By Prof. O. Lubarsch, Berlin.

Originally it was my intention to make some remarks only to what M. Helly has said on the histological findings in the thyroid in cases of exophthalmic goiter. After the remarks of Dr. Biedl I am however compelled to amend these also.

Dr. Biedl has appreciated the method used in the pathologico-anatomical lectures to classify entirely from the morphological point of view. He has further tried to define as the object of pathological anatomy to conceive as sharply and precisely as possible the morphological facts, but not to bother about what they

really mean. I cannot agree with that. As pathologists we can not submit ourselves to such restrictions. But I should think that only the ways should be separate; that, to begin with, indeed we shall have to establish the pure morphological facts, and that later we shall have to find ourselves what they really mean and how far we can make use of them in trying to understand the clinical symptoms. It is true that frequently enough we cannot draw final conclusions from the morphological facts alone, but it is this way which may lead to pathfinding hypotheses, the correctness of which has to be proved experimentally with serological, bacteriological and similar methods. This however is only possible if we have tried to understand the histological findings.

If Dr. Helly has mantained that there is no typical histological picture in exophthalmic goiter, it can be admitted that here, as everywhere, there are certain exceptions. But in the main I must adhere to the opinion that the histological picture as I had drawn it 32 years ago is as characteristic that we may diagnose upon it exophthalmic goiter as conclusively as we can establish the one of — say — progressive paralysis on the plasmatic and haemosiderotic cellular mantles in the brain. Of course it depends on what we regard as the main characteristic features. These are reduction of the colloid matter itself and if present at all of its viscosity, the formation of pseudopapilli and true papilli and the relatively high epithelia within the vesicules. Not characteristic is the crowding of the lymphatic nodules although this feature is frequently met with. It is this general picture which, since I have first established it in the northern German plain, I have been able to demonstrate in more than a hundred cases of exophthalmic goiter in various districts all over Germany and also to make out from the undoubtedly much more complicated picture found in the Swiss type of this disease.

If finally one of our learned friends has tried to establish a connection of the goiter-problem with the tumor-question I can only say that it is necessary sharply to separate the tumors of the thyroid from typical goiter and that, possibly, the goiter-problem is a problem of growth, but certainly not one of tumor-like growth.

It is largely problem of gr

Involution Processes in Goiters of Rats.

By Prof. Wagner-Jauregg, Vienna.

In the two excellent addresses which we have heard and in the discussion we have learned what goes on in the thyroid glands when they become enlarged and when a goiter is developed. However, it would be of interest to know what takes place in the thyroid glands when they again diminish, and it seems as if this question has not been so thoroughly discussed.

In experiments made upon rats, which I carried on in common with Landsteiner and Schlagenhaufer some years ago, I had the opportunity to make an observation in that direction.

We had found out a place in Styria, where the rats after six months, without exception, developed a goiter, and it made no difference as to what water they drank. We had a number of such goitrous rats brought to Vienna, and we killed a number of them in order to examine their goiters. We found the well-known formation of a micro-follicular parenchymatous goiter. The other rats we kept in Vienna and killed them after four months. It was seen that not only the goiters of these last-mentioned rats had become appreciably smaller, although in the meantime the rats had grown larger, but that the histological formation had also become different. The alveoli had become much larger and were filled with colloid.

In the case of these rats the greater part of the original alveoli present must have diminished since, on the one hand, the goiter had become smaller and, on the other, the alveoli had become larger.

Another interesting fact was ascertained through these investigations. Whereas the alveoli of the rats brought from Styria and at once killed contained either no colloid or merely a clot, that took on a blue color, the alveoli of the rats killed after 4 months were filled with a colloid, that colored with eosin, but in a great many alevoli there lay in the center of this colloid mass a small, blue clot, that would color blue, apparently the colloid from the previous phase which had not been re-absorbed.

Goiter and Thymus Gland.

Dr. F. Messerli, P. D. of the Lausanne University
and
Dr. E. Coulaud, Assistant in the Laboratory of Dr. Calmette of the Pasteur Institute in Paris.

The authors desire to call the attention of the visitors to this Conference to the observations, which they have made on the occasion of comparative research work on the thyroid gland and the thymus of white rats in Paris, a region free from goiter, in Strassburg and Lausanne, regions moderately afflicted with goiter, and Zurich, which is rich in goiter. *)

The thymus of the rats appears to pass through a similar hypertrophy as the thyroid gland in goitrous regions. In this hypertrophic thymus epithelial vesicle-like structures have very frequently been observed, which originate from the small thymus cells and these vesicles resemble those of the thyroid gland. The study of the thymus gland ought to be taken up anew in goitrous regions owing to the ascertainment of this fact. The variety of conceptions relative to the duration of the persistency of the thymus in human beings is probably to be attributed to the fact, that the investigations were carried out partly in goitrous regions and partly in non-goitrous ones.

The authors suggest therefore to the anatomical pathologist that he give closer study also to the condition of the other glands with internal secretion besides the investigation of the thyroid alterations, and among these, especially the thymus gland, the changes of which may be standing in close connection with the changes of the thyroid gland.

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*) Research work in the Laboratory of Prof. *Calmette* of the *Pasteur Institute*. (Annales de l'Institut Pasteur, November 1926, volume XL, page 952.)

Concluding Remarks.

Professor Aschoff:

In making his concluding remarks the lecturer must endeavor to bring back to a common point of view as well as possible the various contrasts, which had been brought up in the debate. The difference of opinion between Messrs. Lubarsch and Biedl admits of an easy solution if we declare, that the pathologists have not only the right but also the duty to consider matters from a functional standpoint, but they will not introduce the functional valuation into their nomenclature until the same has been made sufficiently certain by their working in common with the clinicians and physiologists. For this reason we shall confine ourselves to the acceptance of a purely descriptive plan of division, such as the one of Berne is. And that will be an essential result of our convention.

Furthermore, I should like to assert, that the characteristic curve of the activity or of live, such as we see in the fluctuations of weight and dimensions of newly born children, at the time of puberty, in the case of pregnant women etc., has been recognized as conclusive for all parts of the world. Likewise, that the goitrous enlargement is nothing other than a higher placing of this curve. There are perfectly definite histological aspects, which correspond with these fluctuations in the activity. That the puberty swelling takes its course at one time in the form of the parenchymatous colloid struma and at another time more in the line of the diffuse proliferating one, seems to be a regional matter. The further that we proceed from the southern centers of the endemic towards the north, the more preponderating does the proliferating colloid struma become. Exposure to sunlight, warmth and other climatic factors may play a part here. The number of goiters in the newly born also apparently decreases in the same direction very strongly. This question of the goiters in the newly born and that of the so-called proliferating senile goiter require further research work.

Moreover histologists agree unanimously, that the genuine Basedow thyroid gland has a very characteristic structure, which Lubarsch was the first to outline. Whereas we recognize a necessary state of adaptability in the real diffuse goiter, it is here also a question of a pathological condition of stimulation. The struma Basedowificata is accordingly a combination between a condition of adaptation and that of stimulation. We are to be sure, obliged

to admit that the struma diffusa parenchymatosa of juveniles very often has a Basedow-like structure. Here we shall have to endeavor to discover more accurate distinctions in the development of genuine hypertrophy and strongly marked hyperplasia. It is also to be recommended that we expunge the expression «toxic adenoma» from the morphological nomenclature. It reflects a clinical aspect. Instead of that we ought to be speaking of diffuse or adenomatous-nodular struma parenchymatosa, or of struma colloides proliferans, or of Basedowificized struma colloides etc. with thyrotoxic symptoms. In that case we shall at least know what kind of histological structure was before us.

Then comes the adenoma question. If Professor Roussy lays stress upon the impossibility of any sharp division between the incipient nodular hyperplastic process and the perfected adenomas, I can only corroborate this, as I have already done in my address. The same thing, which usually is of weight for the pre-cancerous stages, is of importance here for the pre-adenomatous or pre-blastomatous ones. This is really also the case in the mamma, in the prostate gland, in the pituitary body and in the liver. I am quite in favor of having us introduce for it the Wegelin expression of nodular hyperplastic struma in the histologically descriptive plan, which we hope will be generally accepted. But we must by all means adhere to the fact that it is, however, only a question of the preliminary stage of genuine swellings and that therefore the struma nodosa, as a struma adenomatosa, is something entirely different from the diffuse goiter. If we look upon the adenomas only as the expression of a strumous hyperplasia, then there are no longer any non-goitrous regions in the world. For adenomas occur everywhere, even though frequently merely in microscopic dimensions. Only in a thyroid gland, that is stimulated in a strumous manner and compelled to assume a state of adaptation, they become all the more strongly and perhaps all the more profusely developed. The more vigorous the proliferation of the thyroid gland is, the greater the difficulty will become of recognizing the first stages of the adenoma structure as such and of distinguishing them from hyperplasia. These are Wegelin's nodular hyperplastic colloid strumas, the so-called adenomatoses of the Americans.

The researches for the first indications of adenomas in a latent thyroid gland, which Colleague Meisel has demanded, have already been carried out, the same as the researches pertaining to the percentage of iodine. In this connection I am obliged to learn from

the expositions made at this conference that, contrary to personal experiences (Dr. Schmitz-Moormann) favoring a similar total percentage of iodine in the diffuse struma as in the normal thyroid gland, it has been maintained that the diffuse struma as a whole has an increased percentage of iodine. That too deserves further investigation. There is agreement concerning the relatively small iodine content in the nodules.

Finally cretinism. By having our several addresses arranged in a corresponding manner, we pathologists have clearly emphasized the necessity of sharply differentiating this from the ordinary endemic goiter. Cretinism corresponds not to a condition of adaptation of the thyroid gland, as does the simple goiter, but, on the contrary, to a state of exhaustion of the same. How this condition arises, that is a question, which we pathologists are not able to explain at the present time. But here, also, there appears to be a geographical parallelism, as Colleague Wegelin has said by way of conversation. In those regions where goiter rarely or never occurs in the newly born at all, there also do we rarely or never find cretinism. But with this statement I am already entering upon the line of thought, which belongs to my fellow lecturer Wegelin.

Professor Wegelin:

I am in full accord with the general declarations of Professor Aschoff. It is primarily a question of describing the individual types of goiter morpologically just as accurately as possible. In doing this the pathologist must naturally not be prohibited from endeavoring to bring the histological aspect in connection with the function of the goiter. Moreover, through new histological researches probably many a step of progress may yet be realized, especially if it will prove successful to study more carefully into the secretory process.

In classifying goiters we must hold to the conception of adenoma, inasmuch as many nodules prove to be swellings that are well encapsuled and develop in an expansive manner. They behave entirely independently not only structurally but also chemically over-against the surrounding thyroid tissue. I am able to confirm absolutely what Mr. Meisel has stated on the percentage of iodine in these nodules. In other nodules there is on the contrary

no sharp differentiation and their growth probably does not entirely proceed from itself. Those epithelial proliferations, which have been but little described, such as occur frequently especially in the diffuse colloid strumas and as have been shown us by Mr. Holst, I should like to designate as nodous hyperplasia, or better as nodular hyperplasia on account of their minuteness. They can be the initial stages of genuine adenomas but must not necessarily become developed into such later on.

I should like to express my doubts now as previously to the classification of Mr. Breitner, for it does not appear possible to me that we can draw any conclusion as to their secretion from the shape of the glandular epithelia. The secretory ability is probably sooner diminished just in such a gland with actively proliferating cubic epithelium, inasmuch as the cells discontinue the function during the time of their multiplication. Vice versa a flattened cell does not always need to be secretorily inactive. We also oftentimes find in one and the same struma, and even in the same vesicles, cells which differ greatly in their respective natures, so that the Breitner classification is not applicable.

The strong action of the genuine exophthalmic goiter upon tadpoles, which Mr. F. von Müller has laid stress on, I have missed in 3 out of 5 cases. There are evidently exophthalmic goiters, in which very little or no effective secretion at all is accumulated. The inactive glands gave evidence of very little iodine contents as far as these were examined.

The difference in the French and German nomenclature of the malignant strumas, to which Mr. Roussy has called attention, can probably not be so easily changed; the chief thing is that we each may know what is intended to be meant by the other name. I am, besides, extremely cautious with the diagnosis endothelioma, nevertheless I am convinced, that there are actually swellings in the thyroid gland, which originate from the vascular endothelia.

Regarding the Riedel strumas, which have been mentioned by Mr. Payr, it is certainly not any question here of neoplasms, but of chronic inflammations, the causes of which are surely still very unintelligible.

The Pathologic Physiology of Struma.

The Pathological Physiology of Endemic Thyropathy.

(Endemic Goiter and Endemic Cretinism.)

By Prof. Dr. F. de Quervain, Bern.

Preliminary Remarks.

The clinical and experimental investigation of the problems, which stand in connection with endemic goiter, has in late years led us more and more into detail work, upon the various ramifications, and we have to consider now to what extent the main boughs, to which these branches belong, are firm. The voluminous individual investigations have given us a most important amount of material in facts and a still greater number of hypotheses and theories since the fundamental work of Th. Kocher, Horsley and Moebius. At a discussion, such as that one of to-day, it is absolutely necessary that we take up again the fundamental problems in order to see to what extent they have approached some solution through the researches of recent years.*)

I. Definition and Limitation of the Conception: Endemic Goiter.

As «Endemic Goiter» we understand in general the so-called Alpine goiter, or, more correctly said, that goiter which is to be met with, as far as we are aware, throughout the whole world in the valleys of the great mountain chains down to the plains. The designation «endemic goiter» is, however, an imperfect one, for running parallel with endemic goiter we find in the centers of severest goiter incidence the endemic cretinism. For this reason it is indispensable to include also this latter disease in our discussion.

Even with the designations Alpine goiter and cretinism the conception of endemic goiter is not yet fully expressed. We know, long ago, indeed, that besides the mountain goiter areas we find other regions, in which endemic goiter is not leading to a diminution but to an increase of the thyroid function. For this

*) Regarding particulars, which can not be considered in this short address, attention is called to my paper: «Rück- und Ausblicke in der Schilddrüsenpathologie», published in the «Grenzgebiete der Medizin und Chirurgie», Volume XXXIX, Page 415, 1926.

reason the resident of the Lake districts of the U.S.A. has quite a different idea of goiter than the resident of the Alps or the Himalayas. It seems to be best to comprehend the different types of endemic disturbances of the thyroid gland under the general designation of « Endemic Thyropathy ».

Through this definition the thyroid gland has been put into the center of the discussion. This is admissible for the reason that as a matter of fact the thyroid gland is the most injured organ in endemic thyropathy and because through it a great number of the phenomena can be explained. The endogenous or exogenous intoxication, which probably is the cause of goiter, is able only to influence the organism directly, i. e. without the intermediary of the thyroid gland. An exhaustive discussion of endemic thyropathy must also take up this side of the problem in the sense of the old Virchow conception, as more particularly Ewald, E. and H. Bircher, Scholz and Kutschera have done. This signifies that even the pathological physiology of endemic goiter is not to be treated exclusively from the standpoint of thyroid gland physiology.

The diagram on the following page presents to our view graphically the relations, with which we have to deal.

N represents the goiter noxa, the etiology of goiter as a whole, i. e. the presence of injurious substances and the lack of useful ones, predisposing hereditary factors and so on.

A represents the parental organism as transmitter of the goiter noxa (through the gonads and the insufficiency of the maternal organism).

B shows us the organism of the goitrous individual or the cretin, with exclusion of the endocrine apparatus.

C the thyroid gland.

D the other glands with internal secretion.

The importance of the direction NAB has been proved, at least for cretinism, and the detour NACB, e. g. congenital injury of the thyroid gland of new-borns, has been proved by observation and statistics (Pfaundler).

The way NB from the goiter noxa directly to the organism and the way NDB via the influence of the other endocrine glands to the organism may be imagined theoretically and finds support in the difference between athyreosis and cretinism. A variant NCDB: Influencing of the other endocrine glands via thyroid gland has perhaps a still greater significancy than the way NDB (gonads and suprarenal capsules).

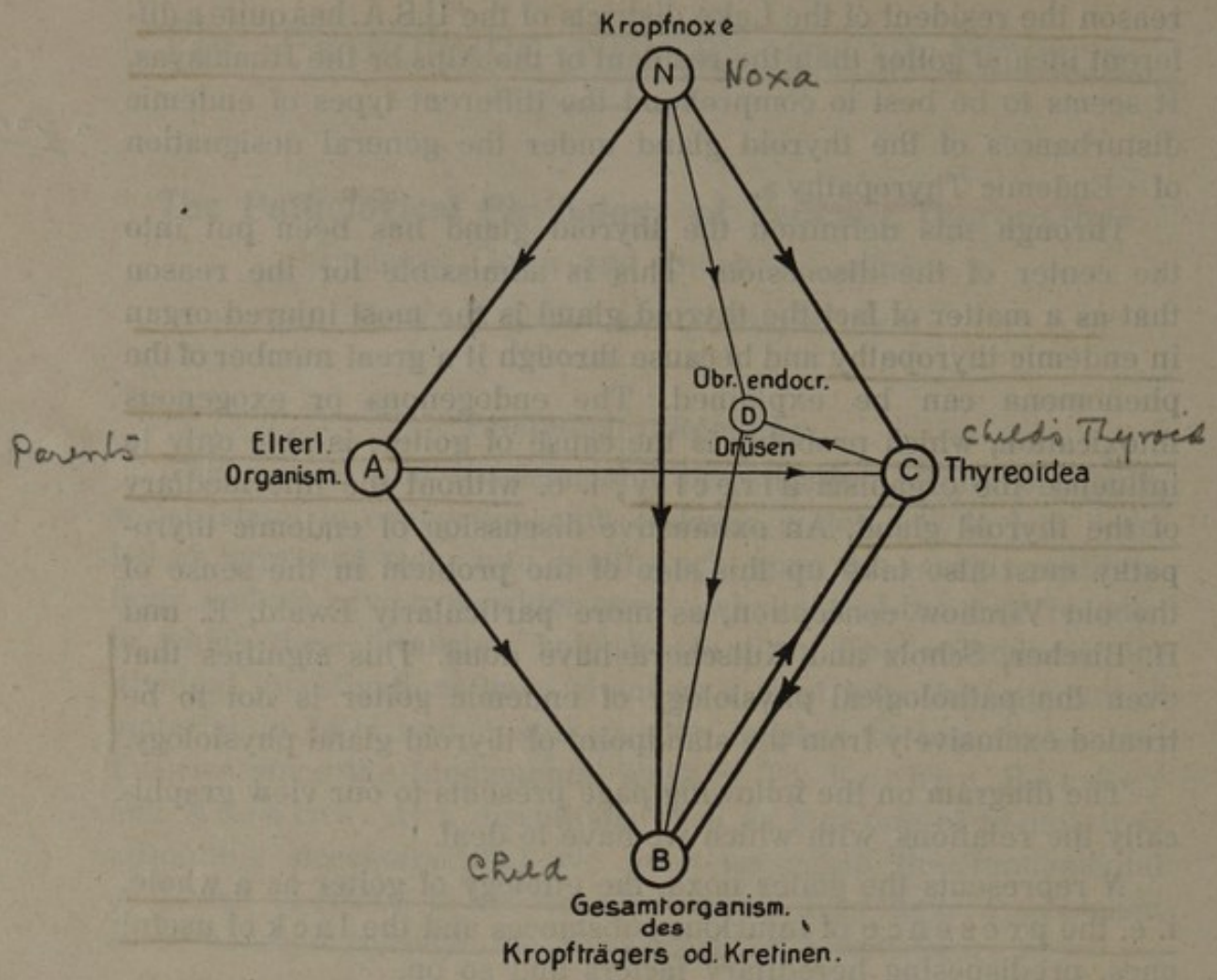


Fig. 1. Diagram of the relations between goiter noxa and the organism of the goitrous individuals.

In the way NCB the arm BC has been drawn in a double sense. According to the conceptions, which are more and more gaining ground, the thyroid gland is overworked and finally damaged by the goiter noxa through the way NBC until hypothyroidism is produced (NBCB). It would, however, be a mistake to overestimate this way as many are inclined to do. The thyroid gland can be injured directly by the goiter noxa, just as well as and perhaps more than the other organism, as we learn from the whole pathology. The atrophy of the thyroid gland, which has been found in cretins without goiter even in very early childhood, speaks in favor of such a direct action through the way NC. In regard to these cases it is not known and could not be ascertained anamnestically in our observations that the atrophy has been preceded by a hyperthrophic stage. We are obliged therefore to postulate the path NCB with the same right as the paths NB and NBCB, as long as such a proof has not been given and as long as it has not been

shown, that a functional stimulus is able to bring an organ directly to atrophy.

In order to avoid any want of clearness, we shall once more call attention to the fact, that we are dealing exclusively with the endemic disturbances of the thyroid gland, being in connection with the goiter noxa, and hence we shall leave out of consideration any trouble being not limited geographically, such as ordinary idiocy, congenital spastic paralysis (Little's disease), mongoloidism, chondrodystrophy, etc., although it is possible for these diseases to be combined accidentally with goiter or cretinism. We specially emphasize this because Kutschera has recently comprised in the conception of «endemic dystrophy» various diseases, which are not confined locally and hence have nothing to do with endemic goiter and cretinism.

The pathological field, which is to be worked out by us, is sharply enough defined through the observations of many centuries and through statistical data, with the exception of several border line discussions. Pfaundler has recently also proved by means of modern statistical methods that there exists some connection between endemic goiter and endemic cretinism. According to his calculations goiter and cretinism show an almost maximal degree of syntropy (correlation) namely 41,6, which signifies that the two conditions are met with some 41,6 times more frequently together in the same individual than could be expected, if they did not have anything to do with one another.

Goitre and cretinism correlation

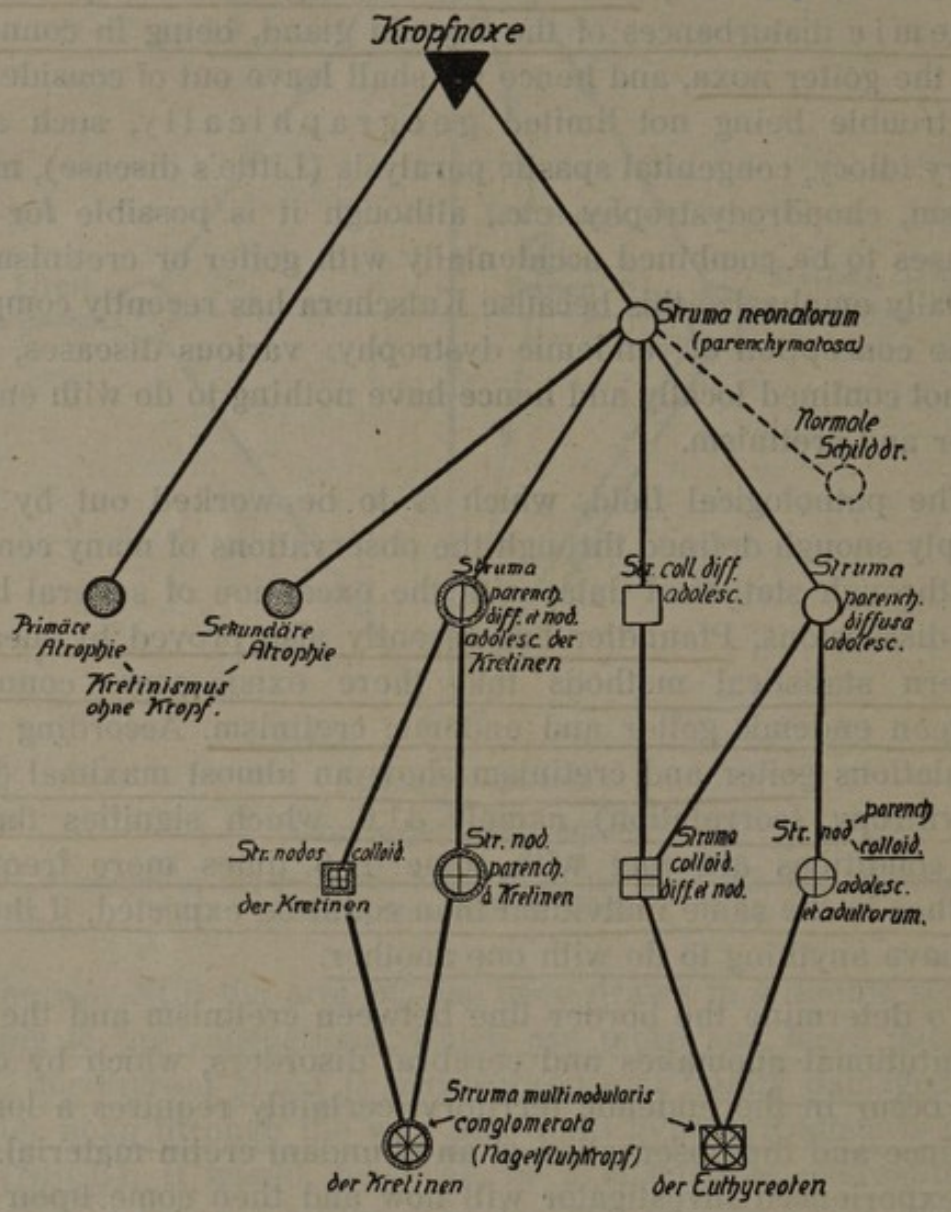
To determine the border line between cretinism and the other constitutional anomalies and cerebral disorders, which by chance may occur in the endemic territory, certainly requires a long experience and the observation of an abundant cretin material. Even the experienced investigator will now and then come upon cases, which it is difficult to classify, notwithstanding the facility of the diagnosis of the average cretin.

The material being the basis of our own investigations is very valuable for this reason. There are indeed numerous of those limiting cases to be found in the State institutions for the poor, besides hundreds of classic cretins and the cases being independent of endemic influence.

We shall introduce our further statements with a diagram showing graphically the relations of the different varieties of goiter to one another, as they have been deduced especially from the

varieties goitre

study of the material obtained in a very goitrous region. This diagram permits us to recognize the rôle they play into the system of the endemic thyropathy.



Atrophy of the thyroid tissue.

Parenchymatous goiter.

Colloid gofter.

Pauci-nodular goiter.

Multi-nodular goiter (Conglomerate goiter, „Nagelfluh" goiter).

Fig. 2. Diagram showing the relations between the different varieties of goiter.

II. Technics of the Formulation of Query and Investigation.

The question, which is to be answered by the pathological physiology of goiter is, briefly put: The bearer of an endemic goiter or cretin of any race: How is he different in the functions of his organism from the normal average in that particular race?

In formulating a reply to this problem the following points are to be considered:

1. General constitution.
2. Behavior of mind and intellect.
3. Behavior of the organs of sense.
4. Behavior of the teguments and appendages to the skin.
5. Behavior of the skeleton.
6. Behavior of the nervous system.
7. Behavior of the circulatory system.
8. Behavior of the sexual organs.
9. Behavior of the blood: a) morphologically, b) chemically, c) physically, d) biologically.
10. Behavior of metabolism: a) nitrogen changes, b) formation of carbonic acid.
11. Metabolism of iodine.
12. Behavior of the goiter substance: a) morphologically, b) biologically.

In addition to the general clinical research ways, we made use of the following methods of control:

1. The determination of the basal metabolism (the consumption of oxygen and the formation of carbonic acid).
2. The rat experiment, according to Asher-Streuli, with the blood of the veins of the arm, the venous blood of the struma and the goiter tissue.
3. The tadpole experiment, according to Gudernatsch, with the substance of the goiter.
4. The determination of the phagocytosis stimulating qualities of the blood-serum.
5. The photo-chemical study of the serum, according to Kottmann.
6. The determination of the iodine level in the blood.
7. Capillary microscopy.
8. The morphological investigation of the blood.
9. The sedimentation rate of red cells.

10. The histological investigation of goiter.

11. The determination of iodine in the same.

III. The three functional Groups.

Even if we do not wish to consider a priori the thyroid function from the standpoint of the basis of the division, this criterion is so prominent that we are forced to use it for a summary classification. We therefore distinguish:

1. The euthyroidic endemic goiter. This manifests in the rat test from a thoroughly effective goiter tissue (colloid goiter) to a little efficacious one (microfollicular adenoma), and around the adenomas a sufficient quantity of well functioning residual tissue. The tadpole test agrees fairly well with the rat test. The tadpole re-acts on the goiter of new-borns and on certain puberty goiters but very little (Wegelin and Abelin), in part because the tissue is poor in colloid. The blood from the veins of the arm shows in the rat test a slight activeness (colloid goiter) or no activeness at all, i. e. it behaves in the latter case like normal blood. The phagocytosis and iodine level of the blood are normal, that is to say, they lie at the lower limit of normalcy.

The haemoglobin content as also the number of red blood-corpuscles are mostly normal, as likewise the number and the differential count of leucocytes, with the exception of a slight increase in the number of lymphocytes. The diminution in the number of blood-corpuscles does not deviate typically from normalcy in the uncomplicated goiter, nor does the Kottmann reaction. The basal metabolism is normal, i. e. with few exceptions it lies within the limits of $\pm 10\%$. In other words it is not possible to ascertain any fundamental deviation from the normal behavior with any of the customary methods of investigation. The thyroid function is normal, whether it is performed by the goitrous tissue (diffuse and nodular goiter) or in the main by the residual tissue (microfollicular adenoma).

2. The endemic goiter with secondary hyperthyroidism. The above mentioned tests give evidence of increased activeness in the goiter tissue in general, with a few rare exceptions, that have been determined by Wegelin and Abelin and Branovacky. The blood of the veins of the arm gives in the rat test a strongly marked positive result, the contrary of the tadpole test. The phagocytosis is increased, the Kottmann reaction shows an abnormally fine dispersion. The metabolism is increased,

sometimes at a very high degree. The clinical aspect proceeds from the simple cardiovascular erethism to the strongly marked aspect of Basedow's struma, whereby the chief distinction from the genuine exophthalmic goiter consists in the absence or in the slight development of the exophthalmus. The secondary hyperthyreosis may accompany every variety of endemic goiter. It occurs most rarely in the center of the endemic area in Berne, e. g., only 2 to 3% of the goiters that are operated on, and more frequently in those districts in which the diffuse goiter prevails, which does not lead to cretinism. In certain regions of the United States of North America the secondary toxicity is said to represent 50% of the whole goiter incidence. They are in part general enlargements, in part toxic adenomas.

The causation of toxicity is to be found very often in iodine treatment, even from the daily dose of 0,5 milligrams on. With a supply of iodine in physiological limits, about 0,05 milligrams per day, the morbidity in Basedow goiter and toxic adenomas is not proved to be any greater than without.

3. The endemic goiter with hypothyroidism and the cretinism. Here the entire constitution, the condition of the intellect, the structure of the skeleton, the integument, the metabolism show a great number of characteristic symptoms, of insufficiency of the thyroid function and even in some cases an almost complete lack of function. The phenomena are mostly not, however, those of congenital athyreosis, so that the co-operation of other factors must come under consideration. Two groups of cases must be distinguished, the characteristic differences of which Maffei and Roesch called attention since 1844:

a) Cretinism without goiter and without clinical enlargement of the gland. These are characterized through dwarfishness, monkey face with a shortened base of skull, insufficiency of the genital organs, deficiency of the intellect from the zero point upwards to a certain degree of common sense, but always a social insufficiency, the skin always dry, sometimes myxoedematous, sometimes atrophic, basal metabolism deep, iodine level in the blood low, phagocytosis somewhat reduced. The thyroid gland is strongly atrophic, both palpatorily and histologically, sometimes with small goiter nodules. Never complete aplasia exists. The atrophic thyroid tissue shows some activness in the tadpole test.

b) Cretinism with goiter. Cretins with goiter show the entire gradation from the goitrous individual more or less

euthyreotic to the perfect cretin with dwarfishness, who differs from the cretin without goiter only through his adenomatous or cystic goiter-nodules. The skin is sometimes myxoedematous, sometimes atrophic, with transition to the normal condition. The basal metabolism is on the average reduced, at times normal (± 10 %) *), phacocytosis normal or slightly reduced, iodine level in the blood reduced in the severe cases.

The goiter is rarely from the colloid, mostly from the parenchymatous type and represents a general enlargement in slight cases of cretinism on children. In the more severe cases it becomes nodular very early with more or less serious atrophy of the scanty residual tissue (Wydler). Similarely to the clinical transition, there is also a gradual transition in the residual tissue of the goitrous cretin towards the behavior of the residual tissue in the non-cretinous goitrous individual, and it is difficult to say in many cases, both from the clinical as well as the histological standpoint, what is the classification of a special case. If Kutschera says of a part of the cretins, that there is nothing the matter with their thyroid glands, it may be that these particular cretins have no palpable goiters. But we can not make any positive statements of the behavior of the thyroid gland without having made a histological study both of the residual and the nodular tissue, and especially the atrophic condition can not be excluded.

Even the histological aspect is not able to decide in border line cases. The really deciding factor is what the organism is able to bring out of this thyroid gland, even when its histology is not completely satisfying.

The explanatory difficulties are not entirely removed with the division into three functional groups, such as we have just outlined. This fact will become evident from a thorough discussion of the three groups.

We shall take up again first of all the group of the euthyreotic goiters. The transitions towards above, in the direction of hyperfunction we shall discuss when we speak of the struma Basedowificata, the transitions downwards, towards hypothyroidism, will require special discussion. We must keep here two matters separate from each other:

a) An episodial underfunction of light grade, that is more or less temporary. This happens to goitrous girls at

*) whereby the results of the researches do not belong to the severe cases all the more as these cases are not able to be examined.

the time of puberty and to women at the climateric period (Hotz, Marañon). Such cases answer to the hypothyroidism first described by Hertoghe, i. e., the «petite insuffisance thyroïdienne» of Leopold Levi. Whether the symptoms are really to be ascribed to the thyroid gland, can only be decided in each individual case by means of careful thyroid therapy. Such symptoms are: dryness of the skin, light oedema of the eyelids, relapses of general oedemas, feeling of cold and cold extremities, uterine haemorrhages, genital insufficiency, arthritis, constipation, headache, feeling of weariness and failure of the memory. We have gained the impression that not only the classical myxoedemas of individuals of middle age, but also the slight episodial manifestations of hypothyroidism, are both more frequent in goitrous regions than in countries poor in goiter.

b) A constitutional type of insufficiency. Notwithstanding the absence of morbid conditions, other than goiter, we nevertheless have the impression that the population in very goitrous regions shows a different physical and intellectual aspect than the racially similar normal population. The appearance of the skin, the entire physiognomy, the psychic behavior, all point towards cretinism, though we could not call these goiter sufferers even semi-cretins. If the gradual transition of this types to that of true cretinism would not exist, we should not immediately think of thyroid insufficiency, as more as the aspect of these cases is distinctly different of that of myxoedema. In accordance with the research work of Heller, Holmgren, Wegelin and others we might assume a tendency towards minus-variants, in contrast with the inclination to plus-variants, produced through the Basedow. These transformations are not to be classed as racial characteristics, since the endemic thyropathy is bound locally, thus contrasting with race. But I do not desire to be understood as not recognizing that the behavior of the endocrine glands play quite generally a certain rôle in the development of the racial characteristics.

We may draw the conclusion from what has been said that the endemic goitrous condition signifies without doubt a pathological damage to the population, even if we do not find in the pathological-anatomical examination any palpable lesion besides the goiter. In this sense the expression «endemic dystrophy» is to a certain degree justified, whatever may be the mechanism of this process.

Here the occasion is also given to touch upon the question of

the goiter heart, i. e., the cardio-vascular symptoms in goiter, which was recently critically discussed by Wegelin.

It is self-evident that we must eliminate everything from this conception, which can be explained even without goiter through the previous history and the pathological condition, but this is perhaps, however, not always sufficiently taken into account.

The greatest part of what remains is to be attributed to hyperthyreotic conditions. These on one side influence the heart via the nervous system through functional hypertrophy and on the other side they act toxically upon the cardiac muscle. The fact, that the action upon the heart does not run parallely to the clinical intensity of the Basedow's disease (exophthalmic goiter), must be attributed either to extra thyroidal co-operating factors or to an individual susceptibility of the heart.

It is impropable that a hypothyreosis, as such, will lead to anatomical hypertrophy of the heart, as more as such a hypertrophy is as a rule absent even in athyreosis. Generally speaking, the hypertrophy of the heart is also not present in young cretins, and in the cardiac changes of older cretins the cause is mostly vascular injuries and other organic changes, independent from cretinism. We can hold the latter responsible only for the flaccidity of the cardiac muscle (Oswald). It is indeed remarkable that we find as a rule the blood-pressure in cretins low.

For the euthyreotic goiter heart there is not much more left according to the anatomical finding that is before us (Wegelin). A part belongs, notwithstanding contradictory views, to the mechanical goiter heart, which we were probably a little overhasty to bury. Other cases belong to an incomplete hyperthyroidism. Of much greater importance are the statements regarding to the goiter heart of the newborns (Feer, Guggisberg, Wegelin) and the fact that there is hypertrophy of the heart in the rat goiter, for which neither hyperthyroids nor mechanical factors are to be thought of. Here we must think either on a dyssecretion, which especially affects the cardiac muscle, or on a hypothetic direct influence of the goiter noxa on the heart. These latter two explanations leave the possibility on hand that even with the adult person there is neither a hyperthyreotic nor a mechanical heart but a so-to-say idiopathic goiter heart, the frequency of which must certainly be very slight according to the pathological-anatomical statements in Berne. Other findings would have to be explained through geographical differences in the goiter noxa, if we desire to enter on an hypothesis anything but firmly founded.

Before we take up the discussion of the other two groups, we ought to premise several general views as to what is to be understood by the terms super-function and sub-function.

In the year 1913 Gley put the question whether there can be any talk of super-function and sub-function in the case of the endocrine glands. He reached the conclusion that these terms are being used too lightly and without consideration on the part of clinics and that a sub-function can only with difficulty be understood in the case of the testicle according to the law of « Everything or Nothing »,discovered by Pézard and himself. In this criticism we are no doubt justified even at the present day in saying that these conceptions are accepted altogether too readily in helping to solve diagnostic difficulties and that useless therapeutic experiments are undertaken too often based upon a doubtful diagnosis « Disturbance of internal secretion ».

If we look upon the super-function as a unitary phenomenon and fail to accept any more definite distinction, we must remember that man and animals can be temporarily hyperthyroidized artificially. With man the gradual improvement of the unquestionably hyperthyroid symptoms of Graves disease proportionally to the reduction of the stand shows that the disorder of the gland is a quantitative one. We are even able to neutralize the blood of the Grave's disease-patients in vitro, as the rat experiment shows (Branovacky), through that of cretins, from which we are obliged to conclude that the one is hyperthyroidic, at least in essential matters, and the other essentially hypothyroidic. With this we have really stated, that we must also accept a hypo-function. We have been emphasizing for a long time that the law of « everything or nothing », which has been described for the genital glands, can have only a limited application as regards the thyroid gland. The limit, over which the function is normal, must with the thyroid gland be further removed from the zero point than in the case of the genital glands, that is to say the range of the hypo-function must be a greater one.

In their latest papers Pézard and Gley have also given some limitations to the law for the testicle and have laid down as a fact that the action of the hormon graduates below the general threshold in accordance with the implanted quantity of testicle tissue, so that for the different effects of the secretion different thresholds (des seuils différentiels) are present. There accordingly is a hypofunction and this follows, as a matter of fact, definite laws in its mani-

festations. Gley applies the principle of the seuils différentiels also to the thyroid gland and endeavors to explain with it the disparity of the phenomena in the «myxoedème partiel» of Brissaud. The animal experiments of Champy and Drzevicki confirm the fact of fractionated action of thyroid preparations on the tadpole. Gley finally in 1925 combines the theory of a plurality of thyroid secretions with that of the «seuils différentiels».

We ourselves have expressed as far back as 1921 the thought of a multiplicity of secretions and have combined with it the idea of an abnormal mingling of the various normal components of secretion (relative dysthyroidism). We are indeed obliged to assume that the secretion conforms to the demands of age, sex and species of animal, and we can imagine that there nevertheless exist within the animal kingdom certain rather fine distinctions even with a far-reaching correspondence of the same and that e. g. the secreted material of the human thyroid gland is not fully adequate for the tadpole or the rabbit although as a whole it indicates thyroid action (Swingle). If we combine this conception with that of Gley of the seuils différentiels, we shall obtain very far-reaching possibilities for the explanation of the so striking clinical disparity of the thyroid disorders. Observations, which have been made by Wegelin and Abelin and by Branovacky in connection with their tadpole experiments appear to give an experimental support to this conception. By reason of general considerations it can be easily imagined that the gland deviates still more from normality under certain circumstances and produces a secretion, that is similar to the normal one but varies from it in its chemical composition, i. e. a genuine dyssecretion, in which the physiological effects are accompanied by certain pathological collateral effects («absolute dysthyroidism» according to our definition of 1921). In whatever form we may imagine this secretion to be, an unripe or over-ripe secretion etc., it is useless to have any discussion about it just now, inasmuch as we do not possess any tangible supports regarding it at the present time. Neither chemical nor histological examination nor experimental research up to now admit of giving any positive proof of any absolute dyssecretion.

Notwithstanding the recognition of the possibility of such a dysfunction, we can not go so far as Lucien, Parisot, Richard and others, who desire to class all functional disorders offhandedly as «dysthyroids». By far the most of the functional disorders, which are known to us manifest very definitely the

character of a «too much» or a «too little», and the «dys» element can refer only to the special aspect of the pathological condition. Having made these explanatory comments we shall now take up the consideration of the second main group.

The hyperthyroid-endemic goiters are, as we have already stated, all to be classed as Basedowificated strumas, whether the Basedowification, the «becoming toxic», concerns a diffuse struma or a goiter nodule.

This is not the place to raise the entire Basedow problem. For this reason I shall confine myself to a few comments, which pertain exclusively to endemic struma.

On the one hand we see that the endemic goiter is, so-to-say, the antagonist of the genuine Basedow. To be sure, the latter occurs also in goitrous districts but all the more seldom, the nearer we approach the endemic center. It accordingly is more rarely found in Berne than in Basel and affects there not more than 1 to 2 % of the cases of struma that are operated upon, if we consider only the native patients.

On the other hand the endemic struma gives us the great majority of iodine-Basedow cases. Whereas incredible quantities of iodine can be borne withouth any thyrotoxic disturbance by the most individuals, who have normal thyroid glands, with goiter sufferers it frequently happens that daily doses of ½ to 1 milligram develop iodine-Basedow, which will last for months if not even for years.

This difference between the normal human being and the goiter sufferer was set down as a fact for the first time in the discussion of the Académie de médecine in Paris in 1860 on the report of Rilliet of Geneva.

But it is also a fact that the struma Basedowica produced by iodine affects only a small percentage of the goiter sufferers, who are taking iodine. Hence we must assume here also an individual predisposition, as even former observations have shown, and occasionally a hereditary one, just as it is the case with genuine Basedow. This becomes latent again after operative removal or the reduction of the toxic tissue, because the patient is tolerant in regard to a normal secretory quantity. The general disposition alone, however, will not help us. The toxic adenoma nodules even at times show at the operation macroscopical changes of a directly inflammatory appearance, so that we are obliged to assume an idiosyncrasy, inherent to the goiter tissue. On the basis of the comparison of these cases with many hundreds of non-toxic adeno-

mas, we should like even to assign just as great an importance to this local predisposition as to the predisposition of the nervous system.

Concerning the struma Basedowificata of Norway and North America I am unable to express any opinion from my own experience. Judging from the reports received and the general character of the goiter endemic, it seems that it is more often diffuse than nodular. Just as it is the case with the endemic struma, so the struma Basedowificata seems also to have its local peculiarities.

The two main facts in Basedowification are, that each variety of endemic goiter, with the exception of the secondary degeneration, is able to be Basedowificized and furthermore, that the Basedowification can come about with and without the action of iodine. Iodine-Basedow and toxic adenoma are therefore just as little synonymous terms as diffuse Basedow struma and genuine Basedow. To look upon struma Basedowificata or at least the toxic adenoma as a hyperthyreosis and upon genuine Basedow as a dysthyreosis (Plummer) facilitates the explanation of many clinical observations. It is, however, a difficult matter to apply it to the diffuse Basedowificized, i. e. originally banal goiter of the North American middle western regions and to similar observations made in our country, though it occasionally may resemble «genuine exophthalmic goiter» histologically. Here there is a distinction between hyperthyreosis and dysthyreosis in the Plummer sense, possible neither in the consideration of the genesis nor in relation to the clinical aspect. For this reason Crile and his followers refuse to accept the distinction of Plummer.

One of the main problems regarding struma Basedowificata accordingly still remains an open question and requires further proof through the application of the different clinical and laboratory methods.

We now come to the discussion of the hypothyreotic conditions in endemic thyropathy: Cretinism without and with goiter.

There are two things here which we ought to be able to explain:

a) The differences between cretinism and dystopic or complete thyreoaplasia.

As Wegelin says, there is no genuine aspect of the athyroid, i. e., a pattern which will fit every case. Even in the congenital athyroid we find distinct gradations in the aspect of the disease, probably resulting from dystopic thyroid remains, that are still present. Nevertheless we can in general say that the individuality

is more severely injured here than in many cretins, who are somatically even severely affected. The myxoedematous aspect is as a rule more sharply defined, whereas the skeleton shows more slender forms than in many cretins, especially such suffering from goiter.

Between the cretins with atrophic thyroid gland and the so-called athyroids the distinctions are not very striking and they can quite easily be explained in that the former always possess still more thyroid gland than the serious cases of thyreoaplasia and that this remnant of thyroid gland degenerates only in course of time. There thyreoaplasia sufferer lives upon the normal thyroid gland of his mother during his intrauterine existence and has suddenly after birth almost nothing to depend upon. The cretin has in the main intrauterinally less of the thyroid gland of his mother, who is as a rule goitrous, than the athyroid individual, but he takes along a moderate supply into the extrauterine life.

The cretin with goiter deviates mostly still more strongly from the thyreoaplastic type, inasmuch as he has at his disposition a greater supply of tissue than the non-goitrous cretin and since the degeneration of this supply goes on more slowly than in primary thyroid atrophy, his skeleton and the genital organs therefore can be better developed and the cretinous face is less strongly marked than in the non-goitrous cretins. To be sure we also find different variations here as, e. g., dwarfish cretins with a relatively slightly pronounced cretin skull and, vice versa, relatively well developed cretins with a pronounced monkey face and myxoedema. The myxoedematous change of the skin is far less strongly marked in the goitrous cretins than in the athyroids. How little, nevertheless, the metamorphoses of the skeleton and of the skin run parallel in the latter the case of a 13 year old girl proves to us. This girl was 51,7 inches tall, with strongly marked myxoedema, moderately deficient in intellect but without any contraction of the base of the skull. She looks not like a true cretin in respect to her skeleton, however she possesses at the normal location no trace of any thyroid gland, as the operative control shows. A lingual thyroid which can not be proved, must here have partially compensated the absence of the normal gland.

The difference between thyreoaplasia and cretinism are, in accordance with what has been said, not so much of a fundamental as gradual nature and the estimation of them is considerably rendered more difficult through the disparity present in both conditions. For an explanation of them we can get along quite

well with the idea of the seuils différentiels. The remaining factors, that are to be considered, we shall take up later.

b) The strongly marked disparity in the clinical aspect of the cretin himself. This has been known for a long time but very little attention has been given to it. The employement of the principle of graded thresholds can explain only a part of the phenomena. In the case of the castrated cock the restitution of the sexual attributes through implantation of the testicles shows a definite order. The dissociation is not an arbitrary one but is governed by distinct rules. With goitrous and non goitrous cretins, the dissociation seems to be arbitrary. We find (at times) on some patients the skeleton disorders more predominant, on some other, those of the intellect, or the deafness, or the myxoedema. The last named is replaced through atrophy of thė skin, sometimes early, sometimes late and sometimes not at all. The mental individuality can be preserved just as well as destroyed in the case of cretinous dwarfs, as with cretins from normal size. This irregularity would be explained easily if we could admit an abnormal composition of the secretory components in addition to the seuils différentiels. It is scarcely necessary to establish the hypothesis of an absolute dysthyroidism. The hypothesis is, however, urged upon us by isolated cases of cretinism with hypertrophic goiter and conditions of psychic excitement. This excitement is neither hyperthyroid nor hypothyroid and is something different from the usual thyroid troubles.

We have tried in the foregoing to explain the phenomena of cretinism exclusively with the thyroid gland as a basis, because this, in so far as we have precise investigations, is the only constant and more or less seriously injured inner-secretory gland on cretins. We have seen, that such an explanation may be sufficient for the essential points with auxiliary hypotheses, which tend in the direction of the development of endocrinological research.

We have not even looked in this particular case for help to the other glands with internal secretion, because there are no anatomical indications for their primary participation. Nevertheless a slight co-participation of such glands — without anatomical proofs — can give to some exceptional cases a special aspect. We should like to lay more stress upon the secondary participation of certain inner-secretory organs, that is to say, on the way NCBD. This applies particularly to the genital glands, the inefficiency of which must again react upon

the organism. The participation of the other inner-secretory glands is nevertheless from such a little importance, that we can not feel justified in considering off-hand cretinism as a pluriglandular disorder.

We may still wonder what the effect is of the direct influence upon the organism exerted through the goiter noxa, that is, the way NB in the diagram? We mention this factor lastly, because we can obtain a general survey only by testing each factor for itself and that in proper succession, in which it is to be reached in a clinical and an experimental control. This, however, has been the least possible up to the present time for the hypothetical goiter noxa, because we are not as yet sufficiently acquainted with its nature. To be sure, E. Bircher has done research work to determine the influence of this noxa upon the heart. For the fundamental problem, which is: «Hypothyreosis or direct action of the goiter noxa», such experiments do not come under consideration, because we cannot keep clear of the function of the thyroid gland without removing it, so that we then do not create a hypothyreosis only but an athyreosis. At the most we could try to ascertain whether the goiter noxa cretinizes, when the thyroid gland remains intact. Neither the experiments of McCarrison nor those of E. Bircher and others give us the right to draw any such conclusion. We must therefore depend on indirect deductions. Is there a something in the clinical aspect of cretinism, which we can explain certainly neither from the basis of the thyroid gland nor any other endocrine gland and hence are obliged to assign it to a direct influence of the goiter noxa on the organism?

We have already mentioned the goiter heart of the Newborn. Here the other explanations fail, and also for the changes in the middle ear and the inner ear in the so-called cretinous deaf and dumbness. Here the goiter noxa might come in.

Is this in part also responsible for the general inferiority of the goitrous population? Does it contribute its share towards giving the cretinistics thyroid insufficiency a special aspect? All of this is possible but is not proved up to the present day. The explanation of this problem can be most accurately ascertained by continuing with clinical, experimental and pathological-anatomical research on a great amount of cretinous material in order to ascertain what is and what is not due to the thyroid gland. In this way the nervous system has been thoroughly studied anatomically for more than a century and also experimentally for

more than 40 years and it was not possible to discover any real specific changes in the cases of athyreosis and of cretinism. In recent times capillary-microscopy has also been resorted to. From our own researches we can for the present only conclude, that as a fact anomalies of varied nature are of very frequent occurence with cretins, especially stunted capillaries, but that they do not have any special characteristics. We are able to find perfectly normal «hairpin structures» in dwarf-cretinism also!

IV. The Relations between Pathological Anatomy and Pathological Physiology of Endemic Thyropathy.

We have, to be sure, repeatedly touched upon the relations between pathological anatomy and pathological physiology of endemic thyropathy, but we desire to summarize the most important conceptions of the present day in a table and then summarize into a few sentences whatever has been in a way defined on the basis of more recent research work, especially that of Graham, Wegelin and Abelin, Aschoff, Hellwig, Breitner, as also those of the Eiselsberg school and on the basis of our own investigations.

1. The Newborn goiter is almost free from iodine and colloid; its function is in the majority of the cases satisfactory, even when it proves to be but little active, as a rule, in the tadpole experiment.

In the cases of subsequent cretinism it probably has in most of the cases the germ of future insufficiency already within itself.

2. In struma diffusa parenchymatosa of childhood and puberty with its insignificant iodine and colloid contents and the active epithelium proliferation we find mostly a euthyroid behavior clinically. The hyperthyroid conditions are observed mostly only in a slight degree, at least in the strongly marked endemic region. They can not be positively recognized as such in the histological structure. Hypothyroidic phenomena are not rare in the area of serious endemic and diminish towards the periphery of this. The functional diagnosis can occasionally also be made here from the histological structure, but not always.

3. With the struma diffusa colloides (macrofollicularis) of the child and adult age we find euthyroidism as well as hyperthyroidism, the latter as a secondary phenomenon. The histological aspect at times admits of a distinction but by no means at all times. In experiments on animals this goiter has a more active effect than the other varieties of endemic goiter. Unsatisfactory functioning is scarcely observable here (Branovacky, Wydler).

4. The struma colloides nodosa or rather diffusa plus nodosa behaves like No. 3, but it belongs to a somewhat higher age. Here we also find almost always a euthyroidic or secondary hyperthyroidic function and only very exceptionally phenomena of insufficiency.

5. The struma nodosa parenchymatosa (microfollicularis, tubularis and trabecularis) manifests as such the most insignificant activity, i. e., it contributes as a rule but little towards the maintenance of the function. The function depends here essentially upon the quantity and quality of the residual tissue, that is on hand, thus contrasting with the colloid struma. If this is sufficient then the bearer is euthyroidic; if not then he is a semicretin or cretin. The struma nodosa parenchymatosa can become Basedowificated, i. e. a toxic adenoma.

V. The Colloid Problem.

In the colloid problem normal and pathological physiology are in very close touch with one another. We can summarize in the following sentences what appears to us at the present day as positive or rather as very probable:

1. The colloid is the morphologically demonstrable secretion of the thyroid gland. It contains, within an excipient of albuminoid bodies, the physiologically effective substance, or the effective mixture, of which the delivery into the thyroid gland is proved by means of experiments on rats, i. e. greater activity of the thyroid venous blood than of the blood of the general circulation.

2. An intra-glandular influence on the blood (Blum, Kottmann, Starlinger) is not excluded by the delivery of a secretion. Every chemical change of the constituents of the blood in the gland itself belongs, however, strictly speaking, within the range of secretion.

3. A detoxicating function of the thyroid gland seems to be probable according to the neutralization experiments of Hara and Branovacky.

4. The visible secretion is a stored-up secretion, the delivery of which into the blood is regulated by means of a mechanism of threshold. In various conditions of intoxication and infection this threshold is reduced, i. e. the gland is rapidly emptied (Roger and Garnier, de Quervain, Sarbach). Administration of iodine elevates the threshold temporarily in the case of hyperthyreotic Basedow goiter (Th. and A. Kocher, des Ligneris, Breitner), that

Synoptic

of the Relations between the Shape and Function

Wegelin (School of Langhans)		Aschoff		Breitner (School of v. Eiselsberg)		Bérard	
path. anat.	funct.	path. anat.	funct.	path. anat.	funct.	path. anat	funct.
Struma diffusa parenchymatosa (microfollic.) especially Struma neonat. et adolesc.	mostly eu, occasionally hypo.	*Str. diffusa* *a)* parenchym. *b)* microfoll. (Counted with the Colloid strumas)	hypo to hyper	Eutrophic hyperrhoic Struma	hypo to hyper	Hypertrophie parenchymateuse	
id. basedowiana	hyper (dys ?)	Struma diff. parenchymat. basedow.	hyper	Hypertrophic hyperrhoic Struma	hyper	id.	
Struma diffusa colloides (macrofoll.) *a)* proliferans *b)* stationary	mostly eu, rarely hypo, occasionally hyper.	Struma diff. colloides macrofollic. *a)* prolifer. *b)* non proliferans	hyper eu-hypo	*a)* Eutrophic hyporhoic Struma *b)* Hypotroph.-hyporhoic Struma	hyper to hypo	Hypertrophie colloide	
Struma nodosa adenomatosa parenchymat. (trabecularis tubularis microfollicul.)	hypo to hyper (basedowificata.)	Struma adenomatosa simplex and basedowificata	hypo dys.			Adénome foetal (according to Woelfler)	
id. *colloides* *a)* proliferans *b)* stationary	id.	Struma nodosa colloides *a)* prolifer. *b)* non proliferans	hyper eu-hypo			Adénome colloide	

Abreviations: eu = Euthyroidism
hypo = Hypothyroidism
hyper = Hyperthyroidism
Dys = Dysthyroidism

Compilation

of Goiter, according to different Authors.

Mc. Carrison		Williamson (Berry)		Mayo-Clinic (Plummer, Wilson, Boothby)		Crile-Clinic (Graham)	
path. anat.	funct.	path. anat.	funct.	path. anat.	funct.	path. anat.	funct.
Parenchymatous goiter	eu to hypo	Physiological hypertr. goiter Heterotrophic vesic. goiter		Hypertrophic Hyperplastic goiter	eu-hyper	Hypertrophic Hyperplastic goiter	eu
Hyperplastic goiter	hyper	Heterotrophic adenoid goiter	dys.	id.	dys.	id.	hyper
Diffuse colloide goiter	eu to hypo, rarely hyper	Heterotrophic vesicular goiter		Diffuse colloid goiter	eu	Colloid goiter	eu to hyper
Adenoma	id.	Simple hyperplastic goiter Heteroplastic goiter	eu-dys.	adenomatous goiter	eu	Fetal adenoma	id.
Colloid adenoma	id.	Prim. perilob. Fibrosis Prim. inter. lobul. Fibrosis	dys.	Colloid adenoma	eu (non toxic) hyper (toxic)	Diffuse colloid adenomatous goiter	id.
Lymphadenoid goiter		Hyperplastic lymphadenoid goiter	Myxœdema				
				Adenomatosis (Wilson, Goetsch)	easily hyper		

is to say it effects the colloid constipation, but on the contrary it reduces this with certain secondary Basedowificated goiters — colloid diarrhoea, iodine Basedow (Breitner). The colloid varies greatly in its valence. It is of high value (as for rat and tadpole experiments) in Basedow goiter, of less value but still of strong action in euthyroidic colloid goiter and of slight value in the goiters of cretins. The function of a gland is represented through the product resulting from the quantity and the quality of the delivered secretion, no matter whether this secretion is stored-up and histologically visible or not.

5. The retention of colloid does not enable us to give any judging as to the secretory efficiency of the gland, but is simply a proof of the fact that more colloid is being produced than delivered. High shape of the cells and the thin fluidity of the colloid give evidence for strong, flat cells and thick viscosity for slight issue, but neither the one nor the other criterion enables us to judge of the quality i. e. the functional value of the secretion.

VI. Iodine in Endemic Thyropathy.

Up to very recent times we only knew of the relative and absolute iodine contents of the thyroid gland in the different varieties of goiter and we were aware, that iodine was contained to the minimal degree in the cells and to the maximal degree in the stored-up colloid (Aeschbacher, Tatum, van Deyke et al.). Since more accurate methods of research have been worked out especially by von Fellenberg, we have also gained an insight knowledge of the iodine-metabolism of the organism. Notwithstanding that we are still at the beginning of our understanding as to these matters, there are certain fundamental facts which can even now be recognized.

In the blood there is a definite quantity of iodine circulating, which is derived from the air and the food and is mostly in organic combination. Certain organs keep back a definite amount of this circulating iodine, of which the thyroid gland retains the most in comparison with its weight, namely about 3 to 15 milligrams (0,04629 to 0,23145 grains) and, as a matter of fact, considerably more in summer than in winter, which fact explains in part the great divergency of the data that have been obtained. The iodine content in the blood indicates great constancy, which according to Veil and Sturm is 8,3 millionth gram in winter and 12,8 millionth gram in summer in every 100 grams of blood. As we see there is

here also a certain seasonal difference. The iodine, that has been introduced into the body, increases the iodine content in the blood rapidly, nevertheless this recedes rapidly, i. e. in 1 to 2 days, to its previous level.

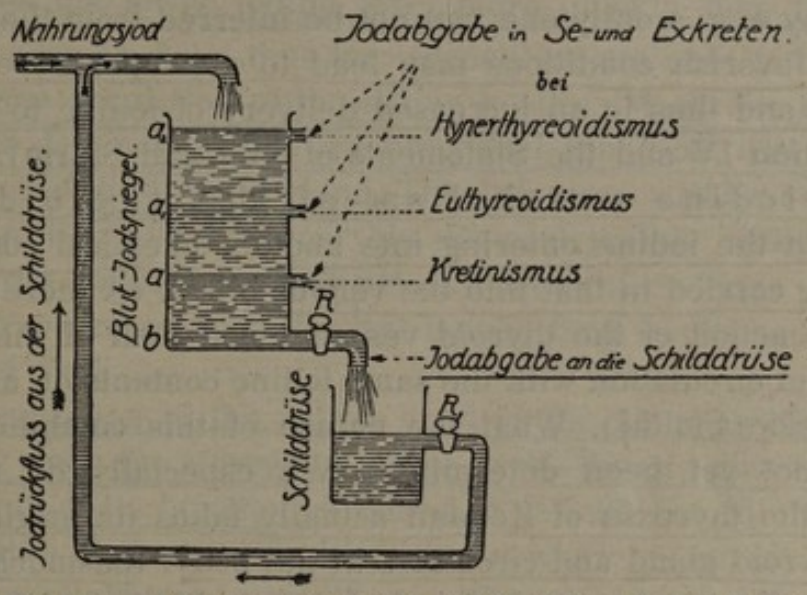


Fig. 3. Diagram of iodine circulation between blood and thyroid gland.

The more intensively the thyroid gland is at work, the greater the amount of the turnover of iodine, that is the further the regulation taps R and R' are opened, all the more the iodine content in the blood arises, with the help of an anatomic regulation of the threshold, — probably the restrictions in the secretion and excretion. Through this it is brought about, that in the blood a certain level will be maintained for the delivery of iodine to the thyroid gland. — The more rapidely we let turn the turbines in an electrical power-work, all the higher we must raise the surface of the water in the reservoir through the closing of the locks, in order to maintain the necessary pressure.

In the thyroid gland the iodine is immediately deposited into the stored-up colloid, since it remains within the cells only to a very slight degree. Glands, that are poor in colloid, are also poor in iodine, whatever may be their functional degree. An elementary consideration will now make clear that the continuous iodine output of the thyroid gland cannot surpass the input through the arterial blood. With the great quantity of blood passing through the thyroid gland — 30-40 times daily the total amount of blood, a delivery excess of 3 millionths of a gram per 100 grams would completely empty the gland in 24 hours. We can imagine that there is a certain periodicity in the secretion, nevertheless this can not reach any high degree, because the stock of colloid keeps very constant, as the histological investigations prove. It is only the hibernating animals, that manifest a very strong seasonal periodicity (evacuation of the gland in

winter). With human beings the differences between the amount of iodine in the blood of the general circulation and that of the thyroid venous blood, lie at present in the approximative limits of methods. (Operative manipulations of the gland!) A short evacuation period of the thyroid gland with increased delivery of iodine, say e. g. a daily one, can not be inferred from them. On the contrary feverish conditions may lead to a temporary evacuation of colloid and thus to an increased delivery of iodine to the blood (See Section IV and the Statements of Veil and Sturm).

The iodine metabolism of the thyroid gland consists in the iodine entering into another chemical combination and being carried in that into the venous blood. (A more energetic biological action of the thyroid venous blood than of the blood of the general circulation with the same iodine contents on an average [Branovacky, Smith]). What the nature of this combination may be, has not yet been determined. We especially do not know whether the thyroxin of Kendall actually takes its origin as such in the thyroid gland and circulates in the body. Inasmuch as there are also albuminous products of decomposition, which are free from iodine, that show thyroid action up to a certain degree, the iodine seems in reality to serve as an activator of this action.

Whether its presence is also as such necessary for the cell activity of the thyroid gland («Betriebsjod») has not yet been proved but can be imagined.

What are the deviations from this behavior, which become manifest in endemic thyropathy? According to the researches, which have thus far been made, the goiter tissue is relatively poorer in iodine than the normal thyroid tissue (Oswald, Kocher, Aeschbacher, Branovacky et al.), whereas the absolute or entire iodine contents of the gland in euthyroidal colloid goiters can exceed the normal iodine contents. In a general way goiters, that are poor in colloid, are poor in iodine. If Basedowificated strumas contain colloid, then their relative and absolute amount of iodine is high. The cretinous goiters are the poorest in iodine both relatively and absolutely, even if exceptionally large specimens may show a normal absolute iodine content. Through iodine therapy the iodine content of a goiter containing colloid can be increased manifold.

The iodine content in the blood is increased in a Basedow goiter (Veil and Sturm) and at the lower limit of the normal in euthyroidal goiters (Veil and Sturm and personal observations). In marked cretins with and without goiter the level

of the blood iodine is reduced to about the half (de Quervain, Smith) and, as a matter of fact, also in the normal iodine content of the food. The cretin excretes, however, artificially taken iodine more quickly than the normal individual, which signifies that he regenerates his lower iodine level more quickly than the latter.

From what we have thus far learned we are able to infer, that an automatic regulation of the iodine level exists in the blood and that this is dependent upon the functional condition, that is to say, the demand of the thyroid gland. This inference was first suggested by Veil in 1925, who had at his disposal mainly euthyroid and hyperthyroid goiter cases but not any cases of endemic cretinism. Our own researches with the last named have confirmed the conclusions of Veil.

The regulation of the iodine level in the blood is thereby not depending upon the storage of iodine in the thyroid gland but upon the intensity of its function. A Basedow patient, accordingly, shows a high iodine content in the blood, even when his supply of iodine in the thyroid gland is a small one. We can not speak here of the other factors, which have an influence (Veil) upon the degree of the iodine level. This level is regulated by means of the storage of iodine in the tissue and through the control of elimination of iodine in the secretions and the excretions. The latter manner is the more important. It allows the organism to absorb without any harm such quantities of iodine, which amount to some 200 000 times the daily requirements, and provides for their rapid elimination, excepting for the physiological necessities. Figure 3 shows us in a diagrammatic manner the circulation of the iodine between the blood and the thyroid gland. It makes clear how the level of the iodine in the blood is differently affected in the cases of hyperthyroidism, euthyroidism and hypothyroidism.

VII. Deviations from the classical Type of Functional Disturbances.

On this subject we shall in conclusion mention in short three conditions, which bear indirectly upon the problem of endemic thyropathy:

1. The nervous cretinism of McCarrison. This has been up to the present time observed in its typical form only in the Himalaya Mountains. It appears to be a combination of cretinism, tetany and Little's spasticity and, according to the observations of McCarrison, is due to the simultaneous injury of the thyroid

gland and the parathyroids. As far as we are able to judge at the present time, it can not be classified in the same category of phenomena as the increase of the tendon reflexes, which have also been observed by us in at least one half of the cases of cretinism.

2. The «instabilité thyroïdienne», as has been especially described by Léopold Lévi, i. e. the oscillating between euthyroidism, hypothyroidism and hyperthyroidism. In the aspect of the endemic goiter it plays no important rôle. The fluctuations observed in cases of struma Basedowificata take place more slowly than with the so-called instabilité thyroïdienne.

We must confess that we are a little skeptical as regards the oscillation of the thyroid gland between the two poles of the functional disturbance and that the accurate proof for such an interpretation of the clinical symptoms is not always given. At all events medical science must refuse to accept the responsability for the polypragmasy, which is at the present time infesting this domain. Numberless patients are being treated in every way with inner-secretory preparations, with whom a careful examinations yields no proof for an endocrine disturbance.

3. The simultaneous appearence of manifestations of superfunction and subfunction. This has been indeed often described, but till now it has not been proved with certainty. If this were to happen, then a relative dysthyroidism must be postulated. All of the cases, that have thus far been observed by us, were super-layers of goitrous cretinism with secondary Basedow, or the transition of a Basedow-complexus into secondary thyroid insufficiency, whereby the cardiovascular lability and the exophthalmos can outlast a long time as, so to say, fixed symptoms.

* * *

Conclusion :

1. The physiopathology of endemic goiter should cover all the morbid manifestations of the goiter noxa in the human body, not only the gross anatomical changes in the thyroid, to which the name of goiter is given.
2. The goiter noxa can affect the structure and functions of the organism,
   a) Indirectly by injuring the genital glands of parents and by functional inefficiency of the maternal organism.
   b) By direct action on the tissues of the body.

c) By injuring the thyroid gland either directly or by functional overwork.

d) By injuring the other endocrine glands, either directly or as a result of injury to the thyroid gland.

3. Taking clinical and experimental facts as a basis, we may divide endemic goiter into:

a) Euthyroid goiter with intermediate stages towards hyper- and hypothyroidism.

b) Hyperthyroid goiter. «Struma basedowificata» in its various forms among which that produced by iodine holds an important position.

c) Hypothyroid forms covering endemic cretinism in one of his clinical aspects.

4. In endemic cretinism are to be distinguished

a) Cretinism without goiter, always accompanied by atrophy of the gland and impairment of growth.

b) Cretinism with goiter, with various degrees of atrophy of the rest of the tissues and varying functional capacity of the goitrous tissue.

5. The striking disparity of the clinical manifestations in the two groups of cretinism may be accounted for by:

a) Hereditary factors,

b) Variations in the earliness and rapidity of onset of injury to the thyroid gland (seuil différentiel of Pézard and Gley)

c) Qualitative modifications of the secretion (relative and, perhaps, absolute dysthyroidism).

d) Primary or secondary involvement of other endocrine glands.

e) Direct, extrathyroidal action of the goitrous noxa.

6. The real extent of the connection in goitrous districts between the affections described collectively as benignant hypothyroidism (anaemia, headache, genital disturbances, enteroptosis, constipation, slight psychic anomalies etc.) and the goitrous insufficiency of the thyroid gland can only be determined empirically in individual cases by the result of treatment. The possibility of a slight dysthyroidism and that of an extrathyroidal action of the goitrous noxa have also to be taken into consideration.

7. The iodine content of the blood is maintained at a constant level within the limits of seasonal variations. The iodine content is determined by the degree of functional activity of the thyroid gland, and for a given intake of iodine is at its highest in Graves' disease, approximately normal in the case of euthyroid goiter and abnormally low in cretinism with or without goiter.

Pathological Physiology of Struma.

By Prof. B. Breitner, Vienna.

The discussion on the pathological physiology of goiter must necessarily presuppose the knowledge of the normal physiology of the thyroid gland. I do not need to emphasize the fact that we have not yet acquired that knowledge. Nor would it seem possible for one person to master this theme. For that reason I should like to make report on only a small section of this subject, to which most profound research attention was given at the Eiselsberg clinic. In order to have a better understanding of the nature of our labor, I should like to make the following preliminary explanations:

De Quervain has recently made a critical study of the numerous researches made on the functions of the thyroid gland and has supplemented these researches with a great amount of material used in all directions. We have occupied ourselves especially with the question of the chemism of iodine.

Notwithstanding the fact that Eugene Bircher and Albert Kocher have made it clear in a most convincing manner, that a great share of the chemism of the thyroid gland is also due to other chemical substances, the vast material, which concerning iodine has been collected for as much as a century, appeared to be more promising for a clarification of these difficult relations, which can be of course only an imperfect one for this reason.

From all that we have thus far ascertained concerning the chemism of iodine, de Quervain has drawn two possible conceptions: Either the iodine «is used only for the intraglandular function of the gland and remains in the gland» or «it is conveyed away as an ingredient of the active secretion and is continuously being replaced».

The question, whether any secretory process takes place within and without the thyroid gland, is accordingly not decided.

On discussing the methods, which are expected to lead to a conclusion, de Quervain establishes as a fact that «from a chemical point of view everything still continues to depend upon

the extractives from the entire gland, inasmuch as it is not possible at the present day to obtain the colloid isolated from the gland». And furthermore: «Whether the greatest part of the iodine is being stored up in the colloid or whether it is added to this only at the delivery of the secretion, we can not positively say from the comparative partial determinations made on the arterial blood of the thyroid gland as also on the venous blood of the same».

With these short quotations a circumscribed complexity of questions is laid down in the most modern conception and by the most qualified authority. I should now like to express my attitude to the same, which is founded on my own investigations.

As long ago as the year 1923 at my instigation Starlinger carried on research work at the Eiselsberg clinic to obtain evidence of a secretion through the testing of the blood of the arteries and that of the veins of the thyroid gland. This aim was not attained. But nevertheless some striking ascertainments along physico-chemical lines were discovered, to which I shall again refer.

In the year 1925 I took up these investigations again and this time I directed my attention towards obtaining evidence of iodine in the blood of the thyroid arteries, the thyroid veins, the veins of the arm and in the goiter substance.

In a number of struma operations blood was drawn from the above mentioned vessels and these different kinds of blood and also the substance, constituting the part of the gland removed operatively, were investigated with regard to the percentage of iodine present.

These tests were carried out by Mrs. Dr. Gundis Rotter, assistant in the II Chemical Laboratory of the University at Vienna, in accordance with the method of von Fellenberg.

The two tables here presented may serve to show you the results:

Table I*)

Clinical Type of Goiter			Presence of Iodine in
Hyperthyreoses, Morb. Basedow	Indifferent	Hypothereot	
0,04 γ; 0,15 γ; 0,06 ; 0,12 γ; 0,12 γ. = av, 0.098	0,05 γ; 0,1 γ; 0,19; 0,1 γ; 0,08 γ; av = 0.104	⊖	Artery of thyroid gland
0,05 γ; 0,05 γ; 0,04 γ; 0,1 γ; 0,15 γ; 0,2 γ. av = 0.098	0,02 γ; 0,15 γ; 0,1 γ; 0,2 γ; 0,15 γ. av = 0.144	⊖	Vein of thyroid gland
0,03 γ; 0,16 γ; 0,05 γ; 0,09 γ av = 0.082	0,05 γ; 0,04 γ; 0,1 γ; 0,11 γ; 0,12 γ. av = 0.084	⊖	Vein of arm
71,3 γ%; 44,0 γ%; 1198 γ%; 3401 γ%.	2310 γ%; 0,73 γ%; 575 γ%; 986 γ%.		Goiter substance

*) Only the positively reliable findings are entered here.

Table II

Morphological-functional Type of Goiter					Presence of Iodine in
Hypertrophically-Hyperrhoic	Mobilized Storage-Goiter	Eutrophically-hyperroic	Eutrophically-hyporhoic	Hypotrophically-hyporhoic	
0,15 γ.	0,075 γ; 0,1 γ; 0,12 γ; 0,12 γ; 0,16 γ.		0,06 γ; 0,19 γ; 0,1 γ; 0,15 γ.	0,05 γ	Artery of thyroid gland
0,05 γ; 0,04 γ.	0,15 γ; 0,15 γ; 0,15 γ; 0,2 γ; 0,15 γ; 0,2 γ.		0,05 γ; 0,2 γ; 0,1 γ; 0,1 γ; 0,12 γ.	0,02 γ	Vein of thyroid gland
0,03 γ; 0,16 γ.	0,05 γ; 0,09 γ; 0,12 γ; 0,13 γ.		0,05 γ; 0,04 γ; 0,1 γ; 0,13 γ; 0,11 γ;	⊖	Vein of arm
71,3 γ%; 44,0 γ%	2649 γ%; 2310 γ%; 1198 γ%; 858 γ%; 3401 γ%.		0,73 γ%; 575 γ%.		Goiter substance

A few comments on these tables are in order:

In the case of 7 patients only the thyroid arterial and venous blood could be examined satisfactorily.

Here, with strongly marked congested glands (Stauungsdrüsen) which manifested themselves as functionally indifferent or as slightly hypothyreotic, there was no iodine found in either of the two kinds of blood.

In those glands, which had to be designated as anamnestically and clinically «storage-glands (Speicherdrüsen) under iodine action» and which accordingly manifested hyperthyreotic symptoms, iodine was found in both kinds of blood, and the percentage of iodine was the greater in the blood of the thyroid veins.

A case of climacteric endocrinic disturbance with rudimentary thyrogenic symptoms showed the circulating blood of an epithelially inferior gland slightly positive.

In a 2nd group the proper investigation could also be made in the blood of the veins of the arm.

The iodine percentage showed the normal amount of 0,1 gr. of iodine in the case of perfect metabolic equilibrium with the clinically indifferent struma. It manifested itself as increasing from the blood of the veins of the arm by way of the arterial blood of the thyroid gland to the venous blood of the thyroid gland with previous iodine treatment of a colloid struma, which was followed by temporary hyperthyrotic symptoms.

In the 3rd group proper blood tests were obtained from the three vessels and the re-dissected goiter substance was also investigated. Here the following ascertainments could be made:

A number of cases, which were in part clinically indifferent and in part more poorly hyperthyrotic after the taking of iodine or in the beginning of a climacteric period, but all being diffuse colloidal strumas, showed, analogous to the cases of the second group an increase of the iodine level of the venous blood of the arm to the venous blood of the thyroid gland. The glands themselves were found to be of high potency regarding iodine (858—3401 γ %).

The second series of the 3rd group, cases of Graves' disease in the climacterium and of genuine Morb. Basedow, gave to the venous blood of the thyroid gland decreasing iodine values with a histologically typical Basedow struma ascertainment.

A more condensed summary of the findings gives us to understand that with euthyrotic storage-strumas iodine is found in every one of the three kinds of blood; that with strumas, that

are characterized functionally as of superior worth, the blood of the veins of the thyroid gland is richer in iodine and that these euthyrotic and hyperthyrotic storage goiters have a parenchyma, that is very rich in iodine.

Even from this circumstance alone the fact that there is a delivery of a secretion containing iodine into the circulation of the blood could be understood. That iodine is also met with in the veins of the body and in the arteries of the thyroid gland, is self-evident if we take into consideration the way to the place of accumulation, the «Thyroid Gland». That it, however, if determined at the same time, predominates quantitatively in the blood of the thyroid veins in all cases, is proved by the fact of delivery.

I come back to the quotation from de Quervain: «The inference of a secretion of iodine from his estimation in the arterial and venous blood of the thyroid gland is taken exception to. For the percentage of iodine ought to be the same in both kinds of blood, making allowance for small fluctuations, if either a lack or an excess of iodine is to appear in the gland in a very short time». This is certainly correct, if we do not take account of the stock of iodine in the gland. With the great reserves of iodine of the parenchyma of the colloidal struma, of which it is really a question here, the process of flushing without a rapid loss can be positively understood. This applies all the more if we take into consideration the minuteness of the quantity; which is several hundredths of a milligram.

The investigation of the venous blood of the goiter simply from a chemical and «biological» point of view (Hara, Branovacky) does not prove the process of secretion, since iodine is found also in the other kinds of blood. The proof is rather to be found only in the constant difference of the quantities. Analogous to the methods of examination of the biological efficacy, as has been carried out by the Swiss authors (Abelin, Wegelin et al.) and especially by the school of de Quervain, Hoche has instituted at the Eiselsberg clinic some feeding experiments with salamanders. In these there was no separation of the kinds of blood according to the clinical aspect. Nevertheless more than 85 % fall to euthyrotic and hyperthyrotic colloidal strumas, so that the result can be applied only to these.

It is as follows:

The material, constituting the goiter, exercises an influence that checks development and accelerates the differentiation and the metamorphosis, just as is the case with the substance of the thyroid gland in the feeding of salamander larvae.

The same effect, as far as the differentiation and growth are concerned, falls to both kinds of blood, viz., to the thyroid arterial blood and the thyroid venous blood, but with the difference, that it is more plainly pronounced in the case of the thyroid venous blood. The metamorphosis appears considerably less accelerated in comparison with the effect of goiter substance.*)

From this we may above all conclude for the problem, which comes here into question, that the specific action of goiter substance exerts also an influence on the blood of the thyroid gland. As this applies likewise to the thyroid artery, it must be taken for granted that there is also an essential factor of the secretion, that is considered as being peculiar for the thyroid gland, contained in the arterial blood of the thyroid gland. This can in the main be only iodine in accordance with our representation. Now it is clear to us on the one hand that the iodine must reach the thyroid glands by way of the arteries. The thyroid arterial blood gives also indications of a measurable proportion of iodine. On the other hand the researches of Abelin, Nagel and Swingle have shown that we are able by means of iodine alone to obtain a similar effect in reference to the metamorphosis as by means of the thyroid substance. Here also it becomes clear that iodine must be the chief efficacious agent. Inasmuch as the efficacy of the thyroid venous blood in the cases taken as a whole appear to be biologically of a higher grade than that of the arterial blood, it seems that here its greater proportion of iodine and with this the fact of a flushing of iodine is found in the supplies stored in the gland.

The results of the biological examination run parallel with those of the chemical analyses. The proof seems to have been given of secretion conducted into the blood with iodine as the essential component of this secretion.

However, the cases of endogenous genuine M. Basedow show low iodine values in the thyroid venous blood and in the thyroid substance. This is probably possible without having any deleterious

*) The experiments were carried out in *Professor Fischl's* institute.

effects from one to the other. If there is a lack of the material for the flushing, it can not be expected in the circulating blood.

The condition of hyperthyrosis, however, can not be explained here by the fact of a predominant secretion. It is only the abnormal constitutional secretory susceptibility of the individual or the functional co-participation of other endocrinic organs or the co-operation of these two factors, that can contribute to a proper understanding.

The secretion of the genuine Basedow gland does contain iodine. The proportion of iodine is strikingly low. But with the special constitution of the individual these low iodine values suffice for the incitation of the hyperthyrotic symptoms.

In this representation the apparently proved secretory process can still be retained.

But new difficulties make their appearance. These are to be found in the possibility of influencing the aspects of disease by means of the intake of iodine.

The rendering the condition worse through the use of iodine in the case of mobilized storage goiter can be readily understood from what has thus far been said. The secretion, which is anyhow of high value, experiences an increase in the amount of iodine, some more secretion can still be activated and the supply of iodine in the gland can be replaced. This is an easy representation, that in only one point requires a limitation later.

The possibility of influencing the aspect of disease favorably in the case of the genuine Basedow goiter through the intake of iodine in accordance with the ideas of Neisser, Zondek, Plummer and Boothby, — becomes an enigma, if we assume the existence of a secretion, that contains iodine.

If with the special susceptibility of the individual to secretory influence the slight iodine quantities in the thyroid venous blood are really sufficient to incite the aspect of hyperthyroidism, then this would necessarily be the case to an increased extent with an intake of iodine. The fact of the secretion seems therefore to be inconsistent with the fact of the favorable efficacy of iodine.

With this the assumption of a localized action of iodine in the thyroid gland would receive support and the theory of secretion, as just now presented, would be discarded.

But the expression of the «slight iodine metabolism», which has up to now been customarily used, must also be dropped. Iodine, which «primarily stimulates the thyroid secretion» (Wegelin et al.), can not be a remedy against hyperthyrosis.

Here the experiments on animals are of service to us. Together with Orator I endeavored to discover the morphological expression of the iodine action in the thyroid gland of the animal experimented upon.

For this purpose a thyroid gland is necessary, the function of which is not normal, for it is well known that the normal thyroid gland can not be appreciably affected by the intake of iodine (Oswald).

The functional disturbance was hoped to be brought about through violent changes as to the removal of the secretion. We therefore took up first of all my experiments of the year 1912. As I can not presume that these experiments and the conclusions deducted from them, which deviate from those inferred by des Ligneris from similar experiments, are familiar to my hearers, I beg you to pardon me if I give a short description of them here.

If the half of a thyroid gland of a dog is extirpated, a plain diminution of the colloid contents in the remaining lobule will be noted. If we give the animal, experimented upon, thyroid substance after the extirpation of the half of the gland, then the colloid contents in the untouched half will be quite unchanged.

These two series of experiments were re-examined by Hedinger in 1922 and confirmed by him. In the year 1913 Blauel and Reich made known their important experiments on rats: If the trachea of a rat is carefully constricted by means of a silk thread, then after a few days a clear colloidal overfilling of the thyroid gland becomes manifest. In 1923 I repeated these experiments with Orator. The results agreed completely with the original experiments, which have since that date been appreciably and valuably expanded by Deucher at the Clairmont clinic in Zurich.

It was quite natural to combine the two series of experiments; semi-lateral extirpation and tracheal stenosis in one act. Then we find the following: The colloid increase, which regularly sets in with artificial tracheal stenosis, does not take place if at the same time a lobule of the thyroid gland is removed.

It is, therefore, seen that we can influence the colloid contents of the thyroid glands of the dog and the rat, by means of experimental manipulations, in such a way that either a stasis, a retention or a flushing is attained. Of the aspect of the cell nothing will be said here.

These limiting cases of engorgement and flushing have induced us to make use of the terms of hyporhöe and of hyperrhöe for the rapid characterization of the condition.

Through these experiments there was accordingly the term «congestion of secretion» (hyporhöe) and «flushing of secretion» (hyperrhöe) coined for an ascertainment, which could be produced at any time in experiments on animals.

As a result of these experiments we can first of all declare:

The thyroid gland of the normal animal gives evidence on an average of an ordinary amount of colloid. If the places, in which the colloid is produced, are very much diminished, then the stocks of colloid in the gland dwindle away. The same happens if I put the organism of the animal under experimentation into the condition of increased metabolic changes. Or in other words:

Each and every form of increased demand on the thyroid gland is answered with a flushing of colloid.

That the nature of this experimental method is with right considered to be an increasing of the secretory requirement, becomes evident from the fact that the flushing away of colloid does not take place with the intake of thyroid substance per os.

The simplest formula, resulting from these experiments, is accordingly:

A lack of colloid in the gland corresponds to an increased secretory requirement of the organism.

The second experimental method, the constriction of the trachea according to Blauel—Reich, puts the animal that is being experimented on into a condition of depressed metabolic change, with which the constriction of the secretory demand goes hand in hand. The effect of this condition upon the colloid contents makes itself manifest in the great increase of the latter.

Here again it was required to show that the aim of the experimental method lies really in the reduction of the secretory requirements. The proof of this could be carried out in that the increased secretory delivery, that was forced experimentally, counterbalanced the colloid stasis. In simple language therefore it may be said:

Restriction of the secretory requirements in the organism is accompanied by colloid engorgement in the gland.

The next step in order was to make a test of the action of iodine upon these two conditions. The results were as follows:

If we supply iodine to a rat after semi-lateral extirpation then the flushing of colloid from the remaining lobule does not take place. If, on the other hand, we deliver iodine to a rat with artificial tracheal stenosis, colloid engorgement will not happen. In other words: By means of the supplying of iodine the experimentally forced hyperrhöe is checked or it becomes a light hyporhoe; the hyporhoe, that is brought about experimentally, becomes hyperrhoe.

This influencing of hyporhoe and hyperrhoe through the intake of iodine has received its clinical and recently its experimental confirmation: De Quervain and Garré could lay down as a fact that through the intake of iodine the colloid of the struma colloides is mobilized and removed. Hellwig has also shown, that the intake of iodine in the hyperrhoic goiter causes colloid stasis. With this the consonancy of the results in the experiments on animals and in the observation in human beings was established.

The noteworthy fact in the clinic and in the experiment was the effect of the iodine treatment.

This antithetical behavior of the iodine action I was only able to explain through the antithetical functional condition of the particular thyroid gland. For this reason I have employed for the characterization of this condition the designation «functional tendency».

The effect of the intake of iodine ensues contrary to the functional tendency of the gland.

If it is a question of a gland, that is forced to an increased secretory flushing, then the iodine acts secretorily restraining and vice versa.

The fact of this mode of operation explains quite easily the results of the dispensation of iodine in the case of the different forms of struma: The eutrophic storage goiter is mobilized, the organism takes in secretion to excess, the hyperthyrotic symptoms make their appearance. In the hyperrhoic goiter the removal is held back, the secretory flushing of the organism is kept in check and the hyperthyrotic symptoms dwindle away.

With this view the undisputed favorable action upon genuine Basedow goiters alone does not coincide, but also the fact, which at first seems so strange, that endogenously mobilized storage goiters are also influenced temporarily through iodine in a favorable manner. Iodine acts upon the latent storage goiter in a secretorily mobilizing manner, that is, injuriously from a

clinical point of view. That is the current procedure with iodine Basedow. It acts primarily in a secretorily obstructive manner upon the storage goiter, which has reached the stage of increased flushing.

It is at all times the functional tendency of the gland, which determines the manner of iodine action.

With these facts the secrets of iodine therapy are in part cleared up. But the secretory theory, which seemed to us to have been proved, can not be so easily brought into correspondence with it. Hence it is very probably for this very reason essential that we make clear to ourselves the processes concerning which we can have no doubt.

If we therefore are looking for the explanation of these facts, we must take into consideration the general iodine action and the particularity of its influence upon the regulating nervous system of the thyroid gland.

H. H. Meyer has established the fact that physical-chemical reactions of living cells run more easily in the direction of the position of normalcy than such that deviate from it. H. Januschke sees here the explanation for the fact, that has been determined experimentally and clinically, that «occasionally a super-functionating organ responds to iodine treatment with a lessening of the function, whereas a sub-functionating organ, on the contrary, responds with an increase of function».

The results of the researches on the basal metabolism in the case of hypothyrotic and hyperthyrotic strumas under iodine action which have been determined by Liebesny give the same story. Iodine therefore appears at one and the same time to be a sedative and also a stimulant. This to a great extent certainly depends upon the dosage. (Neisser, Goldscheider, Rosenow). The second essential factor, however, lies in the functional tendency of the organ.

This functional tendency can be determined either «glandularly» or by the organism as a whole, or both of these ways are possible.

By «glandular requirement» we must understand, that the regulators of the function of the thyroid gland are suffering from some equilibrial disturbance. For this the «Psychic M. Basedow» would serve as an example. The dependency of the formation and removal of secretion on the autonomous nervous system can be considered as proved (Adlersberg, Porges, Reinhardt, Glaser, A. Kocher, Liek, Ostwald et al.).

Recently Susani has pointed out the significancy of the equilibrium of the function of Vagus and Sympathicus for the two component elements of the activity of the thyroid gland, production and removal. The stimulating condition of the sympathicus increases the secretory flushing from the gland, that of the parasympathicus obstructs the removal. The participation of the system, that is under increased stimulation, accordingly determines as regards hyperrhoe or hyporhoe (Susani). This it is, that I have designated as « functional tendency ».

These equilibrial disturbances of the nervous regulators, which have a primary and immediate effect upon the gland, would represent the aetiological moment with the psychically incited glandular M. Basedow (Eppinger and Hess).

The iodine effect is evident: changes in the tendency towards normalcy, a sedative action upon the increased stimulative condition, a restrainment of the increased removal ability.

But the increase in the removal or restraining ability is also furthered through the requirements of the organism. Here also the method can be a two-fold one. It can take its course through the endocrine system. In favor of this are the forms of M. Basedow, which stand in correlation aetiologically with other endocrinic disturbances. This reaction for endocrinic changes of function can come about by way of the nervous system or by way of the circulation of the blood with the help of the « chemical courier ». For this latter possibility we see the case of Eiselsberg, that has become so famous, in which a thyroid metastasis in the sternum of a woman gave evidence of fluctuations as regards the element of size at the time of menstruation. If now in the endogenous manner an increased secretory flushing is required by the thyroid gland, then this develops its stimulating effects upon the sympathetic and parasympathetic system (Asher, Flack, Eiger, Wegelin). The iodine action is therefore also to be understood in this case. In the same way it develops ultimately its influence upon that disturbed activity of the thyroid gland, which is incited through a general metabolic increase.

The action of iodine is in all cases analogous. The primarily or secondarily increased sympathetic tonus is reduced, the flushing of the secretion is restricted, the hyperthyrotic symptoms are rendered more mild or are made to disappear.

If we now were to ask, whether from this point of view the secretion theory is nevertheless tenable, then we can reply with a convincing affirmation.

The increased secretory flushing in all of the forms of Morb. Basedow follows on the basis of the primarily or secondarily increased sympathikus tonus. If iodine is dispensed as a medicament then it develops its action as in every case of nervous equilibrial disturbance at the part of the system that is under the stronger stimulation. This will lead to the retention of the secretion in the case of the hyperrhoic gland. That quantity of iodine, which gets into the thyroid gland at the same time, can therefore not get into action as a higher basic value of the secretion, inasmuch as the secretion is being retained in the gland. If this representation is the correct one, then the transformation of the hyperrhoic into the hyporhoic gland, as was shown by Orator and myself, must also make its appearance in the case of Morb. Basedow.

For the hyperrhoic adolescent struma this stands confirmed through numerous observations. For the Basedow struma Rienhoff, Jr., in Baltimore and recently Schürer-Waldheim at the Denk Department have given the positive proof. The intake of iodine changes the hyperrhoe of the genuine Basedow goiter into hyporhoe.

In the reflection the endogenous aetiology and the nature of the iodine action in the hyporhoic cases appear among the strumas under parasympathetic stimulation.

In consideration of the pathological physiology of the strumas we can conclude that, irrespective of the adenoma structures, the changes in the thyroid gland constitute the expression of a reaction of the organ upon general or local processes of the entire organism. Bircher expressed this in the following manner: «Goiter is a symptom of a generally changed affection of the somatic health condition of man.» In the normal organism the secretory regulators of the thyroid gland are in a state of labile equilibrium. If this equilibrium is disturbed through physiological moments, such as puberty, ovulation, etc., then a participation of the system will gain ground. This will lead to the incitement of the «functional tendency» assisted by this participation of the system (sympathetic, parasympathetic).

The disappearance of the physiological phenomenon, which was originally inciting, leads in the normal organism along the way of self-regulation to the restoration of the equilibrium.

If it is a question of an individual with inherited or acquired inferiority of the nervous system, then there are no functional variations, and either the «tendency», that either checks or increases removal makes its appearance.

Now the action of the thyroid secretion, that is either «too little» or «too much», sets in with all somatic consequential conditions. A «spontaneous cure» does not take place here through the constitutionally insufficient spontaneous regulation, but through the consumption of the real secretion.

Through this way the circulus vitiosus is fenestrated by increased flushing and through that by increased tonicity, the antagonist is strengthened and the secretory flushing recedes.

The medicinal supplying of iodine takes over the mechanism of this «spontaneous cure» under the direct influence of the regulators of the function.

This collective acting of the nervous regulating of the thyroid secretion and the effecting of the thyroid secretion in the organism is therefore the real aetiological moment of all strumas, which for this reason are to be estimated throughout as functional.

all contrô
functional

The disturbances of the equilibrium may also be occasioned through enteral injuries, besides a primary nervous alteration, or through a quantitative change of the conveyance of the most important secretory component element, the iodine. The fundamental method of procedure remains the same.

The representation of the function of the thyroid gland as that of secretory production and secretory removal, which I for the first time stood for in the year 1912, provides the key for this idea; the explanation of the colloid as immature thyroid secretion; the representation of the iodine action upon hyperrhoe and hyporhoe in the experiments on animals.

Their value in new series of experiments, which I mentioned before, led to the strict assertion of a genuine secretory method of procedure in the thyroid gland with iodine as the most important internal ingredient; it led besides to the clinical and physical-chemical characterization of two main forms of hyperthyroidism, with which the division of Chvostek was obtained in another manner.

Even this description is certainly no revelation of the real nature, but only another point of view.

There is no doubt that the hyperthyroses represent the main problem of the pathological physiology of the strumas. And it is just as little a question of doubt, that we are in this matter just at the threshold of a practicable insight here. It is possible that my researches, as reported on here, can be accepted as a small contribution towards the solution of the many problems. I should feel honored if I have been able to perform this service within the

sphere of this important Congress of the Vienna School and above all the Eiselsberg School.

* * *

Conclusion :

1. A comparison of the iodine content of the blood of the arteries and veins of the thyroid and the veins of the arm with that of the goiter appears to prove the existence of a thyroidal secretion escaping into the blood current.
2. Results of experiments made by infusing specimens of blood from these different sources into the larvae of salamanders point in the same direction.
3. Verified facts show that hyperthyreoses may be divided into two groups, a method of division which corresponds in a general way with that of Chvostek.
4. These observations are further in complete agreement with the morphologico-functional types conditioned by «hyporhoe» and « hyperrhoe ».
5. The action of iodine on those suffering from goiter correponds to that which has been observed by experiments on animals, which proves that a careful selection should be made of subjects who are to be treated with iodine.
6. This point of view is based 1.) on the appreciation of the two principal functions of the thyroid gland, namely the production and the elimination of secretion and on the functional adaptation of the gland, and 2.) upon the discrimination between the activity and the output of this organ.
7. Bearing in mind the rôle of the trophic nervous system in the secretory process of the thyroid, the point of view which we here set forth enables us to establish a complete theoretic schema of the functional affections of the thyroid.

Results

of chemical and histological researches on the nature and significance of Jodine in the thyroid gland and in the goiter.

By Albert Kocher, Berne.

We are giving here only the results of our researches which are to be published in extenso elsewhere.

We have examined 256 goiters of various types and 8 thyroid glands of a goiter-free region.

We have investigated the total amount of iodine present, the quantity of albumine present and its iodine content. We can therefore say how much of the iodine present is organic and how much is present as iodine salt. It was exactly investigated whether any iodine had been given before we examined the gland or goiter and the effect of the iodine administered was clinically well established, as to the change in size of the goiter and especially as to the eventual toxic symptoms produced by the iodine administration. Besides pieces of the gland or goiter were used for histological examination.

We first found that the average total iodine content of a nodular goiter when surely never before the examination (1) iodine had been given to the patient, the goiter was from, was lower than the average total iodine content of a normal thyroid gland. The iodine content per gramme of fresh goiter was much (2) lower than the iodine content in one gramme of a normal thyroid gland. Whilst the average total iodine content in a diffuse colloid (3) goiter, even when no iodine had been given to the patient, was higher than the total iodine content of a normal thyroid gland, but the iodine content per gramme of fresh diffuse colloid goiter was (4) usually found lower than the iodine content per gramme of normal gland. The total iodine content as well as the content per (5) gramme of a diffuse parenchymatous hyperplastic goiter was found very low, also when it was from a toxic case (Graves'). Whilst the (6) iodine content of a toxic colloid goiter was found much higher than the average total iodine content of a normal thyroid. Amongst the normal thyroid glands examined it was found that the glands from (7) people living on the seashore contained more iodine than the gland of inland inhabitants. The average total iodine content

of the former being 7.23 milligrammes, of the later 3.76 milligrammes.

Further on, investigations have shown that the iodine content of the normal thyroid gland as well as of the goiter is much higher, (8) when iodine has been given to the subject immediately before examination, than if no iodine had been given. This was found in all different forms of goiter.

In a normal thyroid gland of a subject having been treated immediately before death with iodine, we found a total amount of iodine of 12.0 milligrammes and per gramme of fresh gland 0.33 milligramme.

In nodular goiters (adenoma) having surely never been given iodine we found an average total iodine content of 0.91 milligramme (0.025 milligramme per gramme of fresh goiter) whilst in those that had iodine, the average total amount of iodine was 8.66 milligrammes (0.122 milligramme per gramme of fresh goiter).

In colloid goiters having surely never been treated with iodine, the average total iodine content was found 8.03 milligrammes and 0.104 milligramme per gramme of fresh goiter, whilst in colloid goiters having been treated with iodine preparations, the average total amount found was 20.96 milligrammes (0.28 milligramme per gramme of fresh goiter). Exophthalmic goiters never treated with iodine showed an average total iodine content of 5.87 milligrammes (0.166 milligrammes per gramme of fresh goiter). Exophthalmic goiters treated with iodine showed an average total iodine content of 24.20 milligrammes (0.338 milligrammes per gramme of fresh goiter).

If we examine a normal thyroid gland or a goiter some time after iodine had been given to its bearer, we find the iodine content again lower than immediately after. This shows that the normal (9) gland as well as the goiter eliminates its iodine content partly.

There is however a very noticeable difference in the iodine content of a goiter according to the action the iodine has on the goiter clinically. Goiters that are reduced in size by the administra- (10) tion of iodine contain much less than those that are not.

The average total iodine content of a diffuse colloid goiter never treated with iodine is 8.03 milligrammes and 0.104 milligramme per one gramme of fresh goiter. If treated with iodine before the examination the average total amount of iodine is 29.09 milligrammes or 0.311 milligramme per gramme of fresh goiter, when the size of the goiter is not changed after iodine intake. If on the contrary the goiter gets distinctly smaller after the use of iodine

the average total iodine content is 11.70 milligrammes and 0.138 milligramme per gramme of the fresh goiter, if no toxic symptoms arise. There is a very noticeable difference in the iodine content, if toxic symptoms are produced by the administration of the iodine. If toxic symptoms arise the average total iodine content of the goiter is 19.01 milligrammes and 0.470 milligramme per gramme of fresh goiter, although the goiter is much reduced by the iodine administration. The difference is more especially noticeable in the iodine content per gramme of the fresh goiter. (11)

If we examine the glands of Jodbasedow (Kocher)-cases, even when no iodine has been given for a lenght of time, their iodine content is high: being 21.85 milligrammes in the total gland and 0.262 milligramme per gramme of fresh goiter (see table).

	Average total iodine content	average iodine content per gram fresh substance
Goiters treated with iodine before examination and reduced in size by the treatment	11.70 mgr.	0.138 mgr.
Goiters treated with iodine before examination not changed in size	29.09 mgr.	0.311 mgr.
Goiters treated with iodine some time ago and increased in size since	16.20 mgr.	0.135 mgr.
Goiters treated with iodine before examination, reduced in size but having caused toxic symptoms	19.01 mgr.	0.470 mgr.
Goiters never treated with iodine before examination	8.03 mgr.	0.104 mgr.
Goiters of patients having contracted Graves disease by the use of iodine	21.85 mgr.	0.262 mgr.

Histologically we find that goiters with much eosinstained colloid contain much iodine whilst those with little colloid contain much less iodine. However there is no absolute proportionality between the quantity of iodine and colloid present. The goiters treated with iodine, but not reduced in size contain a great quantity of eosinstained colloid whilst those reduced in size by iodine intake contain very little or no colloid. We can say that in the latter cases a great quantity of colloid has been secreted from the gland causing however in the majority of cases no toxic symptoms at all. (12) (13)

The most stricking histological difference between a goiter containing much iodine and one containing very little is not the amount of colloid present, but the size of the gland follicles. (14) In a goiter containing a great quantity of iodine we find large follicles in great quantity and only a few groups af small follicles whilst in a goiter containing little iodine nearly all follicles are small. The epithelium of the large follicles being cubical or flat, the colloid thick, dark and compact. The epithelium of the small follicles being higher, colloid also present in nearly all small follicles but not compact and lightly eosinstained. But a goiter much reduced in size by the iodine administration shows histologically also the follicles in the greater majority small, the epithelium high, but the greater majority of the follicles contain no colloid. Thus the most striking difference between a goiter never treated with iodine and a goiter much reduced by use of (15) iodine is the difference in the quantity of colloid present. The more reduced the goiter is by the intake of iodine, the more small follicles without colloid are present. In the normal thyroid gland iodine intake causes an increase of eosinstained colloid and if this increase of colloid is considerable the epithelium (16) is flattened and damaged. The same increase of colloid and flattening and damage to the epithelium takes place in those cases of Graves' disease that are improved by iodine intake (Lugol). Such improvement takes place especially in small or smaller glands in Graves' disease.

Our investigations of the quantity of albumen present and of its iodine content, compared with the total amount of iodine present show that not all the iodine present in the normal (17) thyroid gland and in goiters is organic.

The quantity of albumen present varies a great deal in the (18) normal gland and more so in goiters. In the whole relatively little albumen is stored. When much colloid is present more albumen is found. However there is no proportionality between the quantity of albumen and colloid present. Colloid goiters, diffuse and nodular, contain the largest quantity of albumen, while parenchymatous and exophthalmic goiters contain the smallest quantity of albumen. It is very noticeable that exophthalmic goiters contain (19) little albumen even when much colloid is present.

The iodine content of the thyroidalbumen varies like the total iodine content in the normal and goitrous thyroid. There is no (20) proportionality between the quantity of iodine and of albumen present and what is more impor-

tant there is no proportionality between the total amount of iodine present and the quantity of iodine in the albumen. Therefore the iodine content is no index of the albumen present in the gland or goiter. Sometimes the total iodine content of a goiter can be found very high, although the albumen present contains only a small quantity. This is the case for instance in a goiter treated immediately before examination with iodine but not reduced in size and causing no toxic symptoms. We find the same in exophthalmic goiters treated with iodine (Lugol solution) and improved by it. We find here much colloid but little albumen containing little iodine.

As we have shown above, the content of anorganic iodine increases in the normal thyroid gland in goiters when iodine is given before examination, but the amount of organic iodine does not increase proportionally. We find the amount of iodine in the albumen (Thyreoglobulin) varying with the clinical feature of the case. In a goiter having been reduced in size by iodine treatment we find, when no toxic symptoms are produced by the treatment, the iodine content of the albumen (Thyroglobin) normal, whilst when toxic symptoms are produced the amount of iodine in the albumen is very high. This shows that the toxic symptoms do not depend as much from the total amount of iodine present in the gland, as from the quantity of organic iodine in the albumen. When a goiter is much reduced in size by iodine intake large quantities of colloid containing much anorganic iodine and much albumen can be eliminated (poured in the circulation) without causing any toxic symptoms, as long as the albumen does not contain much iodine (is hyperiodized).

The results of these researches throw new light on the significance of the thyroid colloid, the thyroid albumen and especially the thyroidiodine.

The question whether the thyroid colloid as such represents the total secretion of the thyroid gland has not been hitherto solved. Recent histological findings by Williamson and Pearce make it doubtful.

Anderson and Galeotti already presumed two different secretions in the thyroid gland. Müller, Lobenhofer, Bensley and Kraus admitted that the colloid is secreted in liquid form from the cells into the follicular space and thickens there. Kraus and Guillebeau admit a dissolution of the epithelial cells to form the colloid, whilst Wegelin speaks of an active secretion of liquid colloid from

the cells into the follicular space, without dissolution of cells.

We also do not know exactly how the thyroidsecretion, it is the colloid, is secreted into the blood- or lymphvessels, the colloid-like looking substance in the blood- and lymphvessels being not identical to the thyroidcolloid. Hürthle and Matsunaga suppose that the follicular colloid is secreted through intercellular spaces and lately Matsunaga, Williamson, Pearce and Fitzgerald demonstrated intracellular tubules or microcapillaries, distended in cases of hypersecretion. Wegelin, Breitner and Cowdry admit an active secretion backwards through the epithelial cells into the blood- and lymphvessels.

It has not as yet been proved that, what we call histologically, colloid represents really a chemical unity, it is the total secretion of the thyroid gland, and whether it represents really the storage of a thikened secret, being liquified and secreted into the lymph- and bloodvessels according to the demand of the organism.

Macroscopically, it is physically, the colloid is found very different. From the sticky, glutinous, jellylike to the quite liquid thin waterlike colloid, we find all transitory forms. Histologically we find a difference between the colloid in the centre of the follicles and in the periphery, the latter being lighter stained with eosin or van Gieson than the colloid in the centre of the follicular space. Also one finds in the thyroid in some of the follicles colloid stained with eosin and in some others stained with haematoxylin. Troell has lately shown that the thik colloid stained with azocarmin Mallory is red, the thin colloid blue.

Our investigations also show that thyroid colloid is not a chemical unity. Evidently it does not consist of Jodalbumen alone. Iodine is also present in inorganic form. Colloid output does not always mean hypersecretion, we can observe a extensive secretion of colloid causing no hyperthyroidism. The storage of colloid is of importance for the thyroid function, but more so the formation and secretion and especially the amount of iodine present in the thyroalbumen.

On the Coagulation of the Blood in Strumas, in Myxoedemas, in Endemic Cretinism, in Basedow and on its Susceptibility to Influence through Thyroid Extracts and through Iodine Compounds.

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I.

For the study of the coagulation of the blood in conditions of the pathological behavior of the thyroid gland, I made use of the methods for the investigation of the coagulation of the blood, which were described by me some time ago. My researches covered the coagulation time, the interval of time from the moment when the blood was taken from the blood vessel to the moment of complete coagulation, the so-called valence of coagulation, the behavior of a special kind of blood in the face of increasing states of concentration of a substance tending to prevent coagulation, of magnesium sulphate, furthermore the tensile strength, the determination of the laceration weight of the white thrombus by means of the thrombometry mentioned by me and finally also the retraction of the red thrombus. The description of the various methods can soon be looked up in the «Manual of Normal and Pathological Physiology»*) in which I have classified the complete methodology concerning the investigation of coagulation. It would lead too far to enter upon the details now.

The time of coagulation is stated in minutes, the coagulation valence is designated as V and v. It states the degrees of the concentration of magnesium sulphate, at which the examined blood still coagulates completely. The figures indicate the respective percentages of the concentrations. The tensile strength is indicated as g: the moment when the thrombus plate under tension snaps, the laceration weight is read off and thus the tensile strength is indicated. The retraction is stated in millimeters. This shows the height of the column of fluid (serum) from the upper edge of the retracted coagulum to the level of the fluid. It is read off on the retractilometer after 24 hours.

*) Handbuch der normalen und pathologischen Physiologie, volume VI. Published by Julius Springer, Berlin.
Likewise: Schweiz. med. Wochenschrift, No. 7, 1921, and No. 2, 1923.

The data pertaining to normal blood, as defined from a great number of analyses, are:

Time of coagulation 25' to 32'
Coagulation valence V 1,5 v to 4,5
Tensile strength 250 to 350 gr.
Retraction 6 to 8 millimeters.

Adopting this method I have investigated more than 100 cases of struma and conditions of modified thyroid activity and have classified the results in the following manner:

1. Struma with apparently normal somatic behavior.
2. Struma with symptoms of hypothyroidism.
3. Struma with symptoms of hyperthyroidism.
4. Myxoedema.
5. Endemic Cretinism.
6. Basedow.

In the second chapter of my declarations I then compared the results of the examination of the influence of thyroid preparations on the coagulation of some of these conditions and also on normal people. These preparations were taken per os, some contained iodine, others were without iodine. I also grouped here the results of the influence of inorganic and organic iodine compounds and finally of iodine itself, after the reaction of these individual preparations on the blood had been ascertained in vitro. With these researches I wished to ascertain, whether the changes in the coagulation with the various conditions of altered activity of the thyroid gland are caused by the amount of these preparations contained in the blood or by their products of decomposition and whether the amount of iodine contained in these preparations is in any way decisive. Is the behavior of the coagulation in these conditions of altered pathological activity of the thyroid gland due to the amount of thyroid gland secretions contained in the blood or is it here a question of other factors not yet known to us?

I.

The Coagulation with Struma and with Conditions of modified Thyroid Activity.

1. *Conditions of Coagulation with Struma.*

In 31 cases investigated:

The time of coagulation was:

in 5 cases more than 40'
in 11 cases more than 32' . . . prolonged (16),
in 12 cases between 25 and 32' . . . normal (12),
in 3 cases under 25' . . . . . shortened (3).

The coagulation valence shows normal values:

V 0,5 to 2,5 v 1,5 to 4,5,

but nevertheless with the tendency to be rather lower than normal.

The tensile strength amounted:

in 16 cases 250 to 350 g. . . to normal values,
in 13 cases below 250 g. . . to reduced, though insignificantly,
in 1 case more than 350 g. . increased.

Their values correspond approximately to those of the coagulation time.

In about one half of the cases we meet with normal values. The other half comprises reduced values, the increased values constitute a small minority.

2. *Struma with Symptoms of Hypothyroidism.*

There were only 5 cases of moderate hypothyroidism coming under investigation, so that no positive conclusions can be drawn from these few cases. The data concerning coagulation time vary. The coagulation valence has the inclination to rise, the tensile strength likewise.

3. *Struma with Symptoms of Hyperthyroidism.*

There were 11 cases examined. The values of the coagulation time are normal in most of the cases. In one third of the cases it was prolonged. In no case was it shortened. There, accordingly, is a tendency towards the prolongation of the coagulation time. The values of the coagulation valence have a tendency to go down, and the same applies to the values of the tensile strength:

in 4 cases 250 to 350 (normal),
in 5 cases below 250 (reduced),
in 2 cases more than 350 (increased).

4. *Basedow.*

20 cases were examined. The coagulation time was:

in 4 cases more than 32'
in 6 cases more than 40' prolonged (10 cases)
in 3 cases between 25 and 32" (normal) (3 cases)
in 7 cases below 25" (shortened) (7 cases)

In the majority of the cases we find prolonged coagulation times, but there are also many cases with reduced values. The coagulation valences have a tendency to go down. The values of the tensile strength are:

in 6 cases 250 to 350 = normal,
in 12 cases below 250 = reduced,
in 1 case more than 350 = increased.

About two thirds of the cases exhibit reduced tensile strength and one third normal values. Only in one case are the values increased. With Basedow we accordingly meet with reduced coagulation values in the majority of the cases; the more serious the case may be, the lower in general are the values. But we also come across a great many cases, that have reduced coagulation times.

5. *Myxoedema.*

4 cases were examined. Half of the cases exhibited prolonged coagulation times, and the other half shortened ones. Coagulation valences were normal, and tensile strengths were rather increased.

6. *Endemic Cretinism.*

32 cases were examined. The coagulation times were strongly reduced in all cases, and the coagulation valences were strongly increased.

V 1,5—8 v 3,5—12

The tensile strength values were:

in 8 cases 250 to 350 = normal,
in 18 cases below 250 = reduced,
in 6 cases more than 350 = increased.

The majority of the cases showed reduced values.

The coagulation values of endemic cretinism (coagulation time and coagulation valence) are strongly increased with the exception of that of tensile strength, which in most of the cases showed reduced values. It is very striking, that with 26 cases calcification was to be found in the struma. Only with 6 cases it was not possible to find any marked calcification. With the cases that show calcification the reduction of the coagulation time is more pronounced than in those, where lime contents are not positively proved.

Summary.

If we classify the results, that have been determined we find that in the case of strumas having normal somatic behavior the

coagulation values are normal with a tendency towards reduction. With the strumas that have symptoms of hypothyroidism the coagulation values vary, but in general there is a tendency towards an increase. With the strumas that have symptoms of hyperthyroidism the values are normal with a tendency towards a reduction.

With Basedow we find in the majority of cases reduced coagulation values and the more serious the case, the lower are the values. But we also meet with many cases having reduced coagulation times, whereas, contrasted with this, the values of tensile strengths were increased only in one of 20 cases investigated.

With myxoedema there occurred varying values. Those of tensile strength were, however, in general higher but, to be sure, the number of investigated cases is still too small to allow for any positive conclusions.

With endemic cretinism we find very typical values:

Strongly reduced coagulation times, strongly increased coagulation valences, the values of tensile strength are reduced in most of the cases. It is striking that in the great majority of cases calcification of struma parts could be proved. We shall still speak about this extremely important ascertainment.

II.

Concerning the Effect of Thyroidean Extracts upon Coagulation, both those free from Iodine and from Albumen, as also those containing Iodine and Albumen, and also about Iodine and about inorganic and organic Iodine Compounds.

Having now ascertained, that the Basedow disease on the whole reduced coagulation values, to be sure with numerous exceptions, and that in contrast thereto the endemic cretinism has, throughout, strongly increased coagulation values (coagulation times and coagulation valences), whereas the strumas with apparently normal somatic conditions manifest normal values with the tendency towards a reduction; after proving that the strumas with hyperthyrotic symptoms approach Basedow and show an inclination towards reduction, and that the struma with hypothyrotic symptoms incline towards endemic cretinism (tendency towards an increase), whereas myxoedema has not yet been sufficiently investigated for us to obtain a clear idea regarding its coagulation conditions, we wished to ascertain, through the following researches, whether all of these variants of the coagulation relations in the particular conditions of pathological thyroid activity are caused by a change in

the amount of thyroidean substances, respectively thyroid secretion, contained in the blood or whether they are due to other factors still unknown. The following questions arise:

1. Has the proportion of thyroidean extract, its decomposition products, or of thyroid secretion, contained in the blood, an influence upon the behavior of the components of coagulation? Is this influence dependent upon its iodine contents?

2. If this direct influence can not be proved, could we assume that these substances possess an indirect influence upon the coagulation components by causing, in the thyroid gland, an increased mobilization and delivery of thyroid secretion to the blood, and that the coagulation is thereby affected.

3. Have iodine and its derivatives an influence upon coagulation
a) by directly affecting the coagulation components;
b) indirectly by affecting the thyroid gland, causing an increased delivery of thyroid secretion to the blood?

In order to obtain an answer to these questions the following experiments were arranged:

For the investigation we used:

A thyroidean preparation that was free from albumen and iodine, F 200 Ciba, the thyroidine Bourrougs Wellcome, the thyracrine of Oswald, and furthermore iodine and iodine tincture and the organic and inorganic compounds lipo-iodine and potassium iodide. All preparations were first of all tested directly with the blood in vitro as to their influence upon the coagulation: To every 10 drops of blood 3 drops of a solution of the preparation were added (the details of which I can not enter upon here), and the behavior of the coagulation factors were determined according to my combination method. Then I proceeded to the clinical experiment. Various individuals with struma, cretins and normal human beings were fed with the preparation, that was to be studied, and were examined before and after the treatment after 8, 14 up to 30 days.

The preparations F 200, free from iodine and albumen, and the English thyroidine, containing iodine and albumen, were also tested on animals.

Testing of F 200, free from iodine and albumen. (Tab. 1).

The investigation in vitro proved no effect on coagulation. The experiments on animals showed no deflections. The coagulation factors were on the whole not essentially influenced. At the clinical experiment the coagulation time was slightly shortened

through the feeding per os, but the coagulation valence remained uninfluenced. The tensile strength had a tendency to be reduced. With the subcutaneous application the deflections were contradictory and atypical.

Testing of the Englisch Thyroidine (Tab. 2).

One tablet = 0,00279 g. iodine.

The investigation in vitro shows no influencing of the coagulation.

In the animal experiment the coagulation remained uninfluenced in a normal case. With the thyroidectomated animal the coagulation time is prolonged, but the other factors remain uninfluenced. In the clinical experiment there was one case of myxoedema and one of cretinism that were not affected in a typical way. With two normal individuals the coagulation time was shortened, the valence was raised and the tensile strength affected in a non-typical manner, sometimes increased, sometimes diminished.

Treatment, that was kept up for rather a long period, say 4 weeks, with the endemic cretin and the myxoedema, increased the time of coagulation by a little amount, but in correspondence with that it lowered the coagulation valence, whereas the tensile strength was affected atypically. In the case of all three patients, symptoms of iodism had become apparent (viz., accelerated pulse, emaciation, loss of appetite, indisposition, outbreaks of sweat, vomiting, diarrhoea etc.), so that the feeding with thyreodine had to be interrupted.

Testing of Thyreoglobuline Oswald (Thyrakrin). (Table 3).

One tablet = 0,0015 gr. of iodine.

The testing in vitro showed no influence upon the coagulation factors.

In the clinical experiment (a case of weakness of mind, a cretin with struma coll.), the coagulation times were prolonged and the remaining coagulation factors influenced atypically, the valence and the tensile strength sometimes increased and sometimes lowered.

Testing of the Iodine (Table 4).

In vitro no effect upon the coagulation components could be proved.

In the clinical experiment no sign of influence could be proved. A slight, insignificant prolongation of the coagulation periods of

time can not be brought under consideration, since the deflections were too low.

Testing of the Potassium Iodide (Table 5).

The coagulation not influenced in vitro.

In a case of weak-mindedness with struma calcarea and with a female cretin the coagulation was not affected typically when feeding per os. It was the same with subcutaneous injections, which had no effect upon the coagulation.

Testing of Lipo-Iodine (Table 6).

One tablet = 0,123 gr. of iodine.

In vitro no effect was shown upon the coagulation. In the clinical experiment we found after a treatment of short duration a prolongation of the coagulation times and a lowering of the valences; an increase in the tensile strength was tested in the case of cretins. With a longer period of treatment (4 weeks), the coagulation time was increased in one case and shortened in another, while the valence remained unchanged or was increased with the influence on the tensile strength varying.

Recapitulation.

1. The investigation in vitro shows that the thyroidean preparations, those free from iodine and albumen as well of those containing iodine and albumen, have no influence upon the coagulation component factors.

Iodine and its organic and inorganic compounds (lipo-iodine and potassium iodide), show the same reaction.

2. From the animal experiments it results that neither thyroidean extract free from iodine (F 200) nor that containing iodine (thyroidine) exerts any influence on coagulation. Only in the case of a thyroidectomated dog was the coagulation time prolonged through thyroidine.

3. Thyroidean extracts, both those free from iodine and albumen (F 200), as well as those containing iodine and albumen (thyroidine), influenced the coagulation components in an atypical way, if introduced per os. After a longer treatment with thyroidine, the coagulation periods of time were prolonged, the valence, however, was raised. Thyracrine prolonged the coagulation time, while the other coagulation factors remained unaffected.

4. Iodine and potassium iodide, when given per os, do not affect the coagulation, nor does potassium iodide, even when administered subcutaneously. Lipo-iodine prolongs the coagulation

time, lowers the valence, and acts atypically when given for a long time.

We did not succeed in determining a typical influence of thyroidean extracts upon coagulation, either when dispensed direct to the blood in vitro or per os in vivo and absorbed through the alimentary canal. (We are sufficiently aware, from the numerous experiments and from the therapeutic results that these preparations, when administered per os, clearly affect metabolism and certain somatic conditions, in spite of their being split up by way of digestion. Their efficacious components must therefore necessarily get into the circulation).

When added to blood in vitro we found, with all preparations, not the slightest reaction. Neither have iodine and its derivatives any direct influence upon coagulation.

Hence it follows that:

1. The reaction of the thyroidean extracts, taken in per os, does not depend upon the fact that the blood contains these substances or their derivatives. This applies to the varying, the atypical reactions as well as to those that lower the coagulation such as, e. g., after a rather long continued thyroidine feeding, or with thyracrine administered for a short period.

2. As iodine does not affect the coagulation components directly, the iodine contents of the thyroidean extracts are of no consideration in the direct influence upon the coagulation components.

Nor can the action of lipo-iodine in lowering the coagulation, when given for a short time, be attributed to a direct reaction of the iodine contents.

Can we explain the effects of thyroidine, thyracrine and lipo-iodine, which in some of the clinical experiments have been proved to lower coagulation, by declaring that they do not act directly upon the coagulation itself, but they affect the thyroid gland, stimulating it to an increased delivery of thyroid secretion to the blood, and that the coagulation is indirectly affected through the increased delivery of thyroid secretions?

It is not to be assumed that the secretion, which is delivered to the blood fresh from the thyroid gland, reacts differently in regard to coagulation than the thyroidean extracts added to the blood in vitro, because these thyroid extracts must certainly contain thyroid secretion, which is also investigated upon together with the extracts. If this were not the case we should have to assume, that the thyroid secretion in course of time loses its efficiency in power to

affect coagulation and therefore is efficient only in the fresh state. This assumption does not seem to me to be plausible, since it is improbable that the secretion in the extracts should remain effective with regard to its thyrogenous effect and should lose only its power to influence coagulation, inasmuch as such a one is taken for granted.

How, then, is the coagulation-lowering effect of thyroidine, when given for a longer period, or that of thyracrine and of lipo-iodine to be explained, if it has been proved that a direct effect upon the coagulation components is out of question, whether it be through the thyrogenous substances or through the iodine contents of the preparations, and if an indirect effect through the mobilization of thyroid secretion has to be rejected as well?

Since our investigations have proved that a direct influence upon coagulation through thyroid substances or thyroid secretion can not be accepted, we must necessarily look towards other factors for an explanation of these conditions, and those we find in the coagulation doctrine itself.

We know, that the coagulation of any kind of blood can be dependent upon:

1. The amount of a substance, contained in the blood, causing coagulation or arresting it, and

2. the concentration of the blood as regards organic or inorganic substances.

A variety of blood, containing a substance, that causes coagulation, as, e. g., tissue fluid (thrombokinasis), calcium salts etc., has increased coagulation values, whereas, the contents including a substance that lowers coagulation as, e. g., sodium oxalate, magnesium sulphate, hirudine, bile acids etc., lower coagulation values are found.

If we inject a hypertonic common salt solution according to van der Velde or if somewhat large quantities of common salt are taken, then an acceleration of coagulation takes place in consequence of the lixiviation of thrombokinasis from the tissues into the blood.

Now it is a known fact, confirmed by innumerable investigations, that myxoedema and endemic cretinism possess a pronounced inertness regarding metabolism, which leads to a pronounced retention of metabolic products:

The nitrogenous metabolism is lowered, likewise those of the carbohydrates, the changes as regards the salts are diminished. Many writers accept phosphorus-retention. There is thus an abundant storing of metabolic substances in the tissues and in the blood.

The increased concentration of these metabolic products in the blood-plasma is in itself sufficient to account for the increased coagulation values (endemic cretinism), without our necessarily accepting the retention in the blood of substances that cause coagulation.

Another established fact is that of the sluggish metabolism being accelerated in myxoedemas and in endemic cretins by the feeding with thyroidean extracts; thus the metabolism is brought near to normalcy. The change of albumin is increased, parallel to the decomposition of fat, general metabolism is equally increased, the same as the metabolism of lime according to Pern and the excretion of phosphorus according to Scholz, and herewith the diuresis rises.

Through the thyroid feeding, the excretion of a great quantity of stored-up metabolic products and salts is thus brought about and, with this, the concentration of the blood as regards these substances is lowered.

The coagulation components react hand in hand with the action of the thyroidean extracts in promoting excretion and the elimination of the factors, that cause coagulation.

The coagulation of the blood approaches normalcy. Upon this fact depends the indirect action of certain thyroidean extracts upon the coagulation of such conditions. A lowering of the coagulation values runs parallel with the lowering of the contents of metabolic products in the blood.

If we treat a strumous person with thyroidean extracts or with iodine and its organic (lipo-iodine) and inorganic (potassium iodide) derivatives, it can happen that in case of overdosing or of a treatment lasting too long the well-known symptoms of iodism appear. In the end even the aspect of Iodine-Basedow can be developed.

Hand in hand with this there is a lowering of the coagulation values running parallel, as we have shown to be the case with Basedow. Owing to the effect of these preparations metabolism has increased; the secretion of metabolic products has been raised, the concentration of these in the blood has decreased, and phosphorus, calcium etc., i. e. substances causing coagulation, are excreted: The coagulation values fall.

The action of thyroid extracts, of iodine and its compounds upon coagulation is, therefore, not due to a direct reaction upon the blood but

action ? not on metabol

to an indirect reaction promoting metabolism, which leads to an increased excretion of metabolic products, reduces their concentration in the blood and also eliminates out of the blood-plasma substances, that cause coagulation:

Hand in hand with this there is the lowering of the coagulation values.

Here we are involuntarily faced with the question:

Must we under these circumstances assume that there is a specific iodine action upon the struma? Is it not possible to look upon the iodine action, that diminishes or checks the struma, as depending on a simple metabolic action with an increased excretion of metabolic products? Is it not perhaps a question, here, of a more active metabolism, which also becomes evident in the excretory conditions of the thyroid gland in such a sense that it stimulates the increased delivery of secretion and prevents its abundant development?

The behavior of the metabolism gives us also the possibility to explain the coagulation facts pertaining to the various conditions of altered thyroid activity:

With myxoedema and particularly with endemic cretinism:

Sluggish metabolism with retention and abundant development of metabolic products: Increased coagulation values. The ascertainment of calcification of the struma in by far the majority of the investigated endemic cretins indicates that retentions of lime, too, must have been brought about here, which are also capable of increasing the coagulation values.

With Basedow: Increased metabolism with increased excretion of metabolic products: Lowered coagulation values.

With struma manifesting hypothyrotic symptoms: Sluggish metabolism with an inclination towards increased coagulation values. With struma showing hyperthyrotic symptoms: Increased metabolism with an inclination to diminished coagulation values.

With struma having apparently normal somatic conditions, we indirectly and from the tendency towards diminished values come to the conclusion of an inclination towards increased metabolism.

Table of Normal Values.

	Coagulation Time (expressed in minutes)	*Coagulation Valence* (expressed in concentration degrees of $Mg\ SO_4$ solutions) V	v	*Tensile Strength* (laceration weight of the white thrombus expressed in grs.)	*Retractility* (distance of the upper edge of the retracted red thrombus from the level of the fluid expressed in millimeters)
Normal Values	25—32'	V 1—2	v up to 4,5	250—350 g	6—8 mm

Struma with apparently normal somatic Behavior.)*

44'	1	2	200	7	31'	2	3	215	
43'	1,75	4	280	9	30'	0,5	2,5	530	9
42'	1,5	2,5	250	6	27'	1,3	4	350	3
41'	2	3,5	150	6	27'	3	4	300	6
40'	1,5	3	350	12	27'	1,75	2,5		10
39'	1,5	3,5	175	8	26'	2	3	260	8
38'	1,75	3,5	350	4	26'	1	2	270	
37'	1	2	100	6	26'	1,75	2,5	135	8
37'	1,5	2,5	390	8	26'	1,3	3,5	200	6
36'	1	2	250	1	25'	1	2,5	270	5
35'	2,5	4	235	9	25'	1,5	3	225	7
35'	1	1,5	180	7	25'	1,5	2,5	350	5
35'	1	2,5	100	4	18'	1	4,5	135	6
34'	1	1,5	100	1	18'	2	2,5	190	6
34'	0,5	2	100	7	14'	1,5	2,5	260	7
33'	0,5	1,5	230	3					

Summary: Investigated were 31 cases.

Coagulation Time: Over 40' 5 cases } = 16 cases
„ 32' 11 „

Between 25' and 32' 12 cases
Below 25' 3 „

Coagulation Valency: In general normal values with a tendency to become lower.

Tensile Strength 250 to 350 = 16 cases — normal
Below 250 = 13 „ — reduced
Over 350 = 1 case — increased

Struma with Symptoms of Hypothyroidism.

41'	1	1,5	370
32'	1	5	520
31'	1,5	4	237
21'	1,5	6	257
15'	1	1,5	270 (cretinous)

Summary: Coag. Time = non-typical.
Coag. Valency: tendency to increase.
Tensile Strength: tendency to increase.

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*) In all of these tables the order of the normal table has been maintained, namely: If read from left to right the figures signify: Time of Coagulation (′), Coagulation Valency (V, v), Tensile Strength (g) and Retractility (mm).

Struma with Symptoms of Hyperthyroidism.

40'	2	3	400	1
40'	0,5	2,5	131	
36'	1	4,5	173	
31'	2	3	55	(?)
30'	1,2	2	140	
29'	1	2,5	430	10
28'	2	3	250	10
28'	1,0	2	250	7
26'	0,5	2,5	115	
25'	1,5	2,5	280	8
24'	1,5	2	250	6

Summary: Coagulation times with 1 exception (24') over 25' = normal, with one third increased (over 32').

Coagulation Valency: Tendency to reduce.
Tensile Strength: Tendency to reduce.

Basedow (20 cases).

48'	1	1,5	120	6	30'	0,5	4	250	6
46'	1,5	2	350		29'	1,0	3,0	100	4
45'	1,0	1,5		6	27'	1,5		380	3
44'	1	2	150	4	23'	1,5	1,5	180	
41'	0,5	2	125	10	23'	1,0	2,5	75	6
40'	1,5	3	150	4	23'	1,5	3,5	250	3
38'	1,5	4	325	7	16'	0,5	1	246	5
38'	1	2	200	4	16'	1,0	6	150	6
35'	1,5	2	225	7	15'	1,5	3,5	175	8
32'	1	2	175	4	11'	0,5	1,5	275	5

Coagulation time over 40' in 6 cases } — 10 cases — increased
„ 32' „ 4 „ }
25—32' „ 3 „ — 3 „ — normal
below 25' „ 7 „ — 7 „ — diminished

In the majority we have increased times of coagulation, many cases with shortened times.

Coagulation valency: Tendency to become lower.

Tensile strength 250—350 in 6 cases — normal
below 250 „ 12 „ — reduced
above 350 „ 1 case — increased

Two thirds of the cases have reduced tensile strength, one third is normal.

Myxoedema.

35'	1	2	100	4
33'	1	1,5	300	6
14'	1,5	3	410	6
16'	3,5	4,5	300	5

Summary: Coagulation times in part increased and in part shortened.
Coagulation valency: Nomal.
Tensile strength: Tendency to increase.

Endemic Cretinism.
(32 cases investigated.)

					Struma calcarea						Struma calcarea
7'	1,5	8	360	6	+	21'	1,5	4	250	9	+
14'	5	6	165	6	+	15'	2	8	190	6	+
16'	5	6	213	7	+	9'	4,5	8	180	9	+
16'	3	6	160	4	+	17'	3	7	317	7	+
14'	1,5	7	300	7	+	11'	2,5	7	230	7	+
9'	1	12	155	4	+	9'	1	6	170	4	+
11'	5	5	242	6	+	11'	1,5	3,5	150	5	+
12'	1,5	7	130	6	+	15'	2,5	7	90	4	+
12'	1,5	8	280	6	+	12'	3	8	355	4	+
10'	3	7	387	8	+	7'	8	10	257	6	+
11'	1,5	12	160	5	+	24'	2,5	4,5	315	7	uncertain
20'	3,5	8	267	3	+	22'	5	6	265	6	„
14'	2	9	500	7	+	19'	2	3,5	410	6	„
18'	1,5	3,5	85	8	+	17'	1,5	10	140	5	„
16'	1	5	239	7	+	13'	8	8	225	6	„
16'	3,5	7	115	4	+	9'	2,5	7	163	6	„

Summary: The coagulation times are shortened in all cases without exception.

The coagulation valencies are strongly increased:
V 1,5 to 8 v 3,5 to 12

The tensile strength values are mostly reduced, in about one third of the cases normal and in 6 cases increased.

In 26 cases calcification in the struma was proved and in 6 cases calcification was not positively proved. Here the coagulation time has a tendency to be increased in contrast with the cases having calcification.

TABLE 1.

F. 200 thyroidea extract (liquid) free from iodine and albumen. 0,5 cubic centimeters = 1,5 g. fresh gland.

Investigation in vitro.

Na Cl.	F 200	F 200 Na Cl. z. gl. T.
27'	27'	27'

Investigation in vivo.

Animal experiment:

I.

before	20'	1,5	4	156	1	dose: 0,5 ccm. per kilogram of body weight
after	20'	2	5	32	2	

II.

before	20'	2,5	6	49	dose the same.
after	18,5'	2,5	5	42	

Clinical test.

Struma Coll. Hypothr.:

before	21'	1,5	6	57	dose 1,5 ccm. daily for 14 days
after	17'	1	6	100	

Struma calcarea Hypothy.:

before	31'	1,5	4	273	dose 2,0 ccm. daily for 7 days
after	17'	1	4	223	

Endem. Cretin.:

before	23'	1,5	2,5	322	dose 13,0 ccm. daily for 8 days
after	19'	1,5	4	130	

Normal:

before	28'	1	1,5	430	8	dose 8,5 ccm. daily for 8 days
after	30'	0,5	3	215	8	

Normal:

before	23'	1	3	330	dose 7,4 ccm. daily for 8 days
after	13'	1	12	360	

TABLE 2.

Thyroidin Bourrougs Wellcome.

1 Tabl. (5 grains) = 0,324 gr. fresh gland
0,00279 gr. iodine.

Investigation in vitro.

Na Cl.	Thyroidine
25'	25'
19'	16'
19'	24'
11'	11'
1,5 9 80 12	1,0 7 80 11

Investigation in vivo.

Animal experiment:

					I.	
before	20'	1,5	4	156		dose 80 tabl. daily = 1,62 gr. gland per kg. body-weight 10 days
after	18'	2	5	122		
					II.	
before	12'	3	6	58		dose 14 tabl. daily = 0,336 gr. gland per kg. body-weight 28 days
after	21'	2,5	6	65		

Clinical test.

Myxoedema:						
before	38'	1	4	310		
after	31'	1	5	182		3 tablets daily 8 days
after	27'	1	6	294		6 „ „ 8 „
Cretinism:						
before	23'	1,5	2,5	322		
after	19'	1,5	3	530		3 tablets daily 12 days
after	26'	1	2,5	320		6 „ „ 12 „
Normal:						
before	28'	1	1,5	430		
after	8'	1	3	97		6 tablets daily 8 days
Normal:						
before	23'	1	3	330	3	
after	12'	1	9	485	7	5 tablets daily 8 days
Treatment lasting four weeks: 3 tablets daily						
Endem. Cretin.:						
before	14'	2	9	500	7	
after	16'	2	3,5	510	6	
Endem. Cretin.:						
before	9'	1	12	155	4	
after	14'	3,5	6	280	7	
Myxoedema:						
before	14'	1,5	3	410	6	
after	27'	1,5	2,5		10	

TABLE 3.

Thyroglobulin Oswald (Thyracrine)
1 tablet = 0,0015 gr. Iodine

Investigation in vitro.

Na Cl.				Thyracrine			
	24'				24'		
	9'				9'		
	19'				16'		
	11'				11'		
0,5	7	250		0,5	6	360	

Clinical test.

Struma coll. (weak-minded):						
before	7'	1,5	7	180	5	
after	22'	1,5	2,5	280	8	3 tablets daily 8 days
Struma coll. (Cretin):						
before	15'	0,5	2	270	9	
after	23'	1	2	130	5	3 tablets daily 8 days

TABLE 4.

Iodine, resp. Tinctura Iodi.

Investigation in vitro.

Na Cl.				Iodine solution (Na Cl.)			
	21'				21'		
	18'				18'		
	28'				28'		
	37'				28'		
0,5	3	240	6	0	3,5	230	7
3	6	500	11	2,5	7	150	12

Clinical test.

Iodine tincture per os.

Myxoedema:						
before	16'	3,5	4,5	300	5	
after	19'	1,5	4,5	470	6	3 times daily 5 drops 8 days
after	19'	2	5			3 times daily 5 drops 10 days

TABLE 5.

2,5 % solution of iodide of potassium.

Investigation in vitro.

Na Cl.	Iodide of potassium solution			
40'	40'			
	0,5	2	410	12

Clinical test.

Struma coll., in part calcarea (weak-minded):

before	14'	1,5	9	150	8	
after	5'	2,5	4	420	7	0,5 gr. IK daily 8 days

Struma coll. Cretin:

before	15'	2,5	6	140	8	
after	22'	0,5	5	200	8	0,5 gr. IK daily 8 days

Struma adolesc., convalescent after appendectomy:

before	41'	1	3	200	7	
after	42'	1,5	3	120	7	0,5 ccm. 2,5 % solution subcut. 8 days

Struma coll. Cretin:

before	12'	0	6	430	8	
after	12'	1,5	6	470	6	dose administered, the same.

TABLE 6.

Lipo-iodine, 1 tablet = 0,123 gr. Iodine.

Investigation in vitro.

Na Cl.				Lipo-iodine			
27'				27'			
19'				19'			
24'				20'			
6,				6'			
1,5	8	120	10	1,5	7	180	9

Clinical test.

Dose administered: 3 tablets daily à 0,3 gr.

Struma coll., in part calcarea (weak-minded):

before	12'	1,5	8	230	7	
after	26'	1	3	320	6	for 8 days

Cretin:

before	15'	2,5	5	95	4	
after	19'	1,5	4	290	7	for 14 days

Cretin:

before	9'	2,5	7	165	6	
after	18'	2,5	3,5	240	6	for 14 days

Cretin:

before	11'	1,5	3,5	150	5	
after	19'	2	3,5	150	7	for 4 weeks

Cretin (female):

before	13'	8		225	8	
after	11'	10		80	7	for 4 weeks

Remarks

on the

Physiology and Pathology of the Thyroid Gland

by

Professor F. Blum, Frankfort on the Main.

I feel like a heretic here in your forum, which stands particularly for the conception of an internal secretion of the thyroid gland, when I come with my doctrine, now several decades old, of the correctness of which I am now as ever before still convinced, that the thyroid gland does not act as a secretory organ but as a filter in taking the injurious substances out of the circulation and in freeing from poison intraglandularly.

If it has been proved that there is some percentage of iodine in the blood, as has been claimed in many a published report in recent years, then such a determination in no wise justifies us in drawing the conclusion that there is a delivery of an iodine hormone from the thyroid gland. We know that this iodine in the blood takes its origin from three sources. First of all it can come from the nourishment. With the ubiquitous occurrence of iodine in Nature a part of it must certainly be looked upon as « alimentary iodine ». The fluctuations in the percentage of iodine in the blood, which vary with the seasons, if they were to be proved with unobjectionable methods, can with little difficulty be explained from such iodine. The tissue deposits deliver a second part to the blood. Of the iodine introduced into the body in the way of alimentation or medicament, it retains not inconsiderable quantities for a certain period of time without the thyroid gland and only gradually does it give it forth again. My collaborator Grützner and myself[1]) were able to prove that the iodine, that was administered, had not yet been fully eliminated after 12 nor after 20 days. With the permeability of the kidneys for halogen and with the constant slight iodine contents of the blood the iodine was obliged in the meanwhile to be stored up in the body itself,

quite so: due more green p

[1]) Zeitschrift für physiologische Chemie, Vol. 91, pp. 460 etc., 1914, in « Studien zur Physiologie der Schilddrüse »; V. Communication « Kommt Jod im Blut vor? »

after every new intake was out of question. From here it slowly flows off again without having gone through any special conversions. The iodine in the blood can accordingly likewise take its origin from the stored-up amounts of the «iodine in the tissues». Not until we have left these two sources out of question are we justified in ascribing a percentage of iodine in the blood to thyroideal origin. It was only in our investigations (Blum[2]) (Blum-Grützner[3]) that the deviation of the two varieties of iodine had been attempted. Even for this very reason the iodine findings in the blood on the part of other observers lack the proof for the thyroideal secretion of a hormone containing iodine. We ourselves, however, found the blood always free from iodine in the case of our animals experimented upon, which were being starved or fed with food that was free from iodine, whereas the thyroid glands had remained with iodine contents. To this must be added that the positive iodine findings, upon which during recent years the authors based their statements were obtained to a great extent with a colorimetric method of proof (v. Fellenberg), which can not be absolutely depended on with the small quantities that may still come under consideration, after the deduction of the iodine of alimentation and that of the tissue. I have called attention to errors in the number of the Schweiz. medizinische Wochenschrift[4]), that was specially treating of the goiter conference, should like to add here that, under the most ideal experimental which can come forth with the employment of colorimety and conditions, with pure iodine solutions in 0,1 to 0,3 cubic centimeters of chloroform the limits of recognition for a deviation of the color over-against the pure chloroform lies at 0,2 millionth of a gram (occasionally even at 0,1 millionth of a gram). For the characteristic pink color of iodine, however, it moves upwards at least 0,4 millionth of a gram. These are figures, which at first thought appear favorable; but by the last 6 investigators, experts in color and titrimetrically, 2 declared that several tubules, that were perfectly free of iodine, with 0,1 and 0,2 cubic centimeters of chloroform under some distilled water, could be distinguished as regards color from the tubes for comparative purposes without iodine. Such a result naturally prohibits the interpreting of every change of coloration as being iodine. We shall rather be obliged

[2]) «Zur Chemie der Jodsubstanz der Schilddrüse». Pflügers Archiv für die gesamte Physiologie. Vol. 77, 1899, Page 101 and following.

[3]) l. c.

[4]) No. 34. 57 th year, 1927. Page 808 and following.

to hold constantly to the pink coloration as an indication of iodine. The possibility of distinguishing becomes again considerably worse if we bring a layer of a fusing solution of the blood as obtained in accordance with the directions of v. Fellenberg over the extracting chloroform in the place of pure water. Let it be understood that v. Fellenberg himself did not consider blood as an object properly suited for his method.[5]) Over-against this careful spirit on the part of the author himself and in consideration of the limits of recognition already defined, as also in accordance with the errors that have occurred with skilled investigators, the words of praise for the method (among others by Scharrer[6]) appear for the present purpose at least quite devious. For the solution of the difficult question of the iodine of the blood we shall always be obliged to resort to a perfectly unobjectionable method of proof. Colorimetry, however, is subjected too much to subjective impressions than that it should come into consideration for this. I shall say, besides, that with our animals of experiment, as long as we instituted comparative tests with the method of v. Fellenberg we on repeated occasions with it found no iodine in the blood. The method, that was employed by us, is that of Blum-Grützner[7]), the reliability of which in relation to the question of « Iodine or not Iodine » is perfect. Its lower limits of recognition lie at about 4 millionth % with the most careful concentration of the fusing solution (eventually in a vacuum and especially important after neutralization of the acid!) — If we calculate what even 0,4 millionth of a gram, the ideal limiting amount of colorimetry stated above, signifies in the circulating iodine, then it answers to a contents of iodine of 4 millionths %, because it has been obtained from 10 cubic centimeters of blood. This figure, however, would surely signify some 200 millionths gram of iodine if set down as thyroid gland iodine for the entire amount of blood and applied to an adult human being with 5 liters of blood, or in thyroxine expressed with 65% of iodine, 0,31 milligrams of thyroxine. To maintain such contents of iodine permanently must be impossible even for a normal thyroid gland. It would after all

all this is very apt and very sound criticism

[5]) v. Fellenberg. Special issue taken from «Ergebnisse der Physiologie». Vol. 15. Page 193, 1926. « I have tried many different variations with more or less potash, through stronger or slighter heating, especially with blood, without attaining any entirely faultless results. »

[6]) Münchner medizinische Wochenschrift, No. 42, Page 1790.

[7]) Zeitschrift für physiologische Chemie, Vol. 85, Page 430, 1923. «Studies on the Physiology of the Thyroid Gland », I. Information and II. « Methods of Determining Iodine in organic Substances » and III. Information, Vol. 91, Page 392, 1914. « Supplementary Comments on the Method of Determining Iodine ».

have to deliver the quantity of 200 millionths of a gram of iodine at least 3 to 4 times in the course of a day, in order to fulfill this requirements. The absorption and using up of iodine, however, takes place only very slowly, as Blum and Grützner[8]) have shown, whereas the splitting up of the albumin iodatum of the thyroid gland takes place very much more rapidly through the liver and the delivery of the iodine through the kidney. Nor could the intervening deposition of iodine in the tissue protect against early impoverishment of iodine a thyroid gland, that is giving out iodine, without addition from without. Accordingly there is for the present no iodine hormone secretion of the thyroid gland demonstrable in the way of chemical investigation of the blood, even on account of the quantitative conditions.

I have endeavored to recognize the consumption of iodine substance at the center of iodine changes, at the thyroid gland itself. The result was that the second remaining thyroid gland was not, or only a very little, poorer in iodine than the first gland that had been removed at the beginning of the experiment, notwithstanding a system of alimentation as free from iodine as possible or in spite of a hunger treatment in a carefully protected cage for as many as up to 5 weeks.

Summarizing all observations, it follows that in the blood the evidence of normally occurring iodine hormone has not been brought forward and that the long continuance of albumin iodatum in the thyroid gland renders most highly improbable the delivery of a secretion, containing iodine, through this organ.

In addition to these ascertainments there are several others, which are inconsistent with the thought of an inner secretion of the thyroid gland: Romeis[9]) published the fact in the year 1923, that in the Gundernat tadpole experiment the action of thyroxin, which checks growth but accelerates the metamorphosis, is discontinued through the addition of blood. At about the same time we reached a similar result in the Biological Institute with the use of the fluid of wether thyroid and blood: While the fluid alone, if added to the vital fluid of the animals, very quickly brought about the characteristic changes, the similar kind of blood and serum or a high quality of dried blood (haemocrinin) was able to mitigate the injury and with a sufficiently large dose to make compensation for it.

[8]) l. c. Vol. 91. Page 400, 1914, IV Communication: « Schicksal des Jods in der Schilddrüse » and Vol. 110, Page 277, VII Communication: « Jodumsetzungen in der Schilddrüse ».

[9]) Biochemische Zeitschrift, vol. 141, Page 500.

Several illustrations will make this statement clear.

15 days after the beginning of the experiment (1923).

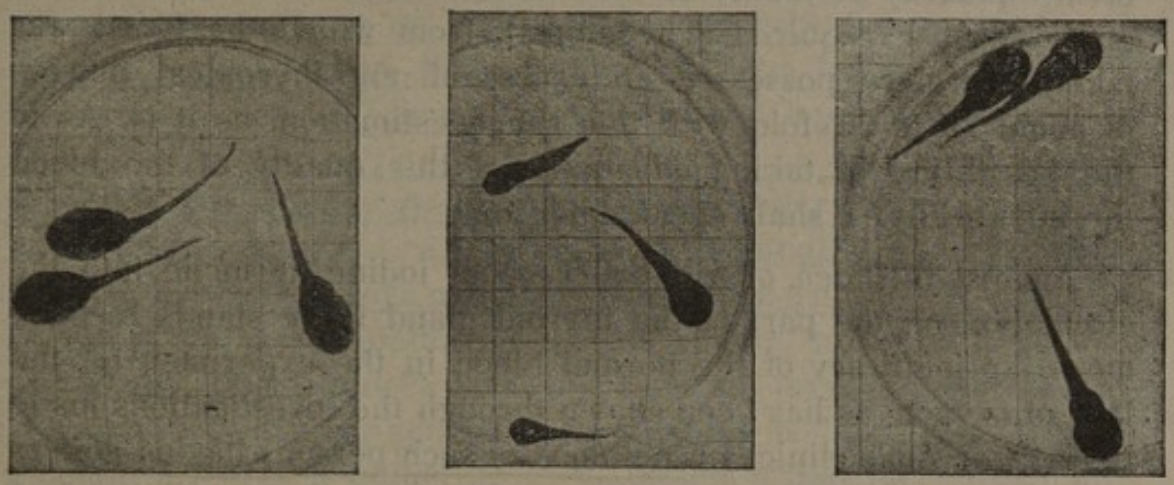

Fig. 1.

without addition — 0,1 ccm. thyroid liquid — 0,1 ccm. thyroid liquid + 0,5 ccm. serum

to every 300 ccm. of water daily (+ 1 particle of meat)

14 days after the beginning of the experiment (1925).

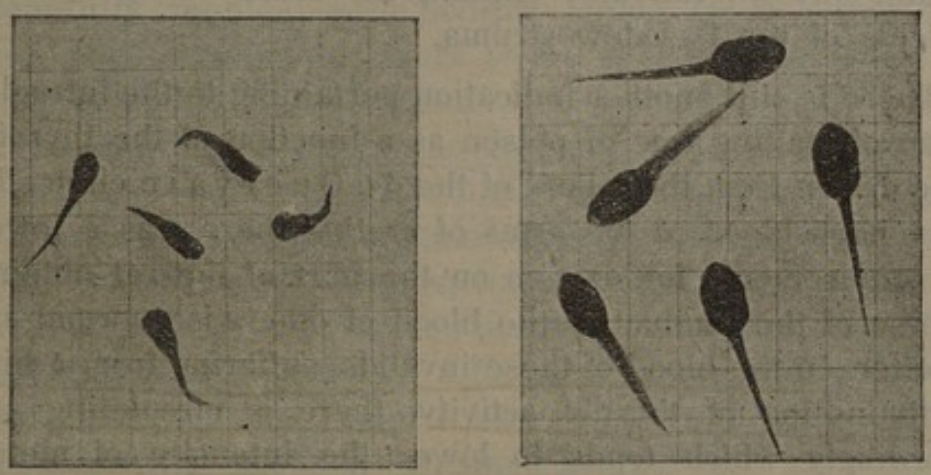

Fig. 2.

Daily 0,1 ccm. thyroid extract + 1 particle of meat — Daily 0,1 ccm. thyroid extract + 0,5 gr. dried blood (haemocrinin)

to every 300 ccm. of water

As we see there are constantly anti-thyroideal substances circulating in the blood, which are able to paralyze certain influences through the thyroid iodine substances and, as a matter of fact, these antithyroideal protective substances are present to an excessive degree. If we now figure out the added quantity of thyroid on the entire gland then there was about from the 20th to

anti-thyroidal substances

the 30 th part of the thyroid apparatus of a wether added. For the compensation, however, there was as a maximum the 400 th part of the quantity of iodine in the whole amount of blood of a full-grown wether required. The animal, from which the blood was taken, therefore possessed an excess of anti-thyroideal powers of about 15 to 20-fold with this rough estimation, as it is. As to the possibility of taking advantage of this quality of the blood therapeutically, I shall speak later on.

Against the idea of a delivery of an iodine hormone into the circulation on the part of the thyroid gland there stands furthermore the inefficacy of the normal blood in the experiment of the lack of oxygen, as has been shown through the investigations made in de Quervain's clinic[10]). The blood of such persons having goiters and especially of Basedow sufferers increases the requirement of oxygen in the rat along the line of the presence of thyroid gland substance; the normal blood does not effectuate any such change. If we draw any conclusion from this without having any prepossession, then this can simply be: The normal thyroid gland holds back its iodine substances; with the invalid it slips away. In this way we can also explain the mostly insignificant iodine contents of the Basedow struma.

There is still another indication pertaining to the intraglandular action of making free of poison as a function of the thyroid gland to be drawn from the labors of the de Quervain clinic: Through the venous blood of the arms of cretins there was a lowering of the requirements for oxygen on the part of the rat obtained, the reverse of the conduct of the blood of otherwise normal sufferers of goiter. In the blood of these invalids, suffering from a high state of diminution of thyroid activity, there is circulating an agent accordingly which tends to lower the intensity of metabolism, which agent is not to be found in the healthy thyroid, because it is drawn from this and freed from poison.

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[10]) Mitteilungen aus den Grenzgebieten der Medizin und Chirurgie, vol. 39 (1926) « Report bearing on the Pathology of the Thyroid Gland », pages 415 to 675. — To the words of Mileta Branovacky (Page 604 and the following) I should like to say that my latest publication, in which I placed the responsibility for tetany and cachexia upon the thyroid gland and the parathyroid glands under the guidance of the former, dates back to the year 1926 and that since that time there have appeared several special labors and two monographs, the first one of the latter in the beginning of 1925, in which I have assigned the little epithelial bodies by all means into the foreground as a result of extensive investigations. (F. Blum. « Studien über die Epithelkörperchen » (Studies on the Parathyroid Glands) etc. 1925. Publishing House of Gustave Fischer, Jena). — My point of view as regards the method of action of the thyroid gland has certainly not undergone any change.

With this process of freeing from poison a special function falls to the iodine: The thyroid gland as the only organ in the body possesses the ability to separate the iodine from the sodium iodide (Blum-Grützner[11]); it de-ionizes it and thereby builds up for it albumin iodate bodies, that are characteristic for it. This power to disengage iodine I have for a long time been designating as «Iodase». If the thyroid gland lacks it, as can be proved to be the case in many greatly degenerated goiters, (Blum, Schweiz. med. Wochenschrift, l. c.) then notwithstanding the supply there is left undone the enrichment in albumin iodate. An accumulation of sodium iodide, however, does not under any circumstances take place in the thyroid gland to any increased extent over-against the remaining bodies. It is only the amount of iodine it builds up in its albumen that the normal thyroidea holds back energetically and permanently. Through this the quantity and percentage contents of iodine of the albumin iodatum gives an illustration of the ability of the organ for iodine transposition. Strumas, which are not able, as a fact, to keep back albumin iodatum with the same tenacity as the normal gland, can, however, be quite rich in albumin iodatum; especially if they have been plentifully supplied with sodium iodide for a rather long time. They have accumulated more of the specific albumen of the thyroid gland within their structure, of the matrix of the later albumin iodatum and in so far as they still possess iodase, they work up iodide of sodium and albumen to their characteristic iodine proteid. Strumas accordingly contain altogether too generally more iodine than sound thyroid glands; but the thyroglobulin mixture contains percentually less iodine, because it is made up of an ingredient containing iodine and a far more important one that is free from iodine. If we remove from the gland with distilled water[12]) the soluble proteids contained therein and separate the portion containing iodine through the semi-saturation with a concentrated solution of ammonium sulphate, then we obtain in this fraction the entire soluble iodine containing proteid. Oswald has designated it with the name «Thyroglobulin», which I have adopted here, although it does not possess every quality required[13]).

[11]) l. c. Vol. 92, Page 360, 1914, VI Communication «Storing and Combining of Iodine in the Organism».

[12]) Distilled water is to be preferred in the process of extraction, because it does not dissolve the serumglobulin, while the thyroglobulin is soluble in it.

[13]) Even the characteristic, here cited, shows forth a difference as compared with globulin. However, as the appellation is only given for the purpose of orientation and not for any explanatory classification with the uniform nature of thyroglobulin, this designation can just as well remain for the present.

Through the intake of iodide of sodium the absolute quantity of thyroglobulin as also the percentage of iodine contained are increased, according to the researches of Blum-Grützner[14]) and those of Strauss[15]).

Iodation values, such as healthy thyroid glands show after the intake of iodine, I have never found with strumas. But it is a fact that occasionally a struma, which may still possess a considerable power to disengage iodine, can store up through iodine feeding very great quantities of albumin iodatum with an iodation value, which is equal to that of a thyroid gland, that had not been fed with iodine. (See Schweiz. medizinische Wochenschrift, l. c. Page 812, Table III).

I accordingly lay great weight, in judging of the iodine changes of the thyroid gland and of goiter, upon the determination of the two factors: Total contents in thyroglobulin and percentage amount of iodine in the thyroglobulin!

The manner of making the estimate has been given in my work in the Swiss Medical Weekly. We must always keep in mind, whether an increased intake of iodine had preceded. If it is desired to test the capacity for iodine changes in a struma, that is to be removed later on, then we must for some time, say about two weeks, before the operation submit it in a suitable manner a number of times to the effect of an influx of sodium iodide. Some 5 to 6 times 0,1 g. NaJ will suffice. The insight into the vital activity of the struma will then become more clear through the investigation outlined above.

In this way I was enabled to distinguish two groups among the goiters, which were placed at my disposal by Colleague Bircher of Aarau: The one group had almost completely lost the power to transpose iodine and its thyroglobulin was extremely poor in iodine notwithstanding a supply; the other group was still in possession to a demonstrable degree of the separating power of the healthy thyroid gland (iodase). Among the goiters of the second category there was, however, in a considerable number the power of retention diminished over-against the albumin iodate prepared intraglandularly, so that the iodine substances could pass off prematurely, as the clinical phenomena of an iodine-Basedow indicate to us.

In previous investigations I laid down the fact, that the thyroglobulin fraction of the normal thyroid gland in different species of animals, but also within the same species, is absolutely not uni-

[14]) l. c. Vol. 92, Page 380 and the following.
[15]) Zeitschrift für physiologische Chemie. Vol. 104 (1919), Page 133.

form in its percentage of iodine; that, however, if we saturate this mixture of albumens, which are iodized to different degrees, with iodine in vitro, we come to albumin iodatum compounds with an amount of iodine, that is constant. From this fact we can therefore conclude, that the thyroglobulin originates from a uniform matrix, which is stored up by the thyroid gland and at which accordingly the iodizing process takes place progressively. In this we can find the reason, why within the thyroglobulin fraction there occurs besides some still unchanged original proteid, such with embodied iodine. In researches on the chemistry of albumin iodatum compounds we, — Blum and Strauss[16]) —, have shown, that the thyroglobulin is able to combine in areolas four atoms of iodine and that two of these enter into the thyrosine part of that proteid. Such a thyroglobulin, saturated with iodine, contains 4.79 % of iodine (D-iodization). The natural thyroglobulin with its scanty percentage contents of iodine of 0 to about 1% must be a mixture of non-iodized original substance with products which have been changed through the iodizing process, which products have absorbed some 2 or 4 atoms of iodine. Kendall had at about the same time shown, by means of alkali splitting up, that the thyroxine is the iodine containing complex of the albumin iodatum of the thyroid gland and looked upon the combination as an iodized derivative of the tryptophane. Between our results and this formula there existed an impassable divergency. Through the knowledge of the constitution of the thyroxine as a Dijodophenyldijodotyrosine by Harrington our conclusion that the albumin iodatum of the thyroid gland must contain four nuclei-iodine atoms, of which two belong to the thyrosine part, is found to be correct[17]). The thyroxine is to be looked upon as the iodine-containing ring-group of the thyroid albumin iodatum. That it represents the secretory hormone of the thyroidea is just as much lacking in proof as is the inner secretion of the thyroid gland. Even if at the assimilation the thyroxine possesses all of the characteristics of the thyroid albumin iodatum, an insight into the vital activities of the thyroid gland has not been created thereby. If we desire to investigate their functions chemically and physiologically, then we shall be obliged to study, in addition to the iodine variations the characteristics of the specific albumen compound of the thyroid gland, that main part of the thyroglobulin fraction to which, iodized, ac-

Is thyroxine active form of the thyro

[16]) Zeitschrift für physiologische Chemie, Vol. 112 (1920), Pages 111 to 166 and Vol. 127 (1923), pages 199 to 207.

[17]) Charles Robert Harrington « Chemistry of Thyroxine ». II Constitution and « Synthesis of Desjodo-Thyroxine ». Biochemical Journal, Vol. XX, page 300.

cording to the researches of ourselves, namely Blum and Strauss, the smallest molecular size of 10 080 approaches [18]).

In almost all strumas there is shifted within the thyroglobulin the constituent proportion between the part free from iodine and the part containing iodine to the disadvantage of the latter. We have to keep before our minds the importance of this accumulation of specific albumen that is free from iodine, if we desire to understand the disturbance in the vital activity of the different varieties of goiter as compared with the standard: In addition to the alteration of the iodine stock, as it comes to the fore in the loss of the power to separate iodine or in the diminution of the atresia power of the thyroidea (presumable « Hyperthyroidism ») [19]), then we must in future take into account the albumen of the colloid, for which it becomes a question mainly with the so-called thyroglobulin, in order to establish an eventual dysfunction. In the determination of the iodine figure of the thyroglobulin we possess a support for the recognition of the soundness of that peculiar proteid. Whereas serum globulin is able to take up at the iodizing 8.3% iodine (A-number) or 6.64% (B-number); serum albumen 8.96% (A-number) and 6.73% (B-number); 6.7 to 6.6% (C and D number), there comes into the thyroglobulin of the normal thyroid gland 6.14% (A-number) or 4.88% (B-number) and 4.79% (D-number).

Does this behavior become changed with strumas? My ascertainments are not yet numerous enough, especially in respect to the different kinds of strumas, to enable me to give a definite final judging. Every act of co-operation in the way of solving this question would be welcomed by me. With perfect positiveness we could say that, according to the results obtained from certain biological researches, there must be some distinctions, — seeing that feeding experiments with cretin goiter to tadpoles frequently showed non-efficiency notwithstanding the iodine residues present, — if we were not to raise the objection, that the presence of blood in the degenerated but plethoric organ

[18]) l. c. Vol. 112, page 164.

[19]) The designation « hyperthyroidism » and « hyperfunction » leads to a completely untenable mental view. The iodine-Basedow, in which a strumously diseased thyroid gland exercises an influence thyrotoxically over the entire organism through the intake of iodine, can naturally truly not be looked upon as a « hyperfunction », but only as an « incompetency ». And, as a matter of fact, with the iodase that is present the retention power of the gland is insufficient over-against the albumin iodatum, which has come forth in abundance. A healthy thyroid gland does not lead to such manifestations of disease even with a great intake of potassium iodide.

had neutralized the influencing of the tadpole metamorphosis through antithyroideal peculiarities. In order to obtain a perfect chemical and physiological conception, we must experiment with unmixed substances, that are as pure as possible. It is therefore necessary to undertake the experiment on the animal not only with the entire goiter, but also with the isolated thyroglobulin. Not until this has proved to be inefficient, and if there results an iodine figure at the strong iodizing which deviates from the normal value, are we able to speak of a dysfunction besides the injury of the iodine metabolism.

And now let us pass over to the question of goiter prophylaxis! That there can be anywhere in nature a lack of iodine substance with the slight iodine requirement of the thyroid gland, which lack could of itself give occasion for the development of goiter, I can not accept. In addition to my statements in the conference number of the Swiss Medical Weekly, I refer to my previous proof of richly iodined thyroid gland in the big game, which was killed in pronounced goiter districts[20]). «The lack of iodine begins with goitrous degeneration; it, however, does not occasion it».

That iodine constitutes exceedingly great efficient therapeutics in thyroid enlargement, is a fact that is contradicted by no one. Its effect-producing mechanism even gives it a specific position; for, since the thyroid gland is able to increase its depoisoning activities by means of iodine, it relieves itself of the accumulated damaging substances. It is at all events imaginable, that when viewed from this standpoint a careful and controlled intake of iodine can be of use, and in a certain sense protective, against a diseased swelling of the thyroidea, even at an early time. If, nevertheless, manifestations of iodine-Basedow appear — a danger which increases with advancing years and with insufficient attention — then let us here proceed for the remedy to the antithyroidal characteristics of normal blood.

Repeatedly, after the dispensing of iodine, in cases of that thyrotoxic condition, which is incorrectly spoken of as hyperthyroidism, above all, however, in severe attacks of morbus Basedowii, I have attained extraordinary success with my protective diet, viz., a system of alimentation without meat but with abundant milk together with an addition of blood, eventually in the form of large doses of haemocrinin.

[20]) Pflügers Archive. Vol. 77, (1899), Page 100.

The origin of goiter even in the Scandinavian countries is scarcely dependent upon the disturbance of the state of equilibrium between the thyroid gland and the antithyroidal powers of the blood; those manifestations, which cause us to think of Basedow are, however, certainly also influenced thereby.

Thoughts on the aetiology of that variety of goiter, which is so disastrously prevailing in Swiss valleys, in Upper Bavaria and in Styria, caused me some years ago to make a comparative study: [21]) « I feel inclined to assume that endemic cretinism bears a relation to the introduction of definite microbes into the human intestines. Just as the fermentation of wine runs differently according to the districts, depending on the special peculiarities of the local indigenous, varieties of yeast germs that are morphologically closely related, so the changes that take place in the intestines can be influenced through the existing particularities of the intestinal inhabitants, that have wandered in from without with the food. If these manufacture a poison, which is injurious to the thyroidea or which can not be overcome by it, then the consequence is the degeneration of the gland and thereupon the poisoning of the organism through entero-toxin ».

Even if it is certain that the unpropitiousness of the living conditions and hygienic errors can act injuriously upon the thyroid gland, I am not able to believe in a multiform vagueness of the goiter noxa which, according to Bircher, puts a cretinoid stamp upon the entire population. Among the flora of the intestines I search for that distributor of poison, to the metabolic products of which the thyroid gland must succumb, since it certainly takes them up but does not completely subjugate them.

The Pathological-Physiology of the Thyroid.

By Friedrich v. Mueller, Munich.

It will be the object of this discussion to emphasize those facts which do not conform to the accepted teachings and which present difficulties in clarification, for it is from these points that we may hope to find new vistas in the study of our problem.

The investigations carried on in Switzerland and in Baden

[21]) Virchow's Archives, Vol. 162 (1900), Pages 404 and following.

showed that endemic goiter, especially adolescent goiter, possesses a low iodine content. The mean iodine content of the thyroid was found to be 9,39 mg. % of fresh gland, that of the euthyreotic (non toxic) goiter on the other hand was found to be only 4,87 mg. % of the fresh gland according to the studies of Dr. Spatz and those of Professor Jansen and Dr. Robert made on thyroid material obtained in the Bavarian Highlands. On the other hand, calculations of the total iodine content of the small normal thyroids and of the enlarged goiters in their material showed that the average normal thyroid contains a total of 3,34 mg whereas the euthyreotic (non toxic) goiter contains on an average a total of 6,75 mg of iodine. Comparable results are obtained on calculating the data from the studies made in Freiburg. Since therefore the euthyreotic goiter especially the adolescent goiter contains on the whole more iodine than the normal thyroid, it appears difficult to refer goiter formation to iodine deficiency. It is true that the iodine content of the blood in persons with euthyreotic goiter is very low according to our investigations in contrast to the increased iodine content of the blood in exophthalmic goiter as found in our investigations as well as in those of Veil and Sturm. Since the iodine content of the thyroid in Basedow's disease is usually abnormally low, it seems justifiable to think of this as due to a rapid outflow of iodine containing secretion from the thyroid in this disease. This assumption agrees with the histological findings of a colloid deficiency and a fluid content in the proliferated epithelial bags. A difficulty is met with at once with this explanation, for the Basedow thyroid has a very powerful effect, at times even a toxic effect in feeding experiments on tadpoles as shown by the experiments of de Quervain. If this disagreement between the iodine content of the thyroid and its biological functioning should be confirmed in detail by further studies, it would be necessary to conclude that other active substances are present in the Basedow thyroid together with iodized thyroxin. This would be equivalent to the assumption of a dysthyroidism. There is no question but that true exophthalmic goiter is a disease «sui generis» which can not be identified with the other forms of hyperthyroidism. The specific histological picture, which the Basedow thyroid offers throughout the gland, speaks for this, whereas the thyroid in secondary hyperthyroidism appears histologically quite different. A liquefaction of the colloid can sometimes be found in Jodine-Basedow it is true, and budding and proliferation of the epithelium, but such signs are found not infrequently in goi-

Iodine-deficiency not false

other 'toxic' substances in thyroid secretion? Graves's

ters without symptoms of hyperthyroidism and no decisive significance can be attributed to them. Neither Dr. Spatz working on the Munich material nor Wegelin working with Swiss goiter could determine surely the presence or absence of hyperthyroidism from the microscopical picture alone.

There is a marked hyperplasia of the thymus in the majority of cases of exophthalmic goiter, whereas thymus hyperplasia is usually absent in secondary hyperthyroidism though there are exceptions to this in both directions.

The different geographical distribution of genuine Basedow's disease from the localization of endemic goiter with secondary hyperthyroidism speaks decisively for a separate position for genuine Basedow's disease. True exophthalmic goiter appears to be uncommon in the centre of the Swiss goiter regions, is not very common in southern Germany nor in the endemic goiter regions of Holland. On the other hand it is much more higly distributed in the goiter free parts of northern Germany and Holland as well as in Denmark. Holst has pointed out that symptoms of hyperthyroidism are strikingly frequent in Norway. Theodore Kocher pointed out this geographical difference.

We immediately meet with a difficulty — how can we decide in any individual case whether a true Basedow or a secondary hyperthyroidism is present? The apparent answer would be that only such cases be classified as true Basedow or exophthalmic goiter in which the goiter developed synchronously with the other symptoms and in which no goiter was previously demonstrable. This definition is not altogether true, for an accurate history of apparently true Basedow's disease will often show that a thyroid enlargement was present in earlier years. True Basedow's disease is differentiated from secondary hyperthyroidism according to Plummer by the exophthalmus and by the peculiar euphoric and restless mental state. I cannot agree with this opinion, for I have often observed all the characteristic eye-signs including exophthalmus and brown pigmentation encircling the eyes in our cases of iodine hyperthyroidism which, as is well known, at the present time are extremely frequent in southern Germany. The psychic manifestations appear to me to be the same in both diseases. Weakness of the lower extremities can be demonstrated in both diseases, often so outspoken that the patients are unable to assume an upright position after squatting. It is extremely interesting that a true peripheral polyneuritis with severe atrophy of the lower extremities and loss of the reflexes may be associated

with this lower extremity weakness. It is well known that anomalies of function and anatomical changes in the genital organs may be present as well in genuine exophthalmic goiter as in Jodine-Hyperthyroidism. Impotence as well as reduction in the secondary sexual characteristics is the rule in both. Both disappear when an Jodine-Hyperthyroidism is cured. The frequency of the combination of goiter and Basedow with myoma and ovarial disease is very striking in the female. One is inclined to assume a disturbance of ovarial function as cause for the abnormal stimulation to proliferation in the uterine musculature, since the uterine myomas recede after exhaustion of the ovaries in the climacterium or following X-ray radiation. Maurer in his communication from the childrens clinic in Munich has shown that the ovaries have an exceptionally high iodine content like the thyroid and I know of cases of uterine diseases in which attacks of auricular fibrillation with delirium cordis appeared regularly during menstruation just as in exophthalmic goiter and in hyperthyroidism.

Iodine in Ovary

One might be tempted to hold up the low iodine content of the thyroid and the high iodine of the blood as characteristics of genuine exophthalmic goiter in contrast to the secondary hyperthyroidism following the use of iodine, for the thyroid enriches itself considerably following iodine treatment. But iodine-poverty of the thyroid in true Basedow is not a rule without exceptions and the thyroid stores considerable amounts of iodine following the treatment of exophthalmic goiter with iodine as has been shown by our studies and those of Neergard. Moreover a high iodine content of the blood is no certain characteristic of exophthalmic goiter or hyperthyroidism, for it is found in goiter unassociated with symptoms of hyperthyroidism, after the use of iodine. I believe that one will not obtain very useful enlightement from studies of the thyroid itself or the iodine content of the blood. Besides the determination of minute quantities of iodine are so difficult that they only give reliable results in the hands of chimists especially trained methods. The difficulties of a clear differentiation between true exophthalmic goiter and hyperthyroidism are very great and in the practice of medicine it will be necessary to reckon only those cases with the genuine Exophthalmic Goiter in which no iodine has been consumed within a corresponding period of time. In many cases of hyperthyroidism we do not know that there has actually been a consumption of iodine. Often the patients are ashamed to confess

I quite agr

a previous treatment at the hands of a charlaton. Sometimes the patients and their doctors are not informed as to the iodine content of their medicine, for example as to the iodine content of Yatren or certain medicines which are used in the treatment of arteriosclerosis, high blood pressure and obesity. At least the most important symptoms are common to true Basedow's Disease and Jodine-Hyperthyroidism, first the increase in oxydation processes which we estimate in the basal metabolism and second the tachycardia, to which is often added during the progress of the disease extrasystoles, and true paroxysmal tachycardia or constant auricular fibrillation.

Heart crises are a very much-feared phenomenon during the course of operative procedures on the Basedow thyroid; i. e. attacks of extreme tachycardia. The assumption seems plausible that an outflow of thyroid hormone into the blood is produced by the manipulations and consequent pressure upon the thyroid gland during operations and that this secretion influences the heart, especially the auricles. This clinical observation could be examined in animal experiments. Although Leon Asher could find no remarkable effect of thyroid gland extract upon the isolated animal heart, my former assistant Dr. Lauter on the other hand was able to produce outspoken effects upon the heart isolated according to the Langendorf method. He found a marked stimulation of the activity of the auricles even up to auricular fibrillation. Kurt Felix repeated these experiments on isolated rabbit and frog hearts in my clinic and could produce with thyroid gland juice as well as with synthetic thyroxin definite toxic injury of the hearth with partiel heart block (2 : 1) and even complete heart block when strong concentrations, 1 : 1000, 1 : 10,000, were used. These hearts began to contract again when the thyroid extract was washed out and could be stopped again by renewed addition of thyroid extract. On the other hand smaller concentrations, 1 : 1'000'000 increased the force and amplitude of the heart beat in Felix and Roberts experiments. It is interesting to learn that Dr. Graiter of Cincinnati has observed partial heart-block with 2 : 1 rythm and sinusarythmia with flutter and fibrillation in Basedow patients. Professor Biedl communicated to me orally that he has produced auricular fibrillation in isolated animal hearts by means of thyroid extracts.

One is compelled to conclude that, since the clinical picture of true exophthalmic goiter agrees essentially with that of Jodine-Hyperthyroidism, Basedow's disease is a hyperthyroidism, i. e. a

quantitative increase in thyroid function, though dysthyroid phenomena play a certain part in the disease. This hypothesis is supported convincingly by the experience of the surgeons. It is true that not every case of exophthalmic goiter is completely cured by a removal of a part of the thyroid gland and not infrequently residual symptoms, as, for exemple, exophthalmus, show themeselves. But the immediate reduction of the basal rate following thyroid gland reduction, moreover the quieting of the heart and of the psyche are so convincing, that one must consider the quantitative element as the most important factor. Moreover, the number of cases is not small in which, following the extirpation of a large part of the thyroid, the picture of hyperthyroidism suddenly goes over into the picture of Myxoedema concomitant with a considerable fall in the basal rate, for example, from + 50 to — 25.

It is true that the nature of Basedow's disease is not fully explained by the assumption of a hyperthyroidism. Such facts as the frequent ocurrence in persons who previously showed nervous stigmata, as the occurrence in many members of the same family and as the occasional combination with typical asthma and other pathological symptoms of an anaphylactic type have suggested that a constitutional nervous fundament is at the bottom of this disease. This opinion has considerable probability in favour of it, but experiments are lacking to prove that such individuals are hypersensitive toward the injection of thyroid extract. Dr. Bauer working in our clinic has found that a given quantity of thyroxin causes the same or higher rise in basal rate in normal individuals as it does in patients with hyperthyroidism. Here then is no evidence that patients with hyperthyroidism are any more sensitive to thyroxin than normal persons. It has been considered that exophthalmic goiter developes on the basis of a sympathicotonic constitution, but we must not forget that the expressions vagotonia and sympathicotonia are nothing but a slogan having nothing or little to do with the anatomical vagus and sympathetic nerves. Symptoms of vagatonia as well as sympathicotonia are both observed in Basedow's disease.

The dangerous symptomatology of Jodine-Basedow is accompanied by a rapid reduction of the goiter. Since the microscopic examination of such goiter points to a liquefaction and absorption of colloid, it is not improbable that the iodine not only activates and liquifies but also causes a resorption of colloid. An other fact stands in some contradiction to this experience. Halsted

action of iodine on colloid

observed that the colloid in the remaining half of a dog's thyroid quickly shrank after the extirpation of the other half, but that this disappearance of colloid could be prevented or could be made to return when the animal were given iodine. He showed with his experiments on dogs that the feeding of iodine would cause colloid to collect in the thyroid alveoli. Following Halsted, other investigators have shown that an enrichement in colloid results from iodine dosage. We therefore see that iodine is able to favour colloid augmentation as well as colloid dissipation. We are here confronted with a puzzle which can only be overcome by means of hypotheses, and for such hypotheses I would like to suggest the German term « Ausreden » or evasion. One can, if so inclined, call upon analogies: insulin furthers the glycogen-storage in the liver and, on the other hand, it furthers the oxydation of sugar and therefore the disintegration of glycogen.

The ability of the thyroid gland to take iodine from foodstuffs and to collect it as supply as well as the striking effect of iodine upon the thyroid has led to different explanations. Many authors consider that iodine is only an activator of the thyroid. This view cannot be maintained since the discoveries of Baumann and Kendall, which have shown that iodine is a component of the active substance of the gland. Kendall's formula for thyroxin as a triply iodized derivative of Tryptophan can no longer be maintained. Harington's constitutional formula of a combination of two thyroxin molecules to each of which two iodine atoms are attached has proved to be the right one, and has been substantiated in the synthetic production of thyroxin. Dr. Baur in my clinic has experimentally shown on animals and on man that this synthetic product brings about the same increase in metabolism and pulse-rate in man and the same phenomena on the animal heart as are produced by thyroid extract. It is therefore justifiable to consider thyroxin as the essential hormone of the thyroid gland.

The fact that the thyroid gland enlarges at very definite periods of life, namely during the school age and during pregnancy, together with the observation that treatment with iodine during these periods practically nearly never is harmful but is outspokenly beneficial, seems to point to an increased need for thyroid hormone during these periods in which enlargement and developement of the body, especially of the genital organs, take place. Our knowledge of cretinism strengthens this opinion: cretinism is probably on the whole conditioned by lack of normal thyroid function, in which we observe characteristic

disturbances of developement and the processes of growth especially in the bones, ear, and the central nervous system. The present exhibition demonstrates convincingly these developemental disturbance on the skull, on the thigh-bones and on the hands etc. The rocking gait so characteristic of cretins is explained by the deformity of the hip joint. The lack of closure of the epiphyses on the clivus as well as on the extremities shows that the possibility of growth was present here for a long time but the stimulus to growth was absent. This stimulus comes apparently largely from the endocrinal glands. Cushing has pointed out the close relation between hypophysis and thyroid gland in this connection.

Hypertrophy of the thyroid has been looked upon as a sign of increased need and this is true to a certain extent. But I doubt whether it is possible to explain every kind of hypertrophy and hyperplasia as a consequence of increased need. Not every stimulation to growth is a symptom of need, for then it would be necessary to explain hypertrophy of the prostate on this basis. Possibly this is in agreement with the observation that goitrous women especially such as have exophthalmic goiter at times bear children which have the sign of a Blastophthoria, that is signs of degeneration of a generalized type which cannot be simply classified under cretinism and Myxodema.

Agreement as to the conception of thyroid adenoma is much to be desired. Plummer goes so far as to declare every thyroid gland as adenomatous in which he can feel a circumscribed nodule, and he speaks of toxic adenoma as soon as signs of hyperthyroidism are present together with nodular thyroid gland. But nodules are present almost always in the goiter of older persons, these nodules exhibiting a similar histological picture as the remaining strumous thyroid. Hyperplasia occurs frequently in the form of nodules and we can follow the formation of such nodules from their beginning, that is from the budding which grows into the ground substance and developes into round nodules. Is it proper to call such nodular hyperplasias true neoplasms in Virchow's term and therefore adenomas? Without histological examination this is certainly not possible and in our clinical terminology it is necessary to confine ourselves to the expression struma nodosa. There exists an other form of nodules, which show on section usually macroscopically a uniform consistency and colour and are notable for their lack of colloid and which have histologically a completely different structure than the colloid nodules. I mean those round structures which do not seem to develope from a circumscribed

formative center, but in which a thick mass of small colloid-free vesicles is observable in the whole of the periphery, which are less frequent towards the center and which there are separated by hyalin ground structure. In this latter condition there is something entirely different, and I propose to confine the expression « adenoma » to these microfollicular colloidfree structures. According to the investigations which Dr. Spatz carried out in our clinic, these nodules are only slightly or not at all effective in tadpole experiments. In fact, according to Dr. Spatz the circumscribed nodules have often less, and only very seldom a greater biological effect than the ground substance. Especially goiter which develops as recidive after thyroid operations, exhibit an exceptionally low content on iodine and a very slight effect upon tadpoles. Perhaps it would be possible to prevent these recidives following goiter operations especially in young people, by giving iodine.

The questions whether, and in what dosage, iodine should be given in the prophylaxis and treatment of goiter and Basedow's disease and whether the minimal amounts of iodine actually preclude an iodine hyperthyroidism are, as is well-known, answered differently. It has been my impression that the amount of iodine is of relatively minor importance, since the larger part of the iodine leaves the body in the next thirty-six hours. The duration of the treatment is more important. The susceptibility of the individual is primarily the determinig factor in the question whether a useful or harmful effect is to result from iodine treatment. At present this question is incalculable. We can only say that a harmful effect from iodine is very infrequent up to twenty years of age and that the benefit prevails in this period of life. From the twentieth year on, harmful effects from iodine become more frequent and especially in the fourth decade, at least in Bavaria, and so in other countries, these harmful effect are so numerous that not infrequently extreme damage is observed following a longer exhibition of the smallest dose.

Goiter and Vegetative Nerve Systeme, Iodine Metabolism, Goiter and Graves Disease.

By Prof. Dr. W. H. Veil,
Director of the University Medical Hospital at Jena.

Ladies and Gentlemen! We are discussing the pathological physiology of the goiter. Apart from the many secondary questions to which the localised peculiarity of the formation gives rise, the chief question for our consideration has regard to those particular laws which, deviating from the norm, have arisen in the physiological course of nature in any organism owing to the presence of goiter. This has been made clear to us in a most exemplary manner in the report of our pathological-anatomical speaker, and particularly by the drawing of the life curve of the thyroid gland. I do not consider it justifiable to put the two diseases (1) Endemic Goiter and (2) Cretinism under one heading. For the combination of these two maladies, although they often do appear together, especially here in Switzerland, can by no means be said to be an unfailing rule. For instance, it hardly applies at all to Upper Bavaria, where I have made my observations from Munich. With regard then to my own experiences I shall confine myself to the consideration of endemic goiter.

Permit me, as a specialist for internal diseases, to treat the matter from a somewhat more general point of view than has been done in the preceeding discussions. A specialist like myself is bound to consider these things in a general way. He must put the single organ on one side, and concentrate on the condition of the organism in general. For here and not in the one particular organ is for him — health or disease. We are only just beginning to be able to judge as to the extent to which endemic goiter can transform normal general conditions. It is for this very reason that up to now goiter research has mostly taken but a small part in internal medicine, but has been chiefly relegated to surgery or to purely practical medicine.

We cannot speak right away of a pathological physiology of endemic goiter. In the first place it implies a special physiological process in the endocrinic region. We doctors must not overlook this fundamental fact, and we must recognize with absolute clearness that in carrying out goiter therapeutics, we not only bring about an

alteration in the physiological conditions, but also that to a certain extent we artificially introduce a pathological condition. It can even happen under certain circumstances, by means of these therapeutics, i. e. the effect caused by these on the organism, that we are enabled to observe the actual pathological physiology of the goiter. This applies to-day in many respects to iodine therapeutics.

The hyperplastic growth of goiter in certain districts, i. e. endemic goiter, assumes for these parts of the earth, as we have already heard, almost the nature of a physiological condition. This also arises not infrequently as the result of surgical therapeutics: that which has been artificially removed soon grows again. Here we have a clear proof of the compelling force of nature to increase glandular growth. It is true that this very often oversteps the limit. This is due to the fact that parenchymatic hyperplasm is particularly favorable to the growth of adenom ganglions. These are the first signs of an actual pathological process, without necessarily involving any immediate change in the physiological condition. Just as this natural force brings about a hyperplastic growth of the thyroid glands, at the same time in a parallel manner it is a hindrance to the development of genuine Graves disease. This double law of morbidity in its positive and its negative form applies, as we have already heard, in general to all districts in which endemic goiter occurs.

Tomorrow, the day of the aetiology of the goiter, we shall discuss wherein this force of nature lies. But it is permissible for me already to-day to endorse the opinion of the speaker on anatomy, that what we are wont to term endemic goiter, if we exclude infectious causes, developes far more on the basis of physical-chemical and purely physical peculiarities of the surroundings, and that in close connection with these, the nerve system, especially the vegetative nerve system and its centres play a very important role.

At the same time, the question of hereditary constitution must not be ignored. There can be hardly any doubt that endemic goiter belongs to the factors which produce constitutional variants. In spite of the favorable possibilities for research as to the hereditary conditions of endemic goiter, we are in possession of very little reliable information with regard to this. But it must be recognised that at this point endemic cretinism comes into direct relation with endemic goiter.

Now what constitutes the physiological fundamental fact of goiter? Our starting point must be the physiology of the thyroid

gland, and Herr Breitner's opinion that we know very little about this is not correct. We are well acquainted with a condition where the thyroid gland is missing. It is just this condition which characterises the fundamental fact of the physiology of the thyroid gland.

I should like here to call attention to only one of the universal traits of this condition, referred to by my pupil Schliephake at the last German Congress for International Medicine at Wiesbaden, where he described the effect produced on the vegetative nerve system by the loss of the thyroid gland. The researches were made at the EKG on dogs in whom the thyroid gland was missing. The results showed a great deviation from the norm in this important process in the vegetative nervous functions of the heart; Adrenalin and Cholin, these activatories of the vegetative nerve system showed a considerable change in their activity and became more dangerous. The vegetative nerve system became the plaything of the moods of such activatories. The stable reserve of the vegetative nerve system had simply disappeared.

From this we may infer that: the hyperplasm of the tissues of the thyroid gland which, when removed, causes insufficient action of the vegetative nerve system, will, on the other hand, increase the stability of the same.

Consequently our first thought must be: the conditions which prevail in the milieu where endemic goiter develops, are in themselves a danger to the vegetative nerve system. Every medical man is aware that the power of resistance of the vegetative nerve system differs according to the telluric and cosmic influences by which it is surrounded. It is not necessary for me to cite the influences of certain special cosmic phenomena on sleep, blood pressure, action of the heart, breathing, on the sensitiveness of the head and on the susceptibility to migrane in districts where foehn is a frequent occurrence.

That goiter is in some way connected with all this is no idle fantasy. In collaboration with my pupil, Alexander Sturm, I have been able to verify the fact that in a person with goiter, the oscillations produced by the seasons of the year in the iodine consistency of the blood are non-apparent, as compared with those in a person without goiter in a goiter district (Munich). This is only one example of the increased stability which the vegetative nerve system acquires through the presence of a goiter, a mere fragment, it is true, but nevertheless, of importance for the conclusions to be drawn with regard to the entire physiology.

In spite of Mr. Blum's criticism we uphold the fact of the existence of an iodine level in the blood. This criticism of the Fellenberg Method is no doubt due to lack of personal experience just with regard to this method. I should be pleased to demonstrate this to Herr Blum in my own hospital. Had the Blum-Grützner method fulfilled their expectations, the Fellenberg method would never have been discovered. This latter method surpasses the former to such a high degree, that it is the only one suitable for application with respect to the biological procedure of the iodine metabolism of the organism. In connexion with this objection to Herr Blum's theory as to the iodine level of the blood, I beg to refer at the same time to other opinions held by him .He spoke of the necessity, when making experiments with regard to iodine metabolism, of giving nourishment free of iodine, and he declares that having used this method he found the blood to be free of iodine. Nourishment free of iodine is an impossibility. How does Herr Blum propose to remove all traces of iodine from the different forms of nourishment? This is also not in the least necessary. For starvation treatment tried both on animals and on human beings has proved with absolute certainty that even under these conditions the blood firmly retains its iodine.

It is this iodine level of the physiological creature that is the characteristic sign of the iodine metabolism in the blood in general. It is a purely endogenous affair. It proves that iodine metabolism undergoes exactly the same process as, for instance, the carbohydrate metabolism.

Already in earlier studies made together with Alexander Sturm, it became clear to us that the thyroid gland is the determining factor for the existence of the iodine level. This fact seems to me to have sustained still further proof through our more recent studies, which will be published shortly. The researches were made on dogs, and the examinations regarding iodine metabolism were undertaken both under normal conditions and under those in which the thyroid gland was missing, and the results then compared together. The removal of the thyroid gland first of all caused a strong effusion of iodine through the urine, also an extreme diminution of the iodine level of the blood, further causing the blood from now on to be entirely dependent on an exogenous supply of iodine: in a state of starvation the very lowest proportion of iodine was apparent, and after partaking of food appeared an increase in the proportion, just as would be the case in a healthy human being.

If we take into consideration this mechanism of the regulation of iodine by means of the thyroid gland, then we must admit that in that compulsory force of nature which leads to the hyperplasm of the thyroid gland i. e. of endemic goiter, the fact is concealed of a regulation of the supply of iodine on a new and larger basis. One might say, that this larger basis involves at the same time a refining tendency in the regulating mechanism. The increased susceptibility with regard to iodine in those districts in which endemic goiter prevails, proves that the entire apparatus has become more sensitive.

For what purpose does the organism require this iodine regulation? In the first place it requires it because it needs iodine, and secondly because it needs protection against iodine.

The protection lies in the regulated discharge of iodine through the urine. Even in a state of starvation this contains a fairly equal amount of iodine. A normal organism manages in a characteristic manner to get rid of any larger quantities of iodine which may have been introduced into the body. In a larger quantity of material under examination, about the same proportion per cent of the amount introduced will be discharged on the first, then on the second and finally on the third day after the introduction of iodine.

The necessity of iodine for the organism, however, does not seem to be determined only by the necessity for thyroxin. Iodine is also an important Ion in the metabolism of the nerve system, especially of the vegetative nerve system, in fact is evidently just as important as the ++Ca, the +K, the +H or the —OH. In contrast to the susceptibility of the nerve system occasioned by overflowing the organism with iodine, its amazing healing power must be emphasised in vagotonic conditions, such as vagusneurose, and more particularly e. g. in bronchial affections and asthma.

But if the organism has once adjusted itself to the enlargement of the thyroid gland in this fine iodine mechanism of its metabolism, then a sudden exogenous increase of iodine has a deleterious effect, because the «workshop» for the production of thyroxin being enlarged, the introduction of iodine into these enlarged spaces leads to a disproportionate production of secretion. This explains the danger of iodine, more especially in districts where goiter prevails, and particularly in those cases in which it is continually partaken of, even in a quantity almost physiological in form, measured according to the conditions of low lying districts.

The exaggerated formation of thyroxin leads at the same time to a far greater loss of iodine externally, i. e. the discharge of iodine

through the urine increases. Graves disease which, on the one hand, involves an increased formation of thyroxin, proceeds in the most extravagant manner with the iodine. This explains the final fundamental truth of which I wish to speak: if, in a case of Graves disease we suddenly introduce a larger quantity of iodine, e. g. 5 gr. JK, then the important fact becomes apparent (again in my researches together with A. Sturm) that this introduction of iodine causes a sudden alteration in the machinery for the endocrinous iodine supply. The thyroid gland, instead of throwing off thyroxin into the circulation — perhaps in the interest of a product of a higher quality than the Basedow thyroxin — retains both iodine and thyroxin simultaneously; the proportion of iodine in the goiter becomes absolutely positive, the symptoms of Graves disease diminish. It is just in this fact that I perceive the proof of the diminution of thyroxin in the circulation, and for its retention in the thyroid gland. The effect may indeed be called magical in the strongest meaning of the word. No doctor would have up to now thought it possible in certain cases which belong in this category — of Thachycardia and Arrhythmia, e. g. one case in my own personal experience of recurrent auricular-extrasystolic form, only distinguishable in the EKg from the perpetua, pulse 160 per minute, — that any other treatment except with « heart remedies » could have had any therapeuthic effect; and yet, nevertheless, just in this above mentioned case, which appeared to be hopeless, the half gramme KJ caused the pulse to become regular, 76 in the minute, and this in the course of one day.

It seems that herein lies the point, in which is to be found the justification and foundation for the characterisation of the cases brougth forward by Plummer, which, just now, not without reason called forth some criticism by Herr Geheimrat Müller. It frequently occurs, that in cases of Struma basedowificata, this retention of iodine discovered by us, and the favorable effect which runs parallel to it, fails to appear after one big dose, whereas a case of genuine Graves disease nearly always shows this reacfion. At the same time we have known cases of Struma basedowificata, (e. g. in an American woman from a place with endemic goiter, in whom possibly an American full salt had basedowed the goiter) in which the favorable effect of iodine as well as iodine retention was positive beyond all doubt.

As already mentioned, we are only acquainted with fragments of the physiology of endemic goiter, but if one pieces these fragments together, it is possible to obtain a living picture of the whole,

above all for the medical man, who is accustomed to think in symptoms, that is in fragments, and to build up on symptoms; we are all the more in a position to do this after the stimulating and vivid description of the pathological anatomy of the organ which has been brought before us.

But this picture will become still more vivid when we succeed in making the echos of this first goiter conference resound in full force in future decades and generations, whose task it must be to garner the seeds sown by us to-day in goiter prophylactics, in a statistic and individual pathological manner.

Supplementary Demonstrations with 6 Curves,

to the lecture of Prof. W. H. Veil,

by Dr. Alexander Sturm, Assistant in the University Medical Hospital at Jena.

You will allow me in connection with Prof. Veil's lecture, by means of diapositives to demonstrate to you the most important results of our experiments with regard to iodine metabolism:

First of all our experiments on a dog in whom the thyroid gland is missing!

Illustration 1. — A normal dog taking strengthning nourishment and liquid to the amount of 500 ccm daily, discharges 400—500 ccm urine, the entire iodine contents of which are 40—60 millionth grammes (the hatched columns show the quantity of urine, the black columns the entire iodine contents in millionth grams). After three days starvation the quantity of iodine in the urine is naturally diminished, does not, however, disappear altogether, but keeps up to 20—30 millionth gram. After a total extirpation of the thyroid gland, which is carried out under most careful treatment of the subsidiary thyroid gland, a strong flush of iodine ensues, lasting more than eight days. As much as 80—120 millionth gram iodine leaves the body. This increased discharge of iodine cannot be explained by the mechanical infusion of thyroid gland juice containing iodine into the blood and lymph channels during the operation, as is shown by the model experiment: an intramuscular injection of thyroid gland juice was given to a dog; the slight increase in the discharge of iodine which this incurred, disappeared after one day. The flush of iodine after the operation

Iodine m
Starvation

Thyroid-
ectomy

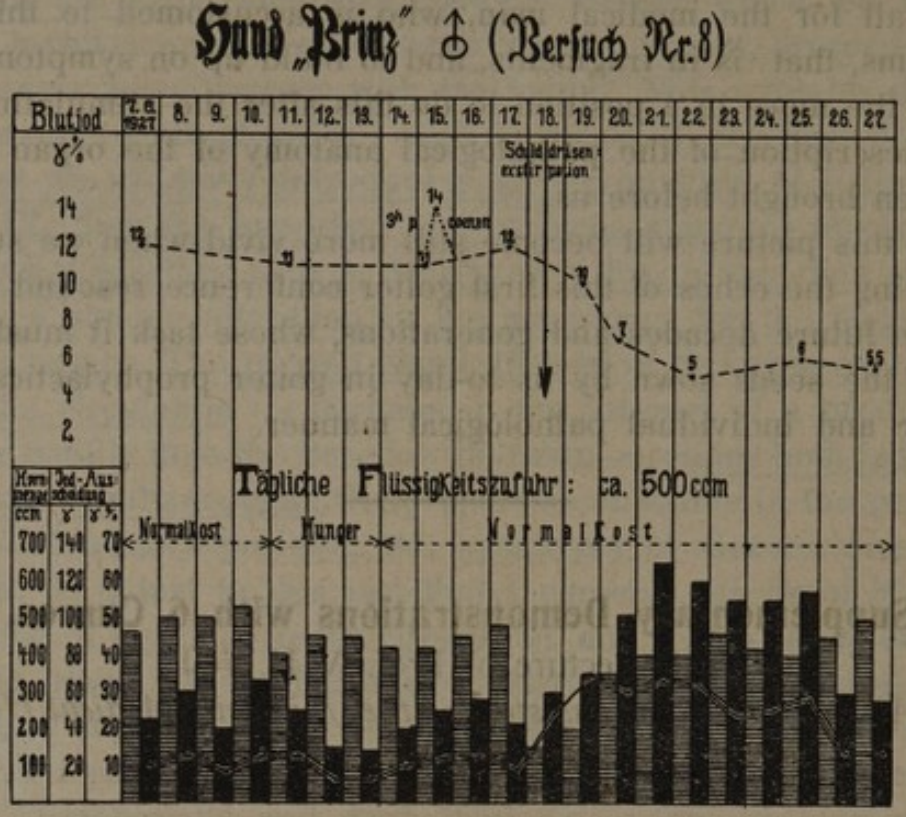


Fig 1.

must therefore be a discharge of iodine out of the body itself. In the pre-experiment period we find an extremely constant iodine level, which goes on existing even in a state of starvation, and is only very slightly increased after strong nourishment. Through the extirpation of the thyroid gland, the iodine level sinks rapidly during the days after the operation, reaching its lowest level on the 5th or 6th day, and keeps at this level for a long time. The lowering of the iodine niveau of the blood is to the amount of about half the quantity discharged.

Illustration 2. — The same experiment in the period when the thyroid gland was missing!

With normal diet, also normal discharge of iodine as in the pre-experiment time. If we let the dog starve for three days, the quantity of iodine discharged in the urine sinks to the minimum degree (5—7 millionth gram). In the blood the low value of iodine is found only in a state of fasting and starvation; after strong nourishment, the quantity of iodine in the blood is raised suddenly to a double and triple proportion of the amount discharged. At this point an actual iodine level is missing. The removal of the thyroid gland seems to bring about an elimination of that factor on which the constancy of the iodine contents of the blood depends.

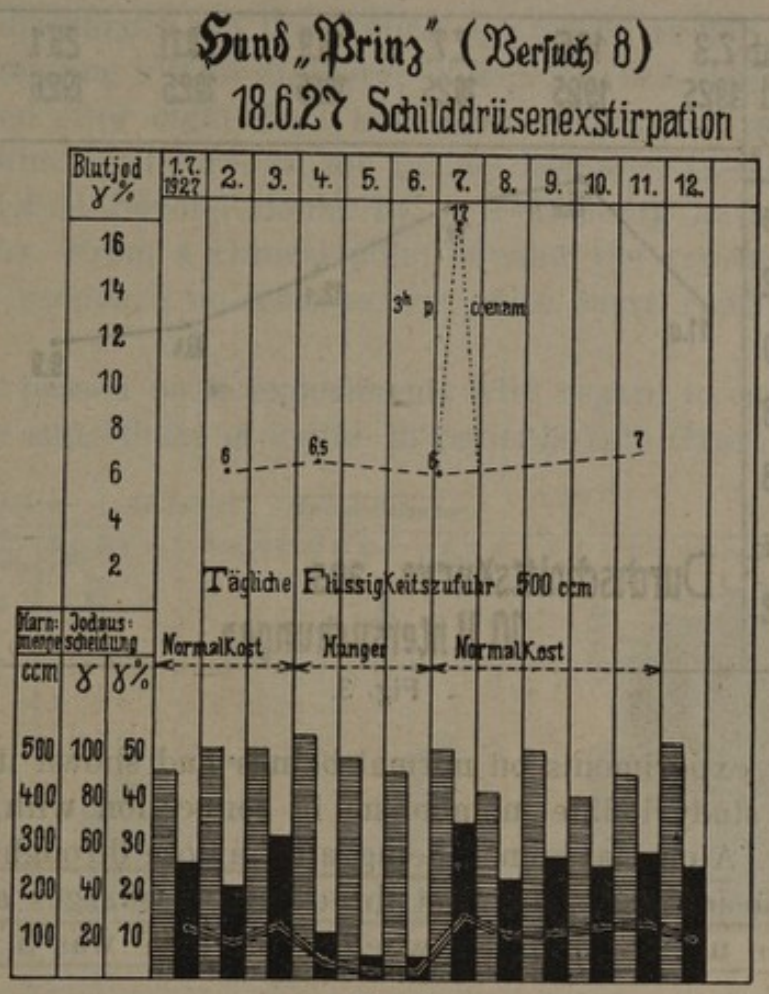


Fig. 2.

Thereby we see what an important role the thyroid gland plays in iodine metabolism; it seems to constitute the regulator in the iodine consistency.

Further I will give you a report of the examination undertaken with a view to verifying the influences of the seasons on the iodine contents of the blood. The examinations were carried out on ten men, all living under the same dietic conditions, in the Romberg Clinic at Munich, and were made by Professor Veil and myself up to the 30th of September 1926. The results were as follows: Season

Illustration 3. — This represents the average curve of the iodine contents of the blood; it rises in May, sinks slowly in November, in January the lowest level is reached. This proves that the iodine contents are obviously influenced by the seasons of the year.

Finally, our experiments with regard to iodine metabolism in hyper-thyreoses!

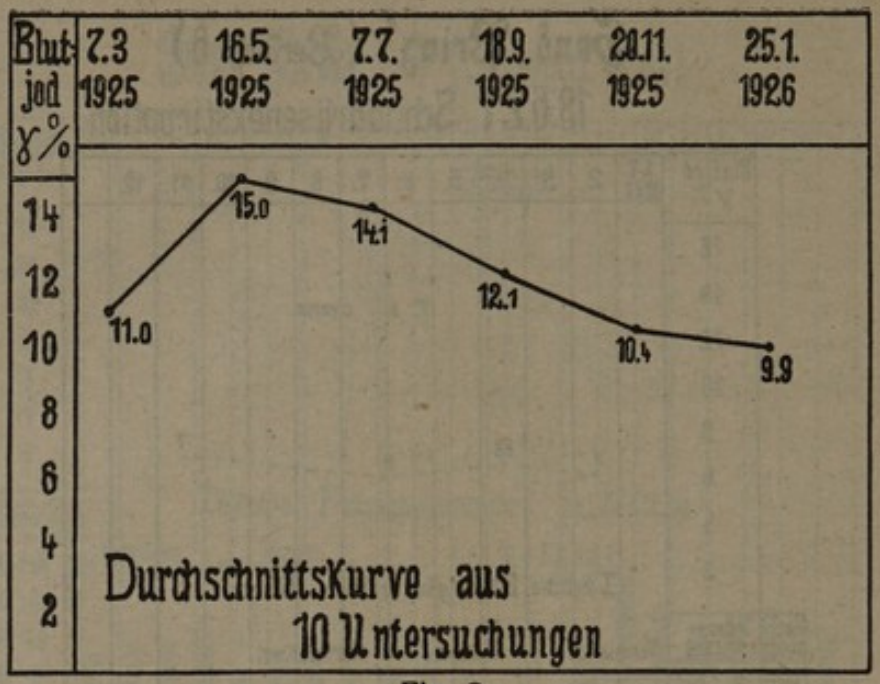


Fig. 3.

Former experiments on normal beings had shown it to be advisable to study iodine metabolism in connection with an iodine superfluity. A normal human being, after a dose through the mouth of inorganic iodine, in the first three days discharges about 75 % through the urine, no matter whether the dose was 5 or 500 mg.

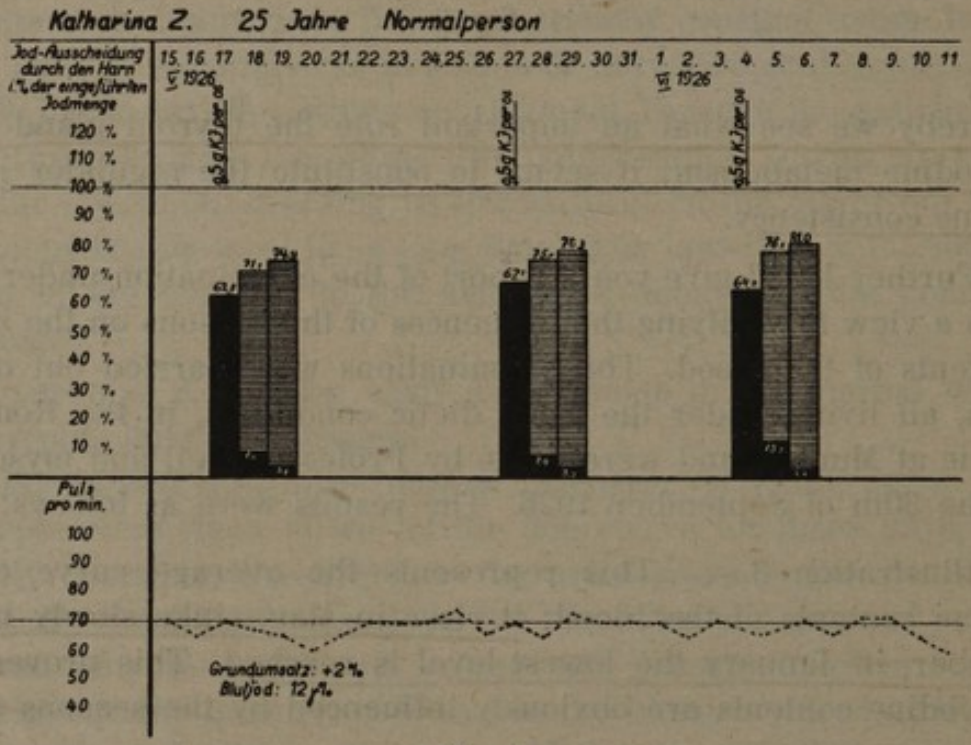


Fig. 4.

Illustration 4. — Shows a normal experiment; 0,5 g Kalium iodine was given per os. On the first day, 62,5 % of the iodine

given was discharged, on the second day 8,6 %, on the third day 3,8 %, this making a total discharge of 74,9 %. This dose of iodine was repeated after eight days, and again after three weeks with similar results. The curve of the iodine discharge as reported by us was verified beyond doubt by v. Fellenberg in subsequent examinations. From a clinical point of view the repeated dosing with iodine produced no reaction, the pulse curve remained quite unchanged.

We now passed on to experiments with regard to cases where there was a superfluity of iodine in patients with Graves disease.

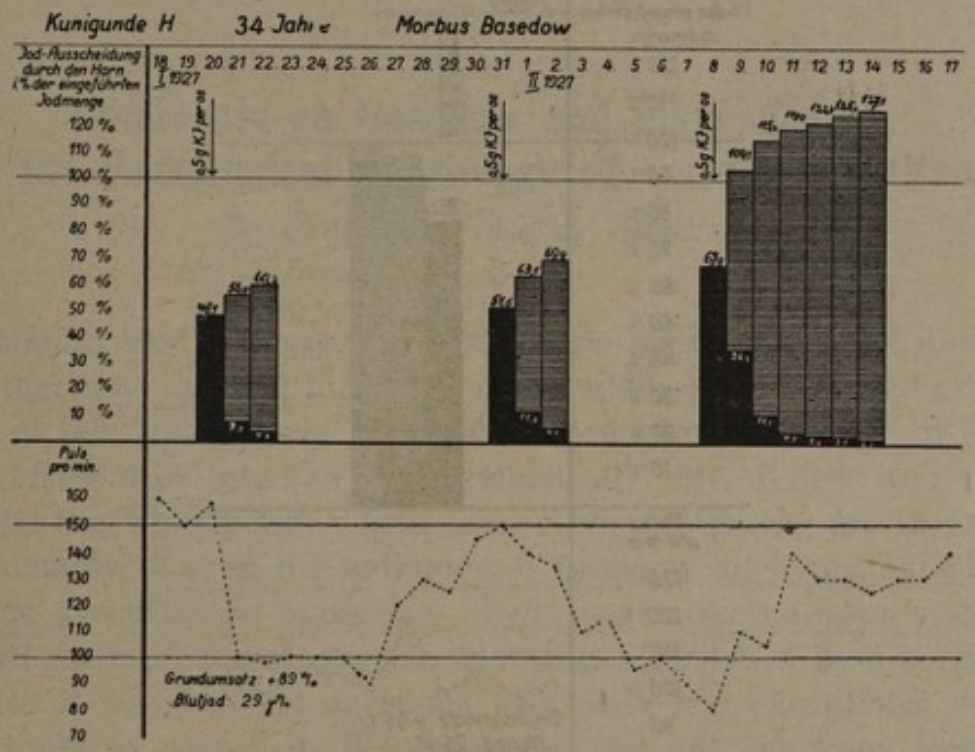


Fig. 5.

Illustration 5. — A patient with all the typical symptoms of Graves disease, suddenly taken ill in the midst of perfect health. After a dose of 0,5 gr. Kalium iodine, followed a most critical fall of the pulse curve, a sinking of the basal metabolism, a substantial subjective and objective improvement. Of the amount of iodine introduced only 48 % leaves the body on the first day, the total, amount discharged being only 60,2 %, thus showing a considerable retention of iodine. The favorable general effect of the iodine ceases after seven days, the pulse curve rises, but can be brought down again by a renewed dose of iodine. The third «push» of iodine produces quite a different result. After the dose of iodine there follows an intense and long flush of iodine. As much as 127 % of the iodine given will be found again in the urine, which

Retention of iodine

means that the iodine retained after the first dose is mobilised and discharged. And this time the favorable clinical effect is missing.

Eight out of twelve cases of Graves disease reacted in this manner. Four cases showed another type of reaction, which is demonstrated in Illustration 6.

After the dose of iodine the general condition of the patient immediately becomes worse, the pulse curve rises, the motory

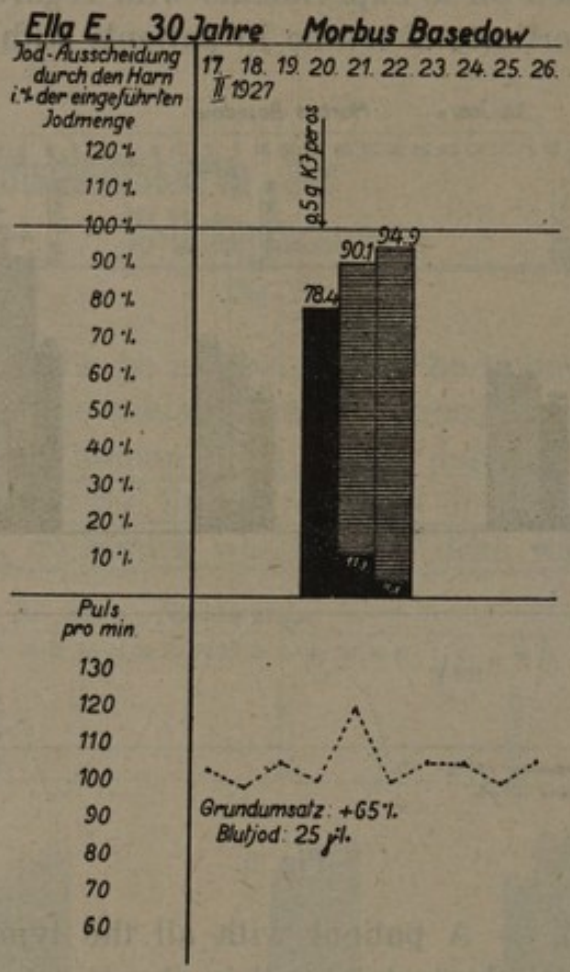


Fig. 6.

restlessness increases. In this case right from the beginning there was an increased flush of iodine in the urine. On the first day already, the body eliminated through the urine 78 % of the iodine given, and a total quantity of 94,9 %; if one takes into consideration that iodine is also discharged from the body in other excrements, then it is clear that the entire quantity of iodine introduced into the body has left it again within three days.

If the aim of our researches with regard to iodine metabolism in Graves disease was at first only physiological, all the more the parallel appearance of the clinical reaction after the dose of iodine

with its irrational behaviour in the discharge of iodine, produced most astonishing results from a clinical-therapeutical point of view. Whereas, the therapeutics for Graves disease consisting of large doses of iodine, as specified by Plummer from Rochester, and, following his example, recommended by Falta and Biedl, are dictated purely by clinical empiricism, the experiments in iodine metabolism supply us from the very first with directions for an individual, gratuated dosing with iodine, and enable us to give up iodine treatment before it is too late in cases where it is obviously not calculated to bring about favorable results.

Chemical control? Iodine-treatment

Comments on Basedow and Myxoedema and the Pathological Physiology of the Thyroid Gland.

By Professor Oswald, Zürich.

I should like to speak on a few of the many matters of discussion, that have sprung forth out of the addresses that were given. First of all let me say that the information imparted by Mr. Breitner has interested me immensely. Mr. Breitner has reached that standpoint, which I have been following for 15 years past, namely, that in the aetiology of Basedow an important place is to be given to the hypertony of the vegetative nervous system. It is all the more satisfactory to have this view taken by a surgeon because it was just the surgeons who, with few exceptions, were disinclined to accept it. We, however, can not get away from a dispositional supersensitiveness of the vegetative nervous apparatus, a hypervegetatony. The experiments on animals show that, and the observations made on man likewise make that clear to us. A human being with a nervous system, that responds normally, never shows any reaction with Basedow symptoms, not even after the intake of rather large quantities of thyroid hormones. All those, who respond to the intake of thyroid preparations with such symptoms, show a stimulus threshold of their vegetative nerves, which can be proved clinically and pharmacologically to have been diminished. There is likewise with genuine Basedow always a hypervegetatony present before the outbreak of the disease. The experimentum crucis of this conception is made evident through those cases, where a notable struma is dispersed under the influence of an iodine treatment, without leading to thyrotoxical

manifestations. I have observed characteristic cases of this sort. I may mention the case of a 64 year old man who was afflicted with a terrible struma, which had been dispersed in a very short time through an energetic iodine treatment, that however had not been recommended by me, and now there was at his neck only an empty pouch of skin, in which a woman's fist could comfortably lie, without having the least indications of a hyperthyroidism become manifest. The careful examination of the patient proved that the nervous system was entirely normal in its behavior. The patient was a well-to-do farmer who had always been accustomed to lead a very hygienic life. A hyperneurotonic person would have under the same circumstances developed a most perfect iodine-Basedow. The great significance of the condition of the vegetative nervous system is in agreement with the fact, that was brought out in the addresses, that the hyperthyroidism does not correspond to any typical histological structure. With the same histological character there can exist clinically a hyperthyroidism or not. An important genetic factor lies really without the thyroid gland. This latter is not at all responsible for everything. A similar discrepancy is seen in the paratoxically simultaneous occurrence of symptoms of Basedow and myxoedema in one and the same individual. The purely thyrogenic conception can not give us any explanation for this, unless it were to branch out to fantastic secondary hypotheses. A satisfactory explanation can, however, be obtained, if we do not consider hypervegetatony as an exclusive concomitant of Basedow and especially if we recognize in hypervegetatony a dispositional manifestation, which precedes the outbreak of the Basedow. If a Basedow passes over into myxoedema and tachycardia, dermographism, general nervousness etc. still continue with the fully developed myxoedema, then it really is not a question of symptoms of Basedow but of the indications of a hypervegetatony that had been present prior to the Basedow, even if it be in a naturally slighter condition.

We find hypervegetatonic characteristics also with hypothyrotics, who have never suffered from Basedow, e.g. with endemic infantile myxoedema. Here we can certainly not speak of Basedow symptoms. To be sure, for the appearance of so-called hyper- and hypothyrotic symptoms, that slough and in part forming layers, which have not seldom been observed in imperfectly and fully developed forms of myxoedema, we have easily made an explanation through the bringing forward the idea of the thyroideal instability. From the standpoint of the plain thyrogenic theory,

based on which it was really brought forward, it is a thing of impossibility, inasmuch as an insignificant plus in the thyroid function, as is required so that in a short time it can pass over into subfunction and alternatingly return and again pass over into subfunction, can never incite hypervegetatonic manifestations in a healthy, non-neurohypertonic human being. As we see, the necessity of an extra-thyroidal moment is also proved here i. e. the so-called hyperthyroidal symptoms are spontaneous, not thyrogenic manifestations.

Some influence of the nervous system makes itself also felt upon the struma itself, though in a different respect, at least the Basedow and the Basedowificized struma. It can be frequently observed that with the exacerbation of the condition of stimulation of the nerves the volume of the struma increases rapidly and with an improvement it just as rapidly diminishes. Here it is a question primarily of an influence upon the condition of fullness of the vessels. The autumn goiters, which can be observed with us, are swellings of this kind because of the nervous system having been rendered worse through the wet south-wind.

I made mention of endemic infantile myxoedema. I should like to explain this term in few words. In previous publications I pointed out that what we designate as endemic cretinism embraces at least two different conditions, viz., one affliction which is throughout identical with the sporadic infantile myxoedema, in which the thyroid gland is hypoplastic, and the goiter cretinism which embraces the cretins suffering with goiter, with whom the characteristics of myxoedema are scarcely or only a little impressed. These two categories react very differently on thyroid medication. The former, which embraces the thyrohypoplastic cretins, as I have called them, or as they can expediently be called, the endemic-infantile myxoedematous, react in extremely more favorable, oftentimes even prominent, manner on thyroid treatment, the thyrohyperplastic cretins, or goiter cretins react practically not at all. Notwithstanding that I am aware that pathologically-anatomically the thyroidea does not enable us to recognize any fundamental difference with these two categories, I should nevertheless like to make a distinction between the two groups from a purely clinical point of view, even if it is only in that sense that they represent the terminal members of one and the same series. Furthermore let me say that the goiter cretins are proportionally more frequent in the center of our Alpine endemic, e. g. in the Cantons of Berne and Aargau, than at the

periphery of the same, e.g. in the Canton of Zurich and those of Eastern Switzerland. We have reason to look upon the goiter cretins as those, who are afflicted the most. I should not like to ascribe the physical imperfections, such as we meet with in the goiter cretins, to, say, a qualitatively modified thyroid secretion, which can not very readily be accepted for general biological reasons, but to tissue products originating from the atrophically degenerated struma tissue, somewhat as they proceed from the carcinoma, but I should like to have this conception considered only in the light of a working hypothesis.

As far as accepting the idea of a multiplicity of thyroid secretions, as has oftentimes been done in medical writings for an explanation of Basedow and other conditions, this appears to me as non-acceptable for the reason that, on the one hand, thyroglobulin cures myxoedema and, on the other hand, the extract from Basedow struma and likewise the thyroglobulin obtained from it do not cause any Basedow in healthy animals. The recognition of the genetic significancy of a pre-existing hypervegetatony with Basedow relieves us from the acceptance of such a problematical and forced « dysfunction » of the thyroid gland, which is in no wise proved.

The fact that iodine is able to improve the genuine Basedow, but on the contrary renders the secondary Basedow worse, can according to my opinion find a solution in the property of iodine in promoting re-absorption. With genuine Basedow the proliferation of the thyroid epithelia is checked, with secondary Basedow the re-absorption of the deposited colloid is promoted. Through the same process there is less thyroid hormone introduced into the circulation in the former case and more in the latter.

As regards the thyroxine I should like to say that it probably contains the metabolism promoting qualities of the thyroid hormone and also its growth promoting, diuretic and still other qualities, but not the properties to increase the demands of the vegetative nervous system, which belong to the full thyroid extract and likewise the thyroglobulin. Therefore it must not be looked upon as the full thyroid hormone. Moreover it does not occur as such in the thyroid gland but it appears as an extreme product of decomposition of the thyroglobulin, as one of the many amido-acids making up the thyroglobulin as well as other albuminous substances, which is, to be sure, typical for thyroglobulin, but perhaps only through its iodine contents.

Remarks on the Pathological Physiology of Goiter.

By Johan Holst M. D., Oslo.

I. Latent and Monosymptomatic Thyreotoxicosis.

With the term of thyreotoxicosis I understand an increased function (with or without dysfunction) of the thyroid gland, and an inundation of the blood with thyreotoxic products. The clinical picture of thyreotoxicosis can in every singular case be regarded as a product of 2 factors:

1. The thyreotoxic influence on the organism.
2. The individually different reaction of the organism on the thyreotoxic factor.

It depends upon the degree of the thyreotoxic influence and on the reaction of the organism wether in the singular case is produced the syndrom of Graves (Basedows, Flajanis) disease or the symptoms of «hyperthyreoidism» or «formes frustes».

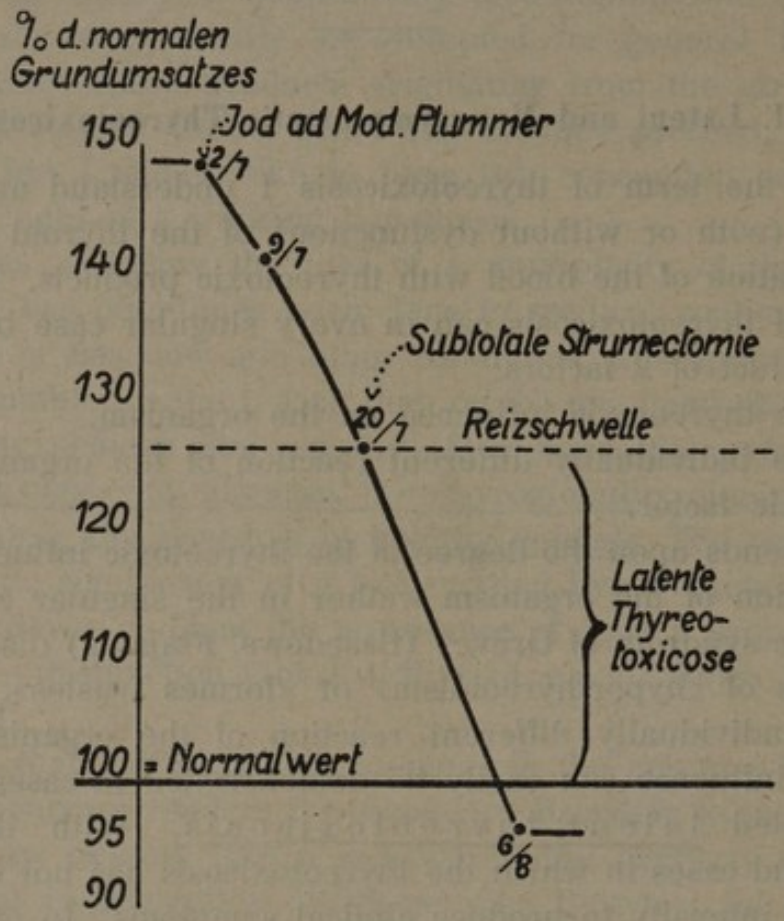
The individually different reaction of the organism on thyreotoxic influence can easily be demonstrated in cases of what I have called latent thyreotoxicosis. With this term I understand cases in which the thyreotoxicosis has not reached the sufficient intensity to produce clinical symptoms. In other words, the thyreotoxicosis has not reached the irritation-threshold («Reizschwelle») for the clinical symptoms, but its presence is demonstrated through the increased metabolic rate. The latitude of the latent stage — the niveau of the irritation-threshold («Reizschwelle») for the clinical symptoms is individually different. In one patient the irritation-threshold can be found at a metabolic rate of +10 (110 % of the normal metabolic rate), in another at a rate of +30 (130 % of the normal rate).

The irritation-threshold of the clinical symptoms and the latent stage of thyreotoxicosis can be demonstrated clearly in cases which are improving under the influence of iodine or surgical treatment. If we in such cases control the metabolic rate during the improvement we will find that in some cases the clinical symptoms disappear at a metabolic rate of +30, in others at +10; in most cases the symptoms disappear at a rate of +20.

The level of metabolic rate where the clinical symptoms disappear demonstrates the irritation-threshold of these symptoms.

From this level the metabolic rate (and the thyreotoxicosis) during the further improvment passes down to the normal through the stage of latent thyreotoxicosis as shown in case I (fig. I):

Fig. I.



Curve showing the metabolic rate (= „Grundumsatz") during iodine and operative treatment in Case I. „Normalwert" = Normal metabolic rate.

Case I. Woman aged 24 years, entered the clinic with fully developed symptoms of exophthalmic goiter. — Metabolic rate +48. — Iodine was administrated (Sol. Lugol. guttae XXXX pro die). In 11 days the clinical symptoms of thyreotoxicosis disappeared, and the metabolic rate was reduced to +26. — The niveau of the irritation-threshold for the clinical symptoms in this case accordingly was +26. Now was performed a subtotal strumectomy, and the metabolic rate in 3 weeks was reduced to —6.

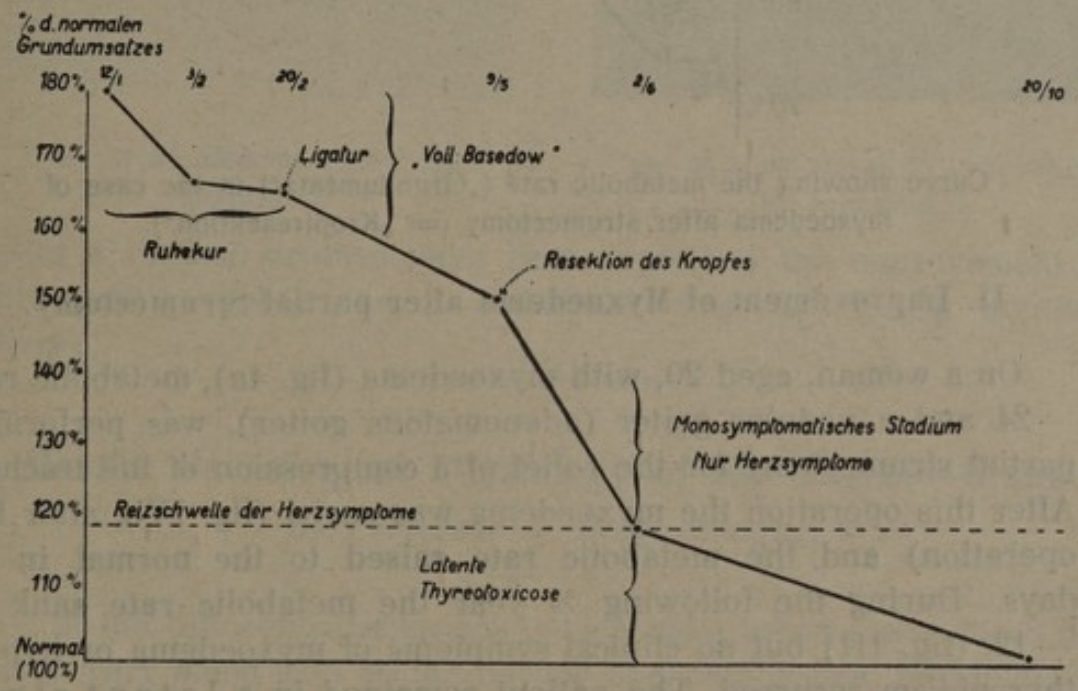
This example shows that we cannot be sure that a patient is cured when the clinical symptoms disappear. The thyreotoxicosis is not cured before the metabolic rate is normal.

Especially for the surgeon it is of importance to know the existence of a latent thyreotoxicosis, because most of the clinical recidivs after surgical treatment occur in cases where the thyreo-

toxicosis has not been cured through the operation, but only has been reduced to the latent stage. If there remains after operation a latent thyreotoxicosis, it shows that the operation has not been radical, and that special precautions are necessary to prevent a clinical relapse.

The niveau of the irritation-threshold of the symptoms from the different organ-systems is also varying individually. In some cases we can see at a metabolic rate of +35 only nervous symptoms, in others only heart-symptoms, in others only diarrhoea. The explanation of such cases what I have called monosymptomatic thyreotoxicosis is, that in these cases the irritation-threshold of the one clinical symptom, or the one group of clinical symptoms present is low, while the threshold for non present symptoms is high. This is demonstrated in case II (fig. 2).

Fig. II.

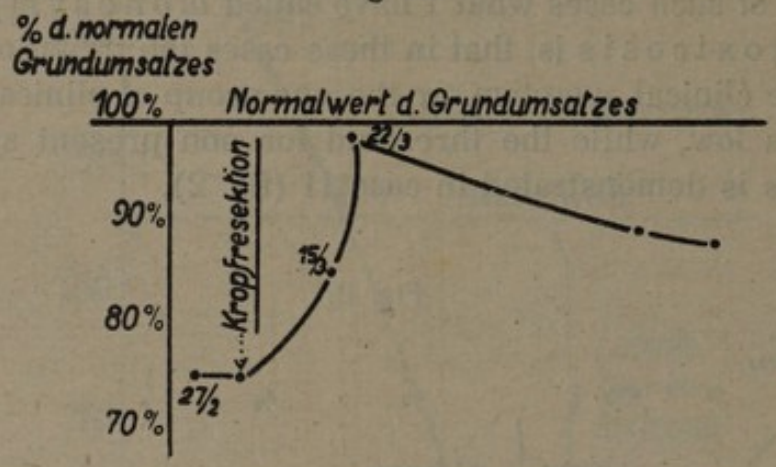


Curve showing the metabolic rate (= „Grundumsatz") in Case II.

Case II. The patient entered the clinic with the classical syndrom of exophthalmic goiter («Voll-Basedow»). Metabolic rate +80. — After a two-stage-operation the thyreotoxicosis succesively improved and passed from the fulldeveloped syndrom of Graves disease through a monosymptomatic stage where only heart-symptoms were present, through the stage of latent thyreotoxicosis, and at last reached the normal.

The above mentioned individually different reaction of the organism on thyreotoxic influence will demonstrate the importance of general constitutional and inherited factors on the development of thyreotoxicosis. The reaction of a neuropathic individual on thyreotoxicosis will be another than that of a patient who before the outbreak of the thyreotoxicosis had a sound constitution. And it may be, that the classical syndrom of Graves disease («Voll-Basedow») in most cases occurs in neuropathic individuals.

Fig. III.



Curve showing the metabolic rate („Grundumsatz") in the case of myxoedema after strumectomy (= „Kropfresektion").

II. Improvement of Myxoedema after partial Strumectomy.

On a woman, aged 20, with myxoedema (fig. 4a), metabolic rate —24 and a nodular goiter (adenomatous goiter), was performed partial strumectomy for the relief of a compression of the trachea. After this operation the myxoedema was cured (fig. IVb, after the operation) and the metabolic rate raised to the normal in 14 days. During the following ¾ year the metabolic rate sank to —12, (fig. III) but no clinical symptoms of myxoedema or hyperthyreoidism recurred. The patient remained in a latent stage of hypothyreoidism.

Thyroid tablets or iodine was never given to the patient.

I suggest that the myxoedema was cured because the partial resection of the goiter has acted upon the remaining adenomata as a decapsulation: The thick capsules of connective tissus surrounding the adenomata have been opened through the resection.

In 1921 J. Hotz has published a case in the «Schweizerische med. Wochenschrift» (Bd. 51, nr. 50, p. 1153) resembling somewhat our patient. The case of Hotz was a cretin who improved

Fig. IVa.

Case of myxoedema before the operation.

Fig. IVb.

Case of myxoedema $^3/_4$ year after the operation.

after a radical strumectomy. Hotz explained the improvement in his case as being due to reduction of dysfunctioning thyreoid tissue.

On the Pathological Physiology of the Thyroid Gland.

By Professor A. Biedl, Prague.

In the different discussions, which have taken place, there has been very much said on the normal and pathological physiology of the thyroid gland, but nevertheless in a fragmentary manner, so that I can consider it as proper for me to make a few comments on this question. Prior to doing so, however, let me expressly emphasize that I have been misunderstood by Mr. Lubarsch, when he expressed the idea that I denied the morphologists the right of discussion on questions pertaining to function. It is just the opposite that I am in favor of. How much morphology is able to contribute in explaining questions of function, is certainly to be seen just from the beautiful results obtained by Williamson, in which we can take such deep interest at the exhibition displayed

here. To ascertain function and to determine the condition of the function is the aim and the task of every medical man, who is of a biological turn of mind.

The pathological morphologist stands in the front ranks in this group of investigators of function. But, according to my opinion, with the present state of our knowledge, he is not in the position of determining with certainty the condition of function from the morphological aspect alone.

It is a matter of deep regret to me that here at this conference there is no particular lecture being given on our knowledge of the physiology of the thyroid gland; especially at a place like Berne, where at the university there is such a prominent specialist and investigator just in this sphere of knowledge as Asher. During the last few years there has been so much real progress made in this department, that we may also expect new discoveries as to the goiter problem. We may simply call to mind such discoveries as the clear separation and synthesis of thyroxine and the carefully investigated relations of the thyroid gland to the remaining organs of incretion. With reference to the thyroxine I should like to remark that I, in agreement with F. Müller, am also of the opinion, which is based on clinical experiences and experimental researches, that we may see in this substance an important and essential, but by no means the only, effective element of the thyroid gland.

The relations of the thyroid gland incretion to metabolism, the powerful rôle which this incretion plays in the regulating of the normal and pathological metabolism, must be taken into consideration to a far-reaching extent, in order that we may more closely approach the goiter problem in its significancy for the entire organism. Researches made in my laboratory could show that we are already at the present time in the position to obtain on a numerical basis not only the basic metabolism, but also the more important total metabolism, at least with animals.

The physiology of the thyroid gland, the behavior of the organ in its relations to iodine, will constitute the productive basis for the iodine prophylaxis and the therapeutics of goiter, which has thus far already given us such fine results. Through a more detailed study of the action of iodine we also expect to gain information on the practical question, which has before this been made clear to a far-reaching extent; namely, that of the possibility of Morbus Basedowii having a therapeutical influence through so-called large doses of iodine, which are really to be looked upon as small doses

in comparison with the quantities of iodine ordinarily made use of. The Lugol method of treatment, which was proposed by Neisser and employed to a great extent by Plummer gives us unexpected favorable results with the genuine Basedow disease. The division of the hyperthyrotic goiter into a toxic and an exophthalmic goiter I certainly consider neither practicable nor correct, but nevertheless I feel obliged on the basis of my own extensive experience to lay stress on the possibility of differentiating different varieties of goiter according to their behavior in regard to iodine medication. In more accurate words, it is here a question, moreover, not of different varieties of goiter, but of different individuals as sufferers from goiter. According to my opinion Basedow is a hyperthyroidism in individuals who are especially organized constitutionally. It is not the difference as to thyroideal function, but the difference of the «Erfolgsorgane», i. e., organs, the reaction of which shows the stimulation of the nerves to them, i. e. in our case of the entire organism, which determines as to whether anyone in case of an increased production of thyroid gland secretion responds with a simple hyperthyroidism or with a genuine Basedow. (Observation at the time of writing: Let me expressly call attention here to the important research labors of Asher and his followers, as also the more recent work of H. Zondek, which go to show that for the action of an incretion the medium and the constitution of the «Erfolgsorgane» are decisive factors.) If Oswald specially points out the significancy of the nervous system in the origin of the hyperthyrotic disease aspects, then he has mentioned one of the factors, which without doubt play an important rôle. The nervous system, however, is only a single one of the factors beside many others in the complex, which I desire to sun up in the designation «Constitution» or condition of the body.

The Significancy of the affected Organ.

By Professor W. His, Berlin.

In consideration of the pathological physiology we must not overlook the fact, that the character and amount of the substance produced by the thyroid gland are not alone responsible for the effect; the condition of the organ in which the effect is produced is of equal importance; this has been extensively proved by H. Zondek and we must not pass by these findings even though they do not solve the problem but only remove it to another plane.

Remarks on the lectures on morphology and function of endemic goiter and on the effect of iodine.

By F. Merke, M. D., Basle (Switzerland).

I wish to begin by referring to the concluding remarks of Mr. Aschoff, concerning the functional value of the different forms of endemic goiter. Mr. Aschoff pointed out that of the endemic goiter only the proliferating diffuse goiter is hyperfunctioning, while all other forms of endemic goiter show no signs of either hyper- or hypofunction. This agrees entirely with clinical observations on the basal metabolism of endemic goiter. Mr. de Quervain classified the endemic goiter without functional disturbance as «euthyreotic forms», formally they were called struma simplex. The basal metabolism of these goiters is «normal», that is to say within a range of —10 % to +15 %. But until today we do not know what in goiterless individuals causes these variations within the «normal» range. It may be a difference in the tone of the sympathetic nerve or individual differences in the function of the normal thyroid gland or differences in the sensibility of the organism to the thyroid secretion. In endemic goiter-districts where we operate daily endemic goiters and where we have occasion to make functional and histological examinations we cannot avoid the conclusion that these functional differences within the «normal» range in goiterous patients are due to a different histological structure of the «euthyreotic» goiters. Our numerous basal metabolic determinations show a certain screwing of the b. m. rate, but the average values seem to be to a certain extent correlated with histological pecularities of the goiter. We found an increasing functional value from the struma nodosa microfollicularis, macrofollicularis and parenchymatosa to the simple diffuse colloid goiter and finally to the diffuse proliferating colloid goiter. These observations correspond with those of Wegelin and Abelin and of de Quervain's school, who showed that in the biological experiment the struma colloides diffusa is more efficacious than the struma diffusa parenchymatosa. For the proliferating diffuse colloid goiter we found a few «normal», many slightly and some distinctly elevated b. m. rates, the average rate

(+ 18 %) for this group exceeds in our material (Basle) the upper «normal» limit. For that we can not deny a certain tendency of this goiter to hyperfunction and we are in agreement with Aschoff's (Freiburg) opinion. At Danzig also this form of goiter seems to produce symptoms of hyperthyroidism while in Holland it seems to be functionally normal (Josselin de Jong). But we want to point out also that in our opinion we are only authorised to speak of hyperfunction if it is proved by an elevation of the basal metabolism. The «slight» clinical hyperthyroid symptoms (except basal metabolism) are too uncertain and their judgement depends too much on the personal opinion of the examiner. They may be present with a normal basal metabolism or absent with an increased basal metabolism. The basal metabolism is the only incontestable criterium of the function also for the euthyreotic goiter. A systematical determination of the basal metabolism in a large series in different endemic goiter districts will probably give an answer for the functional value of the different forms of endemic goiter.

Then I wish to ask Mr. Wegelin who showed us yesterday goiters of hypothyroidism and cretinism whether he has observed in these goiters signs of insufficiency or decreased permeability of the blood capillaries. Mr. de Quervain told us yesterday (as in previous papers) that these goiters often show extremely large arteries. De Quervain's school proved that the parenchyma of these goiters is often active in the biological experiment. This abundant vascularisation and biological activity of the hypothyroid goiter is in contradiction with the presence of clinical hypothyroidism. We suspect that this contradiction might be caused by a degenerative alteration and a decreased permeability of the capillaries. Jaensch demonstrated today the alterations of the capillaries of the fingers in hypothyroidism and cretinism. These observations suggest that similar alterations of the capillaries may be present also in the goiter and may influence the function of the gland. This suggestion seems to be proved by my own observation that is described in the present number of the «Schweiz. Med. Wochenschrift» (No. 35). After sympathectomy on both superior thyroid arteries in a case of hypothyroidism with goiter I found a distinct, though temporary, increase of the function measured by basal metabolic determination. We do not know exactly the effect of sympathectomy on the distant part of the vessel but we know at least that it produces hyperaemia. This hyperaemia could produce an amelioration of the diffusion of thyroid-secret or decrease de

Blood capillaries

"sympathect

Quervain's «limit of resorption». Indeed our experiment seems to prove that a part of the underfunction relies upon a diminished permeability of the capillaries that does not allow a sufficient diffusion of the thyroid-secretion; this diminished permeability may influence unfavorably the production as well as the secretion of the thyroid-secretion.

Finally I want to add a few words to the theory which Mr. Breitner defended so enthusiastically, namely that the effect of iodine is opposite to the functional direction of the gland. This theory may be valid for Breitner's experiment, though some objections against its conclusiveness must be made: the remaining lobe of the thyroid gland of the animal is frequently damaged during the operation and it lies in a hyperaemic wound and furthermore we have to deal with a regenerative hyperplasia in the remaining lobe. But the same effect of iodine on the «hyperrhoic» gland can be demonstrated by another experiment. If we put rats in a meat-safe at a temperature of +3° to +4° C for a period of 3—4 months we can always observe the process of rinsing out of the colloid from the untouched gland. The continuous discharge of heat requires an increased production of heat. The increased demand on the thyroid gland produces a proliferation of the epithelium and rinsing out of the colloid. If we give iodine to these rats (e. g. injection of Lugol's solution) we observe a few days later in the gland an enormous «stuffing» of colloid and a flattening of the epithelium (projection of mikrophotographs).

Breitner's theory is also confirmed by latest researches on the effect of iodine on the exophthalmic goiter gland. Last year we made occasionally small probatory excisions of exophthalmic goiters before we began the preoperative treatment with Lugol's solution (Plummer) and compared them with the histological structure of the gland after the iodine treatment. In agreement with the American authors (Cattel, Rienhoff) we found after iodine administration in the primarily colloidless gland a stuffing with colloid, a flattening of the primarily high epithelium and a storage of iodine. This stuffing with colloid and flattening of the epithelium corresponds to the lowering of the basal metabolism.

To Breitner's thesis, though it seems to be valid for the mentioned experiments with animals as well as for genuine exophthalmic goiter, we must make some restrictions from the clinical point of view. Unfortunately the «hyporhoic» goiters are not all stimulated by iodine to hypersecretion. We know that iodine is not or only slightly beneficial in cretinism and hypothyroidism. This may arise

from an advanced degeneration of the parenchyma; but even when the degeneration is not advanced iodine has mostly no effect on the « hyporhoic » gland (basal metabolism).

Furthermore we know that the effect of iodine is not opposed to the functional direction of the gland in all cases of exophthalmic goiter. In some cases it is not beneficial and further investigations have to clear up, why in these cases it is not effective. There is also to be noted, that even if the iodine is effective the lowering of the basal metabolism does generally not reach the normal rate and that during continuous administration of iodine in exophthalmic goiter the basal metabolism rises again. At present we have no satisfactory explanation for these facts.

The problem of the effect of iodine is still more difficult in iodine- hyperthyroidism. In endemic goiter districts we call « Jodbasedow » the cases of primarily atoxic goiters which become toxic after small or large doses of iodine. This conception of iodine-hyperthyroidism is not identical with the iodine-hyperthyroidism recently described by american authors. They use this term for cases of primarily toxic goiters in which the iodine administration was not beneficial or even injurious. I want to turn your attention for a moment to our observations in cases of what we call « Jodbasedow » (secundarily toxic goiter). In those cases the histological examination always reveals a more or less advanced « basedowification ». We do not believe that this is always caused by iodine, because we generally find in primarily atoxic endemic goiters after iodine treatment degenerative and inflammatory processes (cysts, hemorrhages). In any case the « post iodine » is not always a « propter iodine ». In our endemic goiter we observe not very rarely a « basedowification » without knowing its cause. When it takes place the goiter grows and the patient takes iodine — like all goitrous people in Switzerland — with or without consulting a physician. If iodine is taken in the usually small doses, or — and this seems to be more important — if the iodine administration is frequently interrupted, serious toxic symptoms may appear. The principal cause of these symptoms is the « basedowification » of the gland, which developed before iodine was taken. The « basedowification » causes an abnormal sensibility of the goiter for iodine. We believe that above all the interruption of iodine intake is important for the development of toxic symptoms (as interrupted iodine intake we also consider the administration of iodine once or twice weekly). The treatment of exophthalmic goiter with Lugol's solution taught us that the

interruption of the iodine administration is immediately followed by a stormy change to the worse. Perhaps a similar process happens in the «Jodbasedow», but in a smaller scale. So in these cases it would rather be the interruption than the administration of iodine which is responsible for the rinsing out of colloid.

These are a few restrictions to Breitner's general formule of the effect of iodine. No goiter-theory is perfect. Even Breitner's theory does not pretend to be. But it is the purpose of this meeting to emphasize the most valuable of the observations and theories and to get uniform points of view.

* * *

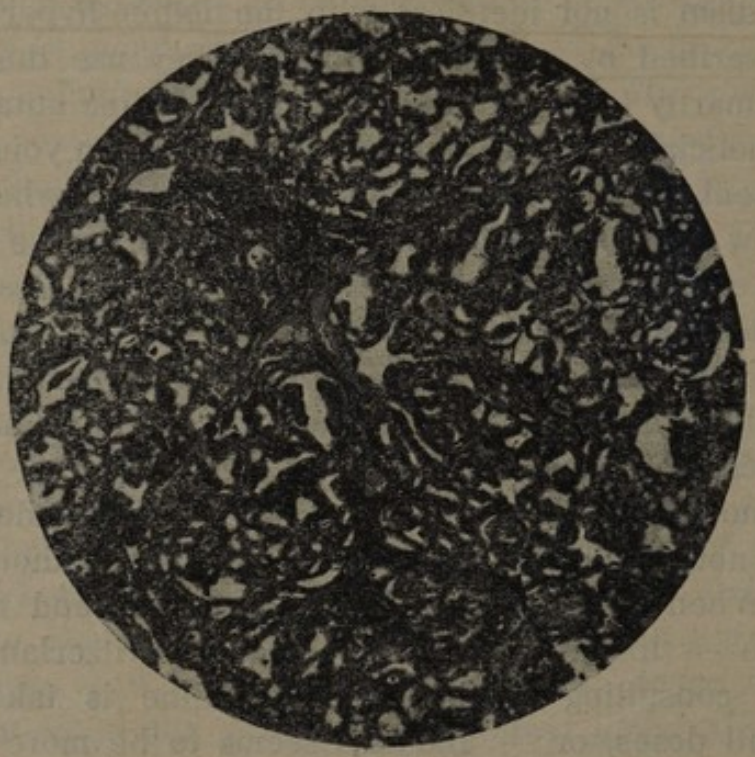


Fig. 1.
Before iodine treatment. Follicles narrow, no colloid. High columnar cell-epithelium Iodine content 0,075 mgr. in 1 gr. fresh gland. Basal metabolism + 72 %.

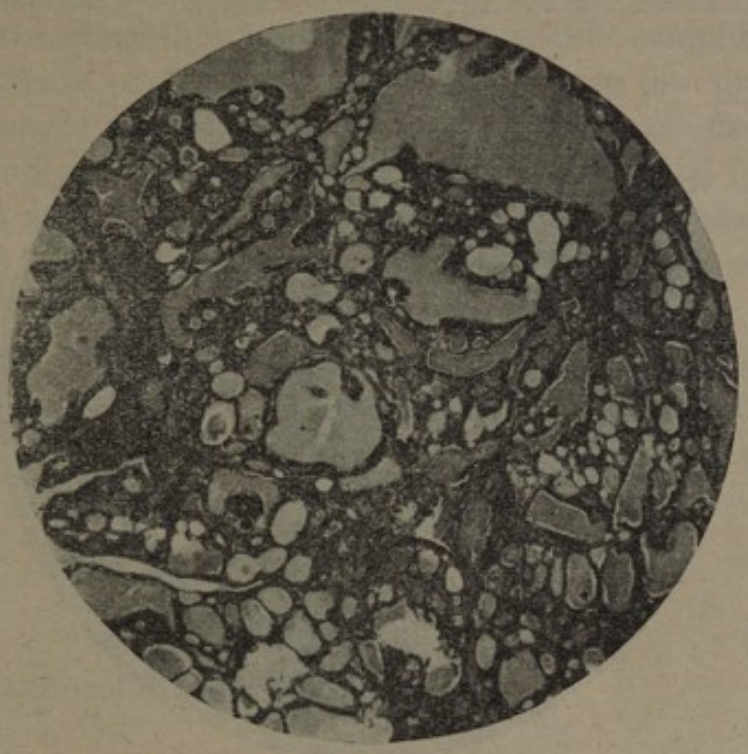
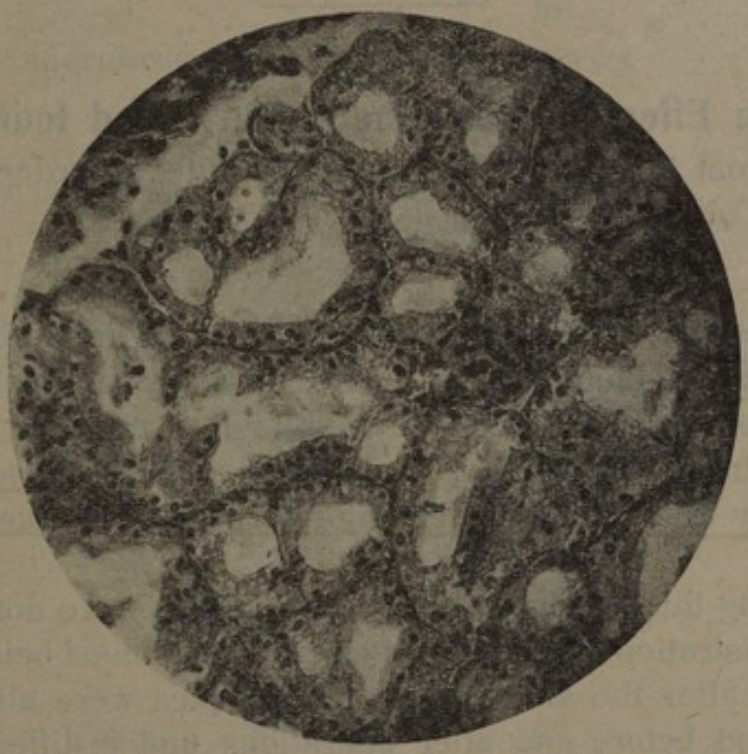


Fig. 2.
After iodine treatment. Follicles enlarged, stuffed with colloid. Epithelium cuboidal. odine content 0,22 mgr. in 1 gr. of the fresh gland. Basal metabolism + 38%.



Season
Heat and cold.
Cold + iodine has the same effect as heat.

Fig. 3.
Thyroid gland of "cooled" rat. Follicles narrow, no colloid. Epithelium high.

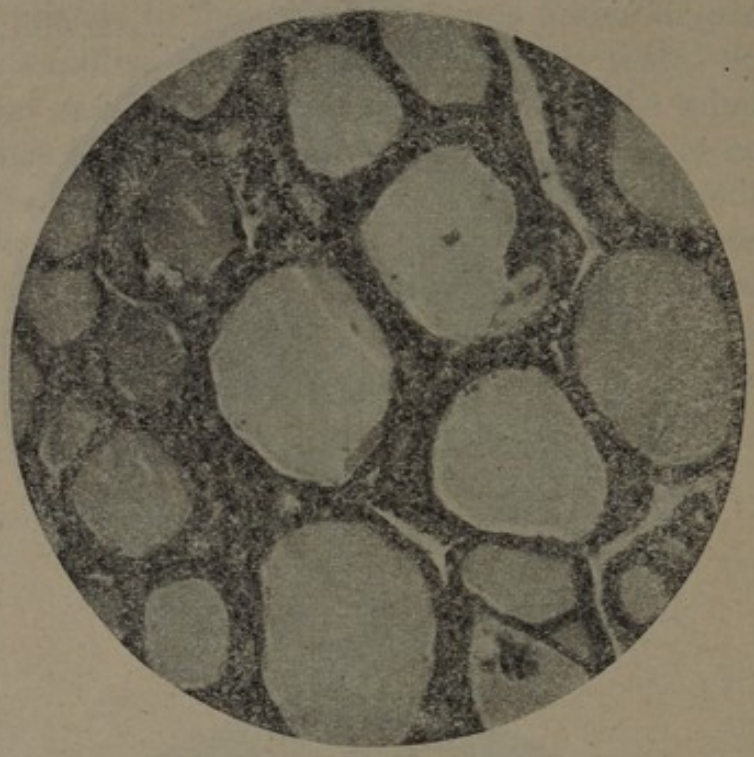


Fig. 4.
Cooled" rat after injection of Lugol's solution. Follicles enlarged, stuffed with colloid. Epithelium flattened.

The Effect of Anaesthetics on Blood Iodine.

From the Rowett Research Institute, Aberdeen.
Communicated by *I. Leitch.*

The fact that anaesthetics may have a marked effect on the iodine content of blood was first noted in the case of rabbits killed with chloroform. The blood of rabbits has normally an iodine content of from 10 γ to 15 γ*) per 100 cc. In the blood sampled immediately after death under chloroform, only a trace of iodine was found.

Following this discovery a few experiments were done on goats with administration of chloroform or ether, the blood being sampled before and after the anaesthetic, and samples were also taken of human blood before and after operations under different anaesthetics. Iodine estimations on these samples have shown that in some cases a very marked rise or fall in blood iodine occurs, a fall

*) 1 γ = 0,000 001 gram.

usually occurring under chloroform and a rise under ether. The results are not altogether uniform, and possible complications are involved in these preliminary observations from the simultaneous administration of adrenalin in some cases. It has already been shown by Veil and Sturm that adrenalin raises blood iodine. The observations appear, however, of some clinical importance, and the investigation is being continued. The following table summarises the results.

The effect of anaesthetics on blood iodine.

Subject	Anaesthetic	Time	Blood iodine: γ per 100 cc.	Remarks
Goat	—	—	42	Before.
	Chloroform.	5 mins.	34	
	»	30 mins.	19	
	»	60 mins.	17	
Goat	—	—	19	Before.
	Chloroform.	15 mins.	13	
Goat	—	—	18	Before.
	Chloroform.	10 mins.	13	
	»	20 mins.	9	
Human.	—	—	48	Before.
	Chloroform.	45 mins.	10	
Human.	—	—	95	Before.
	Chloroform.	40 mins.	Trace.	
				Adrenalin.
Human.	—	—	13	Before.
	Chloroform.	12 mins.	50	Cocaine and
Goat	—	—	16	Before.
	Ether.	30 mins.	18	
	»	60 mins.	18	
Goat	—	—	27	Before.
	Ether.	10 mins.	19	
	»	30 mins.	17	
Human.	—	—	25	Before.
	Ether.	30 mins.	20	
Human.	—	—	19	Before.
	Ether.	12 mins.	18	
Human.	—	—	15	Before.
	Ether.	30 mins.	163	
Human.	—	—	23	Before.
	Ether.	40 mins.	313	

Variations in Blood Iodine associated with Changes in Ovarian Activity.

From the Rowett Research Institute, Aberdeen.

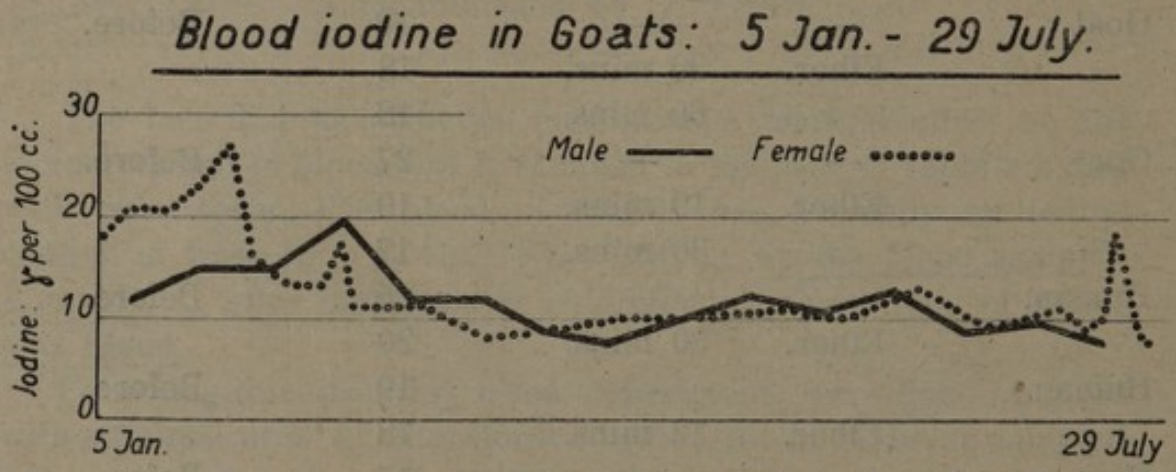
Communicated by *J. Leitch.*

A study of the blood iodine in female goats over a period of almost a year has shown that typical changes occur in the level of blood iodine, and these changes appear to be associated with the sexual cycle.

The blood was sampled every seven days until heat occurred. A sample was taken during heat, and at the second occurence of oestrus, the goats were served. Thereafter during pregnancy the blood was sampled every fourteen days until a short time before kidding (7—14 days), when samples were taken every three days. A sample was also taken as near as possible to parturition.

The results show that a rise in blood iodine occurs during heat. During pregnancy the level of blood iodine is very steady and remains low till immediately before parturition, when a rise occurs. The following graph shows the nature of the results.

It appears that a correlation exists between the level of blood iodine and the sexual cycle in the goat. This is of interest in view of the well-known interaction between thyroid and ovarian function.



In the graph for the female goat, the first two peaks indicate the occurrence of oestrus, the third, at the end, parturition.

Report
on the Physiology and Pathology of the Thyroid Apparatus.

G. Scott Williamson and *Innes H. Pearse*, London.

Introduction.

Work on the thyroid gland, carried out on behalf of the Medical Research Council, London, was demonstrated by Dr. Scott Williamson and Dr. I. H. Pearse. These workers have been turning their attention to function in the thyroid and, from various directions, they bring to bear evidence to show that function within the gland is not a simple cycle, but at least a two-fold one.

Their studies have revealed an intimate relationship between the thyroid and the lymphatics and show that, apart from the common lymph drainage of the neck, there is a specialised thyroid lymphatic system involving the thymus. This specialised thyroid lymphatic system is implicated in one only of the two functional cycles known to occur within the gland.

Demonstration.

1. Relation of the Thyroid Gland to the Lymph System.

Phylogeny. — The simplest form of thyroid is found in Lophius Piscatorius, (Burne [1]). Here, the thyroid is represented by a large cervical lymph sac extending from the angle of the jaw to the pericardium and communicating by a valved passage with the jugular vein. To the inner wall of this sac thyroid follicles are attached. Thus, in its most simple form, the thyroid lymph system is an uncomplicated cavernous sac.

It was shown that the next advance in phylogenetic development involves the lymph sac but not the follicles. In certain fishes (e. g. hake and gold-fish) the lymph sac, by plication, becomes a labyrinth of spaces extending, as before, from the mandible to the pericardium. It thus follows that, in these fishes, thyroid tissue may be found scattered widely in the neck corresponding to the ramifications of the labyrinthine sac. This, in some measure, affords an explanation of the distribution of the experimental hyperplasias produced in the classical experiments of Gaylord (2) and Marine (3) upon Brook Trout.

In the two proceeding types the association between the thyroid and the lymph system is obvious. The next advance is found in the dog-fish. Here both the epithelial elements and the lymph sac share in an advancing complexity of structure. The thyroid follicles are now aggregated to form a compact bilobed mass floating within a lymph sac. But this coming together of the follicles affects their relationship to the lymph spaces. There is created between the aggregated epithelial elements an internal system of narrow or potential spaces (sinusoids), communicating freely with the larger sac. In this fish, therefore, there is an intrinsic and an extrinsic lymph system pertaining to the thyroid organ. Thus, in so far as an intrinsic lymph system (lymph sinusoid) is concerned the dog-fish shows, in simple form, an intimate architecture similar to that postulated by Scott Williamson and Pearse in 1923 for the human thyroid (4).

Is there in the higher vertebrates any homologue of the extrinsic thyroid system of the dog-fish?

In man, Scott Williamson has shown that the intrinsic lymph sinusoids communicate with the large lymph channels terminating in the thymus (5). In support of this, an injected specimen of the thyro-thymic apparatus in the human foetus was shown. The specimen was made by Sir Astley Cooper as long ago as 1832 (6) and is in the collection of the Royal College of Surgeons, England. It was further demonstrated that the tubulate nature of the thymus in some vertebrates (e. g. the pigeon) was well known as long ago as 1850 (Simon [7]). Thus, the probability arises that the thyro-thymic lymph channels, in the higher vertebrates including Man, are the homologue of the extrinsic cavernous lymph sinus seen in the dog-fish.

2. Physiological Activity in the Thyroid Lymph Apparatus.

Microphotographs were shown to illustrate the influence of physiological activity in the thyroid in throwing into relief certain details of the intrinsic lymph system. The perifollicular lymph sinusoids may become filled with substance having the histological characters of a fluid. The spaces when so filled were shown to communicate with a central intra-lobular lymph channel. Thus, the lymph spaces of the thyroid are related to the thyroid epithelium in exactly the same way as the protal blood sinusoids and portal vein are to the liver epithelium. In the thyroid it is a lymph sinusoid, in the liver a blood sinusoid. This being the case it is

necessary to assign to the intrinsic lymph system of the thyroid a very significant physiological function. Can histology help in arriving at an understanding of this matter?

Microphotographs were shown to illustrate that during what these workers have called «secretory activity» (4) in the thyroid there are visible, in the lymph sinusoids, cells of large dimensions, spider-like form and granular content, and that such cells frequently invade the periphery of the epithelium assuming the position of the cellular entities described by Brückner (8) as «cellules basales».

Other microphotographs and drawings were shown indicating that the cytoplasm of these cells invades the epithelium, even penetrating to the lumen of the follicle and thereby giving the appearance of the «intracellular channels» described by Hürthle (9).

Close study of these cells has led to their identification with reticulo-endothelial cells as defined by Aschoff (10). That a reticulo-endothelium should occupy the thyroid lymph sinusoid affords yet another link in the close analogy between the intimate structure of thyroid and that of the liver.

The reticulo-endothelial system in the thyroid organ is called into activity by the secretory function — but what is the relationship of this reticulo-endothelial system to the follicular contents elaborated by the process of secretion?

A series of microphotographs were shown illustrating the connections of the intra-epithelial cytoplasmic extensions of the Reticulo-Endothelial cells with a system of structures first seen by Holmgren (11) and Heidenhain (12) and called by them «Schlussleisten» and described as phenomena of secretory activity. Williamson and Pearse demonstrated that these structures were constant in the thyroid epithelium, remaining closed and unobstrusive when at rest, or when colloid was being produced within the follicle, but opening up to contain a fluid matrix and granules during secretion. Only during this phase was their connection with the Reticulo-Endothelial System so clearly apparent. It was for these reasons that in 1923 having been able to stain the Schlussleisten in their entirety, they named them microcapillary structures (13). There is therefore in the thyroid no such thing as dissolution of the epithelial walls during the effluence of secretion as was formerly postulated (14). On the contrary, there is the active ingestion, by cells of the Reticulo-Endothelium System and their intra-epithelial cytoplasmic extensions, of material found within the secretion follicle, and destined for the thyro-thymic

lymph system. Synchronously with granulation of the microcapillaries, of the intra-cellular channels and of the Reticulo-Endothelial cell-bodies, granules begin to appear in the sinusoidal spaces. It can only be inferred from such a sequence of events that, during the secretory process, some material is conveyed from the interior of the follicle to the special thyroid lymphatics. This material is not colloid.

Thus, there was demonstrated in the thyroid a morphological mechanism which places the lymph sinusoids in direct contact with the contents of the follicles. The mechanism is not altogether unparalleled in the body for its anatomical counterpart is seen in the Deiters cells with their reticular membrane in the organ of Corti.

Embryological studies in the developing mucous membrane of the dog-fish seem to suggest that the inter-relationship between endothelium and epithelium implied in a reticulo-endothelial mechanism of the order demonstrated has a general significance in secreting membranes as well as a local one in the thyroid gland.

Duality of function in the thyroid.

The lymphatic mechanism or pathway of absorption in the thyroid gland is only recognisable as such when the histology of the gland indicates the condition which has been designated « hyperplasia ». This « hyperplasia » is identical with the « Hauptsecretion » phase of Hürthle (9) and the « canaliculated » phase of Aschoff (10) and that which Williamson and Pearse call the phase of « secretion » or « secretion proper » (4).

It is necessary, in understanding function in the thyroid, to distinguish clearly the phase of secretion from other phases; viz. 1) the colloid phase and 2) the rest phase. Histologically the distinction is rendered complete by reference, in each case, to the condition of the microcapillaries within the follicle. In secretion they are full and active, while in the colloid phase they are collapsed and at rest. The features of these two phases were shown by means of microphotographs, drawings and diagrams. The appearances of the rest-phase from which either the colloid phase or the secretory phase may ensue were also depicted. Tissue in the rest-phase is commonly designated « interfollicular tissue ». The presence of the microcapillary network within the solid columns shows however that « interfollicular » tissue is no other than

thyroid epithelium in solid columns without lumen. The existence of the peculiar phase of secretion is well recognised throughout the literature. Recently Wegelin and Abelin (15) and others have studied tissue in this phase and they confirmed the significant fact, already noted by Graham working with Marine (16), that this tissue has little or no biological effect. Williamson has repeated this work using some refinements in technique to secure pure samples of «hyperplastic» secreting tissue. Graphs and photographs of tadpoles prepared by Dr. H. Cunnington were shown indicating that when in a state of purity (i. e. uncontaminated with tissue in the colloid phase), tissue in the secreting phase never has any biological effect and seldom contains any iodine. This finding is in such strong constrast with pure samples of colloid-containing tissue that it must have deep significance.

A preliminary study of the chemistry of secreting tissue adds further significance to these findings. Williamson finds that an acid extract of this tissue gives a reaction with sodium nitroprusside producing a strong green-blue colour. This sodium nitroprusside reaction is only given by secreting tissue; tissue in the pure colloid phase will not give it.

At this point thyroid secretion was contrasted with thyroid colloid. —

Secretion. — 1. Has a characteristic histology.
2. Emerges from the gland via the lymphatic mechanism.
3. Gives a sodium nitroprusside test.
4. Is biologically inactive.
5. Seldom contains iodine (96 % of samples contain no iodine).
6. Has a characteristic pathology; viz. adenoid goitre (17).

Colloid. — 1. Has a characteristic histology.
2. Does not emerge from the gland via the lymphatics.
3. Does not give the sodium nitroprusside test.
4. Is biologically active.
5. Always contains iodine.
6. Has a characteristic pathology; viz. vesicular goitre (17).

The demonstration sought thus on histological, biological, chemical and pathological grounds to show in an unequivocal manner

that there are two cycles of function at least in the thyroid physiology — one is the production of «secretion» and the other the accumulation of colloid by the gland. Only one of these phases of function occupies the attention of the special lymph system, shown to exist in the thyroid apparatus.

Concluding Observations.

Professor de Quervain:

The discussion on the pathological physiology of the thyroid gland has primarily proved to us, that we, even up to the present day, are not yet in the position of welding together the morphological and functional modes of acting of the individual varieties of goiter to a uniform whole, so that a classification could be brought about which could be of service to the international mode of thinking. For this purpose we lack the necessary knowledge concerning the normal functional action, as just the important researches of Williamson and Pearse have shown us, and the possibility is wanting us to make any judgment of the quality of the secretion from the histological structure. For a general classification, that can be of practical use, there remains for the present to us only the purely descriptive method. Experiments, such as those of Breitner and of Williamson preserve their full value as working instruments, but they can only be appreciated as such; they are deserving of thanks, because they demonstrate the way for progress for the individual person and for the cause as a whole.

Going somewhat into particulars, let me state it strongly that the discussion has been preponderatingly concerned with the hyperthyreotic conditions. This can readily be understood, since these conditions are to be found throughout the entire world, whereas the manifestations of goiter endemic, which are accompanied by hypothyreosis, have the disagreeable privilege of being found in isolated geographical regions and can be recognized for general research purposes only with far greater difficulty.

The question of the genuine Basedow was also frequently brought into the discussion, which was a departure from the subject of endemic goiter, that was actually under discussion. We must hold to the thought that this in the pure cases takes its origin without any previous euthyroidal goiter development. In the widest sense,

however, it is connected with endemic goiter through those numerous cases of diffuse hyperthyrotic struma, which occur in the regions of the endemic lowland struma as, e. g., the region of the great lakes in the United States of North America and the Norwegian and Dutch goiter districts. It is still an open question whether these endemics on their part are to be distinguished only gradually or fundamentally aetiologically from those of endemic goiter in the narrower sense, viz., the goiter of the Alps, of the Himalaya, of the Cordilleras with their multitudes of cretinism cases.

The transitions from the genuine Basedow of districts, which are poor in goiter, to the Struma Basedowificata of the goiter regions are not only of a geographical nature, but we also find them present in the clinical aspect. This fact seems also to have become evident from the descriptions of to-day, whereby we to be sure very much regret, that Plummer could not present to us his point of view, which somewhat deviates from ours.

We have made the greatest progress in recent years in the recognition of the fact that iodine is a constituent part of the organism. Iodine has been definitely recognized as a normal constituent of the human body, subject to an exact regulating law in its metabolism, and its relations to the thyroid gland are no accidental ones and likewise none that are merely therapeutical. This will be realised in all spheres of investigation, that bear on the thyroid gland and on goiter. The carrying out of the investigations certainly presupposes careful training in chemistry in order to avoid coming to false conclusions.

A new adjuvant remedy for the investigation of the pathological conditions of the thyroid gland is capillary microscopy. According to our researches it is also easy to recognize the hyperthyrotic conditions. With the conditions of insufficiency, on the other hand, the appreciation of the capillary aspect is considerably more difficult. There are cases of grave cretinism offering a capillary aspect, that is but little modified. Research-work is in this line only in its initial stages. The investigations of Wittneben give us valuable indications, but must be re-investigated in regions of pronounced goiter endemic.

For further epicritical comments on cretinism I call your attention to the demonstrations in the surgical clinic, which will take place at the close of the conference. These will illustrate the points, which Maffei and Rösch gave expression to as long ago as 1844 and which I take the liberty of quoting here in concluding my remarks:

«The cretin is a diseased person, and cretinism is a disease, and no particular human species, which is capable of any propagation through the individuals of this species....

That only very wide experience and patient observation, continued over a long period of time, can enable us to recognize the pathognomical indications and make it possible to detect and distinguish them from the non-essential, accidental ones, that fact hardly needs to be mentioned. That a preconceived opinion, an hypothesis, the belief in a normal type of cretin, in a cretin-prototype, is, nevertheless, very objectionable and can only obstruct any rapprochement towards a certainty, to the truth, is probably equally clear.

Dr. B. Breitner:

As assistant speaker to Professor De Quervain it does not fall to my lot to have the real last word to say. But I beg for your attention to a few summarizing observations. As I was intrusted with the address on experimental researches on animals along the line of pathological physiology of struma, it could not be my privilege to touch upon the question of normal physiology except in a general way. I endeavored to do justice to the subject by immediately conforming to the wishes of the previous speakers, especially those of Aschoff, and gave full scope to the attempt of introducing a uniform nomenclature. Nevertheless, fundamental differences of opinion in this matter appear in many points to have become heightened rather than overcome. Formerly my conceptions of the behavior of the colloid were found fault with by pathological-anatomical authorities, but certainly at the present time these doubts appear to have disappeared. But now the doctrine of the «eutrophy» of cell as taught by Aschoff is being doubted and with this the functional importance is placed in question. This causes me to consider the attempt as shattered that we can reach at this conference for the first time an at least formal accurate definition of the struma problem. Inasmuch as I do not share the apprehensions of the representatives of pathological anatomy and am not able to overlook the compact line of results of experiments on animals, but rather appreciate them with all forcibleness, I am endeavoring once more to describe how the

problem of goiter and the possibility of solving this problem appears to me in the sense of pathological physiology.

The very old fact of the existence of « endemic goiter » compels us to accept a cause that is due to regional circumstances. We are not acquainted with these causes. Wheter they are due to an excess or to a lack of something or whether they are toxins or other factors; these are things which we do not know. The problem facing us, therefore, is: to ascertain what changes this unknown local noxiousness works out in the thyroid gland. Histologically, a genuine numerical hyperplasia corresponds to the macroscopical condition of increased development, wherein the adenoma structure is likewise included. The cell structure as such belongs to the normal type and hence admits of the assumption of a normal function. The growth of the specific parenchyma leads to the one conclusion, that the enlarged gland in the endemic region does more work functionally in comparison with the normal thyroid gland, i. e., the thyroid gland in regions free from goiter.

The reason for this fact can be a two-fold one. Either the individuals in the endemic districts require for any cause whatsoever more thyroid secretion than the persons living in districts that are free from endemic. With this assumption we must look upon the product of secretion of the gland as biologically normal in value and that the needs of the organism are alone increased.

Or: the secretion, which the thyroid gland gives forth in the endemic district, is biologically of inferior quality. For this reason the gland attempts to make good the inferiority of quality through increased quantity. Under all circumstances, however, there is every reason to believe that the cell structure in its totality and individually is a perfectly active organ. Whether this is or is not a false conception, the second characteristic, the colloid, must prove. The struma of the endemic district is free from colloid.

Here again two constructions are possible: The specific glandular parenchyma secretes too little secretion, which is the pathological feature of the gland in the endemic region. Or, the produced secretion is immediately yielded up to the organism, so that the factor of being stored up does not exist. The former assumption places us before a completely new fact, which does not harmonize with any of the others, as they are known from the physiology of the gland. The latter assumption satisfies the conception, that is obtained from the cell structure. It therefore corroborates the assumption of a gland in perfect function, which is, however, either over-exercised or of inferior value biologically.

In order to clear up this cardinal question, on the solution of which our knowledge of endemic goiter depends, I have tried to put the condition of a lack of colloid or of an over-abundance of colloid into a biologically comprehensible form.

All of the experiments on animals, which have been made along this line, which I have spoken of in detail in my address, gave me to understand that the idea of hyperrhoe is that of increased flushing of secretion and the idea of hyporhoe that of an increased process of storing up. According to these experiments on animals the histological aspect of a eutrophic epithelium with a lack of colloid can not be explained in any other manner than at the least normal production and increased removal of the secretion.

The idea, that the goiter of the endemic region is the expression of a functional surplus of the thyroid gland, (not of greater effectuation!), is most clearly evident from the experiments on animals.

It is now a matter for us to choose between the two possibilities of arriving at the foundation of this increased activity. The secretion may be biologically of normal value, but the individuals in the endemic region require a plus as regards secretion. This extra need prevents the storing up and furthers increased production. Such a condition is known to us from the physiology of the gland. A gland, that is free from colloid, suits the youthful organism with its evidently increased demand for secretion. The storing up does not set in until stabilization begins. The taking on of parenchyma in the case of the goiter peculiar to adolescence demonstrates the increased production. This is a possibility.

The second possibility consists in this, namely that the requirement answers to normalcy, but that the removed secretion is, nevertheless, of inferior quality biologically, a condition that is made good through a surplus of production and an increased of consumption.

The circumstance is common to both possibilities, that the goiter appears as a symptom of a general derangement and not as a local diseased condition of an organ.

The proximate immediate inciting factor of this symptom can be looked for in the irritation of the regulators of the secretion of the thyroid gland. According to what has thus far been inferred the condition of the hyperrhoe corresponds to an increase of the tonus of the sympathicus. We do not know through which different factors this can be incited. But the clinical infirmary and the experiments on animals have demonstrated the sedative action of the intake of

iodine and the great experience gained through the prophylaxis of goiter has confirmed it.

The experiments on animals, which have been carried out by Orator and myself, appear to be demonstratory in two directions: in the first place the correctness of the functional conception is demonstrated and, secondly, the sedative iodine action upon the different varieties of the «functional trend» is proved. The maintenance of the theory pertaining to the absence of iodine as to the endemic goiter is with this neither furthered nor rejected but it is shifted to one side, because the sedative action of iodine is brought to the fore. The theory of the absence of iodine is compatible with this idea, but it loses its exclusiveness. The problem of aetiology, of varieties of manifestations, prophylaxis and therapeutics of the endemic goiter, however, is being surveyed from one and the same look-out station.

Iodine absence of

Now, it was emphasized by every speaker, that the Basedow goiter is something toto coelo different and that we have here before us an entirely different problem.

That through is, however, especially directive for me, that all conclusions positively and with like unequivocalness admit of finding application also upon the Basedow problem. In my address to you I brought that thought out in great clearness. By reason of this I hold to my system in particulars, notwithstanding the opposing opinions all the more so, since it has also completely stood the test in the question of relapses.

I emphasize again here as at the close of my address, that my conception is nothing else than a definite, limited variety of view-point, no unveiling of the biological problem. But it appeared of great value to me to reveal at least one such variety, which can make over to us a basis for more profound and, perhaps, finally, to further more successful labors.

Aetiology and Epidemiology of Endemic Struma.

Report on the Aetiology and Epidemiology of Endemic Goiter in France.

By Prof. Léon Bérard and
Prof. Charles Dunet, Lyons

The tourist who, some fifty years ago, travelled in France through the valleys of the Tarentaise, the Maurienne and the Briançonnais, certain regions of the Central Plateau, found himself when alighting from the stage-coach surrounded by an entire population of goitrous individuals and of cretins, proudly exhibiting their necks, which were adorned with tumors more or less voluminous, diffuse or in «cattle-bells», and begging for alms or making fun of the stranger with his «chicken neck» or his «goat's neck». (Saint Lager). The goitrous animals, dogs, cats, mules and goats were numerous in these regions.

Since this epoch, relatively not so far back, people and things have undergone many changes and we can establish the fact in France of a progressive diminution of goitrous endemic, which has changed the appearance of the population of the old so-called «goitrigenous» districts. Even if the hypertrophy of the thyroid gland is still of frequent occurrence there, it no longer constitutes an endemic factor of decadence. And in the course of our recent visits into these regions, we only exceptionally met among young patients with these pitiable monsters, those stunted and dwarfish cretins, myxoedematous idiots with lunatic countenance, which still marred those regions in the last century; and there to-day the majority of the cretins have reached adult age.

I. The Terrestrial Conditions of the Evolution of Endemic Goiter.

GEOGRAPHICAL DISTRIBUTION

In 1900, Lucien Mayet designed a map showing the geographical distribution of goiter in France. Except for some details, this map is practically the same as what would be drawn

at the present time, by taking account of the facts expounded below.

The endemic goiter is raging with variable frequency primarily in thirty-seven of the departments, or states, of France: Upper Savoy, Savoy, Upper Alps, Ardèche, Isère, Rhone, Saône-et-Loire, Upper Saône, Upper Marne, Vosges, Maritime Alps, Ain, Drôme, Jura, Doubs, Upper Loire, Puy-de-Dôme, Vaucluse, Gard, Upper Garonne, Lot, Eastern, Pyrenees, Upper Pyrenees, Cantal, Aveyron, Lozère, Lower Pyrenees, Ariège, Landes, Dordogne, Corrèze, Aisne, Orne, Upper Rhine and Lower Rhine.

This means that in 49 French departments goiter in the endemic state is observed only exceptionally, whereas the sporadic cases seem to have become diffused there through emigration.

Leaving out of question the isolated hearths of the Aisne and the Orne, where the causes of endemic goiter have been attributed to the nature of the calcareous and chalky soil and sub-soil mixed with molasse, the goitrigenous regions are classed into two groups:

a) The one, which is by far the most important, includes the departments of the East, the South-East and the Center from the Marne and the Vosges Mountains to the Maritime Alps, from Savoy to Dordogne, with a maximal proportion of goitrous cases in Savoy, Upper Savoy, Upper Alps, Ardèche and Puy-de-Dôme.

b) The other, much more limited, extends like a strip along the length of the chain of the Pyrenees.

On the whole, the French goitrigenous area, with the exception of several hearths of secondary importance, embraces in its ensemble the mountainous regions, which constitute the western part of the great Alpine system and the Central Plateau.

Its localization does not seem to have varied for some thirty years. The endemic goiter preserves in France the characteristics of sedentarity, for which it has for a very long time been noted in all of the continents. It has only decreased in intensity.

The more exact study of the geographical conditions shows that a whole series of factors, to which some fifty years ago a preponderating rôle was given, such as altitude, location, aeration etc., play in reality only a contingent rôle. — Goiter does not afflict only the poor populations of the deep valleys, which are

enclosed between the high summits and deprived of pure air and of sunlight.

We could multiply the examples of the communities of Savoy, showing that their high altitude does not preserve them from goiter; in Maurienne especially: Montaimart has an elevation of 3776 feet, Bramans of 4100 feet, Albiez le Jeune of 4530 feet, Montpascal of 5100 feet and Albiez le Vieux of 5140 feet.

On the other hand, southern location, perfect aeration, exposure to sunlight are not sufficient elements to check endemic goiter. Many villages, bathed in sunshine on every side, are infested with goiter. In the Jura Mountains the village of Montaigu, which has always paid a heavy tribute to endemic goiter, is located upon a sunny promontory, three hundred or more feet above the plain of Bresse. Many of the endemic centers have been found in the level lands as the Robertsau quarter in Strasburg or at the sea-coast in the vicinity of Toulon and above all in the deltas of some rivers.

Still the evident unchangeability of the goitrigenous area shows that there exists a definite relation of cause and effect between the district and the endemic. This general aetiological factor seems to be of an aqueous origin or nature, a fact which all investigators up to the present time have admitted.

THE AQUEOUS FACTOR.

We shall not be able here to mention all of the facts, that speak in favor of its existence. For a long time in our country the conscripts' fountains have been known, to which the young recruits who desire to escape military service go to drink their fill.

As long ago as 1853 Mgr. Billiet showed that in certain villages there remained exempt from goiter only those families, that drank rain-water, which had been collected in watertight and non-contaminated cisterns.

In 1845 Bozel of 1472 inhabitants had 900 goitrous individuals whereas Saint-Bon, a village situated upon the opposite declivity of the valley and only half an English mile distant, boasted of a remarkably healthy and vigourous population. The municipality of Bozel, which took upon itself the great task of bringing, in casks, the waters utilized by the inhabitants of Saint-Bon, saw in twenty years the proportion of goiter cases

fall to the lowest rate, and at the present moment, after new facilities as to the water have been arranged for, the young generation of Bozel has no cause to envy that of Saint-Bon.

Shall we also mention the case of the horses of the country police of St-Jean-de-Maurienne? These animals, whatever might have been their origin, became goitrous by the end of several months of watering at the well of the country-police. When this well was once for all abandoned the goiter disappeared.

Let us finally point out this fact, which has the value of an experiment of long duration for prophylaxy, of the goiter of scholars and is reported by Viard (Thése Paris 1912). Before 1909, the water that was distributed to the occupants of the former little seminary of St-Jean-de-Maurienne was no other than that of the city, that is to say exceedingly goitrigenous water from the source of Bourieu. Now, every year some 30 % of the seminarists, who had come from Upper Maurienne, a region very poor in goiter, left for their holidays afflicted with goiter, contracted during their academic year. This goiter, moreover, disappeared rapidly without any treatment during the first two weeks of vacation, but invariably re-appeared a short time after their return in October. Every year, however, notwithstanding the curative effect of the holidays, thyroid hypertrophy attained more striking dimensions and oftentimes ended in a definitive goiter.

This annual pseudo-epidemic phenomenon of goiter disappeared once for all when the water of the city was completely given up and the little seminary was provided with a cistern.

The preceding narration ought to suffice to establish in an incontestable manner the existence of goitrigenous waters. This reality, which has been confirmed through numerous analogous documents, gathered in all the countries, has moreover received experimental demonstration through Répin (1911). Some white rats, which had been sent to Saint-Pancrace, a place located below St-Jean-de-Maurienne and very much afflicted with endemic goiter, took in daily for a period of 10 months water originating from a goitrigenous source.

During the same lapse of time some rats, that had remained in Paris, were receiving simultaneously water derived from another goitrigenous source of La Maurienne and brought direct to Paris every two days. All of these animals were killed and all had thyroid glands, which were at least ten times the normal size.

We ourselves made in 1910 analogous observations, though less decisive ones, on dogs, rats and Guinea pigs, supplied at Lyons with water derived from the goitrigenous source of Montaigu (Jura).

The importance of the aqueous factor must no longer be discussed, since we have the excellent research labors of Bircher Sr., Bircher Jr., of MacCarrison, Gaylord et al.

NATURE OF THE AQUEOUS FACTOR.

It is right here where the difficulty lies. The water is evidently only a carrier.

Is it the bearer of chemical substances, of toxical products of inorganic or organic and especially microbian origin?

Is it endowed with special physical properties?

a) **Chemical substances.** The list is altogether too long of all the chemical bodies that have been declared to be present in excessive amounts in the goitrigenous waters. We need state here only the carbonates and sulphates of lime and of magnesia, the pyrites of iron and of copper, the silicates of iron and of magnesia.

All of the researches, so patiently and conscientiously carried on by Saint-Lager between 1865 and 1875, have proved that the salts of lime do not seem to play any essential rôle in the appearance of goiter. According to MacCarrison, the excess of lime in the nourishment of a pigeon and of the rat, other things moreover being equal, would almost constantly provoke in these animals a remarkable hypertrophy of the thyroid gland through an abnormal accumulation of colloid substance in the vesicles. However, lime and magnesia are to be found in abundance in a number of regions, where endemic goiter is unknown. As regards the other substances, no convincing fact has been brought forth to prove their goitrigenous qualities. In 1913, together with Ch. Lesieur and Joseph Chalier, we introduced into dogs either earth from the goitrigenous regions or silicate of magnesia or of iron; it is possible that our experiment was not carried on long enough, for we had no interesting results.

It indeed seems at the present time that the nature of the soil must play only an accessory rôle, inasmuch as endemic goiter has been observed in France as elsewhere in districts, that were very varied both in nature and in origin.

The fact that the greater part of the goitrigenous waters lose their noxious properties through the simple process of ebullition does

not conflict with the purely chemical theory, for ebullition precipitates the salts of ca'cium in great part. Therefore we must not refuse to acknowledge the relationship of the two factors, lime and iodine, in the disorders of the metabolism among the goitrous persons.

b) **As regards the presence of microbian and parasitic agents** we can in France gather evidence only from antiquated works, which were even contradictory and lacking in precision and authority.

The confusion, which the last war has provoked in France, has not permitted us since 1914 to take up again on a sufficiently large scale the entire series of bacteriological investigations, which we had undertaken to do and which would be necessary to throw new light upon the microbian nature of endemic goiter. In a number of goiters in active development, which were perhaps cases of chronic thyroiditis, we have been able to isolate the microbes into: usually staphylocci, streptococci, pneumococci or pneumobacilli, colibacilli, the cultures of which, when injected into the veins of the cervical region of animals such as dogs, rabbits and Guinea pigs, have provoked congestions, hypertrophies or more or less pronounced infection of the thyroid gland. But these facts are not convincing, for the greater part of the nodular or diffuse parenchymatous goiters of young subjects are found to be aseptic.

The microbian infection, nevertheless, acts with individuals, who are predisposed through heredity or through personal causes of thyroid incompetency, to provoke troubles in the secretion of the vesicles and in the circulation of the gland: a number of goiters, already started, become manifest only on the occasion of these outbursts of concealed thyroiditis.

The researches of Répin, published in 1911, seemed to conflict with the microbian theory and, in particular, with the very suggestive facts, observed by Lustig and Carle, Mac Carrison, Bircher, Sasaki, Gaylord et al.

Répin showed, in fact, that all of the goitrigenous waters which he had investigated during several years were practically non-microbian. All of his attempts at isolation of a specific agent resulted only in putting common microbes in evidence, microbes which were no longer to be found when the precaution was taken of drawing water at the very source. But these experiments of Répin do not take account of the possibility of any pollution of the waters, which may happen during their flow far away from their source and which could be responsible for the

endemic goiter. Now, the supporters of the theory of the infectious origin of goiter hold this very pollution responsible. By means of their remarkable experiments, MacCarrison, Gaylord, Bircher, Sasaki have shown that waters, which were pure and without goitrigenous action, would provoke goiter among more than 50 % of the animals subjected to experiment, when they imbibed the waters polluted through the excrements of goitrous individuals or animals.

Likewise, the fact, that hundreds of thousands of goitrous Hindoos, of Thibetans and of Chineses drink only tea or infusions made with boiled water, does not furnish any proof, for we know how numerous are the causes in those countries of alimentary or other contaminations and infections.

« Nevertheless », so say the adversaries of the idea of any goitrigenous infection through the alimentary canal, « the inhabitants of Berne, where we find at least as many as 60 % afflicted with a larger or a smaller goiter, drink water that is not contaminated. On the other hand, the digestive troubles are not particularly frequent in the endemic regions. And a number of districts, in which thyroid fever, dysentery and the diarrhoeas of the torrid countries are constantly raging, escape this epidemic ».

c) **Physical Properties.** It is in consequence of the negative results of his bacteriological investigations that Répin has come to study the physical condition of the goitrigenous waters, especially their radio-activity. Fourteen sources of la Maurienne, of l'Oisans and of the Briançonnais were analyzed with this thought in view. In all these a radio-activity was found, comparable to that of the mineral sources of Dax and of Contrexeville.

Continuing his comparative researches still further, Répin showed that the geographical distribution of the goitrigenous waters agreed exactly with the emergence of the hydromineral sources, both being situated upon the course of the lines of recent fracture of the earth's crust ». (This view is confirmed by Bircher).

But that is only a putting off of the difficulty and these very interesting notions call for new controlling investigations, for many very radio-active waters are not goitrigenous.

There is no crucial fact, which actually permits us to cut the discussion short. The rôle of the aqueous factor appears to be primordial, but we are not able in any respect to foretell anything of its exact nature. It would seem undeniable that in beings predisposed to goiter, the activities of the microbes or of their

toxines play a decisive part. Still the chemical activities must not be rejected, seeing that the experiments made on lime taken in excess in alimentation seem to agree.

II. The Human Conditions for the Appearance of the Endemic Disease.

Age. — Congenital goiter is not so much the exception as the authorities might lead us to believe if we understand this to include all of the hyperplasias of the newly born. Apart from the great thyroideal hypertrophies which do or do not exist with hypertrophies of the thymus gland, and which are to be numbered among the causes of asphyxia of the new-born child, the obstetricians and children's doctors have in France observed a number of cases of moderate but abnormal hypertrophy, observed at the post-mortem examinations of new-born or prematurely born children whose mothers either were goitrous or in the course of pregnancy had shown general or local infections of the thyroid gland. More often, however, the infections incurred during the time of pregnancy, reduce in the child the size of the thyroid system and its power of secretion and entail a more pronounced degeneration towards cretinism. The careful examination of the new-born children of women afflicted with goiter in countries infested with the endemic can show an unquestionable hypertrophy of the thyroid gland, amounting to a proportion of from 30 to 50 %.

Even if it develops at birth or during the first years of life, goiter as a rule begins to become noticeable only on the approach of puberty (goiters of scholars), and only later is it observed at its highest development.

Majet found, when taking up the observations made by Baillarger, that of 13.090 people afflicted with goiter only 2209 were less than 20 years old. This proportion is surely too low, for in the case of most children afflicted with goitrous endemic, the thyroid gland is still too little hypertrophied before the age of puberty to be noticeable at a first glance or at a superficial clinical examination, unless the attention is drawn towards the thyroid gland by some other functional trouble.

Sex. — Goiter in a conspicuous form is much more frequent with women than with men, the ratio being 5 to 3; even before the age of puberty the number of girls afflicted with goiter is greater than that of boys. Later on, this predominance even increases. All the repeated congestions by the thyroid gland in

connection with the ovarian secretion favor the development of goiter. In women these congestive secretions occur constantly and are more or less permanent at the time of puberty. They are renewed at each menstruation. They increase abnormally during pregnancy, above all if it is complicated with blood poisoning or infection. Their development is often greatest after the exertions of child-birth. At the climacteric period finally the thyroid gland is the seat of new congestive secretive developments and trophic disorders, which as a rule do not make a goiter visible that was latent until then, but which very often in quite a bearable goiter cause neoplasic*) degeneration, above all in the nodular goiters, which must be classed among the precancerous lesions just the same as certain adenomatous nodules of the breast.

Heredity. — It is a question here of one of the most interesting factors, perhaps even the most important of all those that encourage the persistency of goitrous endemic.

Having been recognized for a long time, the part that heredity plays needs no longer to be discussed. Therefore we shall only take recent documents into account, referring to our «Treatise of the Thyroid Disease» (Baillière, éd. 1908) for the oldest documents, especially for the relations of cretinism with the hereditary lesions of the thyroid gland.

M. Coulaud (1925) when studying 100 records on examinations of goitrous patients during the last few years in Paris, which could be taken for sporadic cases, ascertained that 13 of them had never lived in a district infested with goiter. But on closer examination of the origin of those 13 diseased people, he found that ten were born of parents native of goitrous districts (Savoy, Puy-de-Dôme, Creuse, Landes), and that two others had Savoyan grandparents. Thus, only one of them formed an exception to the rule.

A great many facts observed by us corroborate and support this idea of hereditary transmission of goiter, in man as well as in the animal (donkey, dog, cat, goat, etc.), which nobody doubts of.

After a couple have left a goitrous district, goiter can still appear in the descendents down to the 4 th generation. This power of transmitting goiter decreases progressively and often very rapidly: A mother who had a cretin child while living in a village infested with the endemic, could after emigrating to districts free of the disease, have a second child that was merely goitrous, then others in whom only slight thyroideal hypertrophies or small

*) *D. Bérard & Dunet*, Cancer thyroïdien, 1 vol. Doris, éd. Paris 1924.

hypothyroid disorders indicated the impregnation. It is also generally acknowledged that after spending the period of pregnancy and of lactation in safe districts, women who are natives of goitrous districts would have normal or almost normal children; for the mother and the child would thus have been protected from the permanent causes of goitrous dysthyroidy. Should the faecal infections be considered the most essential of these causes, how could we account for the fact that they do not take effect everywhere or always in the case of people predisposed to this disease?

When the hereditary predispositions are handed down through several generations, it is only the women who finally remain afflicted. In exceptional cases, only, do we find the father the intermediate agent of this transmission; as a rule it is brought about by the mother, and in two ways:

In the uterus the thyroid gland of the fœtus can be influenced in its structure and its functions by the mother's blood, if the latter has an insufficient amount of vitiated secretion.

After birth this influence is extended, owing to lactation.

This statement is confirmed by experimental facts. The work of Breisaker, Verstraeten and Vanderlenden, of Farkou and Golstein, etc. has, beyond all dispute, established the fact that the maternal thyroideal elements pass into the milk. It is evidently owing to this passing on that the modifications of the epithelium of the fœtal thyroid become clearly defined, making the fœtus predisposed to goitrous degeneration.

Coulaud has demonstrated that rabbits born of healthy parents but suckled by a mother rendered hypothyroidic by means of irradiation of the brain with X-rays showed a very considerable retardation in the development of their thyroid gland.

There is no reason to suppose that in the human species these things should not take place in exactly the same way. When, in addition to the long saturation during the life in the womb, we find a noxious influence of lactation, then all conditions for weakness of the thyroid system have been fulfilled.

III. The Variations of the Endemic in France.

Baillarger had already noted, between 1835 and 1865, the variations of the endemic: whereas it was decreasing in 17 departments, it seemed to be increasing in 26 others.

Fifty years ago, by going through the villages on market days, or by counting the goitrous people after returning from church

on Sundays, Saint-Lager could still find that half of the population of certain hamlets in the Alps or the Auvergne was afflicted by the endemic.

To-day the proportion of goitrous people scarcely rises above ten per cent in districts where the endemic rages with greatest intensity. At any rate, those big, often enormous, goiters, that used to be so frequent, are no longer to be seen to any extent.

In 1900, Mayet estimated the number of goitrous people in France at 400,000; we shall, to-day, not contribute any precise figures, for in these kinds of investigation there are a great number of sources of error. — The fruitless attempt, that we made, has shown us that it is almost impossible to set up exact statistics, and that it would, in any case, require still several years of research and control, owing to the great and increasing emigration movements outside of the endemic zones. It is thus that for 10 years goiter has been making its appearance in industrial cities and centers where previously it had hardly ever been observed.

But it follows, no less, from our conversations and correspondence with physicians practising in goitrous districts for a great number of years, from our enquiries made at the commissions for hygiene and at the centers for invaliding, that the endemic has decidedly been going back, above all during the last thirty years, especially in the following departments: Haute-Savoie, Savoy, Hautes-Alpes, Isère, Ain, Jura, Loire, Haute-Loire, Puy-de-Dôme.

Savoy is still one of the districts most strongly affected by the goitrous endemic; but, whereas during the period from 1887 to 1896 the number of recruits disabled for goiter amounted to 252, the number sank to 101 during the following ten years, and, finally, between 1908 and 1917 only 28 were disabled.

We know that these figures are open to discussion, for the recruiting commission must yield to the increasing necessity for auxiliary service, owing to which people are embodied who are suffering from slight hypertrophies or from small nodular goiters, without any functional disorders, and who, thirty years ago, would have been invalided. — Besides, the recruiting commissions reach only the men, and the number of goitrous women is twice as great.

We have also tried to define the parallel course of cretinism and of goiter in the same district, as they are so closely connected.

In 1864, the report of the French Commission mentioned for the total of the goitrous districts 4346 idiots and cretins among a

population of 271,663 inhabitants; which amounts to a proportion of 16 per thousand.

In 1874, the 86 communities situated on the right and the left banks of the river Isère in Savoy had some 833 cretins among a population of 65,228 inhabitants, that is a proportion of 12.75 per thousand.

In 1900, according to Mayet's statistics, Savoy held the sad privilege of being the foremost department of France as regards the number of its cretins.

In 1908, this number could be fixed, according to Ducoste, at 700 in a population of 253,297 inhabitants, the proportion thus being reduced to 2.76 per thousand. The same communities bordering on the Isère had only 172 cretins among a population of 57,658 inhabitants, that is 2.98 per thousand.

To-day, owing to the loss of men during the war, a loss which affected only the healthy part of the population, this proportion is about 3.10 per thousand.

Thus the parallel decrease of goiter and of cretinism in Savoy is evident. It is not less apparent in the other departments mentioned above.

In the Hautes-Alpes 2 cases of invaliding for goiter were stated for the class of 1923; for the classes of 1924, 1925, 1926: no invaliding. For the class of 1927, one case of cretinism only.

In Isère, 2 recruits were invalided in 1926, and 2 as well in 1927.

In the Loire department, for a period running from 1907 to 1920, about 12 recruits of the 16,800 were invalided for goiter and 44 were assigned to the auxiliary service. From 1924 to 1927 not a single case of invaliding.

In Puy-de-Dôme the same facts were established. From 1923 to 1925, no invaliding for goiter; 3 cases in 1926; 2 cases of invaliding in 1927.

In the Jura only one or two of the 1000 recruits are goitrous.

Now, what causes account for this progressive regression of the endemic?

No campaign, no systematic prophylaxis, ingestion of iodine or of iodized salt has yet been organized by the State, by commissions for hygiene or by the communities. It can not be doubted that the goitrous people, whose number was constantly increasing, upon discovery of their tumor sought treatment by taking iodized organic or mineral preparations, either upon

their own initiative, or through the intermediary of their doctors. But one thing is certain: that no general, official therapeutic measure whatever has been adopted, apart from a few distributions of medicaments in schools, — and still the endemic has regressed.

We consider the following to be the causes of this regression:

a) Improvements in the means of supplying drinking-water for alimentation.

Since the promulgation of the Law of Empereur, in 1903, a very great effort has been made in this direction by many communities. Since that time the number of adductions of water has been raised to the considerable figure of 150, especially in Savoy. Since then, many communities of La Tarentaise, or La Maurienne, those of St-Jean-de-Maurienne, of Ste-Marie-de-Cuines, of St-Pancrace, of Bozel, of Seez, of Planaise, to mention only the most striking examples, undoubtedly owe the disappearance of the endemic in the young generations to the supply of drinking-water.

That does not mean that the noxious sources, the goiter-spreading waters, do not exist any more. Certain less favored communities have kept their old resources as only means of supply of water for alimentation. And still, the endemic is dying out even with them, for the inhabitants, now knowing about the noxiousness of these waters, take greater precautions to preserve the water from external pollutions, when taking and adducting it; and, no longer glorying in big necks they do not use this water without having reduced it by the addition of wine, or by infusing tea or coffee.

In consequence of the industrializing of the valleys and of the progress in the use of white coal, many torrents have been regulated. The waters have been collected, aerated, decanted, exposed in enormous reservoirs to the rays of the sun, thus being purified from the microbes contained therein, especially the anaerobic ones, and have acquired new chemical and physical properties. The water of the Rhone river, though it is goitrigenous in the Canton of Valais, is no longer noxious in France after having emptied into the Lake of Geneva. But above all the greater part of the population, who formerly were out of work during part of the year, can now by their working in factories earn salaries of an amount hitherto unknown. This money is partly spent in improving their food, and above all in buying wine, the consumption of which has

increased a hundredfold in 30 years in certain villages and contributes, we feel sure, towards the decrease of the endemic.

As most of these manufactories have but recently been constructed, they are managed according to the rules of hygiene; almost all of them are supplied with water of fairly unquestionable purity. The workmen, often lodged in new little well-aired houses situated higher up, escape the dampness, the obstruction and the physiological miseries of the wretched lodgings and old cottages. They are no longer during the winter obliged to consume fats that are oftentimes rancid, and badly prepared pickled meat and bread improperly risen, that besides is often mouldy, which are just so many food elements without vitamines. As a rule they consider the improvements in food and clothing before worrying about rational hygiene; but little by little cleanliness and care of the body, even the cleaning of the teguments and of the cavity of the mouth which is so essential, become habits more and more cultivated. The causes of infection and of poisoning, which are of a cutaneous, respiratory and above all of a digestive origin, are thus being more and more reduced.

Food

Hygiene

Fats

Vitamin

b) Emigration.

The increasing facilities of communication, the interpenetration of different regions, that has been conspicuous especially since the war, the forsaking of the country, which is becoming more and more marked, these all play an important part. At present the Alpine districts constitute the emigration regions; there are 50,000 Savoyards in Paris, and more than 50,000 others in the rest of France. A great many young girls leave their communities, at least for a considerable part of the year, in order to take a situation in town, thus escaping the continual influence of the goiter-spreading agent. — They often return to the bosom of their families for a few months during summer, but only to attend to the urgent country work, living in the sun and the open air, and with a sufficient amount of fresh food rich in vitamines. Then, in winter, they once more return to the towns where the endemic can be but suspected, or does not exist at all.

With a certain number of them a slight thyroideal hypertrophy occasionally becomes noticeable, but it can recede from one year to the other; and oftentimes it is scarcely to be noticed, and does not develop at all if the country is not visited too often and for too long a period.

Nor must we lose sight of the case of the number of hamlets afflicted with goitrous endemic, where the inhabitants are more and more struck with the wretchedness and monotony of their lives; they see, adjoining them, more favored districts where manual labor is required and where they are offered a more comfortable existence. More and more are these hamlets being abandoned, and they will soon be almost entirely deserted.

c) Scarcity of Marriages between Relatives and goitrous Persons.

Since goiter is no longer considered, if not exactly an ornament, the token of a privileged race, at least a negligible attribute, marriages either between goitrous people or between blood relations tend to become more and more scarce. Boys and girls marry far off in the villages and towns where they have obtained situations; various kinds of intermixture are thus brought about. As the question of heredity, which weighs so heavily, does not come into question any more, the thyroideal defects are no longer augmented and this too must be considered one of the important causes of the decrease of the endemic.

d) Improvement of General Hygiene.

The populations that even less than fifty years ago, in our Alpine districts, were weakened by goiter, lived under conditions of promiscuity and filth which it is rather difficult for us to conceive now-a-days. Often confined under the ground in damp hovels that were never aired, and unhealthy in the highest degree, living side by side with their cattle that were never cleaned, the inhabitants of these districts were entirely ignorant of the most elementary habits of hygiene. They were thus given up to many kinds of infections and to prolonged general or digestive poisonings.

Since these same inhabitants have learned to separate their lodgings from their stables, and the kitchen from the cesspool, since they have begun to take more substantial food and to drink wine, their robustness and their natural resistance towards the intestinal infections and the poisonings that favor or keep up the endemic of goiter have increased remarkably.

Let us repeat that, by diminishing all the causes of infection and of poisoning, the improvement of general hygiene has been one of the essential factors in the regression of the endemic of goiter.

Epidemiology.

« Epidemics of goiter » have been reported by many writers in every country and at every epoch. — Saint Lager has collected the most characteristic facts in his book. And recently MacCarrison has investigated several such cases in India.

But an analysis of these facts clearly shows that in practically all the cases it is a question of a more or less acute and more or less temporary recrudescence of the endemic, rather than of an appearance of goiter in districts up to then free from it.

These epidemics usually coïncide: either with the change of drinking-water; or with certain food-poisonings; or with the pollution of these waters after the overflowing or the siphonage of certain torrents or of certain stagnant pools; or with the arrival of conscripts or of boarders, in barracks or in schools provided with impure water, especially if these recruits and pupils had, up to then, lived in places free from the endemic. There is really no doubt but that the natives sometimes enjoy a kind of mithridatism in countries stricken by the endemic.

But is it proper to apply the term of epidemics to these morbid manifestations? Now-a-days we take an epidemic to be a kind of cycle, arising through the appearance or the increased virulence of some agent of infection, easily to be transmitted by inhalation, by ingestion or by inoculation, producing during a longer or shorter period an ever increasing effect, — then becoming weaker, either from a spontaneous exhaustion of the poison, or as a consequence of prophylactic and therapeutic measures that have been taken, as serums, vaccines, specific medicaments, etc.

Strictly speaking, we might apply quite a number of these terms to « epidemics » of goiter, without even stretching their meaning too much.

But there are such a number of factors working together in so many different ways, all leading, it is true, to a more thorough disorder of the iodiferous metabolism, that it would no doubt be better to find another name.

IV. The Anatomical Characteristics of Endemic Goiter in France.

We have not made the observation in France, as MacCarrison has in India, that there exists a constant relation between certain anatomical types of goiter and certain causes of endemic.

Apart from those relatively rare cases of goiter, assuming the type of diffuse thyroideal hyperplasia, and operated upon in

children and adolescents, goiter appears in the very great majority of cases in the nodular shape (about 70 to 80 %).

The uni- or pauci-nodular type is decidedly the most frequent. The bulk of the goitrous nucleus varies between the size of a hazelnut and that of a big orange; larger goiters are but an exception. Only rarely do we operate on thyroid glands quite full of numerous nuclei.

The prevailing type is struma nodosa parenchymatosa, that is to say that the endemic appears most frequently in a deviation of the thyroideal tissue towards the adenomatous type. But it seems probable that these adenoma nuclei frequently, we might almost say always, develop in a gland, the consistency of which was already changed, either at the time of birth, or during the first years.

The fetal adenoma (de Wölfler) is not common, coming to scarcely 1/10 of the nodular goiters.

After a phase of proliferation, which is localized not merely to a few vesicles, but to a great number of them, the adenoma keeps a homogenous aspect during a period varying in length; for the epithelial tissue progresses in harmony with the maintaining cellular tissue which supplies it with nutritive vessels.

Almost from the beginning, a capsule, always clearly individualized, separates the adenomatous tissue from the gland with normal or hypertrophied substance.

But when the adenoma reaches a diameter of four to five centimeters, we witness modifications that are essentially connected with circulatory disorders.

The vessels that pass through the capsule resolve, inside the adenoma, into an infinite number of capillaries that are abundant but of precarious texture. They are friable, of fragile structure, easily compressible. At the level of the zone of suffering, symptoms obstructing metabolism are quite the rule; the change of matter slackens, and the cellular proliferation and glandular secretion are abolished, contrary to the subcapsular peripheric zone which remains the only zone of growth in the adenoma.

All the modifications of the central zone are slowly and progressively linked together. They begin with a sero-colloid infiltration; this is accompanied by a rarefaction of the vesicles, by a diminishing of their size, or by their fusion, and finally by their disappearance. An amorphous tissue begins to develop in their stead, it has but little regular cellular tissue and few collagenous

fibres, and these are separated by an abundant amount of interstitial liquid coloring just as diluted colloid does. Superficially considered, this tissue has the appearance of certain myxomas: owing to this, certain writers gave this degenerative variety of adenoma the epithet of adenoma myxoid, which is entirely erroneous.

As the lesions progress, the epithelial element seems doomed to disappear. It is, however, often easy to find the position of the dead vesicles, for their form is preserved perfectly under the shape of completely «disinhabited», rounded cavities.

Later on, when every kind of circulation is definitely abolished at their stage, the tissues of the central zone are given up to total aseptic necrosis, in the majority of cases.

This zone is hollowed with irregular geodes, of sero-hemorrhagic contents, in which it is very difficult to discover, by means of the microscope, thyroideal elements that are very deformed and sometimes even unrecognizable. This progressive decomposition ends in the production of pseudo-cysts which never show the least epithelial covering.

These lesions are very frequently accompanied by hemorrhages which still accelerate the process of necrobiosis by compressing and altering the peripheric adenomatous tissues. The latter are often reduced to a layer a few millimeters thick. At this stage some thyroideal elements continue, existing either as small sized vesicles with a reduced colloid secretion, or as more or less irregular fields.

Having arrived at this stage, goiter does not increase any more by reproduction of its epithelial elements, but by transudation of serum, and by interstitial hemorrhages.

The process of central destruction is most of the time accompanied by a more or less intensive conjunctive peripheric reaction. The capsule, which in the beginning was reduced to just a few conjunctive elements, becomes thick and forms a real barrier separating the actual tumour from the healthy gland, which, nevertheless, at this stage shows a slight hyperplasia of its supporting conjunctive tissue.

Contrasting with this form of parenchymatous adenoma, we have the cystic nodular goiter which is characterized by the predominance of the phenomena of colloid secretion, such as proliferation. This rarer form presents nothing exceptional; it is not, as the preceding form, the seat of progressive degenerative lesions, it evolves ever so much more torpidly, except, of course,

Colloid or cy goitre is less common. (i.e. in Fran

for the complicated cases of infection or of intracystic hemorrhage.

It is, after all, to all the preceding degenerative changes that in the majority of cases goiter owes its macroscopic aspects which are often so different. But under their apparent polymorphism, most of the lesions evolve according to a rhythm that can not be broken off.

The initial lesions are: dysthyroidic hypertrophy, constitution, development of the adenoma and its enclosure in a capsule, all of which directly seem to depend from goitrigenous factors.

However, the secondary degenerative lesions do not, according to our opinion, depend on these factors. They are common, and are solely governed by vascular disorders, the time of appearance, intensity, and extension of which depend, above all, on the rapidity of growth of the goitrous nodule.

From the aetiological point of view which, in this report, we must take, the knowledge of the fundamental and contingent lesions of endemic goiter does, therefore, not lead us to more precise conclusions than does the statement, made above, concerning the causes to be blamed. We find here no process whatever that is characteristic of a microbian infection or of a chronic poisoning through organic or mineral products.

Can the gland, moreover, not react in quite the same way with regard to the most varied kinds of processes apart from the acute and subacute infectious lesions, and apart from certain so-called characteristic reactions of the tissues, such as the huge cell, common nevertheless to tuberculosis, syphilis and the pseudo-tuberculoses? Poncet strongly insisted upon the frequent occurrence of toxibacillary goiters, developing in tuberculous people without specific lesions.

V. Aetiology and Metabolism of Iodine.

To our fellow speakers in charge of the pathological physiology of goiter we shall leave the exposition of the alterations brought about by the endemic, either in the functions of the thyroid gland, or in the general changes of metabolism above all as regards the metabolism of iodine. Nearly all the analytical chemists have ascertained a diminution of the quantities of iodine in

the thyroid gland of goitrous people, and an almost complete disappearance in the gland of cretins and of certain myxoedematous people, in spite of an apparent, often enormous, hypertrophy of the gland, which has developed into extraordinary proportions. This establishment of facts is an indisputable proof that the causes of the endemic are felt first of all, and above all, in this metabolism of iodine.

Ever since the work of Chatin concerning the thyroid gland and iodine, long before the discovery of thyroidine by Baumann and Oswald and of thyroxine by Kendall, and before the synthetic reconstitution of thyroxine by Harrington, the essential cause of goitrous endemic was attributed to the absence of iodine or of iodized combinations in the soil and in the drinking-water. And in order to support this thesis the success obtained with goitrous persons with the iodine treatment is appealed to.

no such thing

But very soon it was acknowledged that this deficiency in iodine, in the soil and the waters, could not be considered the origin of the complete insufficiency of iodine in the goitrous person. In fact, certain areas, afflicted by the endemic, stretch along the sea-shore, where the atmosphere, the plants, and the infiltration waters are rich in iodine. Moreover, all the investigations made by Mr. MacCarrison during the last 20 years, and examined by a number of experimentalists, lead to the following conclusion: If the addition of iodine to nourishment and water prevents the outbreak of goiter or retards its evolution in persons and animals subjected in any other way to the influence of the goitrigenous agents, still a proposition inferring the reverse has no support; the endemic goiter is equally observed in districts where soil and water are lacking in or are abundant in iodine. And where goiter is experimentally produced in animals by the absorption of the intestinal microbes taken from goitrous subjects, or from their toxines, it matters very little whether the ground on which the experimental goats graze, or the water in which trout are kept for experiment, are analytically found to be more or less rich in iodine, provided that they are not contaminated.

All that can be said, is that the goitrigenous agents seem to render the thyroid gland incapable of retaining the iodine and of elaborating the product of its normal secretion, the thyroxine, which is necessary for the equilibrium of the changes going on in the system.

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VI. General Conclusions.

What conclusions can we gather from the facts reported above concerning the aetiology and the regression of the endemic of goiter in France?

First of all that the aetiology of goiter is not univocal.

The endemic goiter is the resultant not of one single cause, but of manifold causes, the isolated or synergetic activity of which no doubt leads to the creation of anatomic-clinical varieties which we are not yet able to identify precisely, and which we put together under the same name.

Without going back to the obsolete theory of the various causes that ended in accepting the activity of more than 50 aetiological factors, we nevertheless admit that, though the aqueous factor is the principal agent, the accompanying causes — physiological misery, defective alimentation, close and foul atmosphere of the unhealthy hovels, poisonings and perhaps chronical digestive infections, etc., play an important part.

It is no less certain that one of the causes of the persistency, if not of the extension of the endemic is due to the following fact: many individuals, deteriorated as regards the thyroid gland, by uniting perpetuate their thyroideal weakness either by begetting children whose thyroideal system is congenitally deficient and who are incapable of assuring the normal changes, or by rendering their descendants extremely more susceptible to the noxious influence of the goitrigenous factors.

As for the water, we do not know whether it acquires its goitrigenous properties from the chemical products, which it contains, from the microbian agents it transports, from the toxines of these microbes, or from a special physical state (radio-activity?); it is impossible to settle the debate at the present time. Only more or less plausible hypotheses can be suggested in this respect. The hypothesis, which attributes to infection the preponderating part, seems to be the most probable one.

Whatever may be the inmost nature, not of the improbable specific factor, but of the goitrigenous factors that are often associated, it seems that all of the latter with their activity disturb the inward metabolism of the iodine, which normally is governed by the thyroid gland; in other words, they bring about a complete insufficiency of iodine.

The process of this insufficiency of iodine is far from being explained; do not some writers even positively refuse to acknowledge it?

Still, the sole fact that the systematic dispensing of iodine might limit the endemic by reacting at the same time on the thyroid gland, on its structure, and on its essential functions, deserves to be taken into serious consideration. Does the other fact, that but very small quantities of iodine suffice to obtain a result, not agree with all that we know about the biochemistry of iodine in the system?

Do the goitrigenous factors effect a change in their interest of the disposable iodine, or do they prevent the system from assimilating this iodine? Do they increase the requirements of the system to such an extent that the proportion of iodine ingested is entirely insufficient? There remain just these many questions to which we are not yet able to give answer.

However that may be, the thyroideal hypertrophy may be considered a compensative functional hypertrophy, secondary to the rarefaction of the iodic combination and to the raw material elaborated by the thyroid gland.

All factors, therefore, which increase the need of the system for iodine are, by contrecoup, important factors favoring goiter, for most of the time it is they that call forth the phenomena of complete insufficiency of iodine and the secondary hypertrophy of the thyroid gland; these factors are above all puberty, pregnancy, lactation, climacteric period.

Still, this conception of the absence of iodine must not let us lose sight of the existence of various goitrigenous factors; a systematic prescription for the ingestion of iodine is not enough to check the endemic. As our study of the causes of regression of goitrous endemic, in France, clearly shows, the fight must be carried into another field which is the social field; every hygienic improvement, whether it concerns nutrition, dwelling, or selection of drinking-water, etc. unquestionably contributes towards the progressive disappearance of goiter.

Moreover, endemic goiter must no longer be considered an affection strictly limited to the thyroid gland, but as a general disturbance of nutrition, appearing first in functional disorders, somnolence, apathy, a slackening of the cerebral function and myxoedema; then it shows itself in thyroideal lesions; these, at

a disturbance of nutrition

first, are curable in the beginning, then, at length become definitive, after the degenerative lesions, studied above, have appeared. Not being caused by goitrigenous factors, these lesions can not disappear when the activity of these factors ceases.

* * *

Conclusions:

In France 37 departments are subject in varying degrees to endemic goiter; in the other 49 departments goiter is only exceptionally met with.

Apart from a few isolated communities in the departments of Aisne and Orne, the goitrous districts are confined to two groups, a small one in the Pyrenees and a big one in the center (massif central) and in the east of France from Northern Alsace to the south of the Alpes Maritimes.

The geographical distribution of goiter in France has not changed during the past thirty years.

Altitude and climate play only a subsidiary part in the genesis of goiter. This is proved by the fact that goiter has decreased in intensity though its geographical distribution has remained the same. No systematic preventive treatment with iodine has so far come to light.

We assume the cause of the decrease to be:

a) The improvement of the supply of drinking water,

b) The increase in the consumption of wine,

c) Emigration (temporary or permanent) from the goitrous districts,

d) Decrease in the number of marriages between blood relations,

e) The improvement in the general conditions of living (personal and general hygiene, improvement of conditions in the home and of nourishment etc.)

Hence we see that there are several causes of endemic goiter. Nevertheless drinking water plays the most prominent part. There are beyond all doubt certain kinds of water which produce goiter.

The action of the goiter-producing water is to be explained by its interference with iodine metabolism, causing relative or complete insufficiency of iodine.

All factors therefore which increase the need of the system for iodine favor the appearance of goiter (puberty, pregnancy, lactation, climateric period).

We regard goiter not as an affection strictly confined to the thyroid, but as a general disturbance of nutrition.

The designation of endemic goiter is a general term covering the most varied affections of the thyroid, which partly take the form of atrophy of the gland, partly that of proliferation of the secretory epithelium as a result of irritation.

The type of endemic goiter usually found in France is struma nodosa parenchymatosa or cystica. Diffuse hyperplasia of the thyroid gland (struma diffusa) is only rarely observed.

Toxic goiter is rare.

New growths in the thyroid gland are also rare. 85 to 90% of the cases of carcinoma in the thyroid gland occur as a result of an already existing struma.

Abstract of report on the aetiology and epidemiology of endemic goitre.

By Robert McCarrison.

Two types of endemic goitre are recognized: 1. the classical type of mountainous regions, variously named parenchymatous goitre, adeno-parenchymatous goitre and chronic hypertrophic goitre, rarely associated with Graves's Disease but commonly associated with cretinism, deaf-mutism and various forms of physical and mental deterioration; and, 2. the diffuse colloid type of the plains and low altitudes, commonly associated with Graves's Disease but rarely associated with cretinism or other stigmata of physical and mental deterioration. The first type is least common in childhood but increases in incidence, in size, and in nodular character as age advances, attaining to its acme about the age of fifty. The second type is most common in childhood, attains to its acme about the age of puberty and lessens rapidly, or gradually disappears, after the age of statural puberty has passed. Both types may occur in the same locality. A third type — the lymph-adenoid goitre — is briefly referred to as likely to be found in Western Countries intermingled with goitres caused primarily by endemic influences.

1. The epidemiological features of the classical type of endemic goitre and cretinism are described; and its relation to geological formations, to food-supply, to iodine-deficiency, to unhygienic condi-

tions of life and to intestinal infection is considered. Evidence is provided of the experimental production of goitre in man, of the experimental production of its complete clinical expression in animals (congenital goitre, cretinism and parathyroid disease), of its cure, and of its eradication from an endemic locality: all by means which indicate a causal relationship of gastro-intestinal infection to this type of endemic goitre. The subsidiary part played by iodine-deficiency in its causation is recognized; and the intimacy of its interaction with other factors concerned in the production of this type of goitre is emphasized.

2. The known epidemiological facts in regard to the chronic, diffuse colloid type of endemic goitre are stated; and the paucity of complete epidemiological surveys or of serious attempts at its differentiation from the classical type of the disease are referred to. The confusion in regard to the causation of the « goitres » and the difficulties attendant on a prophylaxis which is common to them all are considered to be due to this inadequate differentiation. Experimental evidence is provided pointing to the possible influence of a disturbed calcium-iodine-balance in the causation of « colloid goitre ».

3. The dietetic conditions under which the lymph-adenoid type of goitre arises in rats are described. Man is commonly subjected to similar dietetic conditions. The prediction appears, therefore, to be justified that this type of goitre is likely to be common in Western Countries where certain food habits prevail, and that it may be a fore-runner of Graves's Disease or myxoedema. Lymph-adenoid goitre is not related in its origin to iodine-deficiency.

Twenty-two sheets illustrating by charts, photographs and photomicrographs, the various matters dealt with in the Report, and affording a pictorial record of the Author's work on this subject during the past 25 years, are submitted for exhibition.

The aetiology and epidemiology of endemic goitre.

By Robert McCarrison
Pasteur Institute, Coonoor, S. India.

I have to thank the President and Council of the Swiss Goitre Commision for the honour they have done me in inviting me to present a Report on the Aetiology and Epidemiology of Endemic Goitre to this Conference, and to express my regret that it has not been possible for me to do so in person.

Introduction.

With changing conditions of life, improvements in sanitation, protection of water-supplies, modifications in food habits and in food, the character, incidence and sequelae of «goitre» have changed and its geographical limits appear to have widened even within the last 25 years. Formerly it was to be found mainly in hilly regions where persons with large pendulous goitres, and sufferers from cretinism, deaf-mutism and idiocy, were commonly encountered. To-day these grosser manifestations of the disease are less common, even in its old endemic haunts; and instead, we find smaller goitres, more widespread in their geographical distribution and more often associated with thyrotoxicosis. It is only in such localities as Himalayan India and the more remote parts of other mountainous regions where old habits and customs still prevail, and to which the amenities of modern civilization have not yet penetrated, that the classical type of endemic goitre is likely to be encountered in a state of aetiological purity. In these localities goitre-producing influences remain the same to-day as formerly; while in others they have lessened or new influences have been added to them. The constellation of causes which gives rise to goitre is not always the same, nor is the character of the disease identical, in different parts of the world.

Types of goitres.

I recognize two types of endemic goitre differing in their epidemiology, aetiology and pathology. The first is the classical type occurring in mountainous regions, and variously named parenchymatous goitre, adeno-parenchymatous goitre, simple hyperplastic goitre, and chronic hypertrophic goitre. The second is the diffuse colloid goitre which occurs more especialliy in lowland regions. The geographical limits of these two types may meet or overlap so that both may occur together in the same locality; while both may be sporadic elsewhere than in their favourite regional haunts. Intermingled with them there may be other simple, or non-toxic, goitres which are unrelated in their origin to endemic influences; of these I shall refer to one under the provisional designation of lymph-adenoid goitre (a term introduced by Williamson and Pearse, 1925). «Physiological goitre», which may occur in endemic and in non-endemic localities alike, and such terminal phases of the goitrous process as «cystic goitre», «fibrous goitre» and «cal-

careous goitre », will not be considered. I have, therefore, to deal with three types of thyroid enlargement:

A. Parenchymatous or chronic hypertrophic goitre,
B. Diffuse colloid goitre, and,
C. Lymph-adenoid goitre.

A. THE PARENCHYMATOUS OR CHRONIC HYPERTROPHIC TYPE OF ENDEMIC GOITRE.

This is the classical type of endemic goitre occurring in mountainous regions, such as the Alps and Himalayas, in association with cretinism, deaf-mutism and various forms of physical and mental deterioration. It is the type described by the older writers (Malacarme, Fodéré, Coindet, Maunoir, Iphofen, the Sardinian Commission, Saint-Lager, Baillarger, T. Kocher, H. Bircher and many others) to whom all students of endemic goitre are under deep obligation. It is, too, the type which may occur in animals living in captivity under unhygienic conditions of life: as in rats confined in unhygienic cages, or in fish reared in unhygienic tanks or ponds.

Pathological definition.

Pathologically the condition is a true hypertrophy in which the secretory phase of the gland's activity predominates, hyperplasia is pronounced, and many new vesicles are formed. Overstrain ultimately leads to fibrosis, with the appearance in the organ of circumscribed areas of more or less solid glandular tissue (adenomata) or of colloid-containing vesicles (colloid adenomata) or of both; the amount of colloid material in the gland appearing to depend on locality. In its early stages, as in childhood, it is of the parenchymatous type; in its later stages, as in adults, it is of the adeno-parenchymatous type.

In this state of sustained hypertrophy the thyroid is constantly straining to satisfy the needs of the tissues for its active principles but just falling short of doing so; consequently, in regions where the disease exists in a state of aetiological purity, as in certain parts of Himalayan India, evidences of hypothyroidism are constantly to be seen in sufferers from it; hyperthyroidism (thyrotoxicosis) rarely or never. In the pregnant female this sequence of events may result in failure of the maternal thyroid to satisfy adequately the needs of her own tissues, and those of the developping foetus, for the gland's products; especially when some additional burden (fright, mental worry, or attacks of acute disease) is placed on its resources. As a result the foetal thyroid is unduly

stimulated and congenital goitre or cretinism may arise in the offspring: a sequence of events which is equally true of experimental animals.

Epidemiology.

This type of goitre has distinctive epidemiological features: it has its home in the high mountain ranges of the world, prevailing chiefly in their dark and narrow valleys and at altitudes which may be as high as 10,000 feet or more above sea-level. It is essentially a place disease. It prevails with different degrees of intensity in different regions and in different parts of the same region, as in villages, or even in houses, situated adjacent to one another. The intensity of the endemic is subject to fluctuation, being greater at one time than at another. It has made its appearance in places where formerly it was unknown, and has disappeared from others, or persisted in them only as isolated cases; its disappearance has sometimes been noted to follow the canalization of water-supplies and improvements in sanitation. It is especially prevalent in agricultural and pastoral districts, although in many towns in endemic zones it may be rife. It is commoner in the poorer than in the richer classes, and in agricultural labourers than in those of other occupation; many persons may escape it altogether even in regions of high endemicity. It exhibits a distinct seasonal incidence, being more prone to make its first appearance in the spring and early summer months in persons not previously affected, or to undergo further enlargement at this season in persons who already suffer from it. Epidemics may occur in susceptible individuals or in newcomers to an endemic zone, as in school-children or troops, who may acquire the malady in as short a time as 15 to 30 days. There is a marked family predisposition or hereditary tendency to the disease, the children of goitrous mothers being very prone to become goitrous; consanguinity favours its development. It is associated with congenital goitre, cretinism (myxoedematous and tetanic), deaf-mutism and idiocy; these sequelae being as much a part of the endemic as the goitre itself. Apart from congenital goitre the malady is less common in childhood than in later life, but it gradually increases in incidence as age advances attaining to its acme between the ages of 50 and 60 years. In regions of low endemicity it is much commoner in females than in males, while in regions of high endemicity its incidence in the two sexes is more equal. There is a marked tendency to spotaneous recovery in early cases, following their removal from the endemic zone; «first attacks»

rarely proceed beyond a certain point of size, the gland enlarging by a step-like series of seasonal increases; in the endemic zone itself 10 per cent or more of «first attacks» may recover spontaneously, a figure which varies in different localities.

The endemicity of this type of goitre cannot be gauged by the prevalence of thyroid swellings in childhood. Goitre-surveys confined to school-children may accordingly be misleading: they commonly include the slightest swelling of the gland (in some surveys as many as 90 per cent are of this order) which may be either normal to the individual or are of a transitory character not persisting into adult life; and, they may imply a high degree of endemicity of the disease which does not exist. The limitation of such surveys to children is as if we were to attempt the differentiation of the «fevers» by looking only at their beginnings while ignoring their course and sequelae. A proper index of the endemicity of the classical type of endemic goitre is only afforded by (1) the number of goitrous subjects in the general population, or in random samplings of the population at different age periods; (2) the proportion of males to females affected; (3) the number of cretinous children, deaf-mutes and idiots; (4) the number of susceptible new-comers to an endemic district who acquire the disease within a fixed time; and, (5) the size and character of individual goitres. Nothing has done more to confuse the issues involved in the aetiology of the «goitres» than the failure to recognize these criteria on which the endemicity of the classical type of the disease can alone be based.

Causation

From time immemorial this type of endemic goitre has been associated in its origin with water; and even in the present state of discontent which pervades our knowledge of its causation, its relation to drinking-water is generally admitted. The occurrence of the disease in fish, its experimental production in man, goats, dogs and rats, by means of substances contained in water, and outbreaks of it following the consumption of certain waters, are among the most striking proofs of the truth of this relationship. Attempts have been made, from time to time, to explain it (a) by the excessive richness of the water in some chemical ingredient either in solution or in suspension, (b) by the poverty of the water in some chemical substance, notably iodine, and (c) by the presence in the water, either in suspension or in solution, of organic matter (notably pathogenic agents or their products). The soils with which the waters come in contact have likewise been suspected of imparting

to them goitrigenous properties, or of failing to impart to them some chemical substance in sufficient amount to prevent the development of the malady.

At the present time two « theories » have survived from amongst the many promulgated to account for this disease: the first is the iodine-deficiency theory, which sees in the poverty of iodine in the water, the soil, and the foods grown on that soil, the essential cause of goitre; the second is the infectious or toxic theory, which attributes it to some unknown pathogenic organism or to its products. Personally, I have come to believe that the truth lies in a judicious blend of both.

I propose briefly to set out the aetiological facts, as they are known to me, believing that they provide, even in their present incomplete state, a satisfactory explanation of the causation and distribution of this malady and its sequelae, and a rational means for their prevention.

Relation to geological formations.

I have not been able to satisfy myself that any close correlation exists between the endemicity of this disease and certain geological formations, nor that its causal agent is any inorganic substance either in solution or in suspension in drinking-water. In 1848 the Sardinian Commission found that no geological formation excluded the occurence of goitre and cretinism, but that the endemic was met with more frequently on the older than on the more recent formations. This is my opinion to-day. Nevertheless, I recognize that just as variations in the composition and quality of the food of residents in different endemic zones may impart variety to the pathological features of the goitres prevailing therein, so it may be that variations in the chemical constitution of drinking-water may impart variety to the pathological characters of goitre, though not themselves the cause of the disease.

Omitting from consideration such influences as consanguinity, heredity, concomitant infections, and those which may be grouped together as « psychic » factors, the known facts in regard to the causation of this type of goitre centre round three things: iodine, food-supply and insanitary conditions of life ; the last leading, as I believe, to gastro-intestinal infection possibly of a specific kind. The results of our investigations in India dealing with the relation of this type goitre to iodine are as follows:

A. *RELATION TO IODINE.*

a) *Iodine-content of the soil and drinking-water.*

1. In sea-coast, sub-montane and montane localities (ex Himalayan India) where endemic goitre is unknown, the iodine-content of the soil may be very low (less than 5 parts per 10 millions), moderate in amount (25 to 45 parts per 10 millions) or high (100 to 400 parts per 10 millions). The freedom of these localities from goitre is, therefore, related to conditions of life other than the iodine-content of their soils.
2. The iodine naturally present in the soil cannot easily be washed out of it by rainfall or by floods.
3. The richness of a soil in iodine (100 to 400 parts per 10 millions) does not preclude the presence of thyroid swellings — for the most part the so-called « incipient goitres » — in 27,7 per cent of girls and in 11,8 per cent of boys, living, at altitudes of 6000 feet or so above sea-level, in places where endemic goitre and its sequelae (cretinism, etc.) are conspicuous by their absence in the general population. Nor does it preclude the presence of well-marked goitre in approximately 2,5 per cent of school-children; these goitres being unrelated in their origin to endemic influences.
4. In Himalayan regions where the classical type of endemic goitre exists alone, the iodine-content of the soil is, in general, less than 5 parts per 10 millions, although it may sometimes range between 10 and 45 parts per 10 millions parts of the soil. But the disease is not always endemic in villages whose soils are as poor in iodine as those of other villages in which the endemic prevails.
5. There is no evidence that in Himalayan India the incidence of the disease is in inverse ratio to the iodine-content of the soil. In the heart of the endemic zone, as well as in the Himalayan foot-hills, two places adjacent to one another may have approximately the same amount of iodine in their soils yet goitre be endemic in the one and not in the other; or, the soils of two adjacent villages may be equally poor in iodine yet goitre be four times as prevalent in the one as in the other, although the water-supply and conditions of life of the inhabitants are the same.
6. The water-supply of one place may contain appreciable amounts of iodine (300 parts per 100 billion parts of water) and yet goitre be endemic therein; the water-supply of ano-

ther, and adjacent place may contain no determinable amount of iodine and yet goitre may not be endemic therein; the water-supply of two places some miles apart may be the same and yet goitre be present in the one and not in the other.

7. Drinking-water containing 300 parts of iodine per 100 billion parts of water has not prevented the occurence of the disease in endemic form in the presence of a high degree of bacteriological impurity of the water; nor has the consumption of a drinking-water containing 1200 parts of iodine per 100 billions prevented the development of goitre under experimental conditions, in young men who consumed daily large amounts of the unboiled suspended matter removed by filtration or by sedimentation from a grossly polluted, goitre-producing water.
8. The substitution of a bacteriologically pure for a bacteriologically impure water has caused the rapid and complete disappearance of the disease from a place in which it had been endemic for 70 years, although the new water-supply contained less iodine than the old.
9. Iodine-containing salts or substitutes for salt appear to have an influence in preventing this type of endemic goitre.
10. The disease is in general more prone to arise in iodine-poor than in iodine-rich localities in Himalayan India, though iodine-poor localities both in the Hills and in the Plains may be free from it.

The investigations on which these conclusions are based were carried out independently by three chemists (Dr. Newcomb, Dr.Norris, and Mr. Viswanath) whose results were in general agreement. The Himalayan soils selected for study were from localities where my original investigations were made (1902—1911), where the people wer entirely dependent on their own agricultural produce, where there was no importation of foods from outside sources which might have increased the iodine-intake of the inhabitants, where the foods consumed were the same and where — it may be expected — the iodine-content of the soil, and of the water irrigating that soil, would be reflected in the food-supplies. The net result of these investigations is that while a low iodine-content of the soil and drinking-water is, in Himalayan India, frequently associated with this type of endemic goitre this association is not invariable nor is iodine-deficiency in the soil and water the essential cause of the disease.

b) *Iodine-content of the food.*

Within recent years much work has been done on this aspect of the goitre problem, notably by v. Fellenberg in Switzerland, McClendon in the United States, and Hercus and his colleagues in New-Zealand. Their observations appear to indicate that a relatively low iodine-intake is commonly associated with a high prevalence of goitre. This association is, however, not invariable. Few foods are poorer in iodine than Indian polished rices, which contain less than 2 parts of iodine per 10 millions parts of the rice (Newcomb, 1927); yet goitre is very rare amongst the rice-eating races of India although their diet is composed mainly, and somestimes almost exclusively, of this cereal. During the course of my nutritional researches more than 1000 pigeons have been fed exclusively on one or other of 30 varieties of Indian rice. The general effect of these rices on the thyroid gland was to cause a reduction in its size; a very occasional effect was to cause thyroid enlargement. It follows, therefore, that some goitre-producing substance other than iodine-deficiency was present in those birds which developed goitre when fed on an exclusive diet of rice. This substance is either a metabolic or a bacterial toxin or a contagium vivum. Recently I obtained a deteriorated and bacteria-laden rice from a goitrous locality in Burma which caused large hyperplastic goitre in 12,5 per cent of birds fed exclusively upon it: a result so unusual as strongly to suggest that some positive goitre-producing agency — probably bacterial — was present in this rice and not present in others. Its iodine-content was found to be no greater or no less than that of other rices causing a reduction in size of the thyroid gland (Newcomb). Its deficiency in iodine was not, therefore, the essential cause of the goitre from which certain birds suffered.

Similarly, I have found (1927) that while a minority of pigeons develop large hyperplastic goitres when fed exclusively on an iodine-poor diet of American white-flour, the majority do not. The occurence of goitre in the minority cannot, therefore, be attributed solely to iodine-deficiency, but to the action of some positive agency peculiar to the affected birds.

Certain observers (1923) have reported the development within a few weeks of thyroid enlargement in rats fed on an iodine-poor diet consisting of oatmeal, patent flour, linseed meal, calcium phosphate, sodium chloride and distilled water. Recently (1926) I repeated this experiment using large numbers of rats caged under conditions of scrupulous cleanliness; the experiment being

prolonged for several months. No appreciable enlargement of the thyroid gland occurred; but out of 24 thyroid glands examined histologically 50 per cent had small, single or multiple, cysts in one or both lobes of the organ; the number so affected being higher the longer the animals were fed on the faulty food. Thies diet is a very imperfect one, causing in my experiments pernicious anaemia and vesical calculus.

I conclude, therefore, that the association of goitre with a low iodine-content of the food is not invariable, nor is iodine-deficiency the essential cause of the hyperplastic goitres which may occur in experimental animals fed exclusively on such iodine-poor and widely used foods as white flour and rice.

c) *Relation of Iodine to experimentally-produced goitre in animals.*

1. In iodine-poor localities (25 to 45 part of iodine per 10 millions parts of soil and 300 parts of iodine per 100 billions parts of the drinking-water) goitre may develop spontaneously in well-fed animals confined in dirty cages. This is, perhaps, the greastest pitfall in the experimental investigation of the disease. Only the most meticulous cleanliness will prevent the spontaneous development of goitre in laboratory animals in such localities. But cleanliness will prevent it, showing that lack of cleanliness is an important factor in its causation. It can also be prevented by increasing the consumption of iodine proportionately to the unhygienic conditions of life of the animals: as by the addition of potassium iodide, cod-liver oil or iodine to their food. Chlorine acts in a similar way though its action is less certain.

2. In iodine-rich localities (400 parts of iodine per 10 millions parts of soil) goitre rarely develops spontaneously in well-fed animals confined in dirty cages. But in these circumstances the thyroid gland tends to be larger than normal. Thus: two groups of pigeons, receiving the same food and water, were confined (1926) for a period of six months one above the other in the same pen, and separated only by the netted-wire floor of the upper compartment. Through this floor the faeces of those above dropped to the wooden floor of the compartment below which thus became impregnated with the droppings of both groups. At the end of six months the birds in the upper compartment were found to have thyroids weighing, on the average, 89 mgrms per kilogram of body-weight, while those in the lower had thyroids averaging 132 mgrms: an increase in size of nearly 50 per cent. When the experiment was repeated, the wooden floor of the lower

compartment being removed and the birds thus having access to the iodine-rich earth, no noteworthy difference in size of the thyroids in the two groups was observed although the gland was still slightly larger in the less hygienic compartment. In these circumstances the iodine-rich earth appeared to counteract in some way the contamination of the soil resulting from the droppings of the birds.

In another experiment conducted in an iodine-poor locality (1913), the soil of which contained 10 parts of iodine per 10 millions, goats were tethered for many months on the same plot of ground, which in consequence became impregnated with their alvine discharges. Some were muzzled, so that they could not nibble at the polluted earth; these were hand-fed with clean food. Others were unmuzzled, and to these their fodder was thrown on the contaminated ground. Goitre occured among the unmuzzled goats but did not occur among the muzzled goats.

The essential cause of the thyroid enlargements which may result in these circumstances is the polluted state of the soil and of the food and water coming into contact with it. An iodine-rich soil appears to be antagonistic to the septic state of the ground which may result from the long residence of animals upon it, while an iodine-poor soil is not or not to the same extent. This may be due either to a local antiseptic action of the iodine in the soil itself, or to a higher intake of iodine by animals living on an iodine-rich soil and to a similar antiseptic action in their bodies, either by direct action or through the medium of the thyroid gland.

3. But while animals (pigeons, rats, goats, monkeys) confined in dirty cages, or living in insanitary surroundings, are less prone to develop goitre in iodine-rich than in iodine-poor localities they may, nevertheless, do so if their food be illbalanced in certain respects although containing amounts of iodine sufficient for normal needs. Thus: if an excess of butter or of fatty acids be added to an otherwise well-balanced food hyperplastic goitre will arise in a proportion of the animals. This observation, which I made in 1919, has since been confirmed by Mellanby (1921) and more recently by Marine (1924). Similarly, if the food contains an excess of lime small goitres may arise but in this case the goitre is of the colloid type (1923). In these circumstances an increased provision of iodine proportionate to the excessive ingestion of fats or of lime will prevent the occurence of thyroid hyperplasia or the undue accumulation of colloid in the gland and the development of either type of goitre. If the fat added to the diet be cod-liver

oil, which contains iodine in high concentration, goitre will not arise as shown by Mellanby and subsequently confirmed by me.

Goitres resulting in experimental animals from an excess of fats in the food develop earlier and attain to greater size in dirty than in clean cages, in iodine-poor than in iodine-rich localities, and in the early spring months than other seasons.

4. If 10-day old tadpoles be given a diet consisting of caseinogen, white-flour and green pond-weed, to which an excess of butter or of fatty acids is added then the thyroid gland does not assume its functional responsibilities and the tadpoles fail to grow. But if iodine be added to the food in amounts proportionate to the excess of fats then the functional activity of the gland is initiated and maintained and the animals grow normally.

These observations indicate that a sufficiency of iodine and a balanced adjustment between iodine and certain other constituents of the food are essential to the initation and maintenance of the normal revolution of the thyroid gland's cycle of activity, viz: to normal secretion, to normal storage of colloid and to normal resorption or excretion of colloid. They show also that the amount of iodine required by the gland for this purpose depends on the composition and quality of the food and the hygienic conditions of life.

B. *RELATION TO UNHYGIENIC CONDITIONS OF LIFE AND TO INTESTINAL INFECTION.*

1. *The experimental production of goitre in man.*

Eighteen years ago I published my first account of the experimental production of goitre in man. I had found (1904—6) on the Gilgit Fan , in the Himalayas, a series of eight adjacent villages, situated one above the other on the same unprotected water-channels, whose soils (as I now know) were equally poor in iodine, whose inhabitants were entirely dependent on their own agricultural produce, and in which the conditions of life of the people were the same, and the foods in general use the same. The classical type of endemic goitre and its sequelae prevailed intensively in these villages, to all appearances in a state of aetiological purity and uncomplicated by the presence of goitres of other types. The disease did not prevail with equal intensity in every village: there being an increase in its incidence from the first village, where 11,8 per cent of the general population were goitrous, to the last, where 45,6 per cent were goitrous. This increasing incidence was

confined to adults. Goitre was not endemic in a ninth village (Barmis) which received its very pure water-supply from a different source.

Whatever may have been the influences which gave rise to goitre in the first of the Gilgit villages it was obvious that they increased in potency on the way to the last village. Their increase affected adults but not children; it had, therefore, a direct bearing on the production of the nodular (adeno-parenchymatous) goitres with which adults were afflicted. At that time the iodine-content of the soil and water had not been determined, but subsequent investigations showed that the increasing incidence of adeno-parenchymatous goitre was not related to an increasing deficiency of iodine, there being the same poverty of the metalloid in the soils of all villages. It was thought that it might be related to the increasing impurity of the water-supply, all other things being equal. Accordingly the sediment from the water, as it issued from the last village, or the suspended matter removed by filtration through a Berkfeld filter, was administered to young men (volunteers), new-comers to the district, aged between 18 and 22 years (with the exception of myself, who had been resident in the locality for four years and was aged at that time 30 years). The first experiment was carried out in the spring of 1906; it was repeated in the autumn of 1907, again in the spring of 1908, and in the autumn of 1909, with similar results. The subjects of the experiment were encamped on ground containing 15 parts of iodine per 10 millions parts of the soil; they received a drinking-water, containing 1200 parts of iodine per 100 billions parts of the water, which was derived from a source (Barmis) near their camp where goitre did not occur. All were fed alike, and the strictest discipline was maintained. In no case was this discipline infringed. Every morning and evening before the two meals of the day the men drank about 6 ounces of the suspended matter removed from the grosslypolluted, goitre-producing water. In some experiments this matter had been previously boiled, in some it had not. The combined results were as follows:

1. Of 36 young men who consumed the unboiled suspended matter 21 exhibited no change in the thyroid gland which could be detected clinically, 10 developed noticeable goitres, while 5 showed a swelling of the gland of a transitory nature.

2. Of 31 young men who consumed the boiled suspended matter, none showed any increase in size of the thyroid gland. The thyroid enlargement induced in this way had the following

characters: It usually made its appearance between the tenth and the fifteenth day of the experiment; it showed a tendency to fluctuate in size; it reached its point of maximum size between the twentyfifth and the thirtieth day; in some cases it disappeared during the course of the experiment; the swelling was not great nor did it progress in size after the twenty-fifth to the thirtieth day, the tendency being towards its diminution from the thirtieth day onward; it was accompanied, as a rule, with certain subjective symptoms: throbbing in the neck and feelings of fulness and discomfort. (These sensations I had an opportunity to experience in my own person since acquired goitre under the conditions of these experiments).

It will be noted that the characters of the experimentally-produced goitre closely simulated those of « first attacks » of the disease as seen during epidemics or in new-comers to an endemic area in whom the malady may make its appearance as early as the fifteenth day after their arrival and disappear spontaneously in a proportion of them. This circumstance in itself would appear to preclude the possibility of iodine-deficiency being the sole cause of the disease. For had it been, one would scarcely expect goitre to have appeared so soon or spontaneous recovery to have occurred, or that men consuming the boiled suspended matter would have escaped it while 41 per cent of men similarly fed and housed but consuming the unboiled residue acquired it. It can hardly be doubted that some goitre-producing agent was contained in the suspended matter and that this agent had been destroyed by boiling. It is to be noted that water containing 1200 parts of iodine per 100 billions did not prevent the disease in the presence of massive infection of the alimentary tract by this agent although the water was not goitre-producing in its absence. I concluded that a contagium vivum was a responsible factor in the production of goitre and of the nodules which characterized it in the adult population.

It was further demonstrated, by like means in man, that filtration through a Berkfeld filter may render the water innocuous, but that neither boiling nor filtering the water may suffice to prevent the disease unless sources of infection from the soil are rigidly excluded. Water is only a vehicle for the goitre-producing agent or agents; these are rapidly destroyed in water running over non-polluted soil, or over rocks while exposed to air, sunligth and agitation.

2. Goitre in artificially-reared fish.

Marine and Lenhart (1909—10), and Gaylord (1912), found that hyperplastic goitre occurred in artificially-reared trout confined in tanks located one above the other on the same water-supply; the effluent from one tank flowing into the next below it in the series. The incidence of the disease increased from the first to the last tank: 3 per cent of the fish being goitrous in the first tank, 84 per cent in the last (Gaylord, 1912). This observation provided a remarkable confirmation of my own made in man four years earlier. The water supplying the tanks was not in itself goitre-producing, since « fish which lived in the raceway above all houses and which had never been confined in the tanks maintained normal thyroids throughout their lives » (Marine and Lenhart, 1910). Those confined in the tanks were fed largely on liver: a fatrich food, the effect of which on the thyroid gland has already been referred to. Marine and Lenhart concluded, as a result of their observations, that « over-feeding, over-crowding and a limited water supply, were the major factors in the production of filthy, unhygienic tanks or ponds; and the insanitary, unhygienic and filthy tanks are in a very important but still unknown manner associated with the development of thyroid hyperplasia » (1910). With this conclusion I am in complete agreement. But more recently Marine (1924) has stated that « if water is a factor in thyroid hypertrophy » (and he believes it is) « it is due to the absence rather than the presence of some substance » « necessary for the prevention of thyroid enlargement » which, he considers, « would more properly account for the malady than some virus or toxin capable of producing thyroid hyperplasia. » The absent substance he believes to be iodine. But we have just seen that if iodine be absent from the water supplying the tanks (and there is no proof that it is) then its absence is incapable of causing thyroid hyperplasia before the water reaches the tanks; we must, therefore, conclude that the causes of the hyperplasia lay in the tanks themselves and that it was not due to absence of iodine. I do not think that by the use of the word « absence » Marine intends to imply the nonexistence of iodine, but rather its relative insufficiency; if this be his meaning then I agree that there was an insufficiency of iodine relative to the conditions of life in which the fish lived. But these conditions of life were the actual cause of the goitre, and one of them was over-feeding on a fat-rich food, another the « filthy » state of the tanks. It can hardly be doubted that this state was due to, or resulted in, the unrestrained growth

of bacterial or other pathogenic organisms. But Marine (1924) rejects the influence of pathogenic organisms, contained in the water, on the grounds that trout living in the wooden raceways (about 30 feet long) between the tanks, and in the raceway below all tanks, «regularly recovered although living in the most polluted water.» This word «recovered» may convey a wrong impression unless it be understood what Marine means by it. He is referring to the hyperplasia, or state of intense secretory activity of the gland, but not to the thyroid enlargement or goitre. He is, indeed, careful to point out that the fish do not recover from goitre, and in this there is the corroborative evidence of Gaylord (1912). What actually happened was that the hyperplasia ceased to progress, the colloidless, hyperplastic goitres filled up with colloid material, became «colloid goitres» and persisted as such in the polluted water of the tail-race, where the fish were not being over-fed and where they subsisted on such scraps of food as escaped from the tanks. There was no recession of the thyroid enlargement, no disappearance of newly formed thyroid tissue, no cure of the goitre such as occurred when iodine, arsenic or perchloride of mercury was added to the water (Gaylord, 1912). All that happened was that an alteration tock place in the histological character of the goitre. Further, although nine months old fish, which had spent their lives in the polluted water of the tail-race, had thyroids of apparently normal structure yet the gland was larger than normal (Marine and Lenhart, 1911). These fish, like some wild fish living in the vicinity of populated areas, were in fact the subjects of hypertrophic goitre. This in itself indicates that the polluted water, and not iodine-deficiency, was the essential cause of the hypertrophy (a balanced-increase of all components of the organ), and that a supply of iodine sufficient for the turnover of the gland's cycle of activity was reaching it. But when to this effect of polluted water per se other goitrigenous factors, within the tanks, were added — excess of fat-rich food, over-crowding, and confinement in «filthy» tanks — the thyroid then showed intense secretory activity and hyperplasia to the exclusion of colloid storage. Each one of these factors — polluted water, filthy tanks and over-feeding on fat-rich food — is of itself capable of causing thyroid enlargement. Their summation within the tanks gave rise to such intense epithelial proliferation as actually to suggest carcinoma. The tanks were for these fish the centre of the endemic focus of the disease, the tail-race was its periphery; and the character of the goitres in the two locations —

hyperplastic in the one and hypertrophic or colloid in the other — was determined by differences in food-supply and in organic pollution of the surroundings of the fish. It is not safe to assume, as Marine has done, that the degree of infectivity in these raceways was as great as that in the tanks, for the walls and bottom of the «filthy» tanks were impregnated and coated with a material with which Gaylord subsequently produced hyperplastic goitre in rats and dogs; a material which trout, when so confined, are wont to nibble. If we look upon this material merely as a food it was, like an excess of fats, productive of thyroid hyperplasia. But it was a food composed mainly of bacteria and their products. I do not, however, need to labour this point for, as will presently be shown, other evidence has conclusively demonstrated in man himself the goitrigenous influence of bacteriologically impure water; while as Marine and Lenhart have themselves recorded, improved hygienic conditions and the provision of fresh and more abundant water-supply markedly lessened the incidence of the disease in artificially-reared trout.

Marine and Lenhart, and later Gaylord, prevented thyroid hyperplasia in trout by the additional provision of iodine; while Gaylord caused its gradual recession by adding perchloride of mercury or arsenic to the water. Both of these observations I have confirmed in other animals using, however, nascent chlorine instead of perchloride of mercury (1923). It is remarkable how little attention has been paid in the literature to Gaylord's important observation regarding the effect of perchloride of mercury; the tendency ever being to extol the influence of iodine, thus restricting the problem of the causation of the disease to a too narrow field.

3. *Effect of intestinal antiseptics.*

The therapeutic administration of intestinal antiseptics — thymol, salol, B-naphthol and B. Bulgaricus — to the subjects of goitre, without any change being made in their habits of life, their place of residence or their food, was shown by me (1906) to result in the cure of the disease in suitable cases. Briefly, the results were these: All the cases treated were in males; 33 were of three months standing or less; 25 were of twelve months standing or less; and 24 were of a year's standing or more. Of the 82 cases treated 68 were cured or so greatly benefited as to be practically so; while 14 were unaltered or only benefited to a very slight extent. The majority of the cured cases were of less than one

year's standing. These results have been confirmed by Messerli (1916), and more recently by Walton (1924) who has provided the additional observation that the therapeutic combination of intestinal antiseptics and iodine may be more beneficial than either alone.

I regard these therapeutic observations as strong confirmatory evidence of the gastro-intestinal origin of this type of goitre. They show that the administration of such drugs as thymol — the action of which is a purely local one in the gut — is capable of effecting a change in the intestinal flora, in their products, or in their action at the threshold of absorption in the intestinal tract, which may bring about the disappearance of early cases of the disease.

A comparative test of the efficacy of iodine and thymol, carried out in 1905, may be referred to here: Ten young men, the subjects of recent goitres who had arrived in the endemic locality a few months previously and whose goitres were to all appearances the same, were divided into two groups of five each. All were similarly fed and housed, all had the same work to do and used the same drinking water. One group was given iodine; the other thymol. The result was the same in both groups: four cases were cured in each; showing that thymol was as efficatious as iodine. This result is similar to that obtained in trout by iodine and perchloride of mercury.

In connexion with the action of intestinal antiseptics it may be mentioned that eosinophilia is usually a marked feature in early cases of this type of goitre. It may be as much as 20 per cent and is rarely less than 8 per cent. It gradually lessens with the growth of the goitre until in cases of some years standing it is not apparent. The polymorphonuclear elements of the blood are almost invariably reduced in number and the mononuclear elements increased. These observations, which I made in 1906, have been confirmed by Marine, Miller, T. Kocher, Bauer and others. The administration of thyroid substance or of iodine restores the leucocyte count to normal (Bauer, 1912).

4. *Effect of Vaccines.*

Shock doses of vaccines prepared from cultures of faecal organisms — bacillus coli, staphylococcus aureus and a spore-bearing organism — were next employed (1910) in the treatment of early cases of the disease; with what degree of success is shown in the accompanying illustrations. The type of case in

which this treatment was found to be successful was of the same order as that curable by intestinal antiseptics. A like degree of success was obtained with several different vaccines; there was no specificity in their action, although it was found that some, such as one prepared from a dysentry bacillus, were not effective. An essential condition to the succes of this treatment is that the vaccines should be administered in shock doses. Wilson (1925) has confirmed this observation as to the effect of shock doses of B. coli vaccine in causing the subsidence of goitres.

In whaterver way the goitre is caused to disappear, whether by iodine, by thyroid extract, by intestinal antiseptics or by vaccines, the signs of hypothyroidism accompanying it also disappear. All act by relieving the thyroid gland of some portion of its excessive load.

5. *Gaylord's experimental production of goitre.*

As has been mentioned Gaylord (1912) produced goitre in dogs and in rats by the administration of the unboiled scrapings from the water-soaked wooden tanks in which goitrous fish were confined; the boiled scrapings did not produce the disease. Confirmation of my experimental production of goitre in man was thus provided.

6. *Bircher's experimental production of goitre.*

Bircher (1911) fed rats on cooked rice and faeces and obtained definitite changes in the thyroid gland. He also produced goitre in rats by the administration of the residue left on the Berkfeld candle after filtration of goitre-producing water.

7. *Sasaki's experimental production of goitre.*

Sasaki's observations, carried out under the direction of Professor Wilms, in Heidelberg (1912), are as follows:

a) Rats fed on cooked rice mixed with faeces developed moderate-size enlargements of the thyroid gland of a diffuse form.

b) Rats fed on cooked rice, mixed with faeces, to which potassium iodide or thyroidin was added did not develop goitre.

c) Other toxins gave negative results when administered to rats similarly fed.

These results indicate that goitre-producing substances are contained in faeces; and that a larger provision of iodine than is provided by the food, or a larger provision of the products of the thyroid gland than is produced by the gland under certain food

conditions, is required to counteract their action. They suggest also, as do my own experiments on man, Gaylord's on dogs and rats, and the curative effects of intestinal antiseptics, that these goitre-producing substances while harmless in the rectum are harmful in a situation abnormal to them where absorption is greatest: the upper alimentary tract.

8. *My own experimental production of goitre in goats and rats.*

The results of these experiments may be summarized as follows::

c) Goitre has been produced in goats (1910—1911), under strict control, by means of water which was grossly contaminated with the faeces of goitrous persons; the incidence of the disease was 45 per cent.

b) The oral administration to goats (1911) of living cultures of a spore-bearing organism, obtained from the faeces of a goitrous pony, caused hyperplastic changes in the thyroid gland in 57 per cent of cases. The growths were washed off the agar slopes and administered in saline. One animal in the series developed tetanic convulsions and pronounced degenerative changes in the thyroid when fed on the washed agar slopes on which this organism was grown.

c) The administration to rats (1913) of the filtrate obtained from an emulsion of the faeces of a goitrous individual caused goitre in 100 per cent of cases. This result indicated that goitre-producing toxins are contained in faeces; an observation recently confirmed by Rush and Jones (1924). The administration of the residue left on the Berkfeld candle after filtration of the emulsion of faeces likewise caused goitre in 100 per cent of rats. Control rats living in another compartment of the same cage, and similarly fed and watered, did not develop goitre.

d) The administration of aerobic cultures (1913) of bacteria, grown from the faeces of goitrous persons caused massive goitres in 30 per cent of rats. Control rats, similarly caged, fed and watered, did not develop goitre.

e) The administration of anaerobic cultuers of faecal bacteria grown from the faeces of goitrous persons caused goitres in 100 per cent of rats. Control rats, similarly caged, fed and watered, remained goitre-free. The goitres produced in this way showed a marked tendency to fibrotic change and were of small size.

9. * *The experimental production of Congenital Goitre. Cretinism and Parathyroid Diseases* (1913—14).

a) The filtrate of an emulsion of faeces from goitrous persons was administered to a number of female rats, during a period of four-and-half months, as their sole source of drinking-water. A male rat was admitted to their cages from time to time. Twenty-one young were born during this period; of these four were eaten by their parents, three were cretins, seven had congenital goitre and seven had normal thyroids. Five animals had haemorrhagic changes in the parathyroid glands.

b) The administration of aerobic cultures of faecal bacteria to pregnant rats caused congenital goitre in their offspring, but no disease of the parathyroids nor cretinism. When no cultures were given to a goitrous female she gave birth to young with normal thyroids, although when these cultures were given during her previous pregnancy her young had congenital goitre.

c) The administration of anaerobic cultures of faecal bacteria to rats during a period of three-and-half months caused marked congenital goitre in 52,6 per cent of their offspring, and parathyroid disease in 57,8 per cent, but no cretinism. One female subsequently gave birth to young with congenital goitre although the administration of anaerobic cultures had been discontinued during her later pregnancy.

d) The administration to female goats of anerobic cultures of faecal bacteria grown in 2 per cent glucose broth — 10 c.c. of the culture being given to each animal daily — caused goitre in the mothers; their young being dead-born, hairless, ill-developed and the subjects of congenital goitre sometimes of enormous size. Control female goats receiving no cultures and similarly fed, but kept muzzled throughout the course of the experiment, did not develop goitre and gave birth to young which were not goitrous, Certain control goats, similarly fed, which were unmuzzled, became goitrous but gave birth to normally developed young some of which had very small congenital goitres which disappeared shortly after birth.

The incidence of cretinism in the offspring of goitrous rats is approximately the same as I found it to be in the offspring of goitrous women: 3 per cent.

* All these experiments were carried out in a goitre-free locality of which the soil contained 10 to 45 parts of iodine per 10 millions, and of which the water contained iodine in traces only.

These experiments demonstrate: (1) the action of intestinal organisms or their products in causing goitre, (2) the presence in the faeces of a goitre-producing « toxin »* which is peculiarly prone to cause cretinism, and, (3) the fact that by means of faecal material from goitrous persons the complete clinical expression of the « goitre noxa » — goitre in adult animals, and congenital goitre, cretinism and parathyroid disease (the last a pathological feature of « tetanic cretinism ») in their offspring — has been elicited under experimental conditions.

10. *Congenital goitre resulting from thyroidectomy in the mother.*

As is well-known female dogs whose thyroids have been in great part removed prior to, or at the commencement of, pregnancy may give birth to pups with congenital goitre. This condition arises beause of the accumulation in the maternal blood, consequent on thyroid insufficiency, of toxic metabolites which unduly stimulate the foetal gland. In my experiments the same result was achieved by the oral administration of bacterial toxins to pregnant animals possessed of whole thyroids. Crippling of the maternal gland can thus be produced alike by surgical means and by the toxic products of bacterial action. The crippled organ may be helped, and congenital goitre prevented, by the additional provision of iodine, probably because the processes of nutrition and of oxidation of toxic metabolites are thereby greatly facilitated. Iodine-insufficiency in its relation to chronic hypertrophic goitre and its sequelae reminds one of vitamininsufficiency in its relation to beri-beri; an insufficiency of the one favours the action on the thyroid gland of certain metabolic or microbic poisons; an insufficiency of the other admits of the development of certain metabolic poisons which exercise a specific action on the heart and nervous system. The essential cause of both is a positive and not a negative agency.

The observation of Hart and Steenbock (1917) will be remembered in this connexion. No « roughage » was provided in the food of sows thereby producing poorer elimination and increased intestinal putrefaction; congenital goitre was present in their offspring. The provision of roughage prevented the development of congenital goitre as did the additional provision of iodine in the food.

* This term is used in its widest sense and includes ultramicroscopic forms of pathogenic agents.

11. *Influence of bacterial toxins on the thyroid gland.*

The work of Rogers and Garnier, Torri and Crispini (1898), Sejous (1903), de Quervain (1904) and Farrant (1910) demonstrated that bacterial and other toxins were capable of stimulating the thyroid gland to increased activity and sometimes to enlargement; while Galli-Valerio (1913) isolated from the waters of the Jura Mountains an organism — the bacillus pseudopestis murium — which gaused goitre on injection into rats.

12. *Bacteriology of the thyroid gland in goitre*

Tissue bacteriology of the thyroid gland, especially in the hands of Rosenow (1914) and more recently of Cantero (1926), has led to the isolation of organisms of streptococcal morphology in a high proportion of colloid and adenomatous goitres both of man and of dogs. Cantero has reported positive results in 94 per cent of all goitres (50) examined by him. Intravenous injection of the streptococcus into animals caused hyperaemia and swelling of the thyroid gland without gross lesion of other organs, the organism being afterwards recovered from the gland.

13. *The experimental prevention of goitre in man.*

There remains the final proof which I have to offer of the influence of bacterial infection, by way of the gastro-intestinal tract, in causing chronic hypertrophic goitre: In 1913 I undertook the investigation of goitre in a large school situated in an iodine-poor locality in the Himalayan foot-hills where a changing population of about 500 boys and girls resided. Goitre had at that time been endemic in the school for 66 years. So great was its prevalence that in some years as many as 50 per cent of the children were the subjects of noticeable goitres; while after a residence of 8 years about 80 per cent became goitrous. In 1913, no less than 66 per cent of girls above the age of 16 years were the subjects of disfiguring goitres. As a result of my investigations the conclusions were drawn (a) that the disease was due to the pollution of the drinking-water; and (b) that the provision of a pure water would cause its disappearance. Following these recommendations, made in 1914, a new piped-water was introduced in 1918 from a neighbouring town (Kasauli) with the result that within four years the endemic had disappeared; the rapidity of its decline being, of course, due largely to the non-appearance of the disease in new resident pupils. It became necessary then to determine whether its disappearance was due to an increased iodine-content of the new water-supply, all other factors — food, etc. — having re-

mained unaltered. This investigation was undertaken independently by three chemists, two of which found traces of iodine in the old supply but none in the new, while one found 300 parts per 100 billions in both. Clearly, then, the new supply did not contain more iodine than the old but less; and the cause of the disease was, as I had previouly found, the bacteriological impurity of the old water-supply. My prediction that a pure water-supply would cause its eradication was thus fulfilled.

* * *

In this survey of the causation of the chronic hypertrophic type of endemic goitre and its sequelae, I have endeavoured to show how closely it is interwoven with the composition of the food, with the state of the gastro-intestinal tract, with the concentration of toxic metabolites in the system, and with the rôle of the thyroid gland and of iodine (alone or in collaboration with the thyroid) in the phenomena of nutrition and oxidation; and I have endeavoured also to show how closely the goitrigenous action of one factor is interwoven with the goitrigenous action of another. I have provided evidence of the experimental production of this type of goitre in man and in animals, and of the experimental production of its sequelae (congenital goitre and cretinism) in the latter; evidence also of its cure, and of its complete eradication from an endemic locality: all by means which indicate its causal relationship to gastro-intestinal infection. I recognize the part which iodine-insufficency may play in its causation or, more properly perhaps, the part which iodine-sufficiency may play in its prevention; but the essential cause of this type of goitre is, in my opinion, a positive toxic agent derived from the gastro-intestinal tract. Gastro-intestinal infection may not in itself cause chronic hypertrophic goitre in the presence of a sufficiency of iodine, nor may an insufficiency of iodine in itself cause chronic hypertrophic goiter in the absence of gastro-intestinal infection; but when both are present the conditions for the development of this type of goiter are at their optimum. The prevention of the disease and of its sequelae, rests, therefore, on

1. The perfecting of sanitation.
2. The provision of pure and protected water-supplies.
3. Efficient personal hygienie, and drainage of the gastro-intestinal tract.
4. The use of a well-balanced food, containing a sufficiency of iodine in a natural state.

B. THE DIFFUSE COLLOID TYPE OF ENDEMIC GOITER.

There is little precise knowledge as to the geographical distribution and epidemiology of this type of endemic goiter, less as to its aetiology and less still as to its bio-chemistry.

It is that type in which the vesicles of the thyroid are of diverse shapes and sizes, distended and distorted by the accumulation of colloid material within them, and in which evidence of antecedent epithelial hypertrophy and hyperplasia may or may not be present. Following a period of hyperplasia and its cessation colloid may accumulate in the gland in large amount. « Colloid goiters » may arise in this way, as in artificially reared trout and presumably also in man.

The most recent pathological research does not indicate that all colloid goiters are of the above order, nor that diffuse hyperplasia is always a necessary forerunner of « diffuse colloid goiter ». There appears to be a variety of this disease in which colloid storage occurs, without antecedent hyperplasia, to the complete exclusion of active secretion (Williamson and Pearse, 1925). Its cause is to be sought in factors which interrupt the normal cycle of the thyroid gland's activity at the stage of colloid storage. Of these one may possibly be the ingestion of food of low iodine-content or the inadequate assimilation of iodine, although there is, as yet, no statisfactory evidence that this is so. The present-day tendency is to consider « goiters » in general too much from the narrow point of view of iodine; as might a mechanic who considered the efficiency of his engine solely from the point of view of lubrication. It is very probable that the development of diffuse colloid goiter depends on other things besides lack of iodine, and that it is related in some part at least to change in the concentration of certain ions within the cells, plasma and colloid of the gland. In this connexion my own experimental work has provided the following evidence: In pigeons and rats which received an excess of lime in an otherwise well-balanced food, for a period of eight-and-a-half months, an average increase in size of the thyroid occured amounting to approximately 50 per cent. Thus: while the average weight of the gland in control pigeons receiving no excess of lime, was 80 grms per kilogram of body-weight, that in animals receiving an excess of lime was 121 mgrms, or an increase of 51 per cent. The goitres so produced were due to the abnormal accumulation of colloid material in the vesicles of the gland, secretory activity being in abeyance. The vesicles in whole or in part of the gland were greatly distended, distorted in shape, and their

walls much thinned. This effect of an excess of lime, in an otherwise well-balanced food, was prevented by increasing the amount of iodine ingested proportionately to the excess of lime. A similar effect was observed in animals following the administration of iodine in excess, but in this case secretory activity was not in abeyance; it was, likewise, counteracted by increasing the amount of lime ingested proportionately to the excess of iodine. It would seem, therefore, that a disturbance of the calcium-iodine-balance in the food, and possibly in the gland itself, may bear some relation to the pathogenesis of diffuse colloid goitre. I am aware that Aschoff has obtained evidence suggesting that calcium does not increase colloid storage but that iodine makes the colloid more viscous. My ovn experience is, however, as stated. More recently Hewer (1927) has found evidence to suggest that a correlation exists between the H-ion concentration of the colloid and the secretory activity of the vesicular cells. If this be so it is a most important observation.

Diffuse colloid goitre exists in two forms: the acute, which is said to be associated with a high incidence in young males (Berry, 1910; Williamson, 1926); and the chronic, which is one variety of endemic goitre (Plummer, 1921; Williamson, 1926). The chronic or endemic form appears to prevail especially in the plains and at low altitudes: but few serious attempts have been made, so far as I am aware, to define its geographical distribution and to separate it aetiologically from the adeno-parenchymatous type of the disease. Of such attempts the most noteworthy is that of Levin (1924) in the Great Lake District of North America; his results show clearly the different age incidence of the two types; an observation which in itself indicates their different aetiology.

The diffuse colloid type of endemic goitre is most prevalent in children round about the age of puberty; «it progresses with remissions for from three to five years and then regresses to barely palpable, or at least relatively small, dimensions before the twenty-fifth year. Spontaneous recovery after a relatively short course is the rule in the United States» (Plummer, 1922). It has a higher incidence in infancy and childhood, attains to greater size, and regresses later in life, and less completely, in those geographical areas in which it is more prevalent» (Plummer, 1922). It appears to be fairly evenly distributed in the two sexes, there being a slight preponderance in females. It is commonly associated in the same locality with Graves's Disease; but there is little statistical evidence in regard to its association with conge-

nital goitre, deaf-mutism and idiocy, — such evidence as there is suggesting that these are not essential features of the endemic. It is commonly associated with changes at the threshold of absorption in the alimentary tract; thyroxine administered by the mouth may fail to cure it; thyroxine administered intravenously rarely fails to do so (Plummer, 1922).

I have included this brief, and imperfect, account of diffuse colloid goitre mainly to emphasize that «there are two types of goitre with two distinct pathological expressions in endemic zones which may be differentiated by the zone» (Williamson, 1926). My own experience has, however, been confined mainly to the parenchymatous or adeno-parenchymatous type, so that I have drawn on the work of others (Berry, de Quervain, Plummer, Levin, Williamson and Pearse) for this account of the colloid type of the disease. I will conclude this section by the following quotation from a paper by de Quervain, published in 1922: «The histological structure of goitres varies according to the part of the country. In certain countries, especially in level regions, the diffuse colloid goitre, with and without hyperthyroidism, and the exophthalmic goitre predominate. In more mountainous countries the toxic goitre is an exeption, and the nearer one approaches the centre of the endemic area, the less he meeets with the colloid goitre, It is replaced by the colloid-poor, diffuse, parenchymatous goitre in childhood, and by the adenomatous-parenchymatous, nodular goitre with its degenerative forms, in adults.» It can hardly be doubted that these differences in the architecture of the endemic goitres are due to differences in altitude, soil composition, hardness of drinking-water, bacteriological purity of water-supplies, social and personal hygiene, and above all to differences in the quality and composition of the food-supply. This brings me to the last type of goitre with which I have to deal:

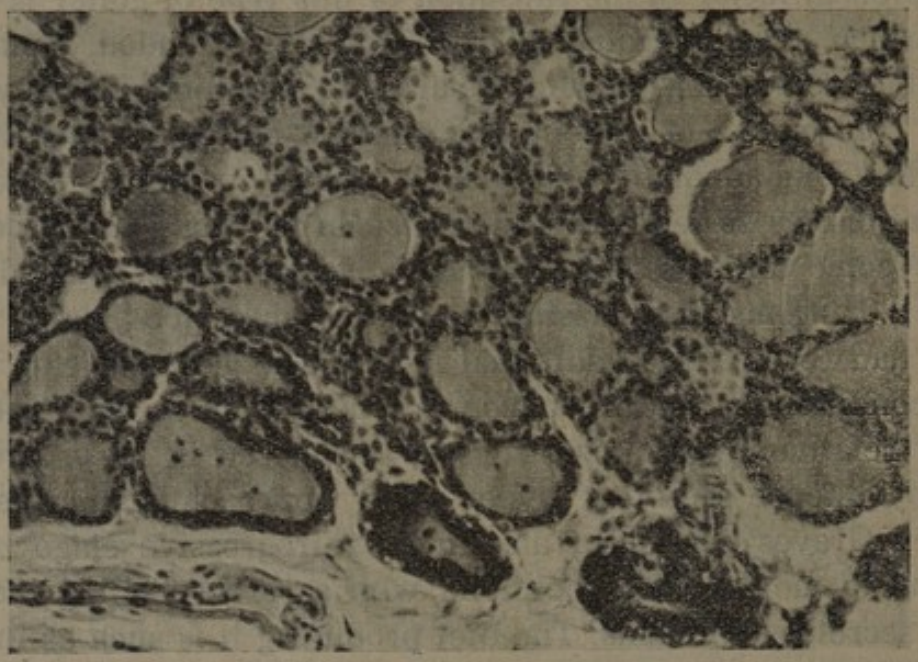
C. THE LYMPH-ADENOID TYPE OF GOITER.

The existence of this type of goiter in human beings has been demonstrated by Williamson and Pearse (1925). Recently (1926) I have produced in rats a state closely resembling it. I desire to bring the experimentally-produced state to the notice of the Conference mainly because of the dietetic conditions which give rise to it and of the probability that similar dietetic conditions may give rise to a similar state in man. Full details in regard to it will be found in the July (1927) issue of the Indian Journal of Medical

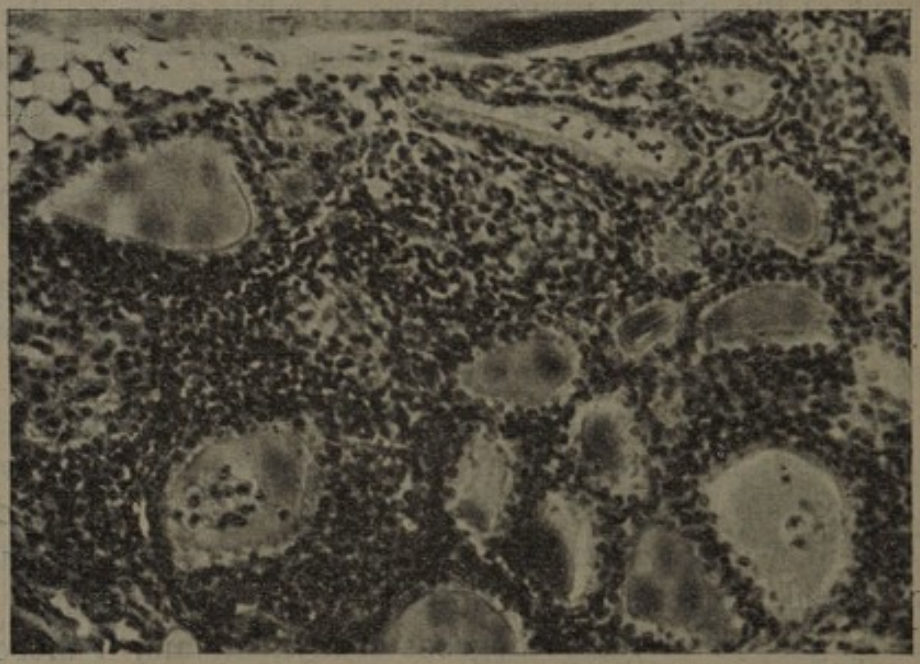
Research. Time does not permit me to give more than a brief account of it here.

The basal factor in the causation of this type of goiter is a diet from which green vegetables and fruit are excluded, containing more than 60 per cent of white flour or vitamin-poor carbohydrate, 20 per cent or less of protein, and fats and inorganic salts (including iodine) in adequate amounts. It occurs in approximately 25 per cent of rats so fed and is unrelated in its origin to iodine-deficiency: some animals acquiring the disease had consumed from 0.4 to 2.6 mgrms of potassium iodide in their food daily, while others had received no additional iodine. The goiter arising under these conditions is more common in female than in male rats and it is of relatively small size. It is characterized in its progressive stage by intense secretory hypertrophy approaching that seen in Primary Graves's Disease; and in its retrogressive stage by exhaustion of more or less epithelia with a corresponding increase of non-secretory elements. The diet producing it is such as induces a physiologically subnormal state of the thyroid gland and of the gastro-intestinal tract; and the changes occurring in the gland are the evidence of compensatory hyperplasia in a physiologically subnormal organ or of the action of « toxins », derived from the intestinal tract, or produced in the course of a disordered metabolism, on a physiologically subnormal organ, or of both.

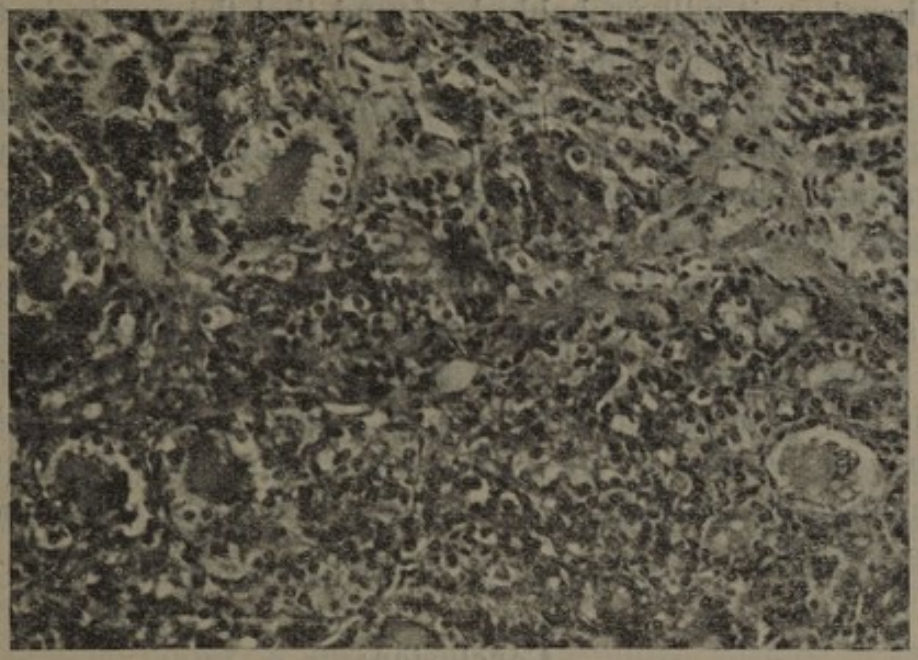
In view of the almost universal use of white flour as the main staple of the dietary in Western Countries, of the wide,spread use of vitamin-poor carbohydrates, and of the scanty use of fresh fruit and green vegetables, it seems probable that this type of goiter will be found to occur sporadically, or even in endemic proportions, among Western Peoples; that it will be encountered in its progressive stage in childhood and in young women whose food contains much vitamin-poor carbohydrate, little suitable protein and less green vegetables and fruit; that its retrogressive stage will be found in older subjects whose food has had similar faults since childhood; that the subjects of its progressive stage will be prone to develop Graves's Disease following such influences as fright, mental worry, pregnancy, lactation and attacks of acute infectious disease; and that the subjects of its retrogressive stage will exhibit greater or lesser degrees of myxoedema. If these predictions should prove to be correct then it will be found that the additional provision of iodine in the food will neither prevent nor cure this type of goitre. These matters can, however, only be decided by clinical, epidemiological observation, and by « goitre-sur-



1.
Normal Thyroid of Rat. Same Magnification as succeeding Figures.



2.
Lymph-Adenoid Goitre. Early Stage.



3.
Later Stage. Intense Secretory Activity: Increasing Fibrosis.

4.
Final Stage. Exhaustion of Epithelium: Great Increase in Fibrous Stroma.

veys» which are not limited to one section of the community — the children — but which take into consideration the whole population and the food habits of the individuals comprising it. Outside the laboratory it will probably be found that the purity in type of this variety of goitre may commonly be obscured by the interaction with the nutritional factors which give rise to it, of other goitrigenous influences such as lack of personal and social hygiene. The varying interactions of these influences may be expected to give variety to the characters of the «goitre» met with in different individuals and in different localities.

It seems necessary to add that since various types of «simple goitre» may prevail in the same locality — some capable of being benefited by the prophylactic use of iodine, some not, and some that may be harmed by it — the indiscriminate use of iodine as a preventative of «goitre» is a procedure both unscientific and dangerous.

* * *

Conclusion:

When I think of the permutations and combinations of the known goitre-producing influences — food deficiencies, food excesses, polluted water-supplies, gastro-intestinal infection, and insanitary conditions of life — and of the possible variety of their effects on the thyroid gland, I feel that in describing only three types of «simple goitre» I have but touched the fringe of the subject. Twenty-six years ago, at a time when our knowledge of the thyroid gland and its disorders was even more nebulous than the most pessimistic amongst us would admit it to be to-day, James Berry (1901) wrote: «But although goitre in most cases is to be regarded as an endemic disease, caused by a definite poison, whatever that poison may be, it is impossible to assert that all cases of goitre originate from the same cause.» I can do no better than conclude on this comprehensive note. Indeed, we now know that «goitre» is a generic term which includes a variety of diseases of diverse aetiology. Future research may, and no doubt will, further subdivide the «simple goitres» clinically, pathologically and aetiologically. But meanwhile we have the means of preventing large numbers of them by attention to the fundemental principles of Nutrition and of personal and social Hygiene.

Twenty-two sheets illustrating by charts, photographs and photomicrographs the various matters dealt with in the Report, and affording a pictorial record of the Author's work on this subject during the past 25 years, are submitted for exhibition.

Aetiology and Epidemiology of the Thyroidian Endemic.

By B. Galli-Valerio, Lausanne.

Under the designation of thyroidian endemic I understand three affections, which prevail in an endemic manner in certain regions: viz.: goiter, cretinism and deaf-mutism. The first type is characterized by general or circumscribed hyperplasia of the elements of the thyroid gland, accompanied by a more or less great degenerescence of the said elements.

The second type is often characterized by aplasia of the thyroid gland, which is accompanied by a series of development disturbances. The third type can be associated either with goiter or with cretinism, but at times it exists without any apparent symptoms of goiter or of cretinism in the regions, where these two affections exist.

Endemic goiter is spread over the entire surface of the earth and was known in the most ancient times, for in the East Indies it was referred to some 2000 years before the birth of Christ. It was considered at first as being localized in the mountains but we know at the present time that there are hearths of endemic goiter in the level country and even at the coast of the sea. It may suffice for me to make mention of the hearth of Monte Cellio right in Rome, the hearth of the coast of Naples, of Sicily and of Sardinia, of England, the Norwegian hearths surrounded by the sea, the hearths of the Algerian coast, of the Bay of Manilla, the Bay of St. Lawrence, of the United States, of Lake Tschad, of the oases of the Saraha, of the middle Chari etc. The climate has no longer any influence, for the endemic is met with in the north as in the south. The orientation of the localities no longer plays any rôle, for there are localities in the Alps facing the south that are ravaged by the endemic. However, according to Balp, unclean and badly ventilated houses would be more favorable for the development of the endemic. The question of race does not play any rôle here, whereas a very important rôle is played by age, the young being more likely to contract the malady. I have in fact always noticed that in the families originating from uninfected regions, which settle in infected regions, it is almost exclusively the young people who contract the infection.

There are very many cases of individual refractoriness and I may from this point of view cite my own case: Although I came

at a very young age into a goitrous region, after having been brought up in regions, where goiter did not exist, I have never contracted it, notwithstanding the complete lack of every precaution to prevent it, whereas my sister under the same conditions contracted it.

animale.

Endemic goiter does not only affect mankind, but also the animals. Thus we have observed spontaneous goiter in dogs, pigs, cattle, horses, rats, rabbits, more rarely in goats, sheep, birds. I have never had occasion to see it in cats. Experimentally we have produced it in dogs, rats, goats and even poultry. Even the cold-blooded animals can present spontaneous goiter, inasmuch as it has been observed in fish of fresh water and of the sea.

While the entire world agrees to recognize that goiter and cretinism are determined by the same cause, Hunziker denies that there is any relation between these two affections and deaf-mutism, but with Wagner v. Jauregg I am of the opinion that all those who have practised in the regions of goiter and of cretinism, do not hesitate to connect deaf-mutism with endemic goiter, as Felix Platter did at the beginning of the 17th century and some statistical data, which I shall cite later on, will confirm this.

To make a thorough study of the epidemiology of endemic goiter, it would be necessary to have exact statistics on its diffusion. Now, these statistics are entirely incomplete for the following reasons:

1. They are prepared upon the bases of military recruitment, and are enormously influenced by the ideas and personal technics of each medical doctor and besides they pertain only to men. Now we are aware that women are much more affected than men: In Switzerland 5 women to one man according to Kocher; in the Himalaya district 2.5 women to each man according to MacCarrison; in England 3 women to one man according to Campbell.

2. As there is a tendency to continue foolishly to look upon goiter and especially cretinism as a disgrace to a country, whereas it is at the present day a disgrace not to treat them, so the cases are not made known and the statistics become very difficult. Cerletti and Perusini would be able to tell you what opposition and what difficulties they encountered when making their masterly investigations on cretinism in Valteline. Just recall to your minds Ibsen's «Enemy of the People» and you will understand immediately the difficulties to be encountered in making such investigations.

Nevertheless we can give here some data: In 1874 Baillarger estimated that there were in France some 500,000 affected with goiter and 122,700 with cretinism, and Mayet in 1900 estimated 400,000 cases of goiter.

The Italian investigation of 1883 reckoned on 128,730 cases of goiter and 14,882 cretins to 9,000,000 inhabitants in Piedmont, Lombardy and Venetia. We can see at a glance that this statement is below the reality for it takes no further account of the hearths of Central and Southern Italy, of Sicily and of Sardinia.

The Austrian statistics of 1900 estimate that there are in that country some 17,286 cretins, which means 64 to every 100,000 inhabitants, but in certain regions there are even 226 to every 100,000 inhabitants.

H. Bircher declares that no malady takes so much vigor from the Swiss army as goiter. From 1875 to 1881 some 12,227 recruits were exempted for this reason. One of my students, Jomini, found at a late recruiting 30.35 % suffering from goiter and 31.13 ‰ cretins and cretinoids, and he was able to ascertain that in the families of these recruits there were cases of goiter, of cretins and deaf-mutes.

In 1883 Kocher found in the schools of Lauterbrunnen 90 % of goitrous children; in those of St. Gall, Steinlin found 61.9% and in some schools of the Canton of Vaud Roux found 121 children of 304 presenting a more or less defined goiter. We estimate that there are in Switzerland even more than 100,000, who are afflicted with endemic goiter. In the schools of the Valteline, Cerletti and Muggia estimate the proportion of goitrous individuals to be between 50 and 70% and in those of Bavaria from 77 to 89%.

Taussig has referred to the frequency of endemic goiter in Bosnia and Herzegovina and a colleague, Dr. Aeschlimann, has mentioned its frequency in Servia.

In other countries than those of Europe we find analogous data. Thus according to MacCarrison in the Himalaya region in a population of 70,000 we find 20 % goitrous and 200 cretins; in Africa at the Moyen-Chari it is estimated that 80 % of the population is afflicted with endemic goiter. The United States, the Andes, Brazil and Central Asia present formidable goiter hearths.

In all of these regions we find many deaf-mutes. Thus in France in 1851 in the endemic goitrous regions we found 129 deaf-mutes to every 100,000 inhabitants, while in the other districts there was a maximum of 56. From Italy come analogous reports, and I have myself determined in Valteline the frequency of what is there called the «dullness of hearing». In the endemic goiter

regions of Austria there were found in 1900 from 101 to 182 deaf-mutes per 100,000 inhabitants. From 1836 to 1840 it was found that there were in Switzerland 30,4 deaf-mutes to every 100,000 inhabitants over-against from 4,5 to 5 in Belgium and Holland, and in 1870 there were 24,5 over-against 8 in the whole of Europe. There were in that year 42 cases in the Canton of Berne and 49 cases in the Canton of Valais. I know of some Italian endemic goiter regions, where the asylums are filled with deaf-mutes. Goiter, cretinism and deaf-mutism can be hereditary or acquired.

If in the majority of the cases the infection has taken place after birth, there are a great many congenital cases. Thus Demme found among 642 goitrous children 37 with congenital goiter. MacCarrison determined through heredity with rats 63 % of goitrous animals and 4 to 5 % of the animals goitrous and marked with cretinism. It is above all the mother who figures in heredity, and there is no doubt that heredity is aggravated through consanguinity. This plays an important rôle for me in the endemic regions from the point of view of both cretinism and deaf-mutism. Oh! The many times that I have been told in these regions on the subject of cretinous or deaf-mute children: they are children of cousins.

But heredity is not inevitable: The offspring of goitrous cretinoids can be very well endowed. I have the impression that oftentimes people speak of heredity, when it is simply a question of the fact that the children have been exposed to the same injurious cause as the parents.

But what is this prejudicial cause, what is the cause of thyroidian endemic?

No malady has given and still gives rise to so many discussions from the point of view of its aetiology and for no other disease have there been so many theories advanced, at least 50, as for thyroidian endemic.

And I consider that it would still require a long time before an agreement can be reached for the simple reason that upon this endemic goiter there are acting in an analogous manner the presence of the determinating factor or the absence of the factor which prevents it, that is to say of iodine.

To expound in extenso all of the theories would lead us too far and I must restrict myself to an outline in dwelling upon the discussion of those, which are at the present time most wide-spread.

Leaving out of consideration those theories, which put the blame on the moon or on alcohol, and the claims of these latter have been very thoroughly crushed by E. Bircher, there remain

for discussion the theories of those who blame the air, the soil, the water, contagion, the lack of iodine.

The rôle, which the air may play, has been by turns attributed to its vitiation (de Saussure), to the excess of humidity (Gosse), to the insufficiency or to the lack of oxygen (Rozan, Lizzoli) and by Chatin, who had found that the amount of iodine diminished with the elevation on the mountains, to the insufficiency of this element. Not one of these theories rests on any foundation whatsoever and that of Chatin collapses at once when we notice that in the mountains goiter is generally more frequent in the lower part than in the upper part of the valleys.

A powerful rôle has been attributed to the soil, which has been time after time blamed for favoring goiter, viz.: argillaceous terrains, calcareous, dolomitic, gypseous and molasse ones, but it has been determined more and more that endemic goiter flourishes on all the various soils, even upon the sands of the Sahara desert. If it happens that it appears more frequently on some soils than on others, this is not due to the soil alone but to the presence of fissures or to the nearness of the underground sheet of water to the surface of the soil, two conditions which tend to make drinkable water impure.

In all of the endemic goiter regions the inhabitants do not hesitate to blame the water. The theory that the water is responsible is certainly the most ancient and the most widespread.

That drinking water plays a rôle in endemic goiter is demonstrated by the following facts:

1. The drinking waters of endemic goiter regions are all of them impure waters, as I myself have had the opportunity to prove.

2. The endemic is more frequent in the lower parts than in the upper parts of the valleys, for the villages situated lower down have their waters more easily polluted by the villages and fields situated a higher level. Thus in the schools of Tyrol situated at an elevation of 3900 to 6200 feet there were 4,74 % of cases of goiter while in those at an elevation of from 2000 to 2600 feet there were as many as 10,95 %. Some analogous observations have been made by me in Valteline, by me and my associate Jomini in Valais and by d'Almeida at Benguela (Angola). It is for this reason that the former physicians in Valteline who had observed the frequency of goiter and cretinism in the villages situated at the delta of the rivers, which flow in from the lateral valleys, had attributed to these alluvial terrains a rôle in the development of endemic goiter.

It is quite natural that occasionally the reverse fact may be verified, but it is not out of question that in certain cases a village at a high elevation could have a bad water supply and one situated lower down have water of good quality.

3. The experimental determination of goiter in dogs, rats, goats and hens with goitrigenous waters coming from endemic regions or with waters, which have been polluted artificially with the excrementitial matters of man or of beast (Lustig and Carle, E. Bircher, MacCarrison, Messerli, Balp, Pighini et al.), while the animals, which received pure waters, did not present any cases of infection.

4. The unquestionable determination made in several places, that the improvement of the water supply made goiter diminish and disappear. The case cited by MacCarrison in the Himalayas is typical: The village of Sanavar which was supplied with infected waters presented 26,50 % of goitrous children, whereas Kassuli with good waters presented only 1,7 %. The purification of the water at Sanavar by chemical means was employed and the goiter diminished. I have known the family of a Russian pharmacist, who had been living for a long time in Turkestan in a district where the water that was consumed was infected by fecal matters and where the entire population was goitrous. This family, however, had completely escaped infection for it had been accustomed to drink only tea. I have made analogous ascertainments in the Italian Alps and have seen at Sondrio that goiter was kept up in the peasant population, which while working in the fields drinks the water of the brooks that get the contents of the outhouses.

disappeared a new re-supply introduced

5. Disappearance of goiter among the fish of the salmon family, if the water of the ponds in which they live is disinfected (Gaylord) and the recovery from goiter in man through the uninterrupted intestinal disinfection, thus neutralizing the goitrigenous cause (MacCarrison, Messerli).

A great many observers have energetically fought against the aqueous theory of endemic goiter, basing their views on the following facts:

1. Goiter can develop in individuals who do not drink any water. — E. Bircher has very well said that goiter attacks the abstinent Mohammedans and not the common Russians, who become intoxicated with vodka and besides, as we shall see later, these cases can be explained through other causes acting with the water.

2. A great part of the Jura regions is supplied only with infected cistern water and nevertheless, goiter is rare there. — But as I have already stated in written form with my deceased collaborator Vourloud, the inhabitants of these regions recognize the fact that their waters are infected, so that they drink very little of it. The evidence is, that goiter there is more frequent among children and even among the rats (Wegelin), that drink all waters. Messerli found goiter common in the valley of Tavannes, where the drinking water is infected, whereas the neighboring places with cistern water presented no cases of goiter.

3. We can find polluted water everywhere, whereas goiter is localized in certain regions. I shall say to this: *a)* Goiter is more spread than is claimed and we are continually finding new hearths. Typical are the new ones pointed out by Campbell in England. *b)* If the goiter agent were a germ or a specific substance, it would be able to remain in the regions of infected waters. *c)* In some regions the injurious rôle of the goiter agent could be neutralized through the abundance of iodine in certain waters or in certain foods. iodine

4. Boitel has called attention that if it was a question of infected waters, there ought to be some parallelism between goiter and typhoid, but some objections may be raised against this: *a)* that he ought to take into consideration not the deaths but the cases of typhoid. *b)* The germs which determine these two affections are not the same, so that the one could very well exist without the other. *c)* Our goiter statistics are entirely incomplete and in some endemic regions the physicians fail to declare the cases of typhoid so that consequently every comparison is out of question. typhoid *d)* The ~~thyroid~~ epidemics very frequently did not originate through the use of water, which is a new cause that makes comparison impossible. *e)* The typhoid epidemics, which originate through the use of water, are oftentimes of a sudden outbreak, of short duration and consequently do not admit of any comparison with endemic goiter, which gives the impression of claiming a slow and uninterrupted infection from the water.

5. The great frequency fluctuations of goiter in certain regions declare against an infection. But all of the infections are characterized by fluctuations and it is not said that goitrigenous water can always be infected in the same proportions.

6. The experimental researchs of Grassi and Munaron, Landsteiner, Schlagenhaufer and Wagner von Jauregg, Klinger and their collaborators all declare against the aqueous theory, for

they have been able to produce goiters in rats and birds placed in goitrous districts but given pure waters or boiled waters and vice versa they have not been able to determine them in healthy regions with waters originating in infected districts. But, besides the fact that these experiments stand in great part in contradiction with those of other experimentalists, who have succeeded in transmitting goiter into rats even at very great distances from an infected region with the water of this particular region, as e. g. at Buénos Aires with the water from the extreme northern part of Argentina, that it is difficult to eliminate all of the possible causes of the infection of the water employed, they simply indicate, as moreover Landsteiner, Schlagenhaufer and Wagner von Jauregg have declared that water is not the exclusive agent of the transmission of goiter. Thus, when Wegelin tells us that he had occasionally more goiter in rats nourished with milk than in those given goitrigenous water, according to my ideas on the aetiology of goiter I am not astonished to learn this, for milk is oftentimes more infected than the most unfit drinkable waters and besides it is often diluted with the most infected waters. Furthermore, very recently Neukomm, in an address held at my institute made it clear that a certain milk, which at the moment of milking contained 352,000 germs per cubic centimeter, at the moment when it was on sale in the dairies it contained 15,041,000. Where is the goitrigenous water to be found that contains as many as this?

But even those, who are ready to admit the origin of goiter through water, do not agree as to the what, which is found in the water and which imparts to it the goitrigenous power. Some attribute it to the presence of salts of calcium, or of magnesium, of silicon and the silicates (Bérard, Pighini), of others containing a toxic substance which would be formed in the maritime sands, a toxic substance of colloidal type, filtrable but not dialysable, decomposed at 158° Fahrenheit (E. Bircher, Wilms) and finally others with specific or non-specific germs and their products (Galli-Valerio, MacCarrison, Messerli et al).

Besides these theories regarding the presence of foreign substances in the goitrigenous water, there is the theory of Répin, which attributes the injurious action of the water to its radioactivity.

I do not have the impression that any demonstration has been given of the rôle of the chemical substances dissolved in the water or of the radioactivity in the development of goiter. If, e. g., the waters containing calcareous salts appear to be favorable for the

development of goiter, I attribute that rather to the fact that the lime presents in abundance fissures, which permit the contamination of the subterranean waters. Of the radioactivity point of view, we may say that no evidence has been given that shows its influence in the development of goiter. The theory of a toxic substance originating from the maritime sands is considerably more interesting and is founded upon the determinations of H. Bircher, confirmed by E. Bircher, that goiter is developed upon the terrains of maritime sands. But as I have said we are more and more determining the presence of goiter upon all soils, consequently this theory can not be accepted in its restricted limits. On the other hand, taken in the wider sense of toxic substances that are found in goitrigenous water and that act upon the thyroid, it is found to agree immediately with the theory of infected water. The infection of the water could be determined by means of a specific agent, but I am more and more of the impression that it is not a question of a specific agent but of a series of germs originating above all in the intestines of man and animals and which, having been introduced into the digestive apparatus with the impure waters, give there toxines, which act upon the thyroid. We know at the present day, as a matter of fact, that a series of toxines of microbes, and even those of the intestinal worms, is capable of determining the lesions of the thyroid gland. This is why goiter could be experimentally provoked not only with the waters of endemic regions but even artificial waters infected with excrements, and this explains also why a constipating diet favors goiter. In Valteline several young men, in order to escape military service, swallowed great quantities of walnut shells which constipated them and facilitated the development of goiter. The great advantage of the impure water theory is that it is not exclusive. In fact, when we accept the goitrigenous rôle of any particular water with the germs of the intestines, we are forced to admit also the possibility of the spread of goiter through the foods, as milk, salads etc., which are by chance, infected by these very same germs, and even through contact with infected matters, as Balp admits for the peasants, who pass their lives in the stables, and perhaps even through contagion from individual to individual as is the opinion of Kutschera and Taussig.

A great advantage of the theory of water infection is that it is in part admitted even by those who are denying the direct rôle of water in endemic goiter, which they attribute to a cause still unknown, for they admit that an infected water, which is consumed

by an individual, who is already in the power of goiter will increase enormously the dimensions and seriousness of it (Grassi).

Another parasitic theory, which has found some adherents, is that of the transmission of goiter through the stings of arthropods. This theory originated through the fact that Chagas attributed Brazilian goiter to the Trypanosoma cruzi transmitted by Triatoma megista. But I agree with Kraus in considering that Brazilian goiter has an origin identical with that of all the other varieties of goiter and the patients of Chagas are only goitrous patients upon whom the trypanosoma infection has been grafted, an infection, which like every infection aggravates goiter. It is upon such bases that the desire has come up to bring into relation with endemic goiter trypanosomas found upon bats of certain goitrous districts.

In more recent times, above all under the influence of Hunziker and Eggenberger, the old theory of Chatin has been re-exhumed, that the cause of goiter must be purely and simply searched for in the insufficiency of iodine in the air, the soil and the foods. Inasmuch as iodine cures and prevents goiter, it is claimed that it is the absence of it which is the cause of the disease. Post hoc ergo propter hoc. This theory would be equivalent to one which might be given us, viz.: As quinine cures and prevents malarial fever, it is the lack of quinine, which determines the malaria. It is interesting to note that an analogous discussion has been taking place for years on the subject of a disease of the cattle of South Africa: The Lamsiekte. Inasmuch as the cattle could be protected against this malady with phosphates, it was declared to be the lack of phosphates which provoked the malady. But Sir Arnold Theiler however observed that the fact that helminthiases are cured with arsenic is no proof that arsenic is the cause of helminthiasis and he has demonstrated that if the phosphates prevent the disease lamsiekte, it is very evidently because the cattle receiving sufficient quantities of these salts have no longer the need of devouring the bones of dead animals upon the pasturages, bones which contain the toxine of the Parabotulinus bovis, the agent of the lamsiekte.

The theory of the lack of iodine as a cause of endemic goiter is founded upon the interesting researches of von Fellenberg, who has determined the presence of a greater quantity of iodine in the soil and foods in the non-goitrous regions than in those where goiter prevails. But these interesting researches simply show that in those places where there is an abundance of iodine the goitrigenous cause can act less easily because the iodine neutralizes it

in its action. But the proof that the absence of iodine is not the cause of goiter is to be found in the fact that the goiter hearths exist even to the sea-coast and Campbell has determined in England, that the localities where goiter is very frequent are right at the coast; that the valley of Brembo with water containing 0.0028 grams of iodine per liter, is a formidable goiter hearth, that some fish of the sea, living in very salty water such as that of the Mediterranean Sea, feeding upon substances so rich in iodine that its quantity exceeds the amount required to prevent goiter in the fish of the salmon family, have exhibited typical goiters (Marsh and Vonwiller). These facts accordingly show that in those regions where the goitrigenous cause is a very active one, even iodine does not happen to neutralize it and that consequently the absence of iodine is not the cause of goiter.

Pighini has moreover established as a fact that mice which are subjected to an alimentation deprived of iodine die very easily, but their thyroid glands are very small and not at all hypertrophied. These experiments, which have moreover been made by other observers, confirm what Wegelin has written in regard to the theory of the absence of iodine, that is to say that as iodine stimulates the function of the thyroid gland its absence must terminate the atrophy and not the hypertrophy of the gland.

The determinations, that are moreover more and more frequent, which have been made on man and the animals of the goiter hearths in the same city and localized to certain quarters (Strasbourg and Robertsau most especially) or in the stables, have smashed completely the theory of the absence of iodine as the cause of goiter.

This very plain theory, which aims to have the rôle of water and of infection through impure foods disappear, is extremely dangerous for the prophylaxis of endemic goiter for it tends to leave aside two elements of prime importance in the fight against endemic goiter, viz.: The good distribution of drinking waters and cleanliness in the preparation of foods and above all of milk and the improvement of the habitations in a hygienic sense.

To recapitulate: I accordingly consider thyroidian endemic an affection due to toxic products of different intestinal germs, toxic products which infect man through the intermediary in the first place of drinking water and in the second place with spoiled foods, especially milk and salads, and perhaps also through uninterrupted contact with excrementitial matters in the stables or with the infected individuals. Aggravated through consanguinity, heredity

and the general bad hygienic and physiological conditions it terminates in cretinism.

Consequently the prophylaxis must have in view not only the diffusion of the iodine antidote but the improvement of the drinking waters and of hygiene in general, as also the gratuitous treatment with thyroidine of the existing cretins, who are still young and are suffering from goiter, for even iodized salt is not adequate against average cretinism.

Conclusion:

1. The causation of endemic goiter (goiter, cretinism and deaf-mutism) is not yet fully understood.
2. Of the numerous theories that which regards drinking water as the cause of goiter is at once the oldest and the best supported by fact and experiment.
   a) Detection of contamination of the drinking water in all endemic districts.
   b) Abatement and disappearance of the endemic under improved conditions of supply of drinking water.
   c) Appearance of goiter in animals which have been watered from sources in endemic districts or with artificially contaminated water.
3. The noxa of goiter in drinking water is either a specific substance, or a specific germ or group of germs, especially of the intestinal flora, which produce toxic substances that act upon the thyroid gland. By consequence disinfection of the bowel is beneficial and a regime favouring constipation the reverse.
4. The drinking water theory does not exclude the possibility of other vehicles for spreading the endemic. In like fashion cholera, enteric fever, and dysentery in all of which the drinking water is usually at fault can equally be conveyed by milk, vegetables, direct infection, etc.
5. The drinking water theory is further in conformity with the views of those who, while they hold that the causa causans of endemic goiter is as yet undiscovered, still admit that contaminated drinking water aggravates goiter.
6. Apart from water supply inbreeding is a predisposing factor in cretinism and deaf-mutism.
7. The theory of the causation of goiter through deficiency of iodine can not be accepted,
   a) because even where iodine is present in excess (sea-coast and sea) goiter may develop.

b) because deficiency of iodine causes atrophy, not hypertrophy of the thyroid.

8. Iodine is merely in some sort an antidote to goiter, as is quinine to malaria. Deficiency of quinine does not give rise to malaria, neither does deficiency of iodine give rise to endemic goiter.
9. The drinking water theory has much to recommend it from the side of prophylaxis as leading to an improvement of the water supply.

The Geographical Distribution of Endemic Goiter.

By Eugene Bircher, Aarau (Switzerland).

In every progress that is made along the line of research and also in every new real fact that is learned, the endemiology of goiter is not, so to say, made more clear to our minds, but on the contrary the difficulties in the way of explanation become more numerous.

In the following statements I shall confine myself in the endemiological question of the goiter problem to a few definite matters. It becomes therewith a question of ascertaining whether and, if so, what variations of a periodical, quantitative and qualitative nature the goiter passes through in its manifestations. Proceeding from the ascertainment of this point the further conclusions as to its genesis can be drawn, and not until then.

Here we, however, must surely observe, that the statistical material, which will be employed for this investigation, is in part of quite varied importance and must be rated with the greatest care in order to avoid the sources of error in this direction as much as possible, if after all it can be said that a comparison still appears possible with a rather large series of numbers.

The subjectively palpatorical diagnosis of goiter in itself leaves open a great subjective and objective range in the estimation of the result obtained and it would be a difficult thing here to set up positive rules, which can pass as general practicable formulas without any sources of error; we must keep our minds open to this fact.

Clinical meth / survey / family

From the medical writings it ought certainly to be learned that the investigations made on recruits give us in general the best general aspect as regards the distribution of the goiter

Surveys in children not intuitive for ex. lim. prevalence

endemic, as it reflects most distinctly the intensity of the illness for a certain region.

With far less distinctness is this aspect marked in the investigations made on school children, as we shall see.

Great difficulties likewise lie in the way if we wish to define the demarcation of the regions that are being investigated; in making further geographically nosological researches we must hold to the idea that only such statistics are of value for the endemiological research, which at least extend minutely down into the data of the individual communities. To simply make mention of the figures for individual districts, circuits, cantons in Switzerland, departments in France or states in North America, as one whole, will lead to such great sources of error, that only with an exceedingly great number of data is it proper to draw any conclusion whatsoever.

It can often happen that the data of goitrous regions get mixed up with those of non-goitrous ones just in such rather large area percentages, so that a very incorrect aspect results as regards the visible representation of geographical distribution.

With such statistics all those changes of the thyroid gland fall entirely out of consideration which have to be looked upon as of a purely functional nature without leading to an essential and palpable enlargement, as this has already been declared by Krehl and others, and the importance and real nature of which are just as little known to us as also their quantitative range can not be even approximately determined and grasped by us. Perhaps it may be possible to establish diagnostic indications with the aid of the fundamental metabolic characteristics, but such investigations on a fairly large amount of material can probably not so easily be carried out for external reasons.

For the circumscription of the definition of the expression of endemic goiter, that is not just properly chosen, there belongs the fact of its being bound down to a definite geographical localization — the sphere of the endemic.

We should, however, like to supplement this definition with the statement that there are other marks of distinction belonging to endemic goiter, besides the enlargement of the thyroid gland, which stand in relations with the latter, even if these relations have not yet been positively ascertained. These are cretinism and the intermediate stages which pass over to the normal human being, the cretinoids, and also the endemic deaf-mutism, which makes its appearance in many places combined with it, and which

appears to be closely related to it. We can undoubtedly assume that with this a particular aspect of endemic goiter-heart must probably be combined, even if it be only of a functional character.

Here it must be established as a fact that the common myxœdema, the athyrosis resulting from hypoplasia or the deficiency of the thyroid gland, can not be classed as belonging to cretinism. The purely hypothyrotic explanation of cretinism is not able to clear up absolutely all phenomena of cretinism, neither those of a somatic nor those of a psychic nature.

If from this point of view we consider the goiter endemics, we shall find according to our present information the following clear endemic centers:

In France the one of the Pyrenees and that in Savoy, a weak center in the Vosges and a very weak one in Puy-de-Dôme, which can almost be looked upon as still being questionable. Out of the territory of Savoy this goiter center extends north of the Alps, on the one side, into Switzerland and south of the Alps to Upper Italy.

The endemic in Switzerland shows above all a less pronounced character in the southwestern districts with the exception of Valais, and further north in the Cantons of Berne and Freiburg increases in intensity very strongly, from where it passes over into the endemic of the Cantons of Argovia and Lucerne, which formerly had a record of very many cretins in contrast with the Cantons of Zurich, Thurgovia and St. Gall in Eastern Switzerland.

Out of Eastern Switzerland the endemic again branches out in two lines, of which one proceeds along the northern slopes of the Alps through Bavaria to Tyrol-Styria, in part northwards into the river valleys down towards the Danube, while the other extends north of the rugged Alps through Würtemberg down towards Franconia.

Considerably weaker in its cretin character does the endemic manifest itself, which extends along the Swiss-Baden Rhine valley towards Heidelberg.

South of the Alps we have at the extremities of the Cottian, Graian and Pennine chain the strong endemic of Piedmont, which continues over into Northern Lombardy, and especially of the Valtelline, then extends through the Venetian territory upwards towards the Carinthian Alps and finally becomes united with the Styrian endemic. The new goiter center in the Maritime Alps near Genoa seems to show up no cretins.

These groups of the endemic are the only ones, which exhibit a strongly marked cretinic character. All other goiter districts in Europe are wanting in cretinism. Here we may mention primarily that phase of goiter, which prevails in the Taunus, in Rhenish Hessia, in East Prussia and in Danzig. Regarding the goiter in England there was never and there is not at present any connection mentioned with cretinism. For the whole of North America the absence of cretinism is reported; likewise for New Zealand and for the Russian goiter in the Ural Mountain districts there are also no definite data to be established regarding any strongly developed cretinism. In large and numerous parts of France, in Sweden and Norway and in the coast goiter in Genoa it is wanting.

It is only Sicily and one small area in Norway which, according to the latest data, manifest a cretinic character.

The so-called endemic goiter with its accompanying structures is confined to this very definite localized area, from which the other goiter centers must be nosologically sharply separated.

In these regions its character is subjected to variations both qualitatively and quantitatively. For a rather long time it had struck the attention of my father and other colleagues that the goiter endemic in the Canton of Argovia is showing in isolated sections a clear and distinct diminution. For Argovia as for Switzerland there are four sets of statistics, which originate from the years

	1875/80	Bircher			
	1884/91	I. Goiter Commission			
	1908/				
	1922/23	Stiner			
	1924/25				
Districts:	1875/80	1884/91	1908	1922/23	1924/25
	%	%	%	%	%
Zofingen	20	17	6,27	10—15	9,6 (4,2)
Kulm	30	18,5	15,27	10—15	11,4 (4,7)
Lenzburg	25	18,1	7,76	10—15	9,1 (1,6)
Aarau	15	11,7	6,61	10—15	11,6 (0,4)
Baden	25	19,6	7,38	20—30	13 (2,8)
Bremgarten	10	14,6	13,7	20—30	29,5 (5,8)
Muri	0,10	10,4	17,32	20—30	25,1 (4,9)
Brugg	0—10	8,3	2,3	5—10	7,5 (2,3)
Laufenburg	0—10	9,1	3,7	5—10	14,7 (4,1)
Rheinfelden	10—20	10,4	5,79	5—10	14,8 (3,4)
Zurzach	5—10	11,6	1,3	20—30	16,6 (2,5)

(The figures within parentheses pertain to those, who are unfit for military service on account of goiter.)

A glance at the Argovian map will suffice to shows us perfectly that in the Wigger area, which was once upon a time very strongly infected, in part in the area of the Suhren valley and very strongly marked in the Wynen valley there has been a diminution of the endemic.

In some individual sections we can speak of a slight or strong increase and in others of the disease being at a standstill, i. e., as having undergone no change, as e. g., in many villages of the Baden district.

On the other hand there is a remarkable increase of the endemic in the Freiamt, which had formerly been relatively afflicted but very little, in the district of Zurzach and in the Eastern parts of the district of Baden.

It appears, however, to be of essential importance that the entire Jura region, which was formerly mentioned as being immune, has also kept itself immune during the course of 50 years, and that the endemic goiter has n o t penetrated into its different districts. There accordingly seems to be both actively and passively an absolute, permanent immunity in those regions.

This variability in the degree of intensity of the endemic can, however, not be a matter of chance. First of all, the fact must be established that it occurs only in a region that has already been afflicted with goiter, that is to say, not in regions that are free from endemic.

It is probable that this variability follows a certain regularity or law, inasmuch as in Argovia an increase is recognized which runs from West to East and accordingly the decrease makes its appearance prominently but distinctly in the western part of the canton.

Likewise in a qualitative sense a most prominent retrogression is to be seen. The number of strongly marked cretins is becoming most decidedly reduced, as my own knowledge of the country and its population as also the results from enquiries among the medical practitioners have shown.

For example, the villages of Gränichen and Suhr, which are in close proximity to us, are not afflicted with cretinism as much as was formerly the case, but only a few individual cretins still bear testimony, that the malady has almost disappeared. But also goiter has experienced there a distinct diminution if only a slight degree. The retrogression of the endemic of cretinism has n o t been numerically determined, nor can this be done, since the comprehension as to the idea becomes extremely difficult here,

if we are to include the many intervening forms of cretinoids within the sphere of our observation. Neither can we here get rid of the impression, based on the material on hand that cretinism also has likewise taken a migratory movement towards the East, but naturally without any essential quantitative increase. Separate, rather small and plainly pronounced cretin centers are still to be seen.

In this connection we should like to point to a histo-geographical relation of the goiter variety in our professional labour district.

We made a report some time ago on our histologically investigated struma material and at that time established the fact that some 80 % of our strumas belong to the nodose variety and only 11 % to the diffuse form, whereas 9 % are of a mixed variety.

Geographically we now learn that the goiter variety in the Rhine valley, i. e. in the northern part of the Jura Mountains, in the Trias formation region, belongs about one-half to the diffuse form and the other half is of a nodose character, while the southern midlands of the Molasse endemic belong with the excessive figure of 87 % to the nodose goiter variety, whereas the diffuse goiter falls entirely into the background. But, nevertheless, we find the Basedow, the carcinoma and Langhans goiters for the far greater part represented almost without exception in the sphere of the nodose endemic. These observations ought likewise not to be considered chance-work, for the further we go from the endemic center the more can we properly speak of an increase of the diffuse variety of goiter and a decrease of the nodose form.

also de-
crease.

For example, Orator claims for the Vienna region preponderatingly 80 % for the diffuse and only 20 % nodose, which is exactly the opposite relation of that prevailing with us in Argovia. In Holland as in England the diffuse forms are absolutely prevailing.

* * *

These afore-mentioned modifications and migratory movements of goiter really appear also distinctly throughout Switzerland as a whole.

Switzerland

The so-called classical goiter region of Switzerland, the Canton of Valais, shows forth quite peculiar conditions in this particular. Upper Valais manifests with certainty a standstill and in part a retrogression of the endemic, whereas the entire section of Lower Valais has experienced, according to the latest statistics of Stiner and Jomini, a very striking increase, which is seen to be two-fold

and even three-fold. An increase, even if it is one of slight degree, is already recognizable in the statistics of 1884/91. From that date on the increase has taken a somewhat more rapid course.

In the Canton of Geneva and in the southern part of the Canton of Vaud, the conditions have in general remained the same. With the latter there is rather a slight increase to be recognized in the Broye valley, but to be sure this lies within the possibilities of error.

A decline of the endemic in the Canton of Freiburg can be recorded; to be sure it is less so in the southern part of the canton but in the northern part the falling off is in part very plainly and strongly marked and has made itself good since 1884 and can readily be recognized in the first statistics of Stiner. It is simply the Saane and Sense districts which show numerically only an insignificant decline of the endemic, even if such is really a distinct one.

The Canton of Berne shows us in its three strongly marked regions, that have frequently come under investigation, viz., Highlands, Midlands and Jura, the following conditions:

The endemic in the Bernese Highlands, one of very pronounced intensity, exhibits in general, as far as figures prove, a stationary condition. To go into particulars we find here and there a slight falling off or we can establish a slight increase, whereby the decline is more frequent than the increase. In the central parts of the canton the decline begins to appear more pronounced, especially in the midlands area, following down along the Aare river from Berne. This falling off is more plainly marked in the statistics of 1884/1891 than in the previous researches, even if we still find some very evident distinctions when compared with previous data.

Again we find the slight occurrence of the endemic plainly and sharply pronounced in the entire Bernese Jura regions or even its immunity. The Neuchâtel Jura districts resemble the former as regards immunity, for here there is found to be in part a slight occurrence and in part an entire freedom from goiter. This almost absolute immunity still extends further down into the Jura regions of the Cantons of Basel-Land, Soleure and Argovia, even if in some individual cases, where the soil might be of a different geological character, as in the Waldenburg valley, the endemic begins to take on a pronounced character, as is likewise the case in the French Jura.

immune regions

From the eastern districts of the Canton of Berne the endemic passes over into the migration towards the East, which was stated

regarding the Canton of Argovia and then, especially in the eastern regions of the Canton of Lucerne in the bailiwicks Sursee and Hochdorf, it shows a very distinct and remarkably strong increase even to the double of the previous figures, which then extends in the neighboring area of the Canton of Zurich into the districts of Horgen and Affoltern, and on continuing more easterly we find it in the districts of Andelfingen-Winterthur almost doubled; but also in most of the remaining regions of the Canton of Zurich there is to be found an increase and only here and there a state of stagnation. This increase continues in the neighboring Cantons of St. Gall and Thurgovia as far as the Lake of Constance very distinctly and in the majority of the districts of the Canton of Thurgovia it reaches the double and even the three-fold in Frauenfeld and Steckborn. This increased ratio is likewise strongly marked in the Cantons of St. Gall and Appenzell, where, to be sure, the southern districts of Toggenburg-Sargans-Werdenberg exhibit the greatest increase, even to the three-fold, while the remaining central regions show only in part as much as two-fold. Considerably slighter, even if it may still be quite distinct, does the increase appear in the Canton of Schaffhausen.

A similiar increase is noticeable in Central Switzerland. It is most strongly pronounced in the Canton of Schwyz, while the Cantons of Glarus and Uri exhibit a stationary condition with a general slight occurrence of the endemic. The conditions in the Cantons of the Grisons and Ticino have likewise remained stationary, and the Canton of the Grisons can be designated as fairly free from goiter and the Ticino as really poor in goiter, if we do not wish to say immune. An endemic, that has been augmenting at a rapid pace since 1870, is found in the Canton of Appenzell.

The increase has accordingly become the most clearly manifested just in those cantons, in which the prophylaxis of goiter has been carried out the most strictly; this is seen in a truly drastic manner in the latest statistics of Stiner.

In summarizing, we find primarily in Switzerland a great state of fluctuation in the intensity of the distribution of goiter, which separately shows a decrease in the number of the goitrous but mainly manifests a considerable increase of goiter. This increase does not appear to proceed in an irregular manner and there seems to be a migratory movement of goiter taking place from the western part of the country to the eastern and to have been shifted from the former center of Central Switzerland to the East.

This shifting remains exactly within the confines of the endemic, as they have for decades been recognized. Certain regions of Switzerland, as the Jura, the Canton of Ticino, the Grisons, have maintained a certain amount of immunity and are fairly free from goiter throughout this era. We must still make the comment that the increase and the distribution of cretinism has not kept pace parallel with it in the eastern parts of the country.

How are these conditions in the other endemic centers? The best statistics along this line we owe to Italy and secondly to France. Stefano Balp was able to determine a falling off from 70 per thousand to 52 per thousand quite generally for the period of time 1874/78 to 1889/93, that is to say for 15 years.

From the time of the first statistics of the year 1848 of the Sardinian commission this decline for Piedmont is seen very distinctly at once. It is in Alba 50 % and in Cunco 77 %; in Salluzzo the conditions have in part remained unchanged. A clear falling off can be seen in the Aosta valley. For the present the cretinism is everywhere falling off very strongly. Turin shows a decline from 8 % to 3 % and Allesandria remains unchanged. Lombardy shows over-against Sormani a falling off from 5,94 to 3,0 %.

A further decline can be seen according to Pighini in

Como from 8.08 % to 3.5 %
Milan from 4.84 % to 1.2 %
Pavia from 2.7 % to 1.7 %
Cremona from 5.9 % to 2.1 %.

Throughout the whole of Lombardy we see a falling off from 6.76 % to 3 %, i. e. about one half. On the other hand it is evident that this reduction gives proof of not being of a uniform character; while in the Province of Bergamo there was in general a distinct falling off to be seen in the different statistics of Sormani 1859/1864, later of Cavatorti, so now the recent researches of Pighini show that the Province of Bergamo exhibits in many places a distinct increase of the endemic among the population, even if in comparison with 1881 there is in general a falling off to be found. In the Province of Brescia itself there is also evidence of an increase in the year 1881; while the districts of Breno, Chiari, Salo, Verolanuova show a diminution, the Upper Chiese, Trompica valley, Val Comonica show plainly an increase in goiter. In the Province of Sondrio an increase is again becoming slowly apparent after a general decrease which extended over the years from 1843 to 1856, which increase in proceeding from West to East is appearing up the valley as a considerable augmentation. Very striking

conditions become manifest in the Province of Udine. The statistics of Sormani and Cavatorti reckoned with 2 to 3 %. According to Volpi Girardini the Ampezzo valley manifests at present figures up to 7 %, whereas the statistics of 1881 still found large parts of the province free from endemic goiter and only isolated little goiter centers were discovered. It appears likewise in the Province of Belluno that the endemic had during the last few decades expanded to a great extent and to have extended up in the Piave valley and especially in Valle Ansiei and Val Biois. Even if it may not be so distinctly, definitely and strongly pronounced, which may probably have some connection with the fact that the statistics are not entirely uniform, it is nevertheless possible to establish in Italy a progression in an easterly direction, while in general the compass of the endemic, but especially also that of cretinism, has fallen off. In a more recent work Muggia is also able to confirm this considerably spontaneous falling off of goiter. Two goiter centers, which were formerly not known, have been described in Italy as new ones. The one is that of Prigioni of Genoa, having in part very high percentages, even such as 30 % and more, and having no cretinism combined with it, while the goiter center, which has been described by Ottonello in Sardinia, is surely combined also with cretinism, judging from the illustrations.

Germany.

More recent comprehensive statistics have not been received from Germany. For Württemberg the same aspect has again been determined according to a recent statistics, which was manifest in all statistics, namely, that the Suabian Jura has remarkably few cases and that here also the recognized immunity has been maintained.

In the Black Forest region there appears to have been a certain degree of increase, which has even been intensified in the Neckar district, and has become strong in the Danube district, while in the Jagst district a strong falling off of the endemic is evident.

In Baden the following can be laid down as facts according to the non-uniform statistics of Weber, Lücke and Merckens. In Northern Baden an increase has been ascertained by Lücke after a temporary decrease at the time of the investigation, which increase is likewise noticeable in Central Baden.

In the Central Eastern part of Baden the endemic has remained stationary, whereby, to be sure, the highest figures in Upper Baden are seen to be in the lake districts. Inasmuch as formerly the lower

Rhine valley was more strongly affected, it is evident that here also there has apparently been a migration towards the East.

Baden, as well as Württemberg, in reality shows a general diminution of the endemic and cretinism has as a whole fallen off considerably. Bavaria shows a medium strong endemic. Concerning variations nothing can be stated definitely, as very frequently the exact data on these questions are wanting. On the other hand we gain the impression that there has been sooner an increase of goiter, which we can also assume for Franconia, according to the figures of Lobenhoffer, whereas the aspect of the genuine cretinism, which Virchow could still show to occur in great numbers, has very considerably receded. The exact localization of the endemic has been determined by Lobenhoffer, and this certainly shows in its turn exact relations to the underlying basis. For Hesse-Nassau similar data have been determined and here cretinism, so to say, is entirely wanting and the endemic of goiter is surely present.

If the figures recently made known by Gersbach are correct, then a very tremendous increase must be considered as being proved for Hesse-Nassau, when taken in comparison with the figures of Pagenstecher. It must certainly be admitted that there has likewise been an increase found for the Westerwald by Pagenstecher since the statistics of Falk. In the Rhine Province and that of the Moselle there really appears to have been a falling off. There are a few more German goiter centers, which we may mention, namely, the Silesian endemic that has so frequently been described during the last few decades, where the cretinous character is completely wanting, and which exhibits four centers: in the Altvater mountain range of Czechic Silesia, in the region of the source of the Neisse of Glatz and along this in Hirschberg and vicinity and in the Waldenburg Reichenbach region; and secondly the Oder region in Upper Silesia. A slight increase seems to have taken place.

The light endemic in the western Erzgebirge has similarly increased, as it likewise has in Bohemia, and it seems to be migrating towards the North. The endemic in Saxony, described by Hesse, is also a weak one. These endemics are to be looked upon as of a very light character. As another strongly infected region there is the Styrian region, which extends along the Alpine chains through Bavaria and Tyrol and Upper Italy. This is less pronounced from Carinthia and Cariola on, from where the endemic extends into the Vienna basin, and sends forth only slightly infected branches into the Hungarian Banates. As to Tyrol we have no

exact statistics, nevertheless the endemic seems to be as strong as it is in Switzerland; this can certainly be claimed for Styria, according to the data of Scholz, and according to recent researches of Schrattenbach it suffers considerably from scholar's goiter.

War and goiter

In the Vienna basin an increase occurred during the course of the war, so that it is probable that here also there was a migratory movement towards the East. We have no data from here concerning cretinism. A goiter center, even if it is not a very great one, is also found in Rumania in the Carpathians and the Transylvanian regions. No truly exact numerical data are on hand. Approximately 30 % of the Rumanian cities and villages give evidence of an endemic, among which there are four that are rather strong and afflict from 10 to 30 % of the population, but even here there is no very extended endemic.

France

The most comprehensive statistical researches were made in France. We find there statistics from the years 1816 to 1825, also 1836 to 1845 to 1873 by Baillarger, 1880 by Chervin and 1887 to 1890 by Mayet. More recent statistics have, to be sure, not been made. The statistics, that have been gathered, taken all in all have a very varied value.

It must first of all be ascertained, in which localities the goiter in France has become widely spread as an endemic, which has afflicted great numbers of the population.

Of the departments of France no fewer than 79 (!) showed in the statistics of 1887 to 1896 a percentage rate of less than 1 %. But with a rate of 1 % we can hardly speak of an endemic, even the rates of 2 and 3 to 5 % can only with the greatest reservation be designated as an endemic, if we wish to draw any comparison with the strongly infected regions of Switzerland, Styria, Italy etc., and they must be classed with the sporadic goiters. The statistics of Baillarger still showed in some 40 departments a rate of 1 % or more of goiter. It is evident that, on the whole, we see in France a spontaneous, plain falling off of the goiter endemic as regards distribution, but there also in the most afflicted regions a distinct falling off to be found.

Viewed from this standpoint we can settle on only three real endemic centers in France:

I. The Savoyan center, which extends towards the South into the Departments of Hautes Alps and Basses Alps, passes over to the North-East into the Valais endemic, extends into the Rhone valley and towards the West, where it connects with

II. the center in the Puy-de-Dôme, which extends over to the West into the Dordogne, and which branches out towards the South into Central-Lozère and Aveyron, but shows only slight prevalency, and extends

III. into the Hautes-Pyrénées, Haute-Garonne and Ariège.

From the Savoyan center an endemic becoming ever lighter and lighter extends down through the Jura mountains into the Vosges, Meurthe and Moselle, and passes quite sporadically via Meuse, Ardennes and Aisne, Oise turning towards the Paris basin and becoming ever weaker and weaker. Nor does there appear to be any cretinism prevailing here, whereas it is very clearly pronounced in part in the three centers, especially in I and III.

In these three centers the endemic does not by far reach the extent of that in Switzerland and Styria, for at the investigations made upon recruits in Savoy the mustering with Mayet was 2 to 4.5 %, with Mayet still 9 to 13 % and in the Pyrénées 0.5 to 1 % or 2 to 6 %. In individual places the figure can naturally be somewhat higher. For example, in 1873 the endemic amounted to 13.37 % in Savoy and had given evidence of an increase ever since 1816, which developed to the double and fell off in the years 1887/1896 to the one fifth.

In the Maurienne the more slight spontaneous diminution of cretinism gave the most distinct expression, and it had gone down quite considerably in the course of 20 years from the research work in 1847 through Billiet to 1867, and similar conditions prevailed in the Tarantaise. The slight endemic, which is strongly marked there similar to what we find in the Swiss Jura regions, only rarely exceeds 5 %, which appear regularly in Lons le Saumier, Arbois, Poligny and Salins at quite circumscribed places.

There endemics likewise show fluctuating figures in the rise up to 10 %, which can be followed by a decline down to a very low percentage figure. But, however, they showed an increase again towards the end of the last century.

The endemic, which extends from the Rhine valley over to Strassburg, seems to show anew an increase there according to Rhein.

The endemic in the Pyrenees shows throughout a considerable falling off, which has remained constant and has not been crossed by any setbacks.

Summarizingly we can say for France that in general the endemic was never such a great one as in other goitrous countries and never attained such a great distribution among the population as

in those countries, but it was always behind them and that there has rather been a less important decline and only very individually can we speak of an increase in Alsace.

From these extraordinarily sharply defined goiter centers, which are preponderatingly combined with cretinism, those centers in Europe must be kept distinct, which take on another character. These are the so-called goiter centers of England, Holland and Scandinavia, with which we must also count the North German, that lies north of the line of the Main and probably also the Silesian-Saxon center.

The Dutch goiter exhibits preponderatingly diffuse varieties and inclines strongly towards Basedowification and can affect in individual districts and places, as Utrecht, Breda etc., as many as 60 to 70 % of the school children. The number of goiters in the recruits can reach 10 %, even if that happens only rarely.

The endemic, which began to break out at the beginning of this century, broke out most strongly in the Province of Gelderland and in the City of Utrecht, whereas the Province of Utrecht is less afflicted. South Holland is likewise slightly afflicted, Overissel and North Brabant about on an average while North Holland appears to be almost free. The endemic indication of cretinism is undoubtedly not to be found in the Dutch goiter. It further appears also remarkable how places and regions which are in close connection with one another behave very, very differently. For this reason it can not be styled an endemic.

In England we come across very interesting conditions. Campell found the highest figures for South-Western England, then up the Severn valley towards Hereford, Worcester. Likewise the old goiter center was found in Central England, from Oxford to Derby. In these regions the figure varies from 8,5 to 12,5%. Northumberland and South-East England are hit the least. These figures pertain to the school goiter and must be considered as being very low. With the recruits the number of goiterous is only 8 in a thousand!

It happens, that England is very strongly afflicted with Basedow goiters, which are to be found in the western part of the country. A sharp division can not be made here. According to their nature the colloid goiters are prominently in the foreground and adenomas appear but very little.

At any rate the endemic is qualitatively (cretinism being unknown) and quantitatively so weak that the English endemic, just

as the Dutch, can not be brought into any relation with any of the remaining endemic centers on the continent. Some rather small variations likewise appear to have taken place.

In Sweden, as in England, there were little goiter centers reported in Dalecarlien (Hallien, Rosander), which among the recruits could rise up to 19 %. The outbreak of an endemic and its decline were described by Hesselgren.

Johannesen established the fact of a correct goiter endemic in Totenswiken, Dedechen, in Modum. In the last-named some individual cretines were found.

For Russia and especially in the Ural, in the region of Perm, then down towards Asia, in Irkutsk, in the valley of the Lena, in the Baickal region and at the Ladoga Lake goiter centers have been mentioned. Further investigations could be wished for in these regions, because we are now very distinctly gaining the impression of a positive endemic.

Some other individual goiter centers were reported from Asia and Africa. From Sumatra Pfister speaks of a distribution of goiter, even if it is a slight one, which certainly attached exclusively a very distinct tribe. In China individual centers have been observed in the mountain ranges, in Eastern Thibet, in North China, also along the slopes of the Himalaya, in Cashmere, Thibet, Ladak and Panjab, in the high plateau of Bengal, Nepal, Madras and Bombay.

With the exception of the data on the distribution in Gilgit and Chitral by MacCarrison no other accurate and particularly numerical data are known, as also such on cretinism. Individual centers are to be found in Asia Minor and recently also in Palestine.

The conditions are quite the same for Africa, where endemic centers have been described as occurring in Sierra Leone. Rather accurate data were gathered by Répin for the Riff territory, Algeria and Morocco. Individual centers are likely to be found in the Southern regions, in Senegambia, in the Upper Niger regions.

Of special interest are the goiter endemics in North America, which did not break out until during the past century, and likewise those of Australia and New Zealand.

Here we must first of all consider the question, whether the American goiter is, on the whole, to be considered identical with the endemic goiter, which we have described for the goiter centers of the Old World. Through the intensive mixing of the most different races and peoples in America a kind of product has arisen, which from a constitutional point of view can certainly not be com-

pared with the European conditions. Moreover, for the whole of America cretinism has nowhere been described.

Nevertheless the American statistics have been very succinctly compiled for entire states and unfortunately do not go into any detailed studies, so that all conclusions must be drawn here cautiously. It is a matter of certainty that the aborigines of America, the Indians, had already been suffering from goiter, so that we can accordingly reckon with local-endemic influences. Besides, the figures are so extraorginarily low, which were collected in the recruiting statistics during the war-time, that it is hardly possible to speak of any epidemic.

The North-Western states Idaho, Oregon, Washington and Montana rank as the highest with something more than 2 %, thus attesting to the fact that here also the specially mountainous parts of the country are hit the most severely. Utah and Wyoming follow closely after with 1.5 %.

These figures are very low and correspond accordingly to the figures, which we find in Holland and in the least affected parts of England. We can hardly speak here any more of a true endemic.

Close to these there seems to be a goiter center at the North-eastern lakes, in Wisconsin and Michigan, as also North Dakota and Minnesota, which has not yet been expressed in figures.

Whatever states follow these show only a state of affliction of ½ %, so that the question must probably be raised, whether it is not possible that there are here only sporadic influences.

If there were found only 11,971 simple goiters which is in round numbers 0.5 %, among 2,500,000 recruits, who were examined, then the supposition is probably in order as to whether it is not simply a question of a purely sporadic outbreak whereby it must certainly be admitted that here and there separate rather strong or strongly afflicted centers may occur, especially in the State of Washington.

At any rate this American goiter can not be compared in a quantitative sense with our endemic European one.

To these simple goiters there are to be added 8,647 thyrotoxic ones, i. e. a ratio of 3 simple to 2 thyrotoxic. Through this relation it is shown that also in a qualitative sense the American goiter is not to be placed upon the same basis with the European endemic goiter. From this fact the consequences of an aetiological and prophylactic nature follow from themselves when making comparative studies.

The data on goiter in the South American states are so defective and in part not up to date, that it is useless to refer to them.

The « Chagas' disease », the triatoma infestans, a purely tropical infectious disease, can scarcely be any longer placed in the same parallel with endemic goiter.

New Zealand was spoken of by English authors in 1810/84 as being free from goiter. According to a quite recent statistical research, made only among school-children, there were 61 % of enlarged thyroid glands discovered, of which ½ (29 %) were in an incipient stage, ⅓ (26 %) small, 5 % of medium size and 1 % were designated as large, but here, to be sure, a definite localizing could only partly be established, in such places where there could be no mistake as to a relation existing to the soil with its geological formations.

It seems to be in order to make here a few comments regarding the school goiter.

The school-goiter can only very conditionally be laid claim to as a criterion for the extension and the intensity of the strongly marked goiter endemic. There can be no doubt that the swelling of the school-child's thyroid gland, which in part appears perhaps mainly in the age of puberty, experiences spontaneously a distinct retrogressive metamorphosis and that the investigations, made among recruits, give a far better aspect of the intensity of the endemic of a certain region than the investigations, made among school-children. This is also a matter to which altogether too little attention is given in the judging of the therapeutic successes.

In New Zealand it is seen, that goiter among recruits occurs only one twentieth as frequently as that seen from the school-children's examinations. The State of New York showed 0.1 % recruit-goiters and 20 % scholar's goiters. In Holland the school-children's goiter showed likewise from 6 to 10 times higher figures than the goiter of recruits. In England the recruit-goiter is also from $^1/_{20}$ to $^1/_{30}$ as frequent as the scholar's goiter. In Styria the relations between the recruit-goiter and the scholar's goiter are as 1 : 2 to 5, i. e. somewhat less distinctly pronounced. The relation in Bavaria is similar to this. For the Taunus goiter the ratio is as 1 : 5 to 10. In the Valtellina we find again a relation of only 1 recruit-goiter to 2 to 5 scholar's goiters.

In Switzerland we see in the Canton of St. Gall a ratio of 1 : 3 to 6, for the Bernese Jura regions according to the figures of Jomini a ratio of 1 : 5 to 10 and in part also higher figures. Similar data can be learned from the school-goiter statistics of Kocher.

It accordingly follows as a fact purely conformable to law, that the school-children's goiter can come without any external influence whatsoever to a decline of 90 to 95 % of its number and that in this case we are probably justified in speaking of a known physiological swelling of the thyroid gland. It is certainly seen that in endemically infected countries this ratio rate is considerably lower than in the other goitrous countries.

But this periodical fluctuation must be observed more than has thus far been the case. An essential fact here is that in regions in which the adults are almost free from goiter, as in the Bernese Jura, in the Taunus and in New Zealand, this swelling in the young people also occurs. With this we must probably also count the Baltic Sea goiter and that of Danzig and the one of Brandenburg.

If we cast a glance over my declarations we find that the quantitative force of the goiter endemic of a periodical as well as a local nature is subjected to strongly marked variations.

This is nothing new in the history of epidemiology, if we think of typhus, cholera, influenza, luës etc.; it also occurs with more constitutional diseases as chlorose and anaemia, a fact which has recently been once more declared.

It also shows locally far-reaching differences. Endemic and again endemic are not the same. We can not even say with a feeling of certainty where the endemic begins and where it ends. It simply shows, that certain regions have been shown the preference by the disease and others have been spared, which is a remarkable fact, and it actually seems to be bound to certain orographic, geological peculiarities. Only within the afflicted region can migratory movements take place. How are these conditions to be declared? We may safely say to this, that none of the attempts, made at the present day to explain this, are completely satisfactory. We are here certainly standing before a very complicated biological process, in which there are still unknown factors playing their respective rôles.

We must not forget that according to the present state of our knowledge of the physiology of the thyroid gland this reacts remarkably easily and rapidly on all possible exogenous and endogenous stimulations in the sense of a strumous change of the parenchyma as of the colloid, so that the most varied factors can produce the aspect of symptoms of thyroid enlargement. Which that one can be, that produces the endemic goiter and the endemic

degeneration, is completely unknown in the present state of our knowledge. Nevertheless it is proper that we search after methods for the clearing up of this matter. We are far from maintaining in its exclusiveness the hydro-telluric theory which was proposed by my late father. As a working hypothesis it has done its duty, as other explanations have done, but in its combinations it can least of all be maintained.

On the other hand, however, it can be said with certainty — irrespective as to what causes of goiter we impute to an exogenous, not endogenous character — that probably in a great many cases the water can be the bearer of the cause of the goiter and that it must be so, even if we are obliged to admit that this is not true for every case. On the other hand it can not be denied that goiter prefers as an under-basis definite geological formations.

This fact appears very obvious to us in the Jura formations.

For the French Jura, for the Swiss Jura and for the Suabian Jura there is in part a perfect and in part a very great immunity against goiter. This can also be laid down as a fact for the Cretaceous and Carboniferous formations.

In contrast with this we find the most pronounced territories to be those of the Triassic shelly limestone and the new red sandstone, which are preponderatingly afflicted; then also the Tertiary formations, where, to be sure, a sharp definition between marine and sweet water formations can not be maintained.

In another form, America, England and the Scandinavian states show themselves affected in the Silurian formation, but here the qualitative and quantitative intensity is much less than in above-mentioned regions. The condensated surface is almost not affected or only very slightly, while the eruptive rocks behave according to the character of their origin.

As a remarkable fact in the distribution, it is seen that the severest endemics are nevertheless bound to the tectonically complicated mountain range districts and there show forth local regional and periodical varieties. A very variable factor must accordingly play a rôle here. All attempts to interpret this rôle have always remained deficient. This fact must be admitted.

For these reasons, to search after the unknown in the genesis of the entire goiter problem, the thesis, which was first propounded by Répin, namely « The Relationship of Goiter with radio-active Radiance », will again surely gain very much in importance. The factors, which bear on the significancy of radio-active radiancy,

have lately been compiled in a comprehensive manner by Pfaundler.

Recently similar thoughts have been expressed as to the question of cancer by Hedwig Th. Wenger and Willibald Melzer and they also called attention to the significancy of geographical radiation effects.

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Conclusions:

1. Endemic goiter is part of a complex pathological manifestation characterized by a distinct geographical distribution.
2. In the countries where it prevails it can present temporary variations of different intensity in the sense of increase or diminution.
3. In the countries where endemic goiter prevails the goiter can vary in its character.
4. Endemic goiter of different countries cannot be compared one with the other, the difference being both quantitative and qualitative. The histological structure is also of pronounced variety.
5. The aetiological factor of goiter and the conditions which favor its prevalence are of a varied nature. One cannot admit a uniform aetiological factor.

Bacteriological and Parasitological Researches upon the Aetiology of Endemic Goiter and Experimental Results.

Preliminary Communication by Dr. André Crotti,
Chief of Staff of White Cross Hospital, Columbus, Ohio, U. S. A.

Gentlemen!

Inasmuch as the time, which has been allowed me for my discussion, is very limited, I shall confine myself to discuss with you the arguments, for which I have at all times stood, and of the truth of which I am still convinced, namely that the cause of endemic goiter is one of infectious origin, truly even parasitical. The arguments, which were advanced to-day in the report of my illustrious professor and teacher, Mr. Galli-Valerio, seem to me very persuasive ones. I accordingly shall not repeat them here. I shall, however, add one more argument.

If it is true that goiter is due to an effort on the part of the thyroid gland, tending to augment its secreting and absorbing surface (from that cause comes its increase of volume), in such manner as to obtain the quantity of iodine necessary for its physiological metabolism, a quantity which is insufficient in the case that is occupying our attention, if we take into consideration the poorness of the iodine contents of the circumambient media, then in this particular case the thousands of goitrous patients operated upon every year for goiters of every description ought all to have the goiters re-appear without exception, since the secreting surface is suddenly reduced through the surgical operation to a small minimum of glandular tissue. We ought in such case to observe an acute insufficiency of iodine, which ought to show itself again suddenly through a return of the thyrodean hyperplasy greater than ever, which is not at all the case, at least in the very great majority of cases. And moreover the environments, in which these goitrously afflicted continue to live, are the same!

It is not true. This is just the point: The hyperplasia is due to + factors which the iodine counteracts, or rather iodine causes the gland to atrophy normally in the presence of certain + factors known to me, proves the gland is functionally efficient. His argument is sound.

My researches, which were commenced in 1910, have extended over several thousands of specimens removed by me in the operation hall and were transported with every aseptic precaution to my laboratory. The investigation of the fresh material was made in the dark chamber. Magnification was 1000 times.

Before beginning the study of these results, I desire to thank publicly Mrs. F. W. Whitmann, my laboratory assistant, who has been working with me for five years and whose perseverance, enthusiasm and intelligence have greatly facilitated the work for me.

I shall discuss with you the results, which have been derived from the study:

1. of fresh material;
2. of waters originating in endemic centers;
3. experimental studies.

In the fresh material we find:

1. a gregarine,
2. a spirille,
3. a flagellated infusorian,
4. a fungus.

Gregarine. What at first strikes our attention is the presence of a very little body, round or oval, surrounded by a halo of light, and which is moving about with great rapidity, a little in every direction. It has a brownish yellow color; sometimes it is

bluish white. It measures scarcely one micron (= 0.001 millimeter). Its constitution is one of a brilliant though opaque mass. It does not contain any nucleous.

If we continue to observe, we see that this little body is subjected to transformations. Its volume becomes greater and it becomes surrounded with a cytoplasmic membrane and, for the first time we are aware that this halo of light was only some entirely transparent cytoplasm. This cytoplasm can be very uniform or very granular. The little body can be in toto of a dull golden yellow coloration or a bluish white one. This coloration remains firm throughout the entire cycle of development.

These little cellular bodies are gametes or sexual elements, as we can see from the following description.

The development follows along two lines: either the asexual or schyzogony type, the reproduction by fission, or the sexual or sporogonous type.

Asexual type. If we observe one of these gametes without interruption for some time, we notice that it is very soon taking on the shape of a typical ovum. The enveloping membrane is decidedly granular, the cytoplasm more or less granular, the nucleus very refringent. This ovum is still very mobile and nevertheless we do not see any means of locomotion as flagella etc.

Little by little this ovum takes on very intense transformations. The form at first becomes larger and longer. The cytoplasm has become more and more finely granular. Between the cytoplasm and the cytoplasmic membrane there appears a transparent space which grows greater and very soon becomes itself divided in two by a fine granular strip of the same nature as the rest of the cytoplasm. The consequence is that we shall then have to do with two transparent spaces, the one internal and the other external. The nucleus has undergone a very fine subdivision and is no longer visible.

Later the whole is considerably stretched out; the anterior part has become widened and the posterior part thinned and raveled out. The granular membrane is accentuated, the transparent internal space has become pressed down and shortened and the transparent external space on the contrary has become considerably enlarged. At the posterior end, for the first time, there appears a small duct or micropyle, answering probably for the sexual needs.

Finally we find ourselves before an adult parasite, which has the form of a Greek vase, somewhat lengthened out and slender,

and measuring scarcely 10 microns. The anterior part has become fashioned into a kind of rostrum which could be called the epimerite; the posterior part, which constitutes the largest part of the parasite, has become the deutomerite. Apparently there is no protomerite existing just as in the Doliocystides. The transparent internal space has disappeared and the granular membrane, which has become a membrane with very small nuclei, is the limiting membrane. The transparent external space is eliminated as a residual body. The micropyle continues to exist. The cytoplasma contains the merozoïtes, which we can detect in transit either in the micropyle or at the anterior part in a very small duct situated between the epimerite and the deutomerite. Once free, these merozoïtes recommence again the asexual reproduction and so it continues.

Sexual Reproduction. Two merozoïtes become fused in accordance with the isogamic type. Which of the two merozoïtes becomes the microgametocyte and which the macrogametocyte? It is impossible to say.

Very soon the nucleus is divided into two parts, and the two nuclei thus formed are in their turn subdivided into two; the cytoplasm does the same, so that we find ourselves before four well-defined segments or sporoplasts, each of which has its own membrane but the four are surrounded by a common membrane. A transversal division is soon formed, which separates the sporoblasts into units of two, which are surrounded by a common membrane. Each of these sporoblasts is in its turn subdivided in order to form four distinct elements but all enclosed by a common membrane. The cytoplasm of each sporoblast is granular and contains a nucleus. The whole constitutes a unit which we shall call tetrasporocyst.

Little by little the tetrasporocyst becomes greater in length and in width. A transparent space appears between the common member of the tetrasporocyst and the individual membrane of each sporocyte and later this transparent space becomes longer and grows greater at the posterior part of the tetrasporocyst, thus giving to the entire ensemble the elongated form of a tennis racket. This transparent space, which contains evidently the nutritive elements, will be later eliminated under the form of residual body.

The sporocytes, which at the very beginning betray themselves only by some segmentations of the tetrasporocyte that are frequently hardly visible, become more and more distinct and assume

the shape of a polygon of from five to six sides. At the center of each sporocyte there appears a small vacuum connected with the exterior by a small duct, in which we find in transit the same small elements, brilliant and movable, as we have seen at the beginning. These are the sporozoïtes.

If this tètrasporocyte disintegrates prematurely, it can frequently happen that we find these isolated polygons in the field of view of the microscope. They very probably correspond to the « polygonal form » discovered by Merk but the true significance of which had escaped him. As for myself, they constitute sporocytes tending towards disintegration without any ultimate function.

At the posterior part of the tètrasporocyst we find sometimes a very oblong capsule containing four small nuclei situated regularly in a straight line. Do we have here some sporozoïtes still enclosed within their residual body or is this already a process of reproduction? I am unable to say.

The tètrasporocyst continues its development and from this moment the processes are almost the same as those, which we have studied in the type of asexual reproduction and of which the ultimate result is the adult parasite described in the foregoing pages.

This parasite is filtrable, offers strong resistance to acids, to alkalis, to cold and to heat. The Giemsa method gives some very good results from the coloration point of view. The best culture medium has been that composed of sterile bile and glycerine. Sometimes it has been possible to see the parasite in the cuts of the goiter fixed by the formaline and stained with hematoxyline-eosine.

Certain characteristics, and above all the fact that reproduction takes place through schyzogony and sporogony, could make us believe that this parasite belongs to the class of Coccidies. But on the other hand, if we consider its form, the presence of an epimerite and of a deutomerite, the elasticity of its enveloping membrane, its amiboïdal movements and above all the fact that the sporogony takes place according to the isogonic type, we hold to the idea that we have before us a gregarine, which probably belongs to the order of the Eugregarinidies. The gregarine, which most resembles the parasite before us is the Gregarina Blattarum.

2. Spirille. We find, more or less constantly associated with the gregarine, a spirochete, which, considering its morphology,

would seem to belong to the genus spirille. It was in the year 1910 that I observed it for the first time.

Its axis is straight and rather rigid; its enveloping membrane is thick and very refringent; the cytoplasm is thick, uniform and also very refringent. Not any granulations, not any nuclei, no divisions or segmentations, not any axial filament, no nodulatory membrane, no flagella.

These spirilles vary in length from 4 to 10 microns. The very smallest forms are found in cultures. Their spirals vary in number but are perfectly regular. Their extremities end in points, which are so fine, that it is often a difficult matter to observe them.

The greater part of the time these spirilles do not have any motion, that is peculiar to them; by way of compensation for this we can without any doubt see that they are moving, although in a slow manner; they then move along by turning upon their longitudinal axis. Thyroxine accelerates to a considerable extent their motions.

Differing in this fact from the greater number of spirochetes, which reproduce by means of transverse division, this spirille in reproducing itself follows the type of longitudinal division. It seems that there can be no doubt that it increases in number in certain centers of culture, as, for example, the broth formed of blood serum and bile.

This spirille, as the gregarine already described, offers very great resistance against cold, heat, the acids etc. Besides it can be filtered.

In some cases, the spirille could be observed with the microscope, as if it was in the interior of the gregarine. Did we have an accidental superposition or a true symbiosis? I can not say.

This spirille has nothing in common with the treponema pallidum nor with the treponema anserinum.

In May, 1926, Noguchi published the description of a spirille, which bears great resemblance to the one described above. He did not look upon it as a living organism, but rather as a flagellum that had belonged to certain microbes and become artificially detached through the cultural conditions.

In my researches this spirille is found first in the fresh material and secondarily in cultures. On the other hand, as was stated above, it seems that there can be no doubt that it increases in number, a fact that could not be the case if it was nothing else than an inert flagellum.

3. Flagellated Infusoria. Besides the gregarine and of the spirille we find a flagellé, which measures in its adult phase from 5 to 7 microns. In general it has an appearance more or less curved; its anterior extremity is obtuse, its posterior extremity is pointed and ends in a long flagellum. The cytoplasm is rather clear and homogenous and is surrounded by an enveloping membrane or well defined periplast. At the anterior extremity of this cytoplasm, there are two little nuclei of chromatine; towards the center there is a small vacuum. Towards the posterior part of the cytoplasm, there is a very small nucleus of chromatine, which represents the kinetoplast. The two constituent parts of this kinetoplast, that is to say, the parabasal and the blepharoplast are not always readily seen. There is not any doubt that we may have here to do with a kinetoplast, inasmuch as the axoneme takes its point of origin in the kinetoplast itself, passes into the convex part of the cytoplasm and turns back towards the posterior part of the organism, ending in the flagellum.

The flagellum is almost two thirds as long as the flagellé or flagellated infusorian; it is small, very active and often in a spiral form; it does not possess any axial filament.

The presence of an undulatory membrane, although probable, could not be established with any degree of certainty.

The motility of this flagellé is very strongly marked.

Method of reproduction. This flagellé is reproduced in two ways:

1. by schyzogony,
2. by longitudinal fission.

Schyzogony. A flagellé approaches a red blood corpuscle or a leucocyte almost at a right angle to the flagellary point, then little by little the entire flagellé becomes inclined towards the cellular body up to the point where the two elements happen to be in close contact throughout the entire length of the flagellé. Then a fusion takes place between the two and the flagellé penetrates and disappears in the body of its host. The protoplasm of the host becomes very granular, and finally there is developed within it a multitude of little flagellés, very active and more or less disposed concentrically, in the form of a rosette, attached by their flagellary points to the central trophic mass, which will become the residual mass after the liberation of the flagellés. Finally the rosette becomes subjected to a process of disintegration, the flagellés are liberated and each one of them is developed into an adult flagellé.

Longitudinal division. The cytoplasm of a full-grown flagellated infusorian becomes opaque, the two anterior nuclei separate and we see a longitudinal division which divides the entire body of the cytoplasm into two parts, so that we obtain two distinct elements, one of which retains the flagellum which does not split apart and the other is without any flagellum. Soon after this the flagellum falls away of its own accord and becomes an inert body, which we can often see floating aimlessly in the microscopic field.

After this has taken place, we consequently obtain two elements that are becoming ever more and more spherical, each containing a nucleus and a kinetoplast, which likewise becomes divided in two at the time of the longitudinal division. These two elements correspond to what is called the « elements of Leishman ».

These elements subdivide into two and embrace the nucleus and the kinetoplast, and the products of this division are destined to become full-grown flagellated infusoria. In fact, from the spherical form, which they had, they become elongated, one side becomes pointed, then a flagellum makes its appearance and finally the full-grown flagellated infusorian is formed.

Fungus. A fourth element presents itself in a more or less constant way in our microscopic studies. It is a fungus.

We first find a rounded or oval cell having a thick enveloping membrane which is very strongly granular, the opaque protoplasm of which contains a great quantity of granulations. For the most part there is no true nucleus to be seen. This cellule measures about 4 to 5 microns; it is destitute of motility and the only movements that can be discovered are of an amiboïdal character.

If we watch this cellule under the microscope for several hours, we see that at a certain spot of this cellule there is produced a small swelling in the enveloping membrane, an enlargement, which proliferates rapidly in length and soon takes on considerable dimensions. Very often this proliferation is dichotomised into branches of first and even of second order. The enveloping membrane and the protoplasm of all these dichotomies preserve the same characters as those observed in the primordial cellule.

Later, the interior of these dichotomies, as well as that of the primary branch, become differentiated and, strange thing that it is, we find ourselves in the presence of a tetrasporocyst, very similar to that described already about the gregarine, so closely that we may ask if this fungus can not be, by chance, the intermediate host of this gregarine.

The study of this fungus has not been pursued sufficiently far to enable us to classify it.

Results of treatment with iodine. In a goiter that has not been treated with iodine, it is generally easy to show the presence of the four micro-organisms. On the other hand, the more the treatment has been prolonged and the more intense, the greater is the difficulty of recognizing them. Moreover, through the iodine treatment, the cholesterases diminish considerably.

Examination of goitrigenous waters. It is well understood that it would be puerile to draw the conclusion that, because there is in endemic goiter a gregarine, a spirille, a flagellated infusorian and a fungus, therefore these elements must be regarded as being the cause of goiter. This method would be too simple.

At that time I reflected that, if it is true that the infection, which causes goiter, is caused by drinking waters, I ought without any doubt to be able to meet with these same micro-organisms in the goitrigenous waters. I then applied myself to a systematic study of waters that originated in certain endemic centers in the United States. The same methods of study that were employed for goiter were applied to this study of the goitrigenous waters, that is to say, the direct study in the dark room, cultures, colorations.

The results obtained were remarkable. As the numerous photographic negatives prove, there is not the shadow of a doubt that these goitrigenous waters contain the same micro-organisms as those which are found in goiter, i. e. the gregarine, the spirille, the flagellated infusorian and the fungus, possessing all the same characteristics as those described for goiter.

Does this happen to be a simple coincidence or rather is it really a relation of cause and effect?

Experimental Studies. If it is truly a case of the relation of cause and effect it ought to be more than probable for us to reproduce goiter experimentally among the animals.

I have made efforts to do this as the table here shown makes evident.

Alimentation Spirille			Inj. Carotide Spirille			Inj. intravenous Gregarine			Inj. intramuscular Gregarine		
No.	*Neg.*	*Posit.*	*No.*	*Neg.*	*Posit.*	*No.*	*Neg.*	*Posit.*	*No.*	*Neg.*	*Posit.*
4	4		2	2		2		2	6	1	5

Total No. of dogs = 14 négative = 7
positive = 7

50 % positives.

1. The animals employed were dogs.

2. The cultures employed were not pure. It was thus far impossible to obtain absolutely pure cultures. They all contain some of the described elements.

3. In the positive cases, the goiter became very appreciable after 60 to 90 days.

After six months or a year it had entirely disappeared and the animals had still remained negative after 4 years.

This causes us involuntarily to think of the summer goiter of strangers.

* * *

General Conclusions.

1. The total absence of iodine as an aetiological factor of goiter is a fact which is far from being proved.

2. There is in endemic goiter, above all in the nodular and cystic varieties, a gregarine, a spirille, a flagellated infusorian and a fungus, which we find appearing in an almost constant manner.

3. These same micro-organisms are recognizable in the goitrigenous waters.

4. With these same elements we are able to produce goiter experimentally in dogs. In our series of 14 dogs the positive results numbered 50 %.

5. I am willing to recognize the fact that the number of experiments made is still too small for enabling us to draw any final conclusions.

6. The inter-relations of these micro-organisms has not been established in a definitive manner. Do we have here independent organisms or rather do they exist in symbiosis or are perhaps some of them different conditions belonging to the same cycle of life; all of these questions have not been solved in a definite way. What seems probable is that the fungus is the intermediary host of the gregarine and perhaps the gregarine that of the spirille.

7. According to the experimental results, it would seem that the gregarine plays a rôle in the production of goiter.

8. The treatment with iodine in a very manifest manner diminishes or even almost completely destroys the flora of goiter. This fact obliges us to reflect when we discuss the relation of iodine in respect to goiter. In fact, instead of having the absence of iodine as the cause of goiter, it becomes very probable that goiter could truly be of microbian or parasitic origin. The iodine

would in such case act as a bactericide. This conclusion would then be in complete harmony with the extremely interesting experiments of Gaylord of Baltimore.

9. These results, which are still very incomplete, are here modestly submitted in the hope that some more authoritative researches than my own would serve to prove their worth or their worthlessness.

Discussion on the Report of Dr. McCarrison

By Dr. Höpfner, Kassel.

In dealing with the physiology and morphology of the healthy thyroid gland we are concerned with a straightforward question. Basedow's disease is a complex condition in which excessive glandular function takes part. It is the same in goiter. The pathology and pathological physiology of the diseased thyroid have to do with a complex in which dynamico-chemical and morphological plastic elements have a share. At the time when we recognize a maximum correlation between the endocrine glands and the diseased thyroid on the one hand, and between the overacting central metabolic processes of the midbrain and their influence on the concord of nutrition and growth on the other (F. Kraus, Nobel and Rosenblueht, Biedl, Bircher jr., Siemens, Zondek and Schiff, Politzer and Stolz, Werner Schulze, Grafe, Breitner, Tschamler, Oswald, and others), there appear definite limits between the normal and the pathological, between the type and its variations of psycho-physical individuality, as of the thyroid.

The work of Werner Schulze shows, and the fact is established, that in development the relations between the structures of the middle and external germinal layers are dependent upon endocrine action and in particular that of the thyroid, whereby, especially in disturbances of orderly development, the endocrine effects on uniformity of growth, chiefly those of thyroid upset, are perceptible. In analogous anatomical points, especially the capillaries of the nail-grooves, we may recognize definite developmental disturbances which ordinarily are associated with changes of psycho-physical individuality. These concern at one time rather the coarse somatic or

reactional structure (even intestinal), at another more the intellect and the foundations of the psychical or nervous modes of response, and from general experience are found most often and most marked in immediate relationship to, and sphere of action of, the grossly damaged thyroid, as in cretins, chondrodystrophies, myxoedema, and most of all in certain forms of infantilism. From this, if we are to get a proper grasp of the problem, must be excluded from the start the wider hereditary defects frequently met with in practice and a source of another varying element which needs to be taken into consideration more in sporadic cases.

The main significance of the midbrain (basal ganglia, substantia nigra, restiform bodies) in opposition or relation to the endocrine system is that it necessitates attentive research into those variants of metabolism, of harmonious growth, of the intellect and psycho-nervous reactions which meet us as facts to be grasped scientifically. (Demonstr.) Of these the best known are the relationships of basal metabolism, the specific effect of protein, the intelligence, mental and physical proportions (Gesell, Dearburn), and the stigmata of the vegetative nervous system (v. Bergmann). As a recent development we must add systematic study of the capillaries of the nail-grooves and intellectual changes which accompany them, together with psycho-nervous reactions, particularly in adolescents.

The question is intimately bound up with the fact that the capillaries of nail-fold in the human subject pass through a definite course of development, which under normal conditions of endocrine influence in « non-goitrous » districts is complete by about the sixth month of life, somewhat the same period in which the boundaries and differentiation of the layers of the cerebral cortex develop, and also the agreement between the somatic and reactive foundation of the body and its metabolic activities, and in which the intellectual groundwork arrives at a definite stage of maturity. I have tested in over 6000 cases, mostly adolescents, the results worked out by Walter Jaensch and Wittneben, and can confirm their findings in all points.

It has been submitted that there are cases of weakness of mind and forms of neurosis allied to cretinism which are characterized by an arrest of the growth of the capillaries at a very low stage as defects related to hypothyroidism. The proof of the correctness of this idea rests in the great significance of the midbrain centers for harmonious growth, corporal morphology, and metabolism, supported further from the therapeutic aspect in the maturation both of reactions and capillary growth effected by glandular

therapy and the administration of iodine; in addition, recently we have seen that many feeble-minded and neurotic cases allied to cretinism are largely amenable to this therapeutic influence, recognizable exclusively in the disturbance of capillary development and as standing in the closest relationship to cretinism.

By means of the capillariscope a new group of endemic thyreogenic disturbances has been discovered by Walter Jaensch, which are to be regarded as equivalents of these. In the literature numerous accounts may be found of cases presenting these trains of symptoms, in which agreement regarding the goiter-theories was impossible from the clinical aspect, and amongst them are known to be many Swiss authors who had been struck by the existence of the relations between endemic thyroid affections and just such bodily and mental defects. In this connection it may again be emphasized that true deaf-mutism, a condition not to be confused with cretinoid or other defects of speech-development, possesses no correlation whatever aetiologically or epidemiologically with cretinism; so far as my researches go these cases present no deep capillary arrest.

The capillary formations urge the acceptance of comprehensive and unescapable conclusions as to thyreogenic action and that of pluriglandular differentiation. The period of development comprises that from the beginning of thyroid function in foetal life up to about the third year (varying in different regions and from hereditary causes). — The regular co-existence of capillary arrest, as the productive stunt-forms, with corresponding defects of intelligence, bodily development, and altered modes of reaction of functional or nervous type, can be confirmed as W. Jaensch and Wittneben have asserted. The endemic presence is a fact for a German «goitrous districts» and equal to a strong equivalent of the more restricted «thyroid disturbances», it constitutes the bio-morphological aspect of the «goiter-problem», the goiter alone is only one expression of the group. — There is no single «goiter-producing agent» responsible in every instance. Much more is it a case of variety of reactions, of midbrain or thyroid origin, recognizable with fair certainty by the capillary structure, together with regional and geological variations of iodine-supply, individual associations whose peculiarity can be determined only by intensive clinical research; for this purpose mere measurement of the size of the thyroid gland is inadequate and unsuitable. It depends upon the special peculiarity of readiness of reactive response and the balance of endocrines. — All those with

goitrous «analogues» are cases for treating with large doses of iodine or with gland-preparations; the prescribing of prophylactic doses of iodine in such is futile and inadvisable; to aim at merely reducing the size of the thyroid strikes neither at the true foundation nor at the correlated conditions present.

The study of the goitrous equivalents with the capillary changes is intimately connected with clinical investigation and the teachings of heredity.

A clinical schema of this new group of relations assigns to the mere state of the thyroid, especially in adolescence, a subordinate position. (Demonstr.)

What Part does Infection play in the Aetiology of Goiter?

By Dr. Fr. Messerli, Lausanne.

Let me first of all express my highest regards to all those, who have addressed us, and in particular those who have treated in such a masterly manner the question of the Aetiology and Epidemiology of endemic goiter, which is still such a complicated one, because it has not as yet been solved.

May I also be permitted to point out the general perfect accord with the four lecturers, with whose conclusions I am in full agreement, as also with those presented by several other speakers, by Dr. Breitner, Professor Oswald et al., considering that what we call «goiter» is only a symptom or rather a syndrome, which can be provoked by a multiplicity of causes.

One of the most important of these causes is without doubt chronical intestinal infection, due to impure waters and eventually caused by infected foods.

Numerous cases of this infection through impure water have already been reported on during the last few years, and we must here recall to mind that the rôle of water as an agent for the transmission of goiter has been known since ancient times. Some of these cases have been mentioned by the noted speakers, who have addressed us on this subject, namely, Professors Bérard, Galli-Valerio and Dr. Bircher. I do not wish to bring these cases up again, but nevertheless ask you to permit me to mention simply one very typical case only, which I had occasion

to notice in 1916 at Gandria [1]), in the Canton of Ticino, Switzerland. This village, in which the entire population was at that time afflicted with goiter, is encompassed by several villages, namely Bré, Castagnola and Corona, where there is no endemic. Now it is a fact that the inhabitants of the village of Gandria had the same kind of nourishment as those in the other villages; it was only the water of alimentation that was different. It is a fact that the population of Gandria was making use for food purposes of the water of the lake taken at the place, directly at the lake shore, before the village, at the very spot where their garbage, excrements etc. were dumped, whereas the neighboring villages were utilizing spring water or cistern water. It does not at all seem possible to the advocates of the theory of the absence of iodine to appeal to it in this case.

The very same is the case regarding the observations made in different villages of Valais [2]), which are afflicted with goiter in varying degrees, although they are neighboring villages and the inhabitants are being nourished with the same kind of food. The waters used for cooking purposes in these villages, situated as they are at the bottom of the valleys and there where the frequency of goiter is the greatest, are almost always infected, either through the villages that are situated higher up the valley or through the cattle of the pasture lands.

I shall mention likewise the hypertrophy of the thyroid gland, which I provoked experimentally upon myself in 1914 by drinking surface water, that came from an infected region in which the endemic was prevailing. This hypertrophy disappeared when I subjected myself for a period of 15 days to intestinal disinfection with salol, taking a dose of 2 grams per day, without modifying my diet.[3]) The diminution or the augmentation of the quantity of iodine, as we see, did not come into consideration in this case.

The different examinations, which I have had occasion to make under the direction of my esteemed master, Professor B. Galli-Valerio, on the goitrous endemic, which investigations were in general completed with the inspection at the place of origin of the waters and with the analysis of them, have enabled me to verify the fact that the alimentary waters of endemic regions in Switzerland were almost always of surface origin and were always in-

[1]) *Revue suisse de Médecine*, Nos 3 and 4, Vol. XVII.

[2]) *Revue suisse d'Hygiène*, 3rd year, 1923.

[3]) *Revue médicale de la Suisse romande*. December 20, 1915. Vol. XXXV, No. 12 and *Fr. Messerli. Le goitre endémique, Lausanne*. 1916, p. 178.

fected. On the Swiss plateau, in the region of the Broye as one of the places where there prevails a severe endemic, the subterranean layer of water that is used for the alimentation of the villages lies entirely at the surface above an impermeable bed of molasse, which here and there crops out. It is not to be wondered at that this water is strongly infected through the inhabitants, the cattle and the watering of the fields with liquid manure, which I have been frequently able to verify among other places also at Payerne, even as long ago as 1913.[4])

But if the infected water can be a cause of goitrous endemic, or even simply a cause of the aggravation of the goiter, it can not be considered as the only aetiological agent.

A series of observations constrains me to insist on the importance of intestinal stasis in the aetiology of goiter.

In a work published as long ago as 1915,[5]) in which I declared that there exists a « thyroidean constipation », I drew the conclusion:

« Diarrhoea (this had already been ascertained by former investigators; A. Trousseau as long ago as 1862 speaks of it in his noteworthy work on medical clinics)[6]) is generally constant in the course of exophthalmic goiter, a hyperthyroidean affection; it can be provoked through thyroidean medication.

« Constipation is habitual in human myxoedema and operative myxoedema, in cretinism; it is frequent with the goitrously afflicted, as it is a symptom that accompanies hypothyroidism; it is suppressed through the thyroidean treatment. »

I had in fact proved that by interrogating and observing goitrous individuals a person had the opportunity of noticing that it was in general a question of people with slow digestion and that constipation was frequently a regular thing with them. A young man even declared to me that « it seemed as if every time, when there was irregularity in the evacuation of his bowels, his goiter increased in size ».

In proceeding to the recruitment and to the examination at the place, I made the discovery that the individuals who are living in the Jura or at the foot of the Vaud Jura, a region almost free from endemic, showed abdominal peculiarities, which were in general

[4]) Thesis for degree of doctor, Lausanne, 1913. Zentralblatt für Bacteriologie, Originale. First section, Vol. 75, 1914, p. 211, and *Fr. M. Messerli, Le goitre endémique*, Lausanne, 1916, pp. 73 and 102.

[5]) *Revue suisse de Médecine*, December 1921, Vol. XXII.

[6]) Page 612.

clearly different from what characterized those domiciled in the Broye, an endemic region. The people of the Vaud Jura have the stomach flat drawn in, non-ptosic, while the ptosic stomachs, broad and in wallet-form, are much more frequent with the inhabitants of the Broye region.

I have likewise confirmed the fact that the children, who are afflicted with hypertrophy of the thyroid gland, exhibited for the most part a voluminous stomach, broad and wabbly, with a muscular atrophy of the rectus abdominis in the lower part of the abdomen, what I call the « stomach of the goitrous youth », though sometimes it is that of a goitrous candidate, and that very frequently the hypertrophy of the thyroid gland has coincided with a period of retardation of the abdominal functions or more often has followed it.

Like MacCarrison[7]) I have been able to determine the gradual diminution of soft goiters in subjecting goitrous individuals to a gentle and uninterrupted purging through the use of laxative lozenges, made up of Aloes 0.05, Resina Jalapae 0.1, Radix Rhei 0.5, one lozenge each evening, or of aloes pills, taking one in the morning and one in the evening, or of pastilles of magnesium sulphate of 2.0 grs., taken morning and evenings. It is a question of a purely mechanical action and not of a real intestinal disinfection.

These last two years I have also observed very clear diminutions of soft goiters by subjecting some young people to abdominal massage treatment and others to abdominal gymnastic exercises practised daily. I made these observations entirely by chance among young people, who were placed under a treatment of physical exercises.

The observation, cited in his report by Professor B. Galli-Valerio that « in Valteline several young persons, in order to escape military service, had swallowed great quantities of walnut shells, which constipated them and facilitated the development of goiter », appears to me to confirm the fact of influence being exerted by the abdominal condition upon the thyroid gland. It is the same with the observations made by Borel, Boez and Freyss[8]), who have shown the frequency of intestinal worms with the inhabitants of Robertsau, a suburb of Strassburg, in which there is a strong endemic.

Worms

These various observations enable me to insist upon the importance of the intestinal period frequently preceding the hyper-

[7]) *MacCarrison*, « The Etiology of endemic goiter », London, 1913.
[8]) Compt rend. Soc. de Biologie, Vol. 92, 1925, pp. 232 and 234.

trophy of the thyroid gland which, in certain cases, seems to be the secondary result of an intestinal infection, whether it be by contaminated water or by another agent as contaminated food, or whether it also be by auto-infection at the time of intestinal stasis. Does the alimentation act as the cause of this stasis? It can without doubt play a rôle, which would deserve to be laid down with exactness.

Regarding intestinal infection, is that to be considered due to one single specific agent? As Professor B. Galli-Valerio, we prefer to believe that the hypertrophy of the thyroid gland is provoked by a series of germs of intestinal flora. How do they act upon the thyroid gland? Through the poisonous matters, which they produce and the neutralization of which would be the function of the thyroid gland, or, as MacCarrison[9]), Klinger[10]) and several American authors believe, through the absorption of the small quantities of iodine necessary, which these germs would deprive the organism of and would also influence the metabolism of the iodine. Or is it a question, as Harries[11]) believes, of a modification of the intestinal flora, which would interrupt the decomposition of the tryptophane into indol and skatol in the intestine, which could have an action upon the thyroid gland, Kendall[12]) having shown that the thyroxine, the active principle of the thyroidean secretion, is a derivative of the tryptophane containing iodine? Or is it a question of another process?

It is not possible at the present time to take a stand for the one nor for the other of these theories and, moreover, as Professor Galli-Valerio has declared, the intestinal infection is probably not the only infection.

Permit me to sum up this brief outline and to observe by way of conclusion that the hypertrophy of the thyroid gland is a secondary syndrome provoked by a multiplicity of causes and appearing frequently at the same time as some abdominal manifestations, or more exactly shortly after them, among which is constipation, and oftentimes corresponding to a ptosic abdominal condition.

Some other organs seem also to be influenced secondarily through these intestinal disorders, as the thymus gland, according to what we have determined with Coulaud, among rats.[13])

[9]) Med. Journ., London, 1922, p. 188.

[10]) Corresp. Blatt für schweiz. Aerzte, 1919, No. 17; Schweiz. med. Wochenblatt, 1921, No. 1.

[11]) Brit. med. Journ., 1923, March 31st.

[12]) Cited from Coulaud, *Revue d'Hygiène*, 1925, p. 21.

[13]) Annales de l'*Institut Pasteur*, Vol. XL, page 952, November 1926.

For this reason I lay stress upon the frequency of the abdominal symptoms preceding the appearance of the goiter and this confirms the theory of infection and especially the hydro-infectious one, and I suggest to you, when you are called upon to attend goitrously afflicted patients, that you do not observe the hypertrophied syndrome of the thyroid alone but to examine the general condition of the patients and especially their abdominal status, to investigate if there has not been a period of constipation or of abnormal working of the alimentary canal coinciding with the appearance of the goiter or whether it has not preceded it.

Along this line of thought a series of new researches ought to be made, which would be a study of the intestinal working of goitrous patients, the frequency of occurrence of constipation in the regions of endemic goiter and those without an endemic, a comparison of the abdominal status of those afflicted with goiter and those free from goiter of the inhabitants of the regions with endemic and those without endemic. Such researches would perhaps be able to contribute their share towards solving the problem of the aetiology of endemic goiter of which the solution still remains to be found. Regarding this last thought we are without doubt all in agreement.

One of our distinguished colleagues of Constance, whose name has for the moment escaped my memory, claimed here that the determinative cause of goiter was to be sought for in the thyroid gland itself. May I be permitted to declare on this subject that it is oftentimes the case that the determinative cause of a syndrome acts from the distance, and to present on this occasion a plan, explaining and reviewing the evolution of goitrous endemic.

I. The prethyroidean (or preparatory) period: General action of the determinating cause upon the organism (preparation of special terrain) or encroachment of the organism through the determinating cause.

II. Provocation of the hypertrophy of the thyroid gland: The determinating cause produces a modification of the thyroid gland.

III. Action of the modified thyroid gland: The modified thyroid gland acts upon the organism in a way to provoke the hypothyroidism (myxoedema both sporadic and endemic).

IV. Combined action of the determinating cause,

of the modified thyroid gland, of heredity and of close blood relationship; provokes veritable cretinism, goitrous cretins and deaf-mutism.

It is strongly possible that the determinative cause which, in our opinion, is an intestinal infection, acts from the distance upon the thyroid gland, which would have as its function the neutralization of the poisons or the supplying the organism with the quantity of iodine, of which it would be deprived through the intestinal flora, or some other function.

The Present State of the Problem of Endemic Goiter in Spain.

By Prof. G. Marañon, Madrid.

Although Spain is one of the countries of Europe in which endemic goiter is of most frequent occurrence but without attaining any extraordinary degrees of intensity, there has not as yet been any study made of the clinical and pathogenical types considered as a whole. With the exception of the «Manuel de Médecine Interne», the publication of which is under my management in collaboration with Professor T. Hernando, the references pertaining to goiter in Spain, as given in both Spanish and foreign books, are very brief or entirely lacking, and sometimes even erroneous. Bircher's map, concerning the distribution of goiter throughout Europe, which is so often reproduced, does not extend further than the Pyrenees. In MacCarrison's map our country is mentioned, but with evidently incomplete and erroneous statements.

This want of information has induced us to present a brief report upon this problem at this conference as a preliminary account of the labours, which have been effectuated for some few years past by the commission which was appointed by the government in 1921 for the purpose of investigating the question of goiter in Spain, over which I preside with the collaboration of Dr. Goyanes since the year 1921.

a) Frequency of Endemic Goiter in Spain.

It would be inadvisable to express any numerical estimate of the number of cases of endemic goiter in our country and claim that it is exact, considering that the goitrous regions are to be found in the mountain districts, which were remote from every sanitary institution until within the last few years, on which account we

could obtain only incomplete statistics. Both the physicians, who reside in these regions, and we ourselves at the time of our visits, which were made personally in almost all of these districts, had to combat against the opposition made against the investigation on the part of the peasants who almost without exception believed that the morbid condition was normal. For this very reason we can not place any confidence in the articles on the «Medical Geography of the Districts of Spain», which are published every year by the Royal Academy of Medicine. Many of these articles pertain to the Asturias, which constitute one of the regions of Spain where we find the greatest amount of goiter.

The statistics of the most important hospital of Spain, the General Hospital of Madrid, which is frequented by diseased people from every country, are no longer of any great value, for they pertain only to surgical cases. The statistics of our department of internal medicine show the following data:

During the years 1925 and 1926 there were 2 men and 39 women who suffered from endemic goiter from a total of 507 patients of both sexes who presented themselves for the first time for treatment at the polyclinic of internal medicine, that is to say some 8 % of the cases. During the years 1926 and 1927 of 754 patients there were 6 men and 40 women, or 6 % of the cases presented, afflicted with endemic goiter. But it is not possible to give any figures as to the general morbidity of Spain, for a relatively great number of patients, who are suffering from disorders of the glands of internal secretion, prefers to be treated in our hospital department.

However, if we compare all of these cases with those which we have obtained and which other investigators have obtained in the strumose regions of Spain, it may be that we should not be very far from the truth in saying that the number of cases of goiter, cretinism and deaf-mutism in our country fluctuates between 10,000 and 15,000, which is some 0.006 of the entire Spanish population.

b) Distribution of Endemic Goiter.

Not one of the mountainous regions of Spain is free from the strumose scourge. We have visited the region of the Alpujarras, in the Sierra Nevada (province of Grenada), the mountains of Gredos, and practically the entire Pyrenees and we have met, without any exception, cases of goiter among the inhabitants of the high valleys of all of these mountainous regions. Goyanes has particularly

described the endemic goiter and cretinism of the Asturias and of Leon, as also of the high valleys of the Alberche and the Tormes (mountains of Avila). Garcia Guijarro has likewise described an interesting goiter center, which is very isolated and less intense, in the mountains of Alto Maestrazgo, which is in the province of Castellon de la Plane (kingdom of Valence).

Nevertheless there are only two important centers of endemic goiter: that of the Pyrenees and that of the Hurdes. This latter region lies to the north of the province of Caceres at the Portuguese boundary. We gave this district our special attention inasmuch as it constitutes for a great many reasons an incomparable field of study of this problem.

Throughout the entire Spanish Pyrenees, from the Mediterranean to the Atlantic, there are a great many cases of goiter. In the Pyrenees of Catalogne we find high valleys, as e. g. those of Ribas and Camprodon, where an endemic of goiter prevails extensively and likewise considerable cretinism.

In the valleys of the Montseny goiter is very abundant, whereas cretinism is almost entirely unknown there (Dr. Bayés Coch). Marimon observed several cases of deaf-mutes in these regions. In the part of the Pyrenees that lies north of the province of Lerida, Portella described an important center of this endemic.

In the Pyrenees of Navarra and of Guipuzcoa, goiter prevails but it is scattered about and is always found in the high valleys, without however attaining a serious character and with very few cases of cretinoid degeneracy.

In the provinces of Vizcaya and of Santander, which are next reached when going from East to West, goiter becomes more frequent, though the cases are still dispersed, with no great centers and with but few cases of cretinism.

In the Asturias and at Leon, the endemic is much more intense and has been investigated in a very thorough manner by Goyanes and Ceniga. Moreover, of a considerable number of cases scattered throughout the entire region and occurring in the countries of low altitude near the sea, there are true centers with a great many goitrously afflicted persons and with all grades of cretins, who have been thoroughly studied by the authors mentioned above. near Sea

The intensity of the endemic grows less at the terminal part of the Pyrenees in the Galice region in proportion as the population is scattered about in the valleys, which are more open and which terminate in the great bays of the western coast of Spain.

The goiter center of the Hurdes is most important in Spain.

It has been carefully studied several times by Dr. Goyanes, by ourselves and by Doctors Vidal Jordana, Olivera and Pizarro, who compose the medical delegation of the Patronat committee, that was established in 1921 for the investigation and the colonisation of this region under the presidency of the King of Spain and in which we took part until the year 1923. Of the 8000 countrymen, who inhabit this region, we may say that one quarter are afflicted with strumose degeneracy. The Hurdes are made up of three long and narrow valleys, in each of which there is a river, that is generally a torrent. The inhabitants of the region build small villages, some of which are located in the lower part of the valleys and others in the higher part of the mountains in terrains, rugged in an improbable manner, formed exclusively of slate and entirely useless for the life of plants and that of human beings, unless it be merely of a transitory nature. Among the population of the lower villages the proportion of the cases of goiter amounts to nearly 10 % of the inhabitants (districts of Caminomorisco, Casares, Mestas). But in the high regions (Pinofranqueado, Nuñomoral, Riomalo de Arriba) this proportion reaches and sometimes even exceeds 25 % (Dr. Vidal Jordana).

A very high number of the goitrously afflicted are also cretins of different degrees of affliction. The cases of imbecility, of deaf-mutism, of infantilism and of nanism are so numerous that they are equal in number to what has been observed in the regions of the entire world where the scourge of goitrous endemic is more severe. Sometimes, during a period of several years, there was not a single subject to be found in the whole district of the Hurdes able to do military service, either because of the extremely small size or because of frequent cases of serious mental weakness. All this adds a special aspect of a tragic seriousness to the inhabitants of this region and has given rise to numerous legends, which have been exaggerated into fantastic proportions in almost all of the accounts of both ancient and modern travellers and even by a great many of the national writers. *)

c) Clinical and Anatomo-Pathological Characteristics of Goiter in Spain.

From the clinical point of view, our endemic is referred to in all of the standard descriptions. There is no doubt that it is much

*) See the detailed report on the distribution of endemic goiter in Spain in my recent work entitled «*El hocio y el cretinismo. Su patogenia y epidemiologia* en España». Madrid, Pal. 2, edit. 1927. See also M. Legendre, «*Las Jurdes. Etude de géographie humaine*». Bordeaux. 1927.

more frequent in woman than in man, a fact that can be clearly seen from the statistics given above.

We have been able to observe that the cases, in which the goiter is extremely voluminous and in general all of the cases that point to the necessity of surgical attention, are relatively rare. It is for this reason that the proportion of cases operated on in our country is relatively small, even if we take account of the fact that the patients, who are generally illiterate, do not take favorably to surgical interventions. In whichever one of the great operative centers of Madrid, whether it be the General Hospital, the Princess Hospital, the Clinic of the Medical Faculty or the Institute Rubio, the statistics of goiters operated on show a lower figure than those of any analogous foreign center whatsoever.

The different types of cretinic degeneracy are also identical with those of the other countries where goiter exists. Its single characteristic is that it is of frequent occurrence in the region of the Hurdes and that, as if to make up for this, it is rare in the remaining goitrous regions of Spain.

We have also observed quite frequently the appearance of types of secondary hyperthyroidism in endemic goiters. Sometimes they appeared spontaneously, especially during the critical period, but almost always they are due to exaggerated cures of thyroidine, of iodine or its derivatives, which had been dispensed as a treatment of goiter itself, or for other reasons, principally against obesity.

My statistics in regard to this subject are very demonstrative: Of 1789 cases of hyperthyroidism, observed from 1915 to July 1927, 397 can be classed in the group of Basedowified goiters and among these 201 are cases of endemic goiter, which had been treated with improper doses of iodine preparations, especially of the tincture. I must state that the iodine treatment of goiter has a venerable reputation in our country, even among the most ignorant classes of the population. This treatment is practised empirically in all of the strumose regions of the Pyrenees, by means of periodical ingestion of two or more doses per day of the ashes of sea-weed, which the inhabitants gather at the sea-coast. The proper dose of this product, which is rich in iodine, is the quantity that can be put upon a 10 centime piece. For several years past this method of treatment is being little by little modified by administering tincture of iodine, a method that appears more scientific but which is much more dangerous, for with this procedure the judicious doses of iodine, that are contained in the calcined sea plants, are replaced by much

greater quantities, which give rise to the occurrence of numerous symptoms of iodine-Basedow, as we have already stated.

In order to understand this relatively great frequency of iodic hyperthyroidism among the strumose population of Spain, it is necessary to take into account the facility with which our race, as all the southern races, becomes afflicted with hyperthyroidism in all its varieties. Nevertheless, and this we are repeating, as well by us as by other investigators, we have noticed these symptoms only in the cases that had been treated with enormous quantities of iodine, and never in the cases where judicious doses were dispensed or some preparations of iodized kitchen-salt.

Anatomo-pathologically our observations coincide with the description of Wegelin and of Aschoff. The goiter takes the nodular or diffuse form, with the usual forms of degeneracy: colloid diffuse, cystic or fibrous, but very rarely calcareous.

The cystic goiter occurs very frequently. The vascular goiter is also very common.

Finally, we ought to add that cancer of the thyroid gland has been observed very rarely with us. Although we have assiduously looked for it, we were able to find only three cases.

d) Pathogenic Considerations.

The conclusions drawn from our studies on the pathogeny of goiter in its relation to the Spanish endemic may be summed up as follows:

Firstly, the telluric theory is not confirmed in Spain, as Goyanes determined for the centers of the Pyrenees and the mountains of Avila. His conclusions may be applied to the goiter centers of Andalusia and the Hurdes.

The hydric factor does not appear to have any important influence either in the goitrous regions of our country. In a village of Alpujarra (Trevelez) Dr. Fernandez Martinez has, for example, informed us that of the two sections, which make up this village, it is only the inhabitants of the high section who are suffering from goiter while those of the low section do not have it. These two sections of the village have different water fountains. They are situated very close to each other and all of the other conditions of life in the village are absolutely identical.

On account of traditional reasons there is a great degree of independence between the inhabitants of the two sections and for a long time even marriages between individuals of these different districts were of rare occurrence. This case appears to be sufficiently typical for hydric influence. However the water of the two fountains originates from the same source, the snows of the Sierra Nevada mountain range, which is not far distant. Moreover, the number of cases of goiter is too small to enable us to form an exact opinion and we shall say further that the endemic disappears rapidly from the entire region, although the water continued to be at all times the same, in the proportion as the communications with the neighboring regions become more easy.

As far as the remaining strumose regions of our peninsula are concerned, we have not been able to draw any conclusions, which could establish a relation between the distribution and the intensity of the endemic and the waters used for drinking purposes.

In the region of the Hurdes analyses have been made of the iodine contents of the most common foods and the results obtained showed that the percentage of this substance contained in them is, perhaps, a little lower than the average found in the other districts of Spain; but it is practically equal to that of the foods which the people consume who inhabit the districts adjoining these inhospitable regions and among which goiter is quite rare.

Almost all of the salt consumed by the people of the Hurdes originates from the market town of Ciudad Rogrigo (province of Salamance); this is used as well in this same village as also in the neighboring region, in which the endemic occurs only very rarely. However, the inhabitants of the Hurdes make use of very little salt in the seasoning of their miserable foods. Many of them continue for long uninterrupted periods of time in eating almost exclusively only raw fruits, principally cherries, or dried fruits, such as dried chestnuts and some vegetables such as potatoes, which they partake of once or twice per day, boiled, and without any other condiment than salt. Up to the time that the Patronat Committee took up its work there was also very little bread and occasionally it was entirely wanting. It is only the less poor inhabitants, who add quite frequently to their dish of potatoes either bacon or other pork products pickled, which consequently are rich in salt. Very few of the people use any oil and still fewer take meat, and that only from time to time. This brief description will give an idea of the small quantity of salt, that is consumed by these people and, as a consequence, iodine which

occurs with the salt must likewise be extremely reduced. This is confirmed, as we shall see later, through the fine results, which Vidal y Jordana has obtained a short time after having instituted the general use of iodized salt.

However, while recognizing the importance of the iodine factor it seems to us that the origin of our strumose endemic can not be attributed exclusively to this factor. The very thorough study, which we have made on the general living conditions in the goitrous regions of Spain, has convinced us that goiter, except the existence of a specific cause which we do not as yet recognize, is found customarily intimately combined with an aggregate of collateral causes, that can be summed up in these two words: poverty and isolation.

All of the strumose countries of the entire world are poor countries and some are even miserable. But in Spain this circumstance attains a value of impressive demonstration, on account of the contrast with the adjacent regions. In the high and humid valleys of the Spanish mountains, where the goitrous centers are found, the poverty of the inhabitants is uncommonly great; in the Hurdes it is beyond all description. And in addition to the poverty there is to a great extent the factor of isolation, which is due to the inaccessibility of the mountains, the great distance between the different villages, to the abominable condition of the roads, the number of which is limited, and, finally, to a climate that is so rigorous during the winter that in certain regions the isolation is an absolute one for many months.

Under these conditions the cause of goiter could be an organic poison or an infectious germ, borne or not borne by the water. But just as certain ones of the well-known infections of to-day are distributed only over miserable localities, respecting as they do the individuals, who are living under good hygienic conditions, so there can be no doubt that the biological agent of goiter, which we do not as yet recognize, has need of the concurrence of the conditions of poverty and isolation, of which we have spoken, before it is able to be fixed in the human organism.

If we wish to specify which of the factors, comprised in the signification of the word «misery», bear a special importance in the genesis of endemic goiter, we shall state in the first place the want and the monotony of the foods. In the Hurdes, where we have an excellent experimental field for the study of endemic

goiter these characteristics of the nutrition attain limits, which are completely convincing. At the time when the Patronat Committee commenced its labors it was beyond all belief that these human beings were able to live years and years on such a precarious and monotonous diet.

This kind of diet gave the belief that the problem of goiter could have very direct relations with the problem of diseases through «deficiency». The people of the Hurdes, and in general all the Spaniards afflicted with goiter, consume considerable raw fruit, above all at certain times of the year, and also not a few vegetables. It is probable that their ration of this kind of vitamines is accordingly sufficient. But, to make up for this, the quantity of proteins of animal origin, as meat, eggs, milk, and of fats is extremely slight. We can even say that, for a great number of the people, this quantity is of no significancy. We must in passing state that in the strumose regions of Spain we did not notice any cases of that illness from deficiency which is most wide-spread in our country, namely, pellagra. In the Asturias pellagra was very prevalent in certain periods, but its distribution stood in no relation with the distribution of goiter, of which this region is one of the principal centers, as we have become aware.

The fact proves to us that, if it is admitted that the factor of alimentary insufficiency plays a part in the genesis of endemic goiter, as we believe it is very probably the case, this factor will be a different one for pellagra as for goiter. But, taken as a whole, the conditions of clinical aetiology and of the medium, in which these two processes develop, are very much alike. According to our opinion, the genesis of pellagra can not be considered in relation with any one particular aetiology, whether it be of alimentary insufficiency or any other. On the contrary, there is in its genesis the intervention of very varied factors and precisely of the type of misery and of isolation, to which we attach so much importance as regards goiter. This point of view is confirmed by the fact, that pellagra in all of the countries where it has existed, including our own, disappeared in the proportion that the general conditions of life became better and that the communications between the different regions became more easy. We shall later speak of the importance of these facts in the disappearance of goitrous endemic.

We explained elsewhere the experimental bases upon which we were able to develop the hypothesis of strumose endemic being considered as a malady of insufficiency. It is not necessary to repeat them here. We shall confine ourselves simply in calling to mind

that it proved to-day that some of the hormones, principally those which occur in organic morphogenesis, and among these the thyroxine, are very closely related, in their biochemical origin, to the nucleo-proteids which the organism acquires through alimentation. In consequence of this, it is theoretically not unreasonable to suppose that a deficient alimentation, in a definite sense, deprives certain glands of the necessary material for the elaboration of their secretory products. Experimentally we are well acquainted with the facts, that were determined at first by MacCollum and verified later on by many other investigators, regarding the possibility of reproducing certain conditions of delay in the growth, which very much recall to mind the conditions due to complex glandular lesions, as those of cretinism, only in depriving the young animals of certain alimentary factors, of which the subsequent addition is sufficient to correct the said retardations. Funk, Gley, MacCarrison, Pittaluga, Borutau, Zondek and we ourselves, have drawn the attention to the probable relation between the problem of the alimentary insufficiencies and certain endocrinic problems. Nevertheless, it seems to me that this hypothesis has not been studied from the point of view of its most interesting aspect, namely, the genesis of goitrous endemics, although we have clinically a number of data, which indicate it.

Besides deficient and monotonous alimentation, poverty and isolation induce to « agglomeration », to crowding together, especially in the long winter months in the hovels, which oftentimes are more pre-historic grottoes than modern dwellings. Finally, there is the question of consanguinity. In these villages where the population pursues its life and has scarcely any social relations with the neighboring villages and in which the poverty even tends to bring about social isolation and independence, the marriages between close relatives are actually very frequent, as also the extra-matrimonial relations, including those between persons of the same family. The study of these serious cases of cretinism and of deaf-mutism always confirm the importance of this aetiological factor.

Finally, some infectious factors are able to co-operate in the genesis of the cretinoid degeneration. The latent focal infections, the pathogenic value of which for the thyroidean maladies we have lately reported on, are very frequent in these regions, particularly the dental infection, which is almost certain, as we have been informed. In the Hurdes there was, besides, up to a short time ago an enormous amount of paludism and of hereditary syphilis, which

disappeared rapidly owing to the labors of the physicians of the Patronat Committee and to the suppression of the mercenary bringing up of the abandoned children of Cacères and of Salamanca. Almost the entire female population of the Hurdes formerly gave itself up to this industry without having medical supervision, which is the reason why the syphilitic contagion was very frequent. This state of affairs has been radically suppressed.

There are a few empirical facts, but of great demonstrative value, which go to endorse our points of view as to the origin of cretinic endemic, namely:

1. In the poorest villages, the individuals in easy circumstances, who, with a certain amount of comfort in a finer house and with a more varied diet, had a normal unconstrained method of living and medical protection against indicated infections, are rarely afflicted with goiter, although they are living under the same conditions and drink the same water as those who are their neighbors. As a matter of fact, from the time that the labors of the Patronat Committee were started there has been no case of goiter observed among the physicians, the school principals and functionaries of every description, who are obliged to live in these goitrous regions.

2. In the Hurdes — and we are taking this region as a striking example of what is taking place in the other goitrous districts — the proportion of cases of goiter is entirely different in the villages of high altitude from what it is in the villages lower down, although they lie near to one another and consequently the climatological, hydric and other conditions are identical. But the difference consists in that the conditions of life in the lower villages are not so difficult, the houses are a little better, the diet is more varied because there are small fields at the banks of the rivers where more vegetables can be cultivated and certain domestic animals raised, and finally their communications with the neighboring regions are made more easy.

3. In all the goitrous regions of Spain we were able to verify from the evidence that we received direct from the physicians, who have had a practice of many years, and from the aged persons of the villages that goiter is diminishing spontaneously in a very definite manner since the past 20 or 30 years (Alpujarras, Mountains of Avila, different strumose regions of the Pyrenees).

Nevertheless, during this period of time there has not been any change of climate, nor of terrain, nor of water; but it is the means of communication, which have changed in such a radical manner, and consequently the mis-

ery and isolation of the inhabitants have become diminished. At the present day regions, which were formerly separated by long journeys on foot, on mules or donkeys, have easy communications with one another by means of roads, which are open to vehicles and sometimes to automobiles. At the time of our first trip to the Hurdes, the wheeled vehicles were entirely unknown in this region.

This facility of inter-communication has brought about a diminution of marriages between near relatives, the introduction of hygienic measures in the manner of living, although still very rudimentary, a more abundant and more varied diet, and, finally, the presence of physicians and the constant communication with the sanitary centers. The diminution of goiter can be attributed only to these causes, for no special campaign was carried on to bring this about, and it is very remarkable that in the villages where, towards the end of the last century, there were 20 % of the population afflicted with goiter, there are now only very rare cases of this malady (Dr. Martinez, de Oviedo, Asturias).

In the great experimental center of the Hurdes no diminution of cretinic endemic has as yet been observed, considering that the sanitary labors were started there only a relatively short time ago. However, we are absolutely convinced that it will disappear before long with one single remedy, namely: roads of communication. This will mean the bringing down the misery and the isolation within tolerable limits.

The clinical study of the cases of cretinic degeneracy convinces us each time more fully of the importance of the pluri-glandular degeneracy, that is admitted by several modern authors and confirmed by our own recent anatomo-pathological investigations. Vidal Jordana lays considerable stress upon the frequency with which the goitrously afflicted and the cretins in the Hurdes present symptoms of derangement of other endocrinic glands, besides the thyroid gland and especially the ovary. It is necessary to note the good results which have been obtained with a mixed organo-therapeutics (thyroidean, ovarian, hypophysary), employed in a very diffuse manner. We have shown above the probable influence of the hypo-alimentary factors in the production of these lesions.

e) Results of the Collective Use of Iodized Salt.

At Madrid we made use of iodized salt, during the last few months and that in a sporadic manner, combined with a very little

quantity of thyroideal extract, which was prepared according to our directions by the Ibis institute of Madrid. The results obtained seem to us to be favorable, if we take into account that there was not much material for study and also that the period of observation was a short one.

The experiments performed by Vidal Jordana in the Hurdes are very interesting. He established, from both the prophylactic and curative point of view, the employment of salt mixed with potassium iodide in the same proportion as we, i. e. from 4 to 7 milligrams of potassium iodide to the kilogram of salt, prepared gratuitously for these experiments by the Llopis Laboratory of Madrid. In the sections of this region where schools have already been established, the administration of the product to the children was entrusted to the teachers. Dr. Vidal Jordana studied for himself the results of this product upon two great groups of diseased persons at Vegas de Coria and Cabezo. According to his observations 60 % of the young invalids afflicted with goiter gave indications of improvement and some were entirely cured. The prophylactic effects were also very distinct, particularly with the young married women, who had previously almost without fail suffered from goiter, when they became pregnant for the first time.

In another group of goitrous patients he made use of pills of potassium iodide and of thyroidine, following the formula of Pighini: namely, sodium iodide 0.01 gr., tincture of iodine 1 drop and thyroid powder 0.02 gr., which he likewise distributed gratuitously. With some groups of women he substituted ovarian powder for the thyroid powder. This treatment gave distinct signs of improvement in 50 % of the cases, particularly in the case of young persons and women, who had shortly before become pregnant. The nodular goiters of the aged individuals do not present any modification.

Upon the whole, from a prophylactic point of view he has obtained very favorable results with iodized salt; likewise from the curative point of view. He has also obtained distinctly favorable results with the iodized preparations associated with organotherapeutics.

As we have already stated, neither the physicians of the Hurdes nor we ourselves have observed any cases of poisoning due to the use of iodized salt. Vidal described some cases of intolerance in the case of young women who received preparations containing thyroidine.

f) Conclusions.

The goitrous endemic appears in Spain in a very diffuse manner but without any other important centers than some in the Pyrenees and in the Hurdes (province of Caceres).

The number of persons afflicted with cretinic degeneracy can be estimated at about 0.006 of our entire population.

Clinically the goitrous endemic of Spain is identical with that, which has been observed in the other countries of Europe. The cases of surgical goiters and the serious degrees of cretinic degeneracy are relatively rare except in the Hurdes.

The telluric theory can not be employed for an explanation of the distribution of endemic goiter in Spain. The hydric theory could be confirmed, perhaps, in some isolated cases.

It is probable that the diminution of the quantity of iodine taken in may exert some influence upon the production of the goitrous endemic, at least in some Spanish centers of goiter, judging from certain food analyses and considering the good results obtained from the employment of iodized salt.

good: very near the truth.

At any rate, the thorough study of the conditions of life in the goitrous regions of Spain has convinced us that in the production of the endemic, the conditions of food, the being crowded together, the close blood relationship and of infection, which accompany want and isolation, intervene directly. It is not possible to determine the degree of efficaciousness of these concomitant causes. It is likely that some of them, as, e. g. deficiency in nourishment, could directly influence the production of the pluri-glandular lesions, characteristic of cretinism. The lack of iodine would then be one of the factors caused by improper alimentation, but it would not be the only one. If considered from the aetiologic and pathogenic point of view, we are accordingly able to a certain extent to compare the goitrous endemic to certain diseases, spoken of as being such «through deficiency», such as pellagra, of which the distribution, the conditions of poverty and of hypo-alimentation, in which it is developed, bring very closely to mind those of the goitrous endemic.

The spontaneous diminution of endemic goiter in Spain, as soon as there is an improvement in the means of communication, which, as a matter of course, leads to the improvement in the conditions of life in the goitrous regions, shows the importance of these factors, as also, on the other hand, the therapeutic importance of the measures of general progress and of the colonization of the goitrous centers.

On the Diffusion of Endemic Goiter in Switzerland.

By Dr. Otto Stiner
(Swiss Federal Board of Health, Berne).

It is a difficult venture to present accurate data on the actual spread of endemic goiter in our country. There are however necessary some statistical bases if we desire to be in the position later on to make any judgment on the results of the far extended effort, which is being made at the present time in different parts of the country, to relieve our people entirely or at least up to the limits of possibility of the goiter, one of our great epidemics. Inasmuch as an oft-repeated, systematic examination of the entire population in accordance with a uniform method is an impossibility, we are obliged for this purpose to continue and further develop the statistical data which we have already collected on the diffusion of goiter among the recruits, the school children and among the patients in the surgical clinics and hospital wards, who come to be operated on. Then we can determine with a certain degree of reliability, after the required time has expired, to what extend we have met with success in the prophylactic and therapeutic measures, which are being carried out at the present time in the form of school prophylaxis and the general prophylaxis of goiter by means of iodized kitchen salt.

In my report to the Commission of Goiter at its session on september 22, 1923, I called attention to the valuable material on the diffusion of goiter, which is contained in the original reports of the sanitary investigation commissions intended for the judgment of men liable to serve in the army and at the same time I showed by means of charts the results of the investigations of these commissions in the years 1921 and 1922 relative to goiter. In former times these results were of little use for judging the general diffusion of the malady, because the statements made in the minutes were confined mostly to those who were unfit for duty on account of goiter.

For a number of years, that is to say, just as soon as the required time was granted for a thorough examination of recruits through a fortunate change of the stipulations regarding the duties of the commissions, their interest has manifestly been directed

towards goiter, and this subject «Goiter», with which our medical men are so conversant, received intelligent study and investigation, first in a few divisional circles then in all recruiting districts, after the thorough examination of the thyroid gland was made a compulsory stipulation in the year 1924. With the profound study and acquaintanceship on the part of the Swiss physicians as a body with the goiter question, that is in so many ways of great importance for our country, we may very readily take for granted that there is in each commission at least one medical man, who is thoroughly familiar with all phases of this question, and that we may for this reason look upon the statistical data collected by this commission as a valuable basis for the judgment of the prevalence of goiter.

The examination of those who are obligated to appear as recruits before the military authorities, which took place in accordance with the military regulations and instructions laid down by the «Oberfeldarzt» (military physician in chief) of the Swiss army with the understanding of the goiter commission, enables us to keep under progressive control the occurrence of the endemic goiter in the entire male population of the age of 19 to 20 years, which means during the years in which we may take for granted that the physiological school and puberty swellings of the thyroid gland do not play a rôle any longer. They constitute the only opportunity for us to gain proper information on the actual diffusion of goiter. The examinations of the school children will not acquaint us any better on this matter so long as we do not have new methods at our disposition, by means of which we can keep separate the normal and pathological function of an enlarged thyroid gland. Unquestionably the fact, that in regions rich in iodine, as e. g. Chaux-de-Fonds, more than 50 % of the scholars in the higher classes exhibit enlarged thyroid glands which in great part recede later on, proves to us that these school examinations offer us material which is entirely unfit for any later judgment of successes with iodine prophylaxis. This is the case because we are not in a position at the present day to show with how many school children of regions poor in iodine, who are affected with the similar swellings of the thyroid gland, the similar causes have called forth this swelling, though evidently entirely independent of the iodine contents of the food. The operative statistics of the clinics and hospitals will only then have any very special value for the judgment of the diffusion of endemic goiter, when the data are classified according to the age of the individual operated on and according to

the causes, which necessitated the operation. The senile goiters and those enlargements of the thyroid gland, as tumors, tuberculosis, haemorrhages, acute inflamed enlargements etc., which can be attributed to other causes than the ordinary endemic noxas, must be eliminated. The most reliable basis for judging the amount of goiter in our population is to be considered at the present time, according to my opinion, the thoroughly carried out examination of the thyroid glands of the recruits, which is made in accordance with uniform instructions. Swiss science is therefore greatly indebted to the Chief of the Medical Service of the Army for having instructed the sanitary investigation commissions to give their special attention to the study of the thyroid gland of the recruits and to execute these investigations in accordance with uniform instructions laid down in collaboration with the Swiss goiter commission.

Surveys in Recruits.

What are? ↓ vide infra

At a session of the research committee of the goiter commission, which was held under the chairmanship of Professor de Quervain and which was attended by Colonel Hauser, Physician in Chief of the Army, instructions were laid down for the judgment of goiter in the recruits liable for military service. These instructions run as follows:

Directions for the Examination of the Recruits relative to Goiter.

all this is good and represents clinical control of the statistical method suggest.

The medical doctor places himself before the recruit to be examined, who is likewise standing. He studies carefully the shape of the neck and looks for the eventual presence of venous dilatations at the neck and at the exposed chest-wall. Then he asks the man, who is undergoing examination, to swallow, in order to bring in this manner to light an eventual deeply seated goiter.

Then he orders the recruit to be seated; passes over to his left side and measures the circumference of the neck. For this purpose the measuring tape is placed at the nape of the neck above the vertebra prominens and encompasses the base of the neck or rather the most protruding point of the same. This measurement is first undertaken by quiet breathing. Then the recruit is asked to press rigorously, keeping his mouth closed, and in the same manner as before a second measurement is made. A difference of 2 centimeters or $^4/_5$ of an inch or more between the two measurements gives rise to the suspicion that there is a goiter rich in vessels or that there is some compression of the cervical veins by the struma, even if inspection and palpation during quiet breathing

apparently seem to indicate only an insignificant enlargement of the thyroid gland. An increase in the circumference of less than $^4/_5$ of an inch does not, however, preclude goiter.

Finally the medical examiner goes behind the party undergoing examination and places his hands around his neck in such a manner that his two thumbs come to rest on the nape of the neck, while he palpates with the index finger and middle finger of each hand the two thyroid lobules with the aim of comparing them. If the shape of the thyroid gland can not be forthwith determined, then the palpation is to be repeated while the recruit is swallowing. If it does not prove successful to palpate the lower pole of an enlarged thyroid lobule distinctly with the finger, then it can be taken for granted that there is a struma profunda, even if the shape of the neck has changed externally only a little.

For the purpose of the summary military judgment those cases are to be looked upon as normal:

a) in which the groove between the trachea and the lateral cervical muscular apparatus is filled out through a slightly perceptible cushion and where the isthmus can be felt as a thin tissue layer before the trachea;

b) furthermore, those cases, in which the thyroid gland can be really easily palpated in its whole compass,

1. where it however does not perceptibly change the contour of the neck,

2. nor extend down into the thorax,

3. nor become strongly distended through pressure (at the most $^4/_5$ of an inch),

4. where there is no difficulty of breathing in the case of great exertion.

The groups a) and b) correspond to the types I and II of the classification of the Swiss goiter commission relative to the school examinations.

In case the thyroid gland can be readily recognized as being uniformly enlarged and if the shape of the neck is obviously changed through its being enlarged and if the neck becomes greatly distended through pressure, then we speak of a diffuse goiter (type III of the Instruction of the Goiter Commission).

If it is possible to palpate separate nodules plainly in a normal or a diffusely enlarged thyroid gland, then the case must be entered as a nodular struma (struma nodosa).

The Results of the Examinations and the Military Judgment of the Goiters with Reference to Fitness for Service.

a) *Entries into the Service Book.*

The types I and II of the Instruction of the Goiter Commission, which are to be designated as normal from the standpoint of fitness for service, are not entered into the service book.

The prominent diffuse enlargements of the thyroid gland (type III of the Instruction of the Goiter Commission), including the so-called «Blähhals», are to be entered as struma diffusa (Str. diff.) into the service book, with a statement of the circumference of the neck and eventual further data (profunda etc.). The fitness for the service depends in these cases on the location of the struma and on its influence upon the trachea and the vessels. Deep location (struma profunda), tracheal compression (difficulty in breathing under exertion) and great development of vessels at the neck will cause unfitness for military service:

Nodular strumas are to be entered as struma nodosa together with a statement as to the location of the nodules, that have a disturbing effect (struma nodosa centralis, sinistra, dextra), and of the circumference of the neck (e. g. Str. nod. dext. 43).

Struma nodosa involves unfitness for military service, in so far as it is not a question of small non-compressing nodules.

In those cases in which strumas of any kind would involve unfitness for the service the recruit is to be sent back for a year, if it were to seem that medicinal or operative treatment might prove successful and the man declares himself prepared to undergo treatment and eventually an operation.

b) *Entries into the Control Registers on the Sanitary Examination of Recruits.*

The condition of the thyroid gland of all recruits must be entered into the control registers for the sanitary examination and not only must the general condition of the thyroid gland be stated, i. e. normal or the nature of any eventual enlargement, but also the circumference of the neck in a quiet state and under pressure in accordance with the instructions stated in the foregoing pages. The circumference of the neck must be added within parentheses.

Examples: 1. Neck normal 38 (39,5).
2. Str. diff. 42 (44).
Str. diff. prof. 40 (41,5).
Str. diff. compr. 41 (43,5).
3. Str. nod. dext. 43 (45).

We can readily recognize from the instruction that it has really been compiled from a practical point of view. In the discussion which preceded its definite acceptance the postulate was made that the dimensions of the surface of the thyroid gland which is made in the examinations of school children ought to be executed also on the recruit, because only these measurements would make a later control possible. This postulate was, however, opposed by the members of the commission, who had had rather considerable experience in matters pertaining to the recruits, for they claimed that these examinations would firstly require a great deal of time and on the other hand would be unreliable from the practical military point of view, inasmuch as a small nodule, which can scarcely have any influence at the whole, might be located in such a place as to render the recruit unfit for military service and also affect the general fitness for work as well as the health more unfavorably than large nodules, if they were to lie in a favorable location and are not too hard. Besides a later supplementary examination would be possible only with a part of those examined, those fit for service, and even there only under great difficulties.

From the reports of the divisional physicians we learn that the goiter examinations in accordance with these directions can take place without any great loss of time, requiring only about half a minute per man with skilled examiners.

The results of the examinations are contained in the following tables I to IV, calculated for districts and in percentage. The data are average figures of the results of the two years 1924 and 1925 and calculated on the basis of 100 recruits.

As we can see from table I goiter is at present exceedingly widely spread throughout our country. In several districts of the great goiter centers we find figures up to 80 % and even higher. If we compare with these the results obtained at former examinations, we must recognize the fact that in more recent years the diffusion has increased. From table II it becomes evident when comparing with carlier compilations, that the intensity of the endemic, the number of serious goiters, has diminished very greatly in the same period of time. In 83 districts out of 186 there were no recruits, who had to be released on account of goiter, and in 24 other districts the number of such sent back on account of goiter did not reach 1%. The average number of those, who were found to be entirely or partially unfit on account of goiter, is 1,3%, a figure which is very small in comparison with those of former days, and yet the requirements for military service have become

Table I

Total Number

of Men found afflicted with Goiter at the Recruitings of 1924 and 1925.

Zürich	%
Dielsdorf	34,1
Zürich	34,3
Affoltern	36,7
Bülach	45,9
Andelfingen	50,6
Winterthur	53,4
Meilen	59,2
Uster	62,8
Horgen	63,2
Pfäffikon	74,6
Hinwil	82,4

Bern	%
Pruntrut	11,4
Ob. Simmental	24,2
Laufen	25,1
Delémont	25,4
Signau	27,9
Konolfingen	30,0
Moutier	30,5
Aarberg	31,0
Laupen	31,6
Fres. Montagnes	31,8
Bern	32,4
Erlach	34,0
Saanen	34,4
Interlaken	34,6
Frutigen	39,0
Biel	42,5
Courtelary	42,8
Oberhasli	43,0
Büren	44,2
Seftigen	44,5
Nd. Simmental	47,4
Neuveville	47,7
Aarwangen	48,7
Nidau	50,2
Burgdorf	50,6
Schwarzenburg	50,9
Trachselwald	53,7
Thun	53,8
Wangen	56,2
Fraubrunnen	64,8

Luzern	%
Hochdorf	32,0
Sursee	34,3
Willisau	45,2
Luzern	48,2
Entlebuch	50,6

	%
Uri	41,0

	%
Obwalden	53,9

	%
Nidwalden	37,4

Schwyz	%
Einsiedeln	15,4
March	17,3
Schwyz	18,5
Höfe	18,6
Küssnacht	22,0
Gersau	24,8

	%
Glarus	41,1

	%
Zug	45,4

Fribourg	%
La Veveyse	16,2
Gruyère	25,0
See	28,3
La Broye	36,0
Sense	39,2
Sarine	46,2
Glâne	58,0

Solothurn	%
Lebern	17,0
Thierstein	20,7
Balsthal-Gäu	21,8
Balsthal-Tal	22,1
Solothurn	22,5
Dorneck	24,8
Kriegstetten	26,1
Bucheggberg	26,6
Olten	30,9
Gösgen	33,9

	%
Baselstadt	20,6

Baselland	%
Liestal	13,7
Sissach	20,7
Arlesheim	21,9
Waldenburg	26,5

Schaffhausen	%
Reiath	39,8
Schaffhausen	45,1
Unt. Klettgau	45,1
Schleitheim	46,4
Ob. Klettgau	49,7
Stein	52,8

Appenzell A.-Rh.	%
Mittelland	60,9
Hinterland	61,8
Vorderland	63,6

	%
Appenzell I.-Rh.	67,4

St. Gallen	%
St. Gallen	35,5
Wil	43,9
Werdenberg	46,8
Rorschach	48,3
Gossau	49,8
Sargans	51,2
Unt. Rheinthal	55,8
Ob. Toggenbg.	56,7
See	61,3
Neu-Toggenbg.	64,0
Unt. Toggenbg.	68,1
Gaster	68,6
Ob. Rheinthal	68,8
Alt-Toggenbg.	69,4

Graubünden	%
Münsterthal	22,5
Maloja	26,4
Imboden	26,7
Ob. Landquart	28,0
Albula	28,4
Bernina	29,8
Inn	30,3
Plessur	32,3
Moësa	32,5
Vorderrhein	33,9
Hinterrhein	35,0
Unt. Landquart	36,8
Heinzenberg	40,3
Glenner	43,1

Aargau	%
Brugg	22,5
Lenzburg	28,2
Kulm	31,8
Zofingen	32,0
Baden	34,3
Rheinfelden	34,5
Aarau	35,4
Zurzach	35,8
Laufenburg	37,0
Bremgarten	59,7
Muri	73,0

Thurgau	%
Bischofszell	38,1
Arbon	39,5
Kreuzlingen	48,5
Diessenhofen	60,6
Münchwilen	62,0
Weinfelden	64,4
Steckborn	68,6
Frauenfeld	69,6

Tessin	%
Blenio	7,7
Leventina	8,0
Mendrisio	8,5
Vallemaggia	8,7
Lugano	16,1
Bellinzona	17,4
Locarno	21,5
Riviera	27,4

Vaud	%
Grandson	5,7
Yverdon	5,7
La Vallée	9,7
Nyon	11,3
Pays d'Enhaut	11,7
Aubonne	11,7
Cossonay	12,8
Orbe	13,4
Rolle	13,9
Morges	15,6
Echallens	16,3
Lavaux	22,0
Moudon	22,6
Lausanne	23,4
Oron	23,7
Payerne	26,0
Aigle	26,2
Avenches	29,0
Vevey	29,6

Valais	%
Goms	9,3
Leuk	16,1
Raron	16,8
Visp	17,6
Brig	29.3
Sierre	41,2
Hérens	51,1
Sion	56,3
Conthey	57,8
Monthey	60,5
Martigny	61,8
Entremont	72,1
St-Maurice	80,4

Neuchâtel	%
Le Locle	12,9
Val-de-Travers	16,3
Chaux-de-Fds.	21,7
Neuchâtel	22,4
Boudry	24,7
Val-de-Ruz	27,3

	%
Genève	25,8

Table II

Number of Recruits

of 1924 and 1925 unfit for Military Service on account of Goiter.

Zürich	%
Horgen	1,6
Zürich	2,1
Bülach	2,5
Meilen	3,0
Andelfingen	3,5
Dielsdorf	3,5
Affoltern	3,6
Päffikon	3,8
Hinwil	4,0
Winterthur	4,0
Uster	5,6

Bern	%
Courtelary	0
Delsberg	0
Erlach	0
Fres. Montagnes	0
Laufen	0
Moutier	0
Neuveville	0
Pruntrut	0
Fraubrunnen	1,1
Oberhasli	1,4
Interlaken	1,5
Biel	1,6
Aarwangen	2,0
Nd. Simmental	2,0
Bern	2,1
Saanen	2,5
Burgdorf	2,6
Wangen	2,7
Ob. Simmental	2,8
Konolfingen	2,9
Aarberg	3,0
Seftigen	3,0
Laupen	3,1
Schwarzenburg	3,3
Büren	3,4
Signau	3,7
Thun	3,9
Nidau	4,1
Frutigen	4,3
Trachselwald	5,3

Luzern	%
Entlebuch	4,5
Willisau	4,8
Luzern	5,8
Sursee	8,0
Hochdorf	8,8

	%
Uri	0,7

	%
Obwalden	1,9

	%
Nidwalden	1,9

Schwyz	%
March	0,9
Schwyz	1,2
Einsiedeln	1,8
Gersau	2,6
Höfe	3,2
Küssnacht	3,3

	%
Glarus	0,1

	%
Zug	1,7

Fribourg	%
La Broye	0
Glâne	0
Gruyère	0
Sarine	0
See	0
Sense	0
La Veveyse	0

Solothurn	%
Balsthal-Gäu	0
Bucheggberg	0
Solothurn	0
Balsthal-Tal	0,3
Lebern	0,3
Kriegstetten	0,4
Dorneck	0,5
Olten	0,8
Thierstein	1,1
Gösgen	2,3

	%
Baselstadt	0,2

Baselland	%
Liestal	0,2
Arlesheim	0,9
Sissach	1,4
Waldenburg	2,3

Schaffhausen	%
Ob. Klettgau	0
Unt. Klettgau	0
Schleitheim	0
Stein	1,4
Schaffhausen	2,3
Reiath	2,9

	%
Appenzell I.-Rh.	0,7

Appenzell A.-Rh.	%
Mittelland	0,5
Hinterland	0,8
Vorderland	1,0

St. Gallen	%
Gaster	0
Ob. Toggenburg	0
Sargans	0
Unt. Rheintal	0
Werdenberg	0,2
Wil	0,4
St. Gallen	0,8
Gossau	1,0
See	1,0
Rorschach	1,1
Ob. Rheintal	1,2
Unt. Toggenburg	1,8
Alt Toggenburg	2,3
Neu Toggenburg	5,3

Graubünden	%
Albula	0
Bernina	0
Glenner	0
Heinzenberg	0
Hinterrhein	0
Imboden	0
Inn	0
Ob. Landquart	0
Unt. Landquart	0
Maloya	0
Münsterthal	0
Plessur	0
Vorderrhein	0
Moësa	1,5

Aargau	%
Aarau	0,4
Lenzburg	1,6
Brugg	2,3
Zurzach	2,5
Baden	2,8
Rheinfelden	3,4
Laufenburg	4,1
Zofingen	4,2
Kulm	4,7
Muri	4,9
Bremgarten	5,8

Thurgau	%
Bischofszell	0
Diessenhofen	0
Steckborn	0
Arbon	0,2
Kreuzlingen	0,3
Frauenfeld	0,6

Thurgau	%
Weinfelden	0,6
Münchwilen	0,7

Tessin	%
Bellinzona	0
Blenio	0
Leventina	0
Locarno	0
Lugano	0
Mendrisio	0
Riviera	0
Valle-Maggia	0

Vaud	%
Aigle	0
Aubonne	0
Avenches	0
Cossonay	0
Echallens	0
Grandson	0
Lausanne	0
La Vallée	0
Lavaux	0
Morges	0
Moudon	0
Nyon	0
Orbe	0
Oron	0
Payerne	0
Pays d'Enhaut	0
Rolle	0
Vevey	0
Yverdon	0

Valais	%
Conthey	0
Entremont	0
Hérens	0
Martigny	0
Monthey	0
St-Maurice	0
Sierre	0
Sion	0
Raron	0,6
Goms	1,1
Leuk	2,4
Visp	2,6
Brig	3,3

Neuchâtel	%
Boudry	0
Chaux-de-Fonds	0
Le Locle	0
Neuchâtel	0
Val-de-Ruz	0
Val-de-Travers	0

	%
Genève	0

Number of unfit Recruits

afflicted with Goiter besides other physical Defects.

Zürich	%
Zürich	7,3
Dielsdorf	8,2
Affoltern	10,5
Bülach	11,3
Horgen	13,6
Meilen	13,7
Andelfingen	13,8
Winterthur	14,9
Uster	19,7
Pfäffikon	27,2
Hinwil	29,6

Bern	%
Pruntrut	1,6
Erlach	3,5
Delsberg	5,3
Laufen	6,0
Moutier	6,8
Ob. Simmental	7,1
Interlaken	7,3
Bern	8,1
Neuveville	8,8
Fres. Montagnes	9,5
Courtelary	9,8
Biel	10,2
Laupen	10,8
Saanen	10,9
Konolfingen	11,0
Büren	11,5
Signau	13,0
Nidau	13,3
Oberhasli	13,4
Aarberg	13,9
Nd. Simmental	13,9
Burgdorf	15,3
Seftigen	15,4
Wangen	15,4
Aarwangen	16,4
Frutigen	17,1
Thun	18,6
Fraubrunnen	18,7
Trachselwald	19,3
Schwarzenburg	24,5

Luzern	%
Willisau	16,5
Sursee	17,5
Entlebuch	17,9
Luzern	18,4
Hochdorf	20,3

	%
Uri	15,3

	%
Obwalden	19,6

	%
Nidwalden	11,5

Schwyz	%
March	7,7
Einsiedeln	8,7
Gersau	10,5
Schwyz	10,7
Höfe	12,2
Küssnacht	14,1

	%
Glarus	10,4

	%
Zug	12,2

Fribourg	%
La Veveyse	5,7
La Broye	7,2
See	10,2
Sarine	12,9
Gruyère	12,9
Sense	19,3
Glâne	20,3

Solothurn	%
Solothurn	4,7
Thierstein	5,9
Balsthal-Gäu	6,0
Kriegstetten	6,0
Lebern	6,0
Bucheggberg	7,5
Olten	8,0
Dorneck	8,1
Gösgen	8,8
Balsthal-Tal	9,4

	%
Baselstadt	4,7

Baselland	%
Liestal	3,0
Arlesheim	5,6
Sissach	7,5
Waldenburg	13,4

Schaffhausen	%
Reiath	10,6
Schleitheim	10,7
Schaffhausen	10,8
Stein	11,7
Ob. Klettgau	11,7
Unt. Klettgau	16,0

	%
Appenzell I.-Rh.	22,3

Appenzell A.-Rh.	%
Vorderland	12,9
Hinterland	15,0
Mittelland	16,7

St. Gallen	%
Unt. Rheintal	10,5
St. Gallen	11,3
See	11,7
Werdenberg	12,2
Rorschach	12,7
Ob. Toggenburg	13,5
Wil	13,6
Gossau	13,9
Unt. Toggenbg.	15,8
Alt-Toggenbg.	16,8
Sargans	17,4
Gaster	18,0
Neu-Toggenbg.	18,4
Ob. Rheinthal	22,0

Graubünden	%
Münsterthal	0
Inn	2,9
Bernina	4,3
Maloja	5,5
Heinzenberg	5,7
Moësa	7,9
Hinterrhein	8,7
Albula	8,8
Unt. Landquart	8,9
Imboden	9,0
Plessur	9,0
Vorderrhein	10,5
Ob. Landquart	10,6
Glenner	10,8

Aargau	%
Brugg	7,5
Lenzburg	9,1
Zofingen	9,6
Kulm	11,4
Aarau	11,6
Baden	13,0
Laufenburg	14,7
Rheinfelden	14,8
Zurzach	16,6
Muri	25,1
Bremgarten	27,5

Thurgau	%
Bischofszell	8,8
Kreuzlingen	9,0
Arbon	9,1
Diessenhofen	15,9
Münchwilen	16,5
Weinfelden	17,5

Thurgau	%
Steckborn	17,7
Frauenfeld	24,3

Tessin	%
Mendrisio	0,3
Lugano	1,2
Blenio	1,7
Bellinzona	1,9
Leventina	2,0
Vallemaggia	2,1
Riviera	2,2
Locarno	3,3

Vaud	%
Pays d'Enhaut	0
Grandson	0,3
Orbe	0,5
Yverdon	1,0
Aubonne	1,1
Echallens	1,2
Cossonay	1,5
Lavaux	1,5
Aigle	1,6
La Vallée	1,7
Nyon	1,8
Vevey	2,8
Rolle	3,0
Oron	3,2
Payerne	3,2
Lausanne	3,5
Avenches	4,2
Moudon	4,2
Morges	5,0

Valais	%
Goms	2,3
Leuk	2,4
Raron	2,4
Brig	6,7
Visp	6,9
Sierre	7,2
Sion	8,2
Conthey	10,1
Monthey	11,7
Hérens	11,8
Martigny	12,8
St-Maurice	12,8
Entremont	14,2

Neuchâtel	%
Le Locle	4,9
Neuchâtel	5,0
Val-de-Travers	5,1
Boudry	6,4
Val-de-Ruz	7,0
Chaux-de-Fonds	7,9

	%
Genève	5,1

Table IV

Struma nodosa

with the Recruits of the year 1924 and 1925.

Zürich	%
Zürich	9,9
Horgen	12,9
Affoltern	13,2
Winterthur	16,8
Meilen	17,5
Uster	19,8
Dielsdorf	21,3
Andelfingen	22,6
Pfäffikon	28,2
Bülach	32,0
Hinwil	38,4

Bern	%
Freibergen	0
Pruntrut	0,7
Delémont	1,6
Moutier	4,5
Konolfingen	6,2
Biel	7,6
Neuveville	7,9
Courtelary	8,6
Aarwangen	9,4
Bern	11,3
Trachselwald	12,0
Interlaken	12,4
Nidau	12,5
Wangen	12,9
Büren	13,2
Ob. Simmental	14,2
Signau	14,2
Erlach	14,3
Seftigen	14,8
Saanen	15,1
Laufen	15,5
Fraubrunnen	16,0
Schwarzenburg	19,3
Laupen	19,6
Oberhasli	20,9
Aarberg	21,1
Thun	24,7
Frutigen	25,7
Burgdorf	25,9
Nd. Simmental	33,5

Luzern	%
Luzern	17,6
Entlebuch	21,8
Sursee	22,7
Hochdorf	24,2
Willisau	31,6

	%
Uri	31,4

	%
Obwalden	15,1

	%
Nidwalden	6,7

Schwyz	%
Einsiedeln	8,3
Schwyz	9,8
March	11,2
Höfe	11,3
Küssnacht	14,1
Gersau	19,4

	%
Glarus	14,8

	%
Zug	14,5

Fribourg	%
La Veveyse	4,4
See	9,0
Gruyère	9,1
Sarine	9,3
La Broye	14,8
Sense	18,6
Glâne	20,5

Solothurn	%
Lebern	1,9
Kriegstetten	3,6
Bucheggberg	4,5
Solothurn	5,6
Balsthal-Gäu	7,1
Balsthal-Tal	8,2
Olten	13,6
Thierstein	14,2
Gösgen	15,0
Dorneck	15,6

	%
Baselstadt	2,2

Baselland	%
Liestal	2,7
Arlesheim	3,3
Sissach	5,0
Waldenburg	7,9

Schaffhausen	%
Reiath	5,8
Schleitheim	8,9
Schaffhausen	9,9
Unt. Klettgau	10,5
Ob. Klettgau	11,8
Stein	12,9

Appenzell A.-Rh.	%
Mittelland	20,3
Hinterland	21,1
Vorderland	22,8

	%
Appenzell I.-Rh.	23,0

St. Gallen	%
Wil	11,2
St. Gallen	13,4
Ob. Toggenbg.	13,8
Werdenberg	18,6
Sargans	21,8
Unt. Toggenbg.	22,1
Neu-Toggenbg.	23,1
Alt-Toggenbg.	23,5
See	23,7
Gaster	23,8
Rorschach	24,4
Gossau	25,2
Unt. Rheinthal	29,3
Ob. Rheinthal	49,2

Graubünden	%
Münsterthal	0
Hinterrhein	3,3
Maloja	4,4
Albula	5,8
Plessur	7,1
Glenner	7,8
Imboden	8,0
Heinzenberg	8,2
Vorderrhein	8,9
Inn	9,8
Bernina	11,6
Ob. Landquart	12,2
Unt. Landquart	19,5
Moësa	21,3

Aargau	%
Brugg	3,9
Lenzburg	8,6
Kulm	9,5
Zurzach	10,1
Laufenburg	12,4
Rheinfelden	12,7
Aarau	12,7
Zofingen	14,3
Baden	17,6
Bremgarten	26,1
Muri	33,4

Thurgau	%
Bischofszell	11,7
Kreuzlingen	14,0
Arbon	15,0
Weinfelden	19,6
Münchwilen	20,8
Diessenhofen	23,0
Steckborn	30,5
Frauenfeld	33,8

Tessin	%
Mendrisio	0,8
Lugano	1,7
Leventina	2,0
Blenio	2,5
Bellinzona	4,2
Vallemaggia	4,3
Locarno	7,2
Riviera	8,8

Vaud	%
Aubonne	0,6
Rolle	0,7
La Vallée	1,0
Nyon	1,8
Lavaux	2,0
Cossonay	2,1
Morges	2,6
Grandson	2,7
Yverdon	3,7
Lausanne	3,8
Orbe	4,0
Vevey	6,3
Moudon	6,7
Pays d'Enhaut	7,0
Oron	7,6
Avenches	10,2
Echallens	10,7
Payerne	11,7
Aigle	14,2

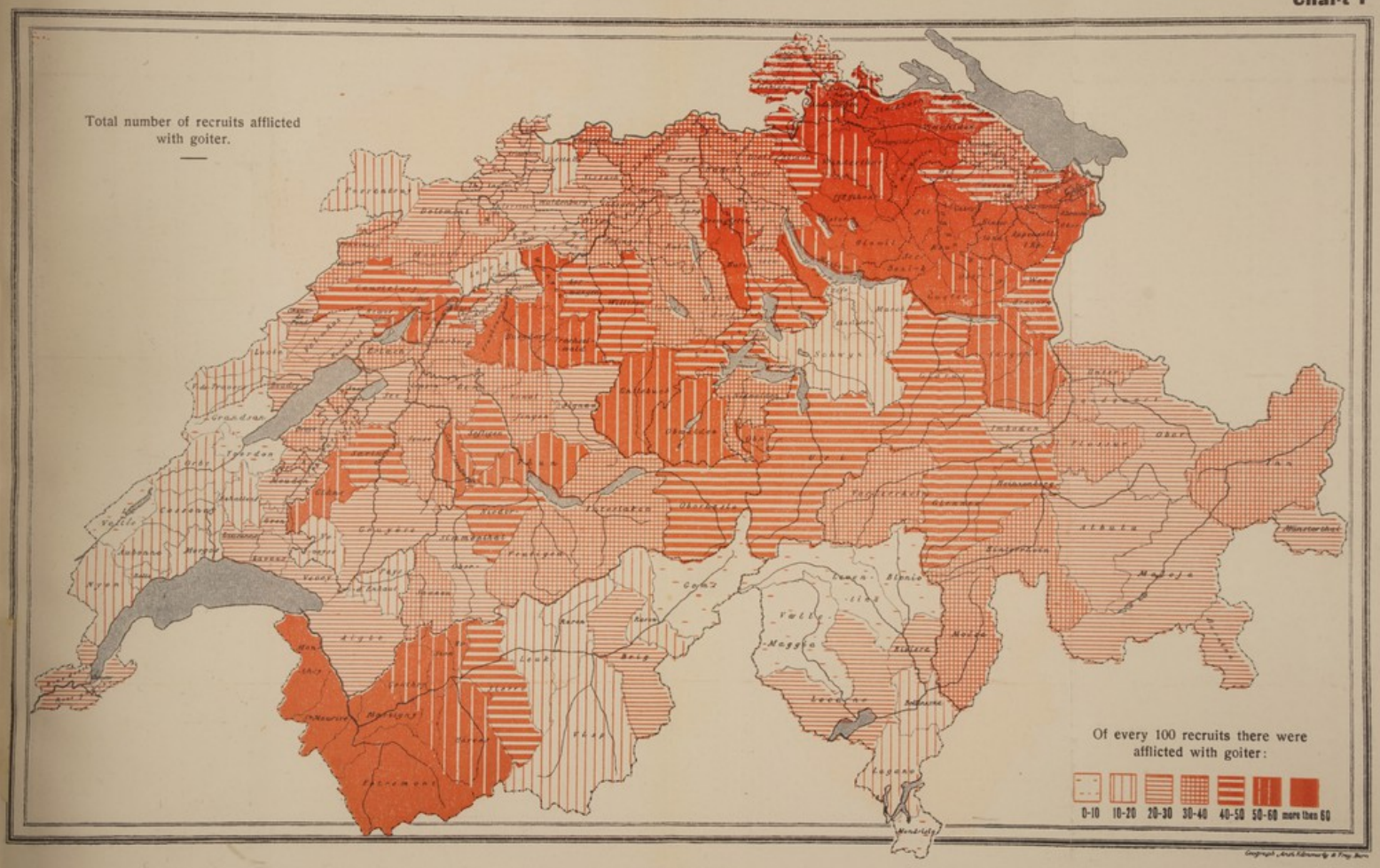
Valais	%
Goms	1,3
Raron	2,0
Leuk	3,2
Hérens	3,3
Visp	3,8
Brig	5,7
Sion	7,1
Sierre	7,2
Monthey	10,1
Entremont	10,2
Martigny	11,2
Conthey	12,2
St-Maurice	19,5

Neuchâtel	%
Val-de-Travers	1,2
Le Locle	1,7
Neuchâtel	2,3
Chaux-de-Fonds	3,1
Boudry	4,5
Val-de-Ruz	4,7

	%
Genève	5,0

The Endemic Goiter with the Recruits of the Years 1924 and 1925.

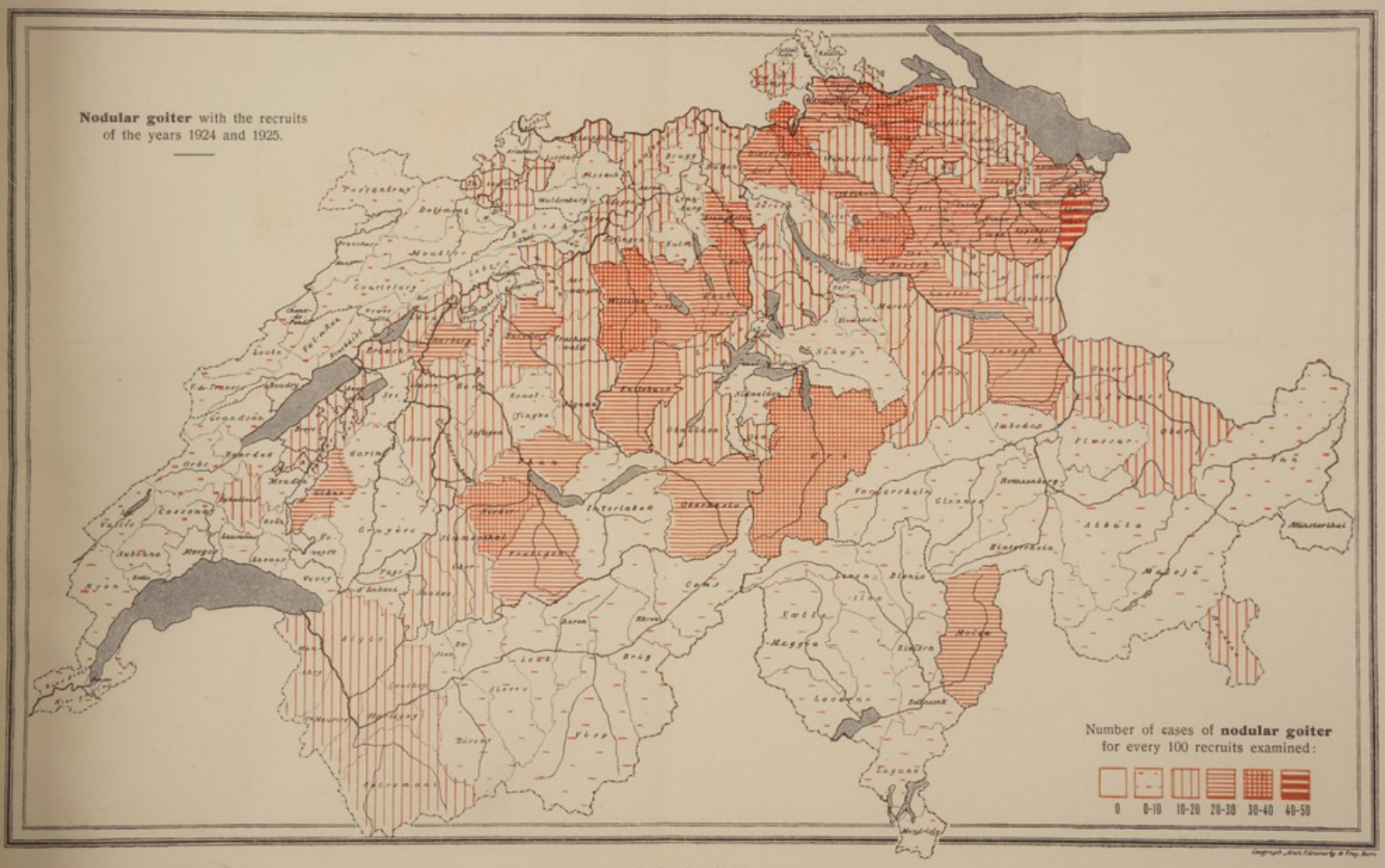
Chart 1



By Dr. Otto Stiner.

The Endemic Goiter with the Recruits of the Years 1924 and 1925.

Chart 2



By Dr. Otto Stiner.

greatly increased in very recent years on account of the more difficult training, that is required for the modern technics of war.

The intensity of the epidemic has also diminished in Switzerland; a fact which is in agreement with the reports coming from other countries, that are afflicted with goiter. What is specially brought up in our memories, when we hear any mention made of mountain goiter, viz: the abnormal shape and enormous size of the goitrous thyroid glands, is beginning to get more rare. It is moreover not our montainous regions, which supply the great number of recruits freed from military service on account of goiter, but on the contrary the low-lying strips of land and especially the large goiter centers situated in the high plateau lands.

Two striking regions, where we find the frequency of goiter increasing with a lower location, are the Rhone valley as far as Martigny and the Rhine valley up to the Lake of Constance. These regions truly vouch for the observations, which had already been reported by Professor Galli-Valerio, that there is an increase of goiter cases in descending from the high regions.

But we can also see from the table and chart No. 2 that the intensity of the endemic, the seriousness of the goiter variety takes a reverse course. For example we find in the highest situated regions of the Canton of Valais from 9,3 to 17,6 % of goiter patients, whereas the low-lying regions exhibit even as many as 80%. Nevertheless there was not a single recruit sent back as unfit for military service from the very low-lying regions; not until we reach the high lying districts, that have for the Canton of Valais the lowest average figures for goiter, did we find that a certain percentage of the men was sent back. The conditions at the Rhine bear a certain similarity to this, in so far as it pertains to the Cantons of Grisons and of St. Gall. The total number of goiter sufferers in this part of the river valley is very high, even up to 60 %, but of the 56 % of recruits who were drawn from the district of the Lower Rhine Valley and who were afflicted with goiter, not one was rejected, and of the 69% of the upper Rhine Valley district only 1,2% were sent back.

In the high plateau lands goitrous conditions and unfitness for military service plainly run along parallel lines. The great goiter centers in Central Switzerland, viz: Lucerne and the southern part of the Canton of Aargau, and in Eastern Switzerland, viz: the southeastern part of the Canton of Zurich and the western parts of the Cantons of Thurgovia and St. Gall, exhibit the greatest percentages of unfitness for military service on account of goiter.

N.B

Now-a-days goitre is the widespread tid. more less in the mountains the reverse is the case in valleys and plateaus the severity not widespread distribution zum Land.

In the Lower Alps this law is less pronounced. In the Lower Alpine regions of the Cantons of Berne and Lucerne the percentages of sufferers from goiter run quite high, approximately up to 50 %, and the number of those unfit for service is correspondingly high, up to 5,3%. On the contrary in the Canton of Appenzell, which is so seriously afflicted with goiter, i. e. with some 60,9 to 67,4%, the number of those recruits sent back as unfit on account of goiter, is relatively low, viz.: from 0,5 to 1%.

For the purpose of gaining ready information regarding the results of the goiter research I have presented them in two charts. Chart No. 1 exhibits the total number of recruits, in whom some modifications of the thyroid gland had been discovered and Chart No. 2 gives us the numbers of those afflicted with struma nodosa. It appeared to me to be a matter of the greatest importance to gather data on the diffusion of the nodular goiters. The populations of our typical endemic regions had always been making a distinction between the nodular goiter and the diffuse swelling of the thyroid gland, and even at the present time we may now and then have to listen to a strong protest, if we venture to tell a patient that he is afflicted with goiter, whereas he is of the opinion that it is merely « a thick neck » and insists on the correctness of his opinion because no nodule can be felt in this thick neck. This layman's point of view is constantly receiving more support anew through the constructions of the pathologists, that the nodules in the struma nodosa are to be looked upon as adenomas, i. e. as genuine tumors. Perhaps the time will come when we shall ventur to make a definite distinction between the adenoma of the thyroid gland and the conception « goiter », which is too general and too vague for modern science. Such differentiation has already been made for the other neoplasmas of this organ.

The adenoma of the thyroid gland ought very likely to be appreciated differently from the diffuse struma from an aetiological point of view also. The survey over the diffusion of struma nodosa, which is presented in Chart No. 2, will give evidences for this view, which has previously been declared by McCarrison and other investigators. Whereas the opinion that was expressed no longer ago than at the last session of the goiter commission, viz:, that the rather surprising frequency of goiter in some of the regions of the French part of Switzerland originates from the « Confédérés de la Suisse allemande », lacks as a whole any and every proof whatsoever, it does not hit far from the mark in regard to the origin of the relatively few nodular strumas. Those afflicted

with these strumas have to a great extent German-Swiss names, which plainly betray their origin from our endemic regions. It is not a question here of goitrous immigrants. If we know how many German-Swiss, quite especially the Bernese peasants who have for a long time been dwelling in these regions, have been preserving their mode of living and manners and particularly their nutritional customs through many generations, then we can find an explanation for the tendency to a definite goiter variety, which can be distinguished from that of the original natives of the region. Whether we ought not rather to look upon the matter of heredity, so often mentioned in the aetiology of goiter, for which just such families transplanted from endemic districts in non-goitrous regions are taken as evidence material, as a simple conservative maintenance of the former manner of living, might be decided without any great difficulties right in the relatively small and easily controlled strips of the Neuchâtel and Bernese Jura Mountain regions.

In certain regions it seems remarkable to us to observe the parallel course of goiter in general and nodular goiter in particular, but in other regions there is a strong divergency. The Canton of Uri has 41,0% goiter cases as a whole of which 31,4% are nodular struma; while on the contrary in the Glenner district, which also lies at a high altitude in the mountains of the Canton of Grisons there are in 43,1% of thyroid enlargements only 7,8% permeated with nodules and in the Valais district of Hérens of 51,1 % not even more than 3,3% etc.

Relative to the intensity of the goiters there are still greater differences. I have already stated, that in 83 districts out of a total of 186 there occurred no exemptions from military service on account of goiter in the years 1924 and 1925 and that such exemptions in 24 other districts were less than 1%. The total number of the recruits, that were declared to be unfit on account of goiter, was 1,3%, whereas in the year 1886 it was still 11,4%, in 1891 8,7% of all definitively examined recruits (Hunziker). It can probably not be looked upon as a matter of chance that, coincident with the great economic boom, which Switzerland enjoyed at the beginning of the second decade of the present century, the severe varieties of goiter also grew less and less in number, viz., in 1911 and 1912 there were 2,9% recruits respectively unfit for service owing to goiter. The explanation for this condition is to be seen directly in the betterment of the standard of life of great numbers of the population, which is proved for that period.

* * *

Frequency of Goiter in the border regions of the Cantons of Freiburg and Vaud, according to Dr. G. Décoppet.

It could be taken for granted that the precise examinations of the recruiting commission would throw light on several matters which had from time to time come up for discussion within the pale of the goiter commission. In order to have the much contested question of goiter conditions in the Freiburg-Vaud boundary regions cleared up, the Swiss Federal Service of Health instituted some special examinations in addition to those of the official recruiting commission. These examinations were undertaken by a specialist, who came from the surgical clinic of the University of Berne. The results of these investigations are illustrated in the accompanying diagram.

We can see from the diagram that the assumption does not hold, that goiter ceases at the western boundary of the canton of Freiburg and that the Canton of Vaud, which is supplied with the salt

of the Bex salt works alleged to contain iodine, is free from goiter, but that the inhabitants of the Vaud enclave which is entirely surrounded by Freiburg territory, who differ but little in their mode of living from the Freiburg population, are exceedingly goitrous. We may say right here that the Vaud members of the goiter commission had even a long time ago declared that the Bex salt does not contain any iodine and that the Canton of Vaud is not free from goiter.

Naturally some attention was also given to the question as to how those villages and districts, whose names have become almost famous in medical works because of their being entirely or quite free from goiter, compare with the goitrous regions in regard to the critical judgment of their young men by the recruiting commission. Some quite surprising condition were found here, which seem to urge a revision of the researches that are looked upon as supporting the aetiology of the lack of iodine.

Th. von Fellenberg in his day took upon himself the great labor to investigate the distribution of iodine in the world about us by making a thorough study of the different material at his disposition. In doing this he also analyzed a number of articles of food derived from villages on the one hand that were alleged to be free or almost free from goiter and on the other hand foods from goitrous regions, and in the former he found a high percentage of iodine and in the latter a low one. In this manner he created an apparently certain basis for the assumption that goiter is due to a lack of iodine in the alimentation.

von Fellenberg chose for his comparative investigations the Jura town of La Chaux-de-Fonds, which in his opinion was, as a whole, free from goiter, and the Emmental village of Signau, in which goiter is prevalent, and furthermore in the Jura mountains of the Canton of Aargau the villages of Effingen, Hornussen, Kaisten and Hunzenschwil, of which the first named has scarcely any cases of goiter, the second more and the third and fourth considerable. According to the data collected by the recruiting commission this classification is not entirely correct, at least it does not apply to the young men of these villages, who are twenty years of age. La Chaux-de-Fonds is found by this commission to be by no means free from goiter or specially poor in goiter cases and on the other hand Signau was not found to be excessively rich in goiter; in chart No. 1 the district La Chaux-de-Fonds and Signau had even to be classed in the same category, 20 to 30%. La Chaux-de-Fonds

exhibited 21 % of the recruits as afflicted with goiter and Signau 28%. Effingen also is not free from goiter.

There are undoubtedly differences in the amount of goiter cases in the villages selected by von Fellenberg for comparison, but these are so insignificant, as e. g. in La Chaux-de-Fonds, which is rich in iodine, and Signau, which is poor in iodine, so that these places, as also the districts in which they are situated, are not fitted to be used for comparative investigations with the aim of supporting the aetiology of the lack of iodine. More important distinctions are only to be recognized in the nature of the enlargement of the thyroid glands: La Chaux-de-Fonds has 2,7 % of nodular struma and Signau some 10,7 %. If we therefore assume that there is an injurious influence upon the thyroid gland through a lack of iodine, then we are obliged to make the qualification that it is not the enlargement of the thyroid gland, which is dependent on the lack of iodine (for that is also to be recognized in children of regions rich in iodine, e. g. in La Chaux-de-Fonds in more than 50%), nevertheless it is but the degenerative processes in the thyroid gland, the formation of the adenomas.

In making a judgment on the alleged bases of the aetiology of the lack of iodine of the endemic struma, there is moreover a great mistake being made, inasmuch as no attention is given to the fact that the Fellenberg investigations were made in regard to the raw foods, such as they can be obtained in the market, and not to prepared foods, which the housewife places upon the table. In the present age of general traffic the investigations made on the foods cultivated in any village must be considered as an insufficient basis for the judgment of the alimentation of the population, and hence they are still less of any value for any expert opinion on the food that is actually consumed, i. e. of the foods that are served at table.

Professor Gigon has given us a model in his labors on popular alimentation as to how such investigations are to be carried out. He deserted the broad path of the doctrine of alimentation and came down into real practical life. For his determinations as to the nutritive value he did not resort to the textbook data on foods but obtained the p r e p a r e d f o o d s from the family dinners of different circles of the population, and instead of the official reports on the index and the market he examined the housekeeping books of these families.

We can never discuss in real seriousness the question, whether the lack of iodine is the cause of goiter, before we are in posses-

sion of suitable investigations on the contents of iodine in the foods that are ready to be served at table and not of the foods that have been bought at the market, which to a great extent are never consumed in a raw state.

In the little area of land, which constitutes our country, we have four linguistic regions. Swiss of the German, French, Italian and Rhaeto-romance languages are living side by side, but with their language they have also preserved their special characteristics and their customs. The system of alimentation and especially the manner of preparing the foods is quite different in the four linguistic regions. I have already on another occasion expressed the idea, how advantageous it would naturally be, right here in our country where the contrasts are so close to each other, to institute comparative studies on popular alimentation and the consequences of errors. These investigations would, however, have to be made not only in scientific institutions, but also in the households of the different linguistic regions.

If we penetrate into the secrets of the kitchen, with which the investigator is not very familiar, then we recognize above all in the German section of Switzerland, that certain foods in being prepared for the table are cooked in a manner, that no longer any proper account can be taken of the original contents of any substance whatsoever. This pertains especially to a number of foods known to be rich in iodine and vitamines.

To illustrate with an example I shall repeat here the directions for the preparation of spinach, as they are given in the cook-book of a well-known German-Swiss school of domestic science: «Wash the spinach, cook for a short time in boiling salt water, then put into the strainer and cool it by pouring a considerable quantity of cold water over it. Now it must be pressed out lightly and finely chopped.» As we see the water in which it has been boiled passes off through the «strainer», then this great quantity of cold water, which was used for the cooling, is poured off and even pressed out of the spinach. We can hardly expect that any iodine or other easily dissolvable substances have remained in the spinach. Other articles of food, especially almost all of the vegetables, are treated in a similar manner, except a few which are eaten raw.

In this manner great quantities of valuable constituent parts of the articles of food, such as iodine and other mineral substances are removed and other materials as e. g. a great part of the vitamines are destroyed. The want of these latter could probably play at least as important a rôle in the origin of goiter as the relative

deficiency of iodine, according to the researches of McCarrison and my own experiments on animals extending over a period of many years. The vitamines are in part quite thoroughly destroyed, owing to the habit of the house-wives to add soda to certain articles of food, so that they will cook the quicker. It is well known that the vitamines are very rapidly destroyed in an alkaline substratum, even those which are most heat-proof in the presence of acids.

In the Romance parts of our country, at least in the villages and in the original native population of the cities, the system of alimentation is considerably different from that in the German part of Switzerland. There are contrasts to be seen in the preparation of the food articles, which are specially rich in iodine and at the same time in vitamines, from which it becomes evident, without taking for granted that any decisive differences exist in the original ingredients of the foods, that French Switzerland, the Canton of Ticino and large parts of the Canton of Grisons, which were settled mainly by Romance populations, have an entirely different system of alimentation from the real endemic regions and probably just for this reason are entirely or almost free from goiter.

The fundamental difference between the German-Swiss cuisine and that of Romance Switzerland lies in the fact that in the latter the foods containing iodine or vitamines are subjected to no improper cooking, such as is prescribed in the cook-books of the German-Swiss cook. The main dish of the dinner in the ordinary household of Romance Switzerland is the potage or minestra, which is a soup containing in considerable quantities the season's vegetables plainly dressed, boiled and served at table. It is evident that, prepared in such a manner, the valuable secondary foodstuffs, which really impart to the foods the stamp of perfect alimentation, are preserved and not thrown away, as is learned from the recipe just given as an example, or destroyed as in other kitchen customs.

The soups of the German-Swiss household contain cereals as their chief constituent, more particulary in the form of manufactured preparations, or perhaps rice, in which case very finely polished varieties are preferred. As a «green» additament chive comes exceptionally into question. The vegetables are served at table each for itself and were mostly prepared according to the method described for the spinach.

In certain regions, which are sorely afflicted with goiter there are still other bad habits of nutrition, which have for many decades been fought against by judicious physicians. For example, in the regions of Eastern Switzerland, in which the chief center of endemic

goiter lies at the present time, a perfectly white loaf of bread is demanded and in some districts, which exhibit more cases of goiter than the neighboring districts, a white polenta is desired, i. e. a food that is prepared from white Indian meal, which has been completely freed from the seed-case and embryo germ. In the Highlands of the Canton of St. Gall Hoffmann has found dental caries occurring far less frequently than in the northern sections of the canton. This would include also the endemic and especially the nodular struma, as can be seen from the accompanying tables and charts. In the former regions the population consumes nutritious black bread made of maize, while in the latter fine wheaten bread is preferred.

White bread

* * *

That goiter is primarily a disease caused by malnutrition is contested by nobody. It does not do to judge the alimentation of a country with so much traffic, as we have in Switzerland, only according to some of the articles of food that are produced in the country itself, especially because of the exceedingly varied method of preparation given to the foods before they are served at table. The relations of endemic goiter to the lack of iodine as also to the lack of vitamines, if I may be allowed to refer to the previously expressed opinion on another mode of origin of goiter, can be readily explained from the quality of the foods eaten, not of the articles of food. In Romance Switzerland goiter occurs relatively seldom; the foods that are consumed there contain in accordance with the preparation an abundance of mineral matters (including iodine) and vitamines. In German Switzerland, where goiter occurs very frequently, the mineral substances (including iodine) and the vitamines are removed in great part out of the articles of food or even destroyed as a result of the entirely different mode of preparation, before the foods are served at table.

Disease ? Malnutrition

In my opinion the investigations of Fellenberg must be extended a great deal more than has thus far been done over the foods of different circles of population and country districts, which foods have been prepared in accordance with definite recipes, before we can properly understand the question of iodine in our alimentation in a way that is consistent with all conditions. The ultimate successes in the prevention and cure of goiter probably depend more on a suitable revision of the cookbook than on new scientific achievements.

Comments
on the Aetiology and Prophylaxis of Goiter.

By Professor Dr. W. Kolle, Frankfort on the Main.

The endemic goiter, concerning the aetiology and prophylaxis of which we are having discussions here, is in my opinion not to be considered due to an agent of infection in the sense of being an infectious disease. As a proof of this idea let me state especially these facts:

1. It has never been observed that in non-goitrous regions there was any transmission of the disease from a goitrous individual upon a healthy person, not even in the case of an intimate living together as e. g. husband and wife and children.

2. Goiter can not be transmitted from animal to animal, neither through feeding nor through the injection of struma substance.

3. If human beings come from regions that are free from goiter into endemic goitrous localities and there get a struma, it is oftentimes observed that the same goes down again without the employment of any medical measures, when these persons return into the non-goitrous regions.

During this conference almost all theories, which have been advanced for the origin of goiter, have been brought forward, and besides several hypotheses have also been mentioned, for which there are relatively few essential proofs. We see such a variegated aetiological picture before us, so that we can from the beginning say: Such a variety of causes can not give rise to such a typical disease. I therefore arrive at the conclusion that all of these causes, which have been given, are simply accessory causes or factors, which produce the predisposition for the goiter noxa or rather the goiter development. For we of course are aware that a predisposition is necessary so that the goiter noxa can develop its action. If this were not the case, then in endemic goitrous regions all individuals would be afflicted with goiter. We see, however, that many persons in such goitrous districts are spared from this affliction of goiter. All of the secondary causes mentioned, such as elevation, unilateral nourishment, lack of vitamines, close blood relationship, heredity, injury to the nervous system, infectious diseases, cases of poisoning, uncleanliness, hygienic abuses etc., are simply auxiliary factors, which create the predisposition.

However, throughout the entire discussion I have heard no stringent evidence against the theory, that the absence of iodine, as the recent investigations make it appear very probable if not positively certain, is the dominant cause for the origin of goiter. The theory of the lack of iodine up to the present time is seen to harmonize with all facts, especially with that of local distribution. It also receives strong support through the researches as to the iodine-content of drinking water, the soil and the plants, as they have been first followed out by von Fellenberg and have been recently carried out further by other investigators. The objections, which had been brought forward against the method of determining the amount of iodine, employed by von Fellenberg, are certainly not tenable. For, if we are working constantly in accordance with the same method, we shall obtain comparable results, even if the method in itself contains certain sources of error. It is not only possible to eliminate the errors mathematically with the aid of interpolations, but they will always frequently recur with the individual investigations and as a matter of fact more or less in the same direction.

I take this opportunity also to report on a few experiments, which were instituted by Dr. Stiner, Dr. de Mestral and Dr. Vannod in the Swiss Goiter Commission, of which at that time Th. Kocher, the never to be forgotten master of goiter surgery and the champion of goiter research, and likewise Th. Langhans and later Wegelin were members.

The experiments were carried out with goitrous water almost at the same time with Bircher's feeding experiments on rats. We exposed rats in different localities of Switzerland at that time, and as a matter of fact in goitrous regions, e. g. in Valais, the Bernese Highlands and the Emmental, and also in regions that were free from goiter, e. g. in the Jura Mountains. The rats were then nourished in part with water drawn from so-called goitrous streams, which was given to some of them boiled and to others unboiled, furthermore with milk and water, with milk alone, with mixed foods and with a meat diet. Our experiments did not turn out with such uniformity as those of Bircher and even at that time they inspired us with the thought that there are existing in the case of rats exceedingly strong individual differences regarding goiter noxa and goiter development, exactly as with man.

It furthermore became evident that not only those rats which in goitrous regions had received unboiled water, but also those, which were receiving boiled water, became goitrously afflicted and

no such thing as absence iodine

see Stiner just what it does not do

now definitely disproven

see Stiner criticism in v. Fellenberg p. 389 ff.

I saw these

*

*: I saw these experiments in 1912. Because of the way in which they were carried out, of the condition of insanitation in which the animals were kept — the results

that on the other hand individual rats, that had received unboiled water, gave no indication of goiter. Furthermore, some of the rats, which had received only milk, had goiter and likewise rats, fed with boiled milk, had in part goiter and vice versa, some that had been fed with raw and boiled milk remained free from goiter. All of these facts give testimony as well against the idea of poisoning as against the infectious nature of struma, but they all admit of being brought into complete harmony with the theory of the absence of iodine.

It is also interesting that in individual districts, which are in general free from goiter, the rats exposed by us there also became goitrous, e. g. in the elevated regions of the Jura, rats that had been fed in part with milk and in part with water. The geological behavior of such regions is, to be sure, no entirely uniform one and the conditions are very complicated. There are also in regions, in which the soil and the water contain sufficient iodine, some interstratified districts, in which, whether it be secondary or primary, a certain absence of iodine as regards the soil and the water is prevailing.

I should also like to draw attention to the fact that iodine was introduced with the Chile salpeter, that contained iodine, into many countries, which, in order to cover the requirements of nitrogen in the soil, had been using Chile salpeter since the introduction by Justus von Liebig of rational fertilizing methods. Since the introduction of artificial fertilizers this source of iodine for the soil has disappeared. Where intensive cultivation of the soil is being followed, as is the case in many parts of Germany and where the soil is anyhow poor in iodine in consequence of the geological conditions, this falling away of the iodine supply is of especial significance for plants, animals and human beings. There is danger of impoveration of the soil. As a matter of fact it seems that an increase of strongly marked goiter has made its appearance more particularly among the schoolchildren, but there are also incretorial disturbances, which perhaps stand in relation with a dysfunction of the thyroid gland as a result of the absence of iodine. However the hunger blockade of Germany, which developed its actions during the war and for a considerable time after the war, has probably occasioned the predisposition for goiter with many, who in Germany are especially predisposed for such irregularities in alimentation. The addition of iodine to the fertilizer, in order to satisfy the demands for plants, animals and man, is a question that deserves attention.

Ground idea

That the theory of the absence of iodine, nevertheless, has thus far been the best established theory as regards the origin of goiter is learned best of all from the experiments, which have been made with the dispensing of iodine in the endemic goiter regions, particularly among schoolchildren. We already have learned of favorable experiences from the various countries. Disturbances on account of the small quantities of iodine do not appear at all to come into question here or, if they do, with an exceedingly small percentage of human beings. With these no dispensing of iodine must take place. The great decrease of struma endemica among schoolchildren, who are provided in goitrous regions with tablets containing a small quantity of iodine, is exceedingly striking. It is just such experiments that ought to be followed up under medical supervision. At the same time the addition of iodine to the table salt in goitrous regions and the giving of iodine, whether in the form of concealed or in the form of open prophylaxis, must however be further looked into. It would be very gratifying if it would be done everywhere as is done in a few countries, e. g., in Switzerland and Upper Bavaria, if as comprehensive statistics as possible would be collected on the occurrence of goiter, with separate data for school-children and for older individuals, furthermore on cretinism and on the results of the iodine prophylaxis.

The theses of Messrs. Wagner-Jauregg and Silberschmidt contain all that can be said on the iodine prophylaxis of goiter. The conclusions are scientifically correct, namely, the dispensing of iodine to the population with ordinary kitchen salt (pure table salt) and with tablets, containing a small quantity of iodine to the school-children. The iodine prophylaxis is to be looked upon as successful and harmless, in so far as we have thus far been able to judge.

Notes on the Epidemiology and Aetiology of Goiter and Cretinism.

By Th. Lang, M. D., Munich.

The German Institute of Psychiatrical Research (Deutsche Forschungsanstalt für Psychiatrie) at Munich (Kaiser-Wilhelm-Insti-

tut), through its genealogic-demographical section, on the request of the Bavarian government and the district authorities of Schwaben and Neuburg, has been carrying out, since May 1925, extensive investigations on goiter, cretinism, idiocy and deaf-mutism in the Allgäu, a part of Bavaria where those affections are most endemically prevalent. The plans on which the inquiries are proceeding have been supplied by Professor Rüdin, director of the aforesaid section.

On the one hand, it is intended to determine by accurate inquiry the endogenous factors of the affections named among families and tribes; on the other hand, and as far as the frame of the investigation will allow, attention is also to be given to the exogenous factors. The material for the family tests has been collected by us through inviting notifications of any mentally abnormal subjects from all localities within the districts investigated, viz. those of Lindau, Kempten and Sonthofen, notifications we obtained with rather uniform completeness through the competent officials, such as parish authorities, schoolmasters, village doctors, auxiliary teachers etc. The persons thus recorded, and their families, were personally visited by my predecessor, Dr. Ernst, and in each case a diagnosis was drawn up, respectively, on cretinism, idiocy, senile dementia etc. Cretinism was diagnosed only in the presence of somatical characteristics, without regard to mental deficiency. The material was proceeded upon according to Weinberg's method of employing test-subjects, i. e. examinations started in every instance with the actually recorded persons. Thus, from notifications received and visits made up to now, amounting to about one half of the prospective total, we have obtained 182 cases of cretinism, 252 of mental deficiency, besides a few smaller groups of cases which were left out account, such as pure deaf-mutism, hardness of hearing, schizophrenia etc.

The examinations were moreover extended to 111 subjects having undergone operation for goiter, and to their families. Finally, 155 railway employees, natives of Allgäu, and their families, have been amongst others examined comparatively.

A statement as concise as possible may here be given of a few initial results that seem to us worthy of consideration and as extracted from the bulk of the examinations, aiming, as these are, at the total comprehension of parentage and consanguinity among the test-groups:

In the first place, and at variance with the principle advanced by Taussig: « no cretinism without maternal goiter », we diagnosed

* This principle would be better expressed as:
" no cretinism without maternal thyroid insufficiency

goiter only in a percentage of 77 of mothers of cretins: 23 % of the mothers of cretins in the Allgäu are and have been exempt from goiter. It should here be added that we have numbered as a goiter case every statement concerning a former enlargement of the thyroid gland, e. g. «thick neck (Bläh-hals) at the first birth» and so on. A second classification bore on the connection between the prevalence of cretinism and mental deficiency on the one, and the size of a locality on the other part. (Tab. 1.)

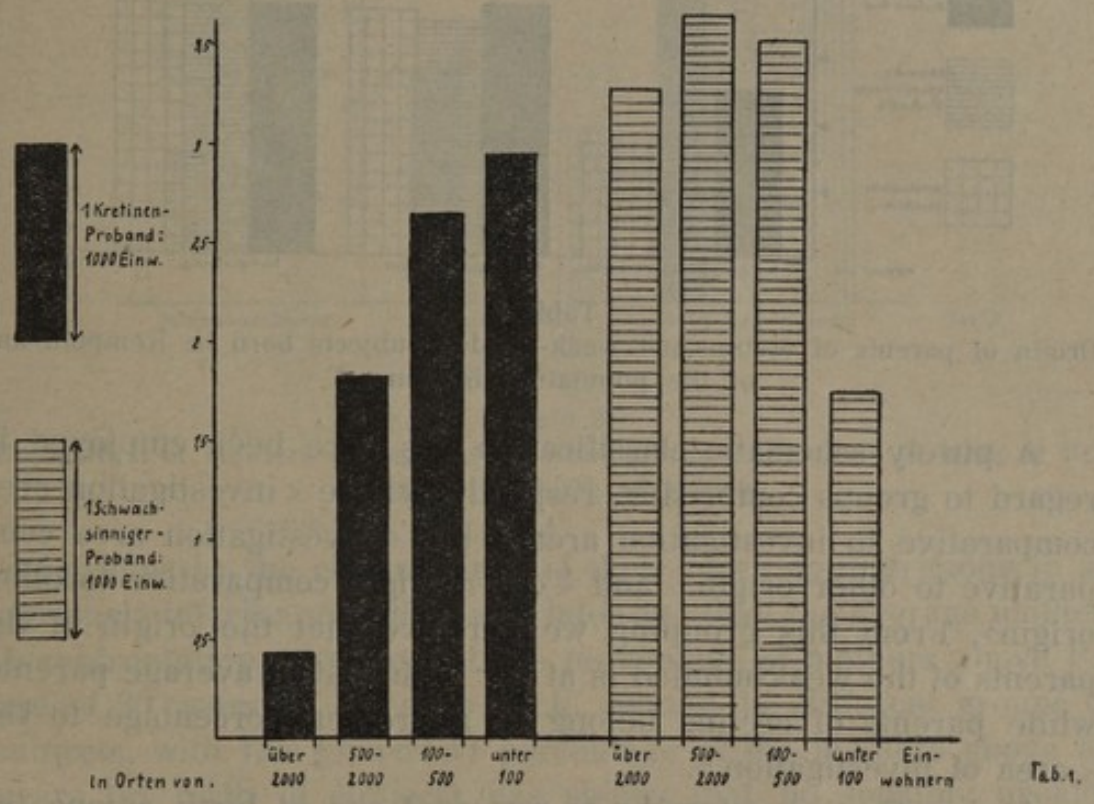


Table 1.
Relation of prevalence of cretinism and mental deficiency to size of locality.

Within the area most efficiently investigated, viz. the district of Kempten, we have classified 99 cretins and 148 mentally deficient subjects correspondently to the size of their places of birth and in confrontation with the total number of inhabitants of all localities of a respectively similar size in the same district. As a result, we noticed a regular increase of cretinism in an inverse proportion to the size of localities. As regards prevalence of mental deficiency, no such connection was discernable. An obvious explanation for this would seem to lie in the fact that the smaller villages are generally situated at elevated altitudes and that cretinism be found prevalent in this relation, i. e. that size of locality be of no importance. This inference would however be in contra-

diction with the circumstance that only 33,32 % of our smallest cretin-centers (with less than 100 inhabitants) are situated at more than 800 meters above sea-level, as against 36,66 % of the villages with 100 to 500 inhabitants.

A synopsis as to the origin of parents of cretins and weak minded subjects born in Kempten town in relation to its average population is furnished by Table 2.

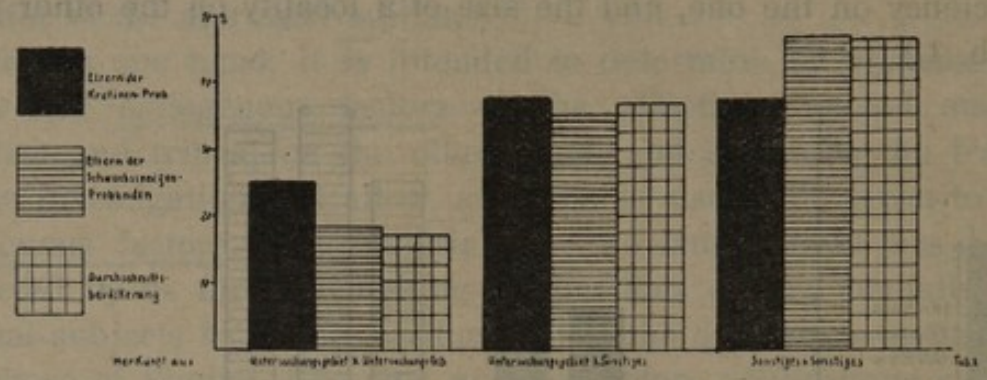


Table 2.
Origin of parents of cretins and weak-minded subjects born in Kempten and of the population in general.

A purely schematic classification has here been employed in regard to groups comprising, respectively: the « investigation area comparative to investigation area », the « investigation area comparative to other origin » and « other origin comparative to other origin». From this grouping we perceive that the origin of the parents of the weak-minded is at par with that of average parents, while parents of cretins belong in a greater percentage to the « area of investigation ».

A classification referring to maternal age at birth among the different groups of subjects, viz. of cretins, weak-minded, goiter-operated, and, on the other side, subjects belonging to the rail service, was also effected. In the junior groups — « up to 30 years » — we find a stronger contingent of mothers of goiter-operated subjects and of railway servants, which may be considered as belonging to the average population of the Allgäu; whereas, in the senior groups — « 31 to 40 years » and « over 40 » — the mothers of cretins, as well as of weak-minded subjects — these latter, though, in a lesser degree — are more pronouncedly represented. A differentiation between mothers of cretins and of cretinoid subjects shows, on the other hand, that the former are in greater number among the senior age-groups than the mothers of cretinoids. We might be induced to explain this prevalence of mothers of cretins and weak-minded subjects among the senior

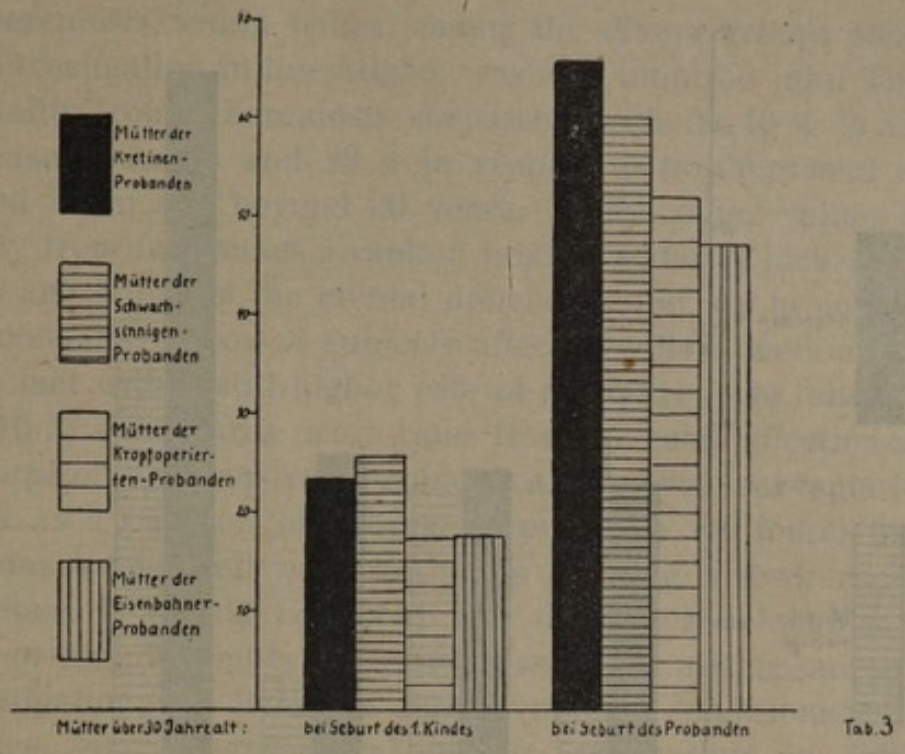


Table 3.
Repartition of mothers among the different groups of subjects at birth of first child and at birth of subject.

age-groups by the circumstance of their reaching matrimony in an obviously inferior condition, at a later age than the average mother. A confrontation, however, of the percentage of mothers above the age of 30 years at first birth, among the different groups of subjects, with the general percentage of the mothers above 30 years (at birth of subject) has shown that no sensibly greater proportion exists of mothers of cretins and weak-minded subjects, having reached maternity at advanced age, as against that of such mothers among an average population; but it showed, nevertheless, that the elder classes of mothers take a proportionally larger share in the procreation of a weak-minded individual and, even more so, of a total cretin, than in the production of an average population *). We have therefore to consider the higher procreative age of a mother as a factor tending to favor the birth of a cretin.

age of the mother

A further differentiation was established in respect to the position of cretins and weak-minded individuals in the order of births; here we have, naturally, not limited our count to the immediate subjects of investigation, but included also the secundary

*) Our tribal series having been established in each case with an investigation subject as a starting point, the comparison between the two groups here in question cannot but be considered precarious and approximative.

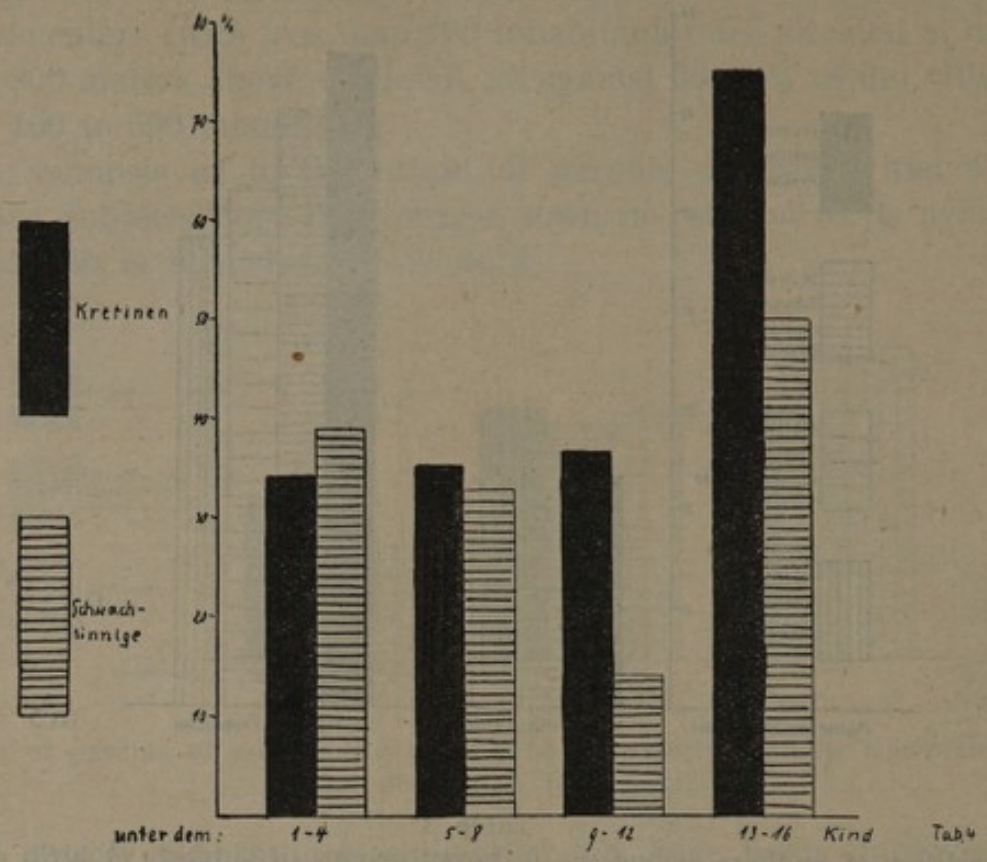


Table 4.
Position of cretins and mental deficients in the order of births.

cases traced within the tribes of cretins and cretinoids. The totals thus gained we confronted with the totals of all births, generally, occurring in the same respective order and which, along with the subjects of investigation, were eliminated from observation only at ages above 5 years. In cretinous families, a continuous increase of cretinage can be observed as in parallel ascendancy with the progressive order of births. The families of the weak-minded, however, would show a steady proportional decrease of mental deficiency until the 12th birth.

Both these groups share, at all events, a complicity in the production of abnormal subjects in connection with successively late births. In the present classification, as well as in that relating to parental origin, a distinction results regarding cretinism and mental deficiency, from which, however, we do not wish to conclude that a closer connection might not exist, all the same, between certain forms of mental deficiency and cretinism. It is to be pointed out that we have classed as mental deficients all the weak-minded subjects found exempt from physical characteristics, and categorized as cretins all persons thus marked, regardlessly of the gravity of mental defects, if at all existing. (See Table 4.)

Tuberculosis within tribes, among the divers groups subjected to our investigation in the Allgäu, was also inquired into: The rate of mortality from tuberculosis surpasses, with its 16 % in respect to deceased parents and 26 % in respect to brothers and sisters deceased at an age beyond 20 years, all the other values found. Mortality from tuberculosis ranked next in order of incidence with parents and tribes of the mental deficients, and, up to now, it was only among the tribes of subjects affected with dementia praecox that we met with a still higher rate of mortality from tuberculosis, viz. 31,16 %. As regards death-rates from the same affection among our groups of goiter-operated subjects and railway servants (which we took as a paragon of average population) we found them to tally remarkably well with the rates existing elsewhere among populations. It should be noted that the tribes belonging to the cretins, mental deficients and railway servants, among our subjects of investigation, are living in rather uniform conditions and surroundings, viz. in agricultural callings and mostly in dispersed farms or villages; in the case of railway servants only, tribes are in a greater proportion to be reckoned among the industrial and artizan workers.

A comparison effected between two graphics: the map of « tallness », based on Ranke's survey of army recruits of 1875, and Weichardt-Schlittenhelm's map of goiter diffusion in Bavaria — showing, on the one hand, as regards Southern Bavaria, the existence of a great number of tall individuals and, on the other hand, in the very same districts, a strong prevalence of goiter — has prompted me to investigate, upon a sufficiently abundant material, the contingency of a correlation between goiter affection and tallness. On the basis of data — unfortunately available only for a small part of Bavaria — all the recruits born in the districts of Kempten and Sonthofen and mustered in their respective district-court from 1905 to 1914, have been classified according to height, goiter affection and fitness for service: a pronounced increase of goiter frequency was found to be concomitant with increasing height. The prejudice which is frequently taken against the accuracy of military statistics, is not borne out, in my opinion, in the case of goiter occurrence, this anomaly being never overlooked at medical examinations, were it only on administrative grounds, since it has to be strictly taken into account in connection with the narrowness of uniform collars. Moreover, it has to be considered that a survey carried out upon a sufficiently large amount of material, must

— even admitting inexactitude to a large extent as to the figures of frequency of the somatic characteristic — produce nevertheless a correct proportional statement on the subdivision of groups, the latter having naturally to be regarded as of uniform accuracy or inaccuracy, as the case may be.

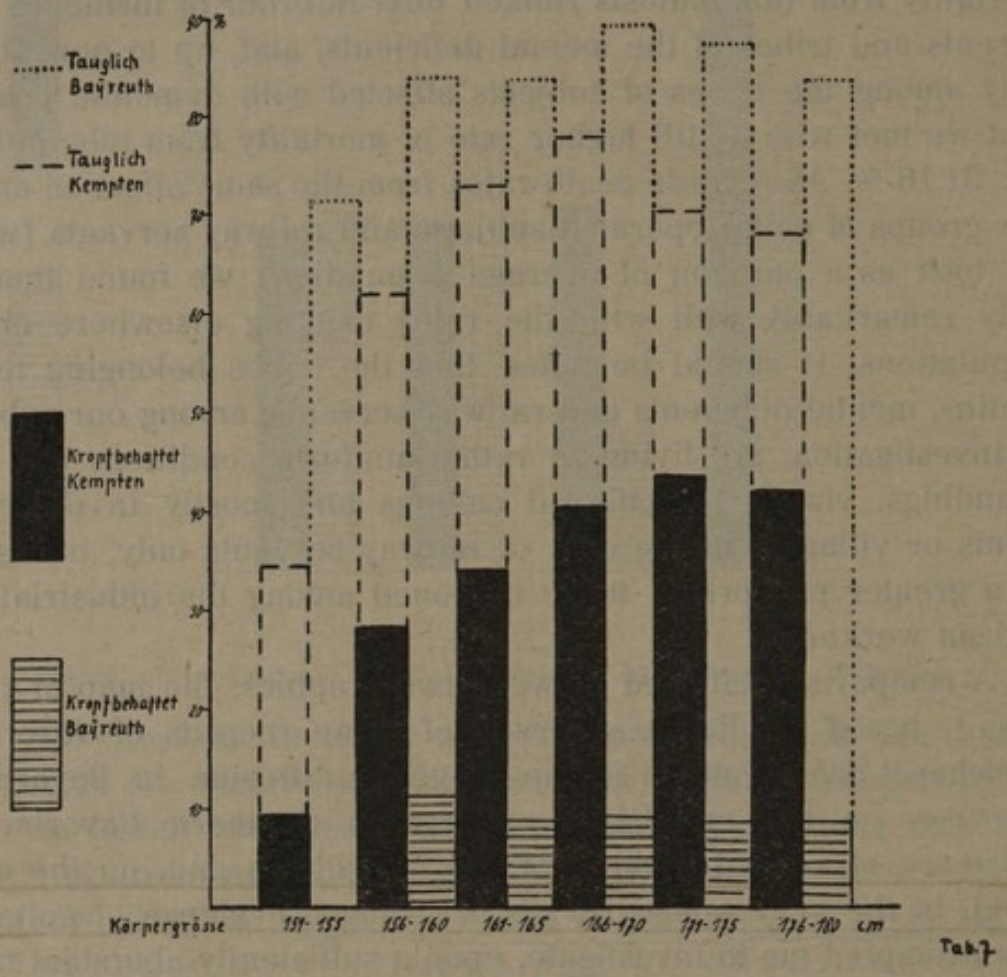


Table 5.
Goiter prevalence, Height of body and Military fitness in a goiter endemic area (Allgäu) and in a non-endemic area (Upper Franconia).

Since it had been possible to establish a correlation between goiter and size of body, in a district presenting so strong a goiter endemic — the adult native population of the Allgäu is affected to the extent of 35 % — it became naturally interesting to probe a non-endemic, or scarcely affected, territory as to a potential similar correlation. The town and country district of Bayreuth was chosen therefore and confronted with an endemic district of equal size, viz. the town and country district of Kempten. In the Bayreuth district — showing a goiter frequency of about 8% only — no correlation between goiter and tallness of body was noticeable (Table 5). Recrutes measuring « less than 150 cm », as well as those « above 180 cm » are left out, owing to the

fact that in both these categories unfitness had been declared prima facie in almost every case, and goiter, therefore, hardly taken account of.

The further question of a possible connexion between goiter frequency and cranial index — similarly to that found to exist between the former and tallness — was gone into on the basis of material afforded by the post-mortem reports of the « Rechts der Isar »-Hospital of Munich, readily put at our disposal by Professor Dürck; no reliable material of sufficient extent having been available within the Allgäu region. The material thus investigated by us would show an increase of the goiter affection in connection with brachycephaly: whereas, among dolichocephalous subjects, goiter affections numbered 14%, they rose to 22 and 23%, respectively, among the hyper- and ultrabrachycephalous. It must be pointed out, however, that our material has been yet on too limited a scale to permit of a definitive deduction being drawn. The aforesaid investigation had for its basis 894 post-mortem reports of the year 1925 on subjects above the age of 20 years. The repartition of the cranial index of the investigated material in respect of dolicho-, meso- and brachycephaly having been found to agree exactly with the values ascertainded by Ranke among 1000 skulls of Old-Bavaria (correlative coefficient of both curves: 0,97), we may consider our Munich material as representative of an average Old-Bavarian population.

In the interpretation of the correlations thus obtained, one might primarily be lead into the assumption that hypertrophy of the juvenile thyroid coincide with the greater length of body of its bearer, or, inversely, that in tall individuals, the greater stress resulting from a strong tendency to growth would have occasioned a strumous enlargement. The fact, however, that this correlation of goiter prevalence and tallness has only been ascertained in an endemic district leaves yet room for the conjecture — in presence also of the greater goiter frequency found up to now among hyper- and brachycephalous individuals — that endemic goiter take its hold with a certain partiality on the ground of a racial predisposition of the inhabitants of an endemic center.

The theory of goiter origin propounded by Répin and Pfaundler, finally, would seem to allow of the surmise that the actinic influences on goiter development, assumed by these authors, do not defer manifesting themselves until extra-uterine

life, but might already exert a directive action at the time of conception, or during intra-uterine development. We have therefore classified all the 20 year old recrutes of the years 1905 to 1914 from the districts of Kempten, Lindau and Sonthofen according to month of birth, goiter affectedness and fitness for service: The dates of birth of the individuals affected with goiter were not found to be equally distributed along the year, but a curve, presenting two apexes and two lowest points, has resulted: goiter frequency was found to exist most markedly among those born in January and May, together with those conceived in April and September. The total number of individuals classified amounted to 3105.

The fluctuations of the curve are quite compatible with the margin of faultiness if the simple square average of faultiness is assumed, but they will not withstand the assumption of the triple square average. An analogous curve was obtained in the classification of 5891 recruits born and mustered in the city of Munich, according to goiter frequency and month of birth, a curve whose apexes, however, were shifted (in relation to the Allgäu) by one month, respectively. As with the recrutes native of the Allgäu, goiter frequency among these Munich subjects was found to be lowest with those born in autumn. In resuming the whole material so far classified as to month of birth, goiter frequency and fitness for service — a total, that is to say, of 10,685 recrutes mustered in the years 1905 to 1914 in the administrative districts of Kempten, Lindau, Sonthofen, Füssen, Tölz, Miesbach and Munich city — we find the curve of fitness to run pretty evenly along all the months; the curve of goiter affection, however, presents two apexes and two lowest points. The lowest goiter frequency is shown also in this case to exist among the individuals born in autumn, i. e., accordingly, conceived in the winter.

With the interpretation of the two latter curves, the question will naturally arise also as to whether any possible modifications in diet and manner of living of the mothers — concomitantly with the different seasons — may not exert an influence. We regret that the material till now collected, as concerning congenital strumae, does not suffice for a classification to be made with a view to ascertaining whether these bearers of a congenital struma be born more or less frequently within a certain season.

A more definite interpretation of the results of investigation here presented would not seem to be called for, since we are un-

able to say to what extent results, analogous to those we have obtained in the Allgäu, might be forthcoming from other parts and proceeding, perhaps, from a more comprehensive material. We hope, moreover, to deal more precisely with these questions at a time not too remote, i. e. on the occasion of the publication of the results of the investigations in their totality.

Maternel Influence an Etiological Factor in Endemic Goiter.

M. O. Shivers, M. D. Colorado Springs, Colo. U. S. A.

In discussing the maternal influence as a causative factor in goiter it must be understood that it should be considered as only one of the many agents in the production of thyroid disease and not the sole cause.

The chief difficulty in determining the maternal influence in the etiology of endemic goiter lies in the fact that we possess too little actual data, having in the past depended on determinations not substantiated by recorded cases.

In some sections of the United States large numbers of animals suffer with « big neck » or goiter and a large per cent is lost — rate running as high as 70%, particularly in the Northwest. If iodine is given to the mother while she is carrying her offspring no such phenomenon exists.

Pregnant animals: iodine in.

Kalkus, working in the Meshon Valley, State of Washington, U. S. A. where congenital goiter is prevalent among animals, showed that he was able to produce goiterous or normal kids from the same ewes by giving or withholding iodine during pregnancy, showing conclusively that the mothers influence the development of goiter in the offspring. Hart and Steinbach experiments were equally conclusive when carried out on pigs.

Mc Carrison in « Experimental Production of Congenital Goiter » 1913, 1914, states « The factor of the presence of goiter in the mother is of great importance in the genesis of congenital goiter in the offspring. Not only were 100% of the offspring of goiterous mothers born with congenital goiter but also congenital goiter occurred in two kids born of control mothers which had acquired goiter in pregnancy ».

Baillarger (1873) made a survey of France to determine the incidence in various regions and in his report discusses the in-

fluence of heredity. He found children of goitrous parents had a predisposition to develop goiter although they were not subject to endemic influences. These cases will develop goiter if the hereditary influence is strong enough. This familial influence was also evident in the instance of goiterous persons who left an endemic region and yet their children born several years later were found to have goiters. These children, having the predisposition to develop goiter in an endemic region, did not show goiter symptoms at birth but developed a goiter during childhood.

Vallery-Radot (1922) found thyroid heredity principally transmitted through women and in the cases of Basedow's disease they oberserved similar cases of heredity occurring in several generations and affecting several children in one family.

Simon Levin, State of Michigan, U. S. A. — in an unselected group he found 1146 goiters in 1783 persons. He investigated the histories of these cases for the localization of the disease in families and he found that in the case of 22,2 per cent of the patients the fathers had goiters, in 85,4 per cent the mothers were affected and in 67,6 per cent of the cases the children showed the disease.

J. M. Summers (1915) summarizes his observations of many family histories in which goiter was very prevalent, by stating that there are too many family histories showing a high incidence of the disease to disprove the inheritance of it.

Bess Lloyd's survey to ascertain the frequency of occurrence of diseases of known hereditary tendency in two large populous centers in the United States of America noted that a study of family histories for as many as four generations showed the familial tendency to goiter to be more noticeable the second and third generations.

E. E. Holland, State of Indiana, U. S. A. gives a very full report and discussion on hereditary goiter manifested in five consecutive generations, thus contributing to the literature information that is most instructive and convincing on the subject of heredity.

J. Earl Elise notes that if a mother has goiter her offspring will suffer from congenital goiter or that it may be manifest by a weak thyroid in the child that later in life will develop a goiter more readily than in the normal individual.

All authorities, chief of whom were Marine and Kimball U. S. A. agree that in the prevention of goiter in man, the administration of iodine to the pregnant mother will prevent the development of goiter in the offspring, showing conclusively that the mother is a great factor in the etiology of goiter.

Hertzler states that « the familial occurence of goiter is a common observation. Whether this is due to heredity of environment or a biological heredity is another question. It is common to see a number of members of a family affected. I have had a grandmother, the mother and three daughters consult me at the same time. Most likely heredity plays a prominent part. Not infrequently there is a family type in that all members affected become so at the same age. Some families do so at an early age, say below fifteen, others again at a late age, say after thirty ».

Ernest Jones, London (1917) discusses occurrence of goiter in parent and child. The problem of the occurrence of various thyroid affections in members of the same family is an extremely interesting and obscure one. He records a personal case and urges a report of cases so as to complete our knowledge on this subject.

I have noted that goiter becomes more toxic as the number of generations are affected. For instance the grandmother at 70 showed her first cardiac manifestation, the only daughter at 56 and the four grandchildren were toxic at 19 — 26 — 31 and 32 — sex equal in number. The girls became toxic earlier than the boys, the girls in the second and third decades and the boys in the fourth.

I have a large group of families in which we have been able to study the heredity feature in three generations in the Rocky Mountain section of the U. S. A. — the original member of each family developing goiter while living in other sections of the States.

Many investigators are positive that goiter is not often inherited and consider family history as unimportant, others after careful study of many cases are convinced that heredity is a prominent factor. So-called goiter districts are on the increase in the United States of America. It is quite evident that only three generations are necessary to develop a goitrous focus. There must be some reason why daughters of goitrous mothers develop thyroid disease. Certainly a higher per cent of girls than boys become victims of abnormal thyroid. A communication from Mrs. G. states « in regard to the goiters in our family, mother has had one, two of my sisters, I have a goiter, and our two girls, also Mr. G. Our two boys, 12 and 14 years of age do not show signs of goiter at this time ».

No one should question the maternal influence as an etiological factor notwithstanding the fact that no absolute explanation of how it takes place has been put forth. Is it a difference of thyroxin needs of different individuals, or the inability of the mother to produce sufficient thyroxin to meet the requirements of the foetus, or is it direct transmission of some infection to the offspring after

birth in the children who do not suffer from congenital goiter? Surely there must be some reason why if a mother has goiter many of her girls will develop the disease and virtually all the girls and a good number of boys in the third generation will become affected. A most interesting fact is that the family need not remain in the locality where the original member developed the disease. They can be removed to another community and the peculiar phenomenon remains unchanged. It is further interesting that no other family in the same block or locality will develop the disease in the new community, while goiterous grandmothers have many goiterous offspring although buying groceries from the same store and drinking from the same water supply as their more fortunate neighbors. It seems if the above phenomenon could be explained a starting point in the cause of goiter could be obtained.

If we accept Rosenow's theory of selective action of bacteria then any organism might be a causative factor in any group of cases. For example a mother suffering from goiter might be a victim of colon vaginitis. By caring for her offspring she could easily infect especially the girl babies. This may account for the frequency in girls over boys. We have been able to isolate colon bacillus from the vaginal secretion of a large number of young girls suffering from goiter. No attempt has been made to produce goiter in animals from this group of patients. The vaginal canal may be one of the normal habitats of the colon bacillus, yet it may be proven one of the avenues of infections of the thyroid gland.

genital infection.

Do the reproductive organs play an important part in the maternal influence of goiter, or is the vaginal tract an avenue of infection and the girl babies become victims of the disease in this manner, thus elimitating the maternal influence as a causative factor? I think not.

1. There seems to be sufficient data to prove the maternal influence as a factor in the origin of goiter.

2. The method of inheritance has not been definitely established.

3. The so-called Mendelian law does not account for all the phases of hereditary goiter.

On the Causes of Endemic Goiter.

By Prof. G. Pighini, Reggio-Emilia (Italy).

My personal contribution to the study of the aetiology of endemic goiter is based upon direct observations made in endemic localities in the regions of Belluno and Brescia, and, more especially, in the Province of Reggio-Emilia, as well as on laboratory experiments undertaken in the Psychiatrical Institute of Reggio-Emilia.

From observations carried out on the spot I have gained the conviction that an immediate connection exists between the consumption of certain waters for alimentary purposes, and the endemic. A very cogent documentation of this close relation is accessible to anyone, for instance, in the upper Valle del Torrente Secchia (Prov. of Reggio Emilia) in that part of the valley, that is to say, which comprises the vast gypseous banks of Triassic origin and through which percolate the waters consumed by the local populations (from wells, brooks, springs and the torrent). Those waters abound in mineral elements, the aforementioned Triassic rocks, an ancient calcareous formation, having undergone transmutation through various mineral agents and among which predominate sulfurous gases; numerous mineral springs are in fact emerging at the basis of the Triassic banks and discharging into the Secchia torrent. The water carried by this torrent is exquisitely goitrigenous: supplies of it having been taken in large bottles to my laboratory at Reggio-Emilia, I found it producing thyroid enlargement and degeneration in white rats that were kept on it. All the inhabitants of the hamlets situated on the banks of the torrent and making use of its waters in their hydric alimentation, are afflicted with goitrous cretinism. Not one of the families of millers established all along its course — from the upper end of the Triassic gypseous zone and beyond it, throughout the valley — can claim indemnity from the atrophy, and it is not difficult to find cases of deaf-mutism, mixoedema, cretinism, among the members of those poor miller families.

A further proof of the fact of those Secchia waters being acutely goitrigenous may be deduced from the circumstance that none of the families of millers living in the zone above the

aforesaid gypseous Triassic banks, where the torrent runs between the strata of « macigno » sandstone, of which the so-called Eocene rock of the upper Apennines is formed, not one of the families consuming the waters permeating it is affected; neither there, nor in the villages situated at the foot of the Apennine crests is endemic goiter met with any further. The endemic, instead, follows the torrent down the valley and all along its course, even beyond the exquisitely endemic zone; and it is a very demonstrative fact that the waters of the torrent, in emerging from the valley to spread laterally and subterraneanly into the plain, are feeding the wells of the neighbouring villages — among them Salvaterra, Magreta, Marsaglia — there to propagate the endemic with the same characteristics as those prevailing in the high mountains.

No goitrigenous waters are carried by the other Apennine torrents in that neighborhood, such as the Enza, the Parma, the Baganza, the Taro, on the one side, and the Panaro, on the other.

The aqueduct providing the town of Reggio-Emilia obtains its supply subterraneanly from the Enza torrent, and these waters are proved to be innocuous, while the province of Modena had to renounce the use of the Secchia waters, they having been recognized to be goitrigenous in their subterranean courses at Magreta. Miller families immigrated from the regions of neighboring torrents into that of the Secchia were found to have contracted the endemic within a short time. Such of the Secchia millers, vice-versa, as had passed to the Enza mills — and who were known to me — recovered from the endemic before long.

I have insisted upon this typical example as illustrating the close correlation of the waters consumed and the endemic, being of the opinion that, preferably to general observations, special studies ought to be pursued in determined and circumscribed zones, within which it will be possible to discern the pros and cons of the many theories obtaining in respect of the aetiology of goitrous diseases.

Having considered the general hygienic conditions of the populations of those regions and the chemico-biological qualities of the waters consumed, I was able to convince myself that a solid ground is wanting for the assumption held by the sustainers of the exclusive goiter genesis concerning infiltration from stables or faecal sediments: no bovine animal, above all, is kept in the hamlets of millers ranged along the Secchia. The scarse villages there existing are situated at great distance from the Secchia banks, and few

herds only can be met with in that region, deprived as it is, almost entirely, of pasture ground and coppice, even in the parts not consisting althogether of bare rock. Moreover, the limpid waters of the Secchia torrent, examined by me in large proportions, were not found to contain germs or impurities to any greater extent than those of the neighbouring non-goitrigenous torrents, and I do not think there can be question, in regard to the former, of contamination from excrementitious or faecal materials.

Nor is it consistent, concerning the Secchia waters, to impugn a deficiency of iodine, since in repeated laboratory experiments carried out by me after the methods of von Fellenberg and Paolini, the presence of iodine in these waters has been proved without exception; the proportions vary from one half to the one thousandth part of a milligram per liter (the latter minimum having been ascertained in spring, when the affluence from melting snows is at its height. Besides, the fact of many chloro — sodic — magnesian — sulfuric springs discharging into the Secchia torrent, renders the presence of small quantities of iodine — analogously with other similar springs — presumable).

As a result of further experiments, pieces of rock taken from the banks of the Val di Secchia have yielded — on treatment with immune water — a distillate which has produced typical strumae upon some chickens and white rats to which it was given, and of which strumae I have deposited some specimens in the present exposition. The water, therefore, may be held in all probability to have extracted from those grounds a chemical element acting upon the organism in provoking the degeneration of the thyroid.

* * *

But, what is the nature of that, or those, toxico-degenerative principle, or principles?

That is the problem! —

I believe that the question may be answered when a complete chemical and physico-chemical examination will have been made of waters that have proved to be goiter-producing.

Up to now, I have not found myself in a position to carry out such investigation, but hope to be able to do so, at some future time, with the collaboration of a proved chemist.

Meanwhile, I limited myself to experimenting with various chemical substances that have been met with in different riverine waters, some of which belonging to the composition of the Secchia torrent waters, and I have thus completed the experiments made

with other substances selected according to certain determined criteria.

Those experiences are referred to in detail in my recent works, and several histological preparations of thyroid alterations encountered have been presented to the Exposition of this international Conference.

My researches have resulted in proving that the chemical substances which, in being administered to animals orally or by means of injections, may produce thyroid alterations resembling those characteristic of certain stages of human goiter, are in great number.

Among the inorganic principles I shall here refer to the salts of selenium, tellurium, borium and fluorate; among the organic substances many amines could be named, such as hydrazine, p-Phenylene diamine, guanidineacetic acid, histamine, choline, also some fatty acids, among which the oleic, butyric and propionic acids.

Of some of these substances, experimental pharmacology has demonstrated that they are being methylated within the animal organism; selenium and tellurium, for instance, go through the urine as methylselenium and methyltellurium, while guanidineacetic acid is transformed into methylguanidine-acetic acid, i. e. in creatine (which then passes into creatinine).

His and Hofmeister, already, had admitted such methylation within the organism to be possible as effected by a preformed methylic group, acting as a methylic ether acts «in vitro» — such as, e. g., the chlormethyl or the iodomethyl — upon these bodies, in transforming them, that is to say, into methylated composites.

As to the transformation of the guanidineacetic acid into creatine, it has, further, resulted from the researches of Stuber and Schenk that its methylation is brought about by means of the iodic principles of the thyroid: in fact, in an animal the thyroid of which has been removed the said transformation does not occur any longer; while, if the animal deprived of its thyroid is treated with thyroid extract, or with a serum from a healty animal, containing the active principle of iodine, or, even, by a simple iodic cure, creatine is again found in the urine.

It is thus demonstrated that it is to the thyroid, and to its iodic principles especially, that the main action in that methylation has to be ascribed.

As regards the fatty acids, also, which we have experimented,

the occurrence of chemical substitutive reactions through the iodine of the organism may be contemplated.

Iodine might be acting, also here, as it does «in vitro» when there is question of determining the so-called «iodic number» of non-saturated fat.

Thus, my researches have to a large extent been conducted with the purpose of experimenting on the thyroid such substances as might be attacked chemically by the iodized hormones of the thyroid itself; to observe, in other words, the behavior of the thyroid in the case of the organism becoming intoxicated from substances which may be supposed to enter, also within the organism itself, a chemical reaction with the iodine on combining with the hormones of the thyroid.

Among these substances, there are, as said before, those which the organism is able to methylate, viz. the guanidine-acetic acid, the selenium, the tellurium, the boron; various amines which «in vitro» react with the halogene paraffins — of which the methyl-iodide is the most active —; and, furthermore, some fatty acids which also react with iodine.

We have seen how all these various substances turn out to be reacting, each more or less than the other, upon the thyroid; some of them, owing to their elevated toxicity, evince degenerative reactions, whereas they produce only from highly attenuated doses those reactive hyperplastic forms illustrated in my works.

In assuming this mechanism on the part of the iodic principles of the thyroid, we have to anticipate an alteration of the gland in each case where abnormal substances are circulating within the organism, and capable also of entering with the aforesaid principles a chemical reaction.

But, in what manner is the alteration of the thyroid to be determined?

Here, again, we navigate among hypotheses.

To remain on what I have verified in initial strumae, the primary reactive phenomenon in the gland is that of the congestion of its capillary perifollicles, their colloid acquiring a greater fluidity and tending to be reabsorbed by the circulation.

The glandular parenchyma, under these new conditions, exhibits signs of an embryonal reawakening, whence the mitoses, the epithelial new-formations etc., which are to be met with at that first stage. The hyperplastic (of Basedow type) of the gland would take place only — as Marine has justly observed — in the case

of a rarefication of its iodic content, bringing it to a point below 0,10 %.

According, then, to the theory here evolved, the pathogenetic basis for goitrous disease might be represented, not by the mere hunger for iodine, but by an intoxication responsible for inducing iodine hunger in the organism.

* * *

From the sum of the observations made — to which I have to add the experiments on nutrition carried out upon white rats on a diet deprived of iodine, and which gave me athrophic thyroids, instead of hyperthrophic ones, as a result — the following provisory conclusions may be drawn:

1. Goitrous cretinism is in direct correlation with the consumption of certain determined goitrigenous waters.
2. The active principles of such waters are, probably, not represented by any specific germs, but by chemical substances, elaborated, may be, by micro-organisms having a toxic influence upon the organism and, simultaneously, in a direct manner upon the thyroid.
3. Those toxic substances, very likely, enter into action with the iodic compounds of the organism and, more especially, with the iodized hormones of the thyroid.
4. Many substances, either foreign to the organism or generated by it, abnormally in certain physico-pathological circumstances — such as the climateric, during pregnancy, or in the course of exophtalmic (Basedow) goiter — may enter a reaction with the iodic principles of the thyroid; and, therefore, a plural genesis of goiter should be admitted, i. e. one connected with various causes which, though differing among each other, would produce similar effects.
5. Those goitrigenous substances are in all probability contained in the potable waters of endemic territories, though, perhaps, in quantities to be termed infinitesimal. In some places, as, for example, in the goitrous zone of the upper Val di Secchia, the abovesaid substances reach the waters through certain chemical components of the local ground dissolving in them, while in other localities they might also come through other channels.

6. I am not as yet in the possession of sufficient data to venture an affirmation as to whether any one among the many substances experimented by me may be seriously taken into consideration in connection with the aetiology of goiter. Further analytical researches upon the chemical and bio-chemical compositions of goitrigenous waters are necessary, and the possibility should be kept in view that the agents to be investigated might be elements of rare occurrence and active, perhaps, in quantities exceedingly small.

I agree, may be very thesis

I am glad to find that my present conclusions agree in great part with those of my learned colleagues who have preceeded me in this discussion; with the thesis sustained, that is to say, by Professors Bérard and Galli-Valerio, regarding the correlation of the endemic and potable waters; with that of Prof. Bérard, in particular, as concerning the connections between the goitrigenous agent and the iodic metabolism directed by the thyroid, and, finally, with the thesis propounded by Prof. McCarrison and Bircher as to the manifold nature of the agents capable of provoking goitrous affections.

Epidemical Goiter and Avitaminosis.

By Dr. Marcel Rhein, Strasburg.

What I am about to state to you is neither the result of experiments nor that of observations; it is knowledge gathered through the reading of old works that treated on the aetiology of endemic goiter. For there are few diseases about which we possess such a profusion of former observations. They are only awaiting to be utilized.

I should like to contribute here some thoughts upon that particular appearance of endemic goiter, which we call the epidemic goiter. It is not necessary for me to explain to you what is meant by epidemic goiter. It is distinguished from the ordinary endemic goiter through the fact that it afflicts simultaneously a greater or less number of individuals living together under the same roof as, e. g. in barracks, boarding-houses, orphan asylums and prisons. Moreover, it appears very unexpectedly, in 10 to 20 days, from which fact arises that other name of 'acute goiter. The number of observations that were made in the course of the

epidemic Goiter

very acute epidemics of Basi-thyr

19th century is rather considerable. Excellent and numerous accounts of these have appeared principally in the Military Medical Review (Recueils de Médecine militaire). Laveran, military physician, to whom we owe the discovery of the haematozoa of paludism, has compiled them in his « Treatise on the Diseases in the Armies ». In our days, epidemic goiter is seeming to become more rare. It even seems to have disappeared from the armies. It still sometimes appears in boarding houses and orphan asylums.

This is not a dangerous disease; the great attention which is given to it in pathology is above all of a theoretical nature, for every viable theory of endemic goiter must embrace this special manifestation, which is the epidemic goiter. Diverse explanations of epidemic goiter have been attempted particularly in relation to the special conditions of military life, but as soon as we endeavor to apply them to the epidemics, which occur elsewhere, e. g., in prisons, they lose their value entirely. In reality, there is no satisfactory explanation of epidemical goiter.

What we can look upon as positive information in the observations made regarding epidemical goiter can be expressed in a few sentences: 1. The epidemical goiter has always appeared only in the regions, where endemic goiter prevails, e. g., in France at Briançon, at Annecy, at Clermont-Ferrand, at New Breisach and elsewhere. 2. The officers and sub-officers of the regiments or battalions afflicted have at all times remained unafflicted, even those who had been living in the midst of the troop. 3. Not the slightest contagion on the part of the civil population through the afflicted soldiers has ever been observed nor, moreover, of other soldiers of other unafflicted regiments, who hat been placed promiscuously among the diseased soldiers. (There is on that question a very interesting and conclusive experiment made by the military physician Czernicki). 4. No simultaneous appearance of goiter has ever been observed among the civil population accustomed to use for drinking purposes the same waters as the afflicted soldiers, which proves the complete failure of the theory of the hydric transmission of the goitrigenous principle, at least in the epidemic goiter.

Among former observations I have found two of particular interest and which, as it seems to me, give us the key to the enigma of epidemic goiter. Both of them date back to the 18th century. The one was related by Simonin in his « Medical Topography of Nancy »

Vitamin Deficiency might work to produce "epidemic" goiter in this way: a positive goitrigenic agent which can

and is in relation to the thesis of the military doctor Valentin, entitled as follows (I intentionally am giving the exact title): « Dissertatio medico-chirurgica de struma bronchocele dicta et hemeralopia ». Valentin observed about 700 cases of epidemic goiter in the time from 1784 to 1789 and an equally high number of hemeralopia cases among the soldiers of Ste. Catherine barracks at Nancy. It should here be recalled that we understand by hemeralopia the blindness occurring at the close of day (Night blindness), especially uncomfortable for the soldier on guard, as it prevents him absolutely from distinguishing anything even in moonlight.

vitamin deficiency

The other analogous case is found noted in Thouvenel, « Treatise on the Climate of Italy », a work which appeared in 1792. Thouvenel relates, in speaking of epidemic goiter, that the observation has frequently been made of the occurrence of epidemic goiter and hemeralopia in the garrisons stationed upon the banks of the Rhine.

We accordingly see on two occasions a coincidence or an alternation of epidemic goiter and of hemeralopia. Do we have here simply a fortuitous coincidence, or are the same causes at the bottom of two diseases so different? I believe in this latter way of looking at the question. For the treatment of the two diseases has likewise strong analogies. This is principally alimentary: in hemeralopia, beef liver, and in epidemic goiter an augmentation of the rations and allocations of wine are indicated; later on the iodic treatment was added. Now, we know to-day that hemeralopia is an avitaminosis disorder and even one of the most genuine examples: keratomalacia and hemeralopia appear when there is a deficiency of fat and disappear rapidly after ingestion of vitamine A, called also liposoluble factor A. In that case, by analogy, would we not likewise be able to apply the idea of avitaminosis to epidemical goiter? I answer in the affirmative. This would explain 1. the immunity of the officers and sub-officers, of whom the alimentation, and on that question there can be absolutely no doubt, was more varied and better than that of the private soldier. 2. The non-contagion of the civil population which possesses likewise the means of taking nourishment a little more according to its inclinations.

Everything takes place in the epidemic goiter as if, in consequence of a special avitaminosis, the organism was much more susceptible to the influence of the goitrigenous principle. It is, as it were sensitized. It is the endemic goiter rendered much more

Subjection to such deficiency, might, therefore, cause the "Epidemic". Compare here-there.

swift and simultaneous upon organisms that are prepared in common.

This attempt to explain epidemic goiter as an avitaminosis finds a real support in the hypotheses and recent experiments on the aetiology of endemic goiter. I should like first of all to call attention to the opinion of Mr. Stiner, who on different occasions has described endemic goiter as an avitaminosis, and to a very recent work of Mr. McCarrison who, with the aid of nourishment deprived of vitamines, has succeeded in developing goiters in white rats. You are likewise able to see, along the same line of ideas, in this exposition, a beautiful preparation which was brought from the Institute of Professor Huguenin, made by Miss von Fischer, which shows thyroid glands of white rats that had been fed with, and without, vitamines. Professor Silberschmidt has likewise in his report called to our minds in persuasive language the important rôle of vitamines in the development of goiter.

Hemeralopia as well as scurvy have frequently been observed in the crews of ships at sea, but epidemic goiter never. It remains riveted to the land and even to special kinds of ground, to the goitrigenous soils or, in order to continue in the thought which I have drawn from the study of the distribution of goiter in Alsace, to the sub-soils with special hydro-geological conditions, as, e. g., subterranean flowing sheets of water, which are at no great depth. The avitaminosis renders the organism susceptible to the attack of the goitrigenous principle, which must still be fully determined. The avitaminosis performs the functions of a mordant. Numerous relations between the internal secretion and the vitamines are already known to us, I refer to the works of Mr. Abderhalden and of Mr. Biedl; the described relation would still have to be added to those.

For that reason there is also the almost complete immunity of the wild animal in respect to the endemic goiter — which has been observed by many authors and above all by the lamented scholar B. Grassi — it becoming goitrous only when kept in captivity in a country where goiter prevails and as it is not able to select nourishment according to its desires. I call your attention in regard to this subject to the beautiful preparations of Professor Huguenin, shown here, and I refer to the interesting work of Mr. Fox, of Philadelphia, which contains a great number of observations of goiter in wild animals kept in captivity.

Can we place under the same head of ideas the epidemic goiter of the trout, which has made such great ravages in the United

States? Is it provoked by a too uniform system of alimentation, which we understand means the same as alimentation without vitamines? Mr. Marine explained this at the Congres of Comparative Pathology at Paris, in 1912, as the effect of an aphysiological alimentation. Should this prove to be the case, it would be a fine example of comparative patho-physiology branching out from the fish and the birds up to the mammalia.

What is it that we can derive from this way of looking at it: an avitaminosis or an aphysiological alimentation as the cause of epidemical goiter?

1. For the investigation of the goitrigenous principle, it will afford the experimenter a much more accurate test; his experiments will proceed much more rapidly when he will use animals that have been made sensitive. Nevertheless, it will be necessary to determine the best composition of the food required to produce sensitiveness.

2. The idea as stated could give an explanation of the variations in the intensity of endemic goiter and principally of the strong augmentation towards the end of the war and after the same, in the countries, in which the food had to be rationed (a goiter wave).

The War & Goiter.

3. With respect to the prophylaxis, we are impelled to let the nourishment be as rich as possible in vitamines and as varied as possible, a thought which has already been advanced by Mr. Stiner. Is it due to its wine, that France owes its great diminution of goiter? (Professor Bérard drew attention to the extensive consumption of wine in the French villages.) It appears to me that this might be possible.

I herewith bring my remarks to a close. Without refusing in any respect whatsoever to recognize the great importance of internal iodine in the physiology of the thyroid gland, in the origin of goiter and in its prophylaxis, I believe that the idea of avitaminosis or aphysiological nourishment throws a new light upon the problem of goiter.

See Memoir

* * *

Recapitulation.

Among the earlier observations on epidemic goiter it is fitting to mention two as being particularly interesting from the aetiological point of view.

The one was reported by Valentin in his thesis of 1789 which bore the title: « Dissertatio medico-chirurgica de struma broncho-

cele dicta et hemeralopia ». Valentin noticed at the same time, from 1784 to 1789, a strong epidemic of goiter and of hemeralopia among the soldiers of the Ste. Catherine barracks at Nancy. There were more than 700 cases examined.

The second observation was mentioned by Thouvenel in his « Traité sur le Climat de l'Italie », dated 1797, in which he relates that he has frequently seen acute goiters in combination with hemeralopia in the garrisons of the Rhine.

This coincidence of the two diseases both of which have an epidemic course, does not seem to be an accidental one. Since hemeralopia is an avitaminosis, a similar origin must be admitted for epidemical goiter. But, whereas hemeralopia and the other classical avitaminosis, scurvy, have been seen a little everywhere, even upon ships at sea, epidemic goiter remains riveted upon the goiter districts. Everything occurs as though a special avitaminosis made the organism more sensitive in regard to the goitrigenous principle. The primary cause of epidemical goiter, as for the endemic form, is the goitrigenous cause, which is still unknown. The avitaminosis performs only the function of a sensitizing body in the epidemic appearance of goiter. The immunity of the officers and non-commissioned officers, as also the non-contagiousness of the civil population in the epidemics of garrisons easily admit of this explanation. To that circumstance is also due, without doubt, the strong recrudescence of goiter during and after the war in the countries which were obliged to allowance their foods (Wave of goiter).

These ideas find a sound support in the observations and deductions made by Mr. Stiner on the endemic goiter and in the recent experiments of Mr. McCarrison. Perhaps we can even bring into connection here the epidemic goiter of the trout, which has been described by Mr. Marine as the consequence of an aphysiological alimentation.

It follows that in the experiments on the aetiology of endemic goiter, the investigator will have every interest to feed the test animals without any vitamines, so as to render them as sensitive as possible in a very short period of time.

In regard to the prophylaxis, it is summed up in a system of alimentation, which is as varied and as rich in vitamines as possible.

The Aetiology of Endemic Goiter.

By Dr. Maurice Freyss, Strasburg-La Robertsau.

In accordance with the request of Professor Galli Valerio, I desire to state in a few words what the ascertainments are, which have been made in France in the Department of the Lower Rhine in regard to the aetiology and the distribution of endemic goiter.

The work of Dr. Rhein entitled «The Distribution of Endemic Goiter in Alsace», which was published in 1923, and the explanatory chart to go with it, make it clear to us that in the Departments of Upper and Lower Rhine there are two very distinct zones, which are goitrous, namely, the valleys of the Vosges Mountains and a broad strip of land which extends along the Rhine. In the Department of Lower Rhine this strip of land corresponds, as it seems to me, to the region between the Rhine and the Ill rivers. The entire intermediary part between the slope of the Vosges and the region of the Rhine is about uninfected, above all in the region which constitutes the terrace of Loess, where the sheet of subterranean water is very deep. It is just the contrary of what we find between the Rhine and the Ill, where the subterranean sheet is found to be two or three meters below the surface and in certain districts even less.

Since the year 1924 we have carried on an inspection of schools in the Department of Lower Rhine. Up to that time it existed only in the cities, especially at Strasburg. The results of the examination of the schoolchildren of the two years 1924 to 1925 and 1925 to 1926 enable us to determine anew to what extent the disease of goiter is spreading in this department. I have become convinced by the statistical data that what Dr. Rhein had observed is perfectly exact. Moreover, I have been able to state precisely the frequency of goiter for certain regions. The result for the department as a whole is: in 1924 to 1925: 4.1 % palpable goiter, 3.3 % visible goiter, 0.97 % goiter, that was strongly hypertrophied; in 1925 to 1926: 3.8 % palpable goiter, 2.7 % visible goiter, 1 % goiter, that was strongly hypertrophied. There was no real difference between the two years.

The relatively low percentage is due to the almost complete absence of goiter in the intermediary region between the Vosges Mountains and the Rhine river and to the fact that the frequency

of goiter has diminished in the valleys of the Vosges Mts. for reasons analogous to those, of which Professor Bérard has spoken in his report; namely, improvement of hygienic conditions in general, better selection of the sources of water, influence of tourism and emigration. In many of the valleys there are still some cretins but they are for the most part aged individuals and they are becoming more and more rare.

I do not desire to confine myself principally with the goitrous region which extends along the Rhine. This is unquestionably the region, where goiter is at present the most prevalent in the department and where it has even in some places increased. In the region of Markolsheim, down the stream from Colmar, I found more than 40 % of goiter among the schoolchildren. At Markolsheim itself the medical inspector of the schools found 54 palpable goiters, 44 visible ones and 10 strongly hypertrophied ones in 241 children. The hygienic conditions of this region seem to be evidently bad ones, and the possibility of infection through the subterranean sheet of water is evidently greater than elsewhere.

I now pass over to the Robertsau region, where I have been studying the goiter question for some twenty odd years and since 1924 in collaboration with Professor Borrel. Tourdes found among the schoolchildren of the City of Strasburg in 1854 some 7 % with goiter and among the schoolchildren of the Robertsau, at the gates of the city, some 19 %.

Krieger, Woehrlin and Fischer discovered in 2630 schoolchildren of the city in 1883: 32 % afflicted with light cases of goiter, 6.4 % with medium sized goiter and 2.2 % with strongly developed goiter. At the Robertsau in 566 schoolchildren there were 44.2 % cases of light goiter, 7.7 % of medium sized goiter and 1.6 % of strongly developed goiter. At the present time it is necessary, so it seems to me, above all to point out the great difference which exists between the frequency of goiter among the schoolchildren of the two suburbs, situated upon the border of the terrace of Loess, namely Kœnigshofen with 10 % and particularly Kronenberg with 2 %, and of the suburb of Robertsau with 22.2 % (1924 to 1925).

The study of the aetiological conditions of the goitrous endemic of the Robertsau region has shown up defective hygienic conditions of this center. The level of the subterranean sheet of water is from 2 to 3 meters below the ground, a fact which I have been able to determine through some open wells, that are still to be found in this place. At certain times the level varies only a little, but when

the Rhine rises it occasions strong oscillations. It is accordingly a question of a subterranean layer of water, which is in motion (Dr. Rhein), and is contaminated by the numerous draining-wells, which are formed from the overflow on account of the cesspools; besides, by the dung, the liquid manure, which is employed in great quantities by the market-gardeners and the cultivators. It is among the market-gardeners and the cultivators and secondly among the wives of workmen, that I have observed most frequently the goiter and also the most voluminous forms of the fleshy goiter. On the other hand, I have never seen any of them among the boatmen who go on entire days' journeys to look for gravel on the islands of the Rhine.

The urban canalization of potable water was installed at la Robertsau a long time ago, but a part of the population does not make use of it and prefers the water of the wells, which have a variable depth say from 4 to 7 or 8 meters, i. e. from 12 to 24 feet. That these waters are of a very bad quality has many times been proved by the analyses made at the Hygienic Institute.

As school medical officer I was able to ascertain that 66.4 % of the schoolchildren, who were afflicted with goiter, were drinking in 1924 the water of the wells that were fed by the subterranean sheet of water, and 33.6 % the water of the municipal water system. Other ascertainments made it clear that 61 % of the goitrous children were living on the ground-floor. Accordingly we see that goiter prevails among individuals who live near the ground. The significance of an unhygienic dwelling in regard to the aetiology of goiter has oftentimes been noticed. At la Robertsau there are very many low houses, constructed nearly level with the ground, in which it is necessary to descend a step in order to enter them. I have frequently found other symptoms of endocrinian disorders among the inhabitants of these dwellings: among the young girls at the time of puberty, and among adults and old people cases of chronic, disfiguring rheumatism, attributed by Leopold Levy and by Rothschild to a thyroidean incompetency.

As a class of young girls of about 10 years of age at the school had made an impression on me because 18 out of 30, say 60 %, were afflicted with goiters of considerable size, Professor Borrel suggested that the stools of these scholars should be examined. Worms These observations were conducted over 60 scholars in all, who were goitrous. Through these researches, not only was the frequency of infestation made obvious but likewise the indications of infestation. This latter fact was indicated through the number of

eggs, that were found for 100 microscopic fields in analogous conditions of observation.

For the sake of making a comparison, the search for the eggs of helminthes has also been made in the feces of young girls, who were not afflicted with goiter and who were attending a school of Strasburg under normal conditions of urban alimentation. There was no goiter at the school.

Whereas 90 % of the young girls, who were living in a goitrigenous district, presented indications of intestinal parasites, only 25 % were observed in the district, that was non-goitrigenous. The intensity of the infestation can be understood still more from the comparison of the average indications of infestation, which are as high as 93.4 % in the goitrigenous center and only 30 % in the center that is free from goiter. Among the goitrous children there were 51.7 % infested with ascaris, 80 % infested with trichocephales and among the non-goitrous there were 5 % infested with ascaris and 20 % suffered from trichocephales *).

Must we accept the thought that this verminous infestation of the intestinal canal, which appears to be one of the best indications of digestive contamination (Borrel), is the only aetiological cause of goiter, as it has been observed among schoolchildren? I do not believe that this is so. As has been brought up many times in the course of this conference, there are a number of causes, which can be combined. These little girls were approaching puberty, their entire nervous system was being put under a strain every day at school. (Professor Veil has shown the significance of the nervous system in this question). Above all, they were living in a center where goiter is at all times endemic.

The conclusion, which we can drawn here, is this: that in a goitrigenous center, we must not forget to search for helminthiasis among the goitrous individuals, of keeping the intestinal tube clean, and of prescribing an anti-verminous cure in advance of the treatment with iodine preparations, if it will still be necessary.

In this report, I am in perfect accord with Prof. Galli-Valerio and with Doctors Messerli and Folley. Our various researches lead us to the same conclusions.

In 1924 I frequently observed women between 25 and 40 years of age, with whom goiter became developed or augmented in volume at the same time that they were affected with general fatigue

*) Conditions étilogiques de l'Endémie goitreuse de la Robertsau. Par A. Borrel, L. Boëz et M. Freyss. Comptes-Rendus des Séances de la Société de Biologie 1925, p. 232.

and with anaemia. The examination of the feces brought to view eggs of trichocephales. I do not believe that this worm is always as inoffensive as we in general imagine. As far as I am concerned, I did not see any symptoms of hyperthyroidia, as Dr. Folley did, but rather hypothyroidia with anaemia and fatigue. The investigation of helminthiasis in the goitrigenous regions is our problem for the future. We shall then see if our ascertainments will be confirmed.

I wish to add that I was able during the years 1923 and 1924 to establish as a fact that there are « years of goiter », i. e. years, in which this endemic takes on greater proportions, or where it assumes even the character of an epidemic, only to lose anew its intensity and its frequency little by little as is the case in the epidemics of the contagious diseases in general.

In the years 1923 to 1924 I not only observed numerous cases of goiter becoming developed and increasing rapidly in volume in some schoolchildren and some adults, but likewise in a score or more of dogs. The symptoms were the same in both man and dog, and in some cases the development of goiter could be observed simultaneously in both.

The observation of two goitrous litters of a female fox-terrier is particularly interesting. In the first litter the goiter was well developed, but I was able to make it completely disappear in one of the female dogs by means of the ordinary iodine treatment, administered in milk. The second litter was strongly goitrous from birth. Two male dogs perished just as the little children die who are afflicted with the goiter of the newly-born, concerning which Professor Aschoff has spoken. One female dog of this litter was saved, because it had been brought to the Institute of Hygiene. A third litter was completely uninfected with goiter in 1925. It is on this account that I acknowledge that the epidemical character, which the goitrous endemic at Robertsau had assumed in 1923 to 1924, came to an end in 1925.

In two cases I saw a goiter being developed almost simultaneously in man and dog. A man of 29 years of age, who was often in contact with the dog of the house, made efforts to find me because his neck was enlarging at a rapid rate and so preventing him from buttoning up his collar. A treatment with an iodine preparation caused the goiter to disappear in a few weeks. An examination of the dog of the house revealed the fact to me that it was the bearer of a voluminous goiter. This dog was acquired for scientific research work and its direct successor possessed no sign of goiter, but that one living in the same kennel for a year or more, has

finely developed a goiter anew, while drinking only water from the urban canalization.

(3) Another interesting case is that of a sculptor of 45 years of age and his dog. He also came to consult me for a goiter that was swelling very rapidly. The iodine treatment with very small doses caused this to disappear almost completely in three weeks, but thereupon the symptoms of intolerance for iodine became manifest in all their violence with emaciation, tachycardia, nervous agitation. In this case I conceived the idea of giving likewise small doses of iodine to the very goitrous dog, to the dog as well as its master. The dog manifested exactly the same symptoms of intolerance towards iodine, with marked emaciation, agitation etc. It became so ill-natured that it became necessary to kill it. Unfortunately I arrived too late to be able to make an examination of the thyroid gland.

Goiters and Infections.

By E. Folley.

Goiters are divided into two great groups.

1. Those which are present during life, but disappear at death. To these goiters belongs the Basedow or exophthalmic goiter.
2. Those goiters, which are present during life and still continue to be present on the corpse. The endemic goiter belongs to this second group.

The Basedow goiter is caused by an infectious disease, and in two cases it was possible to inoculate mice with the diseased matter, but it could not be transmitted in series nor could it be cultivated.

The endemic parenchymatous or cystic goiter attacks only such persons, who have been attacked by two infections, that are entirely independent one from the other, and whereby each particular infection must attain a definite degree of seriousness. A system of therapeutics, which reduces these infections without entirely removing them, attains the complete disappearance of the parenchymatous goiters, but oftentimes is free from influence upon the cystous ones.

infections

Basedow Disease.

The Basedow disease has been called exophthalmic goiter, but this designation does not apply. The goiter and the exophthalmus are here only secondary manifestations occurring in the course of an infectious disease, one of the chief results of which consists in its being attended by an excessive expansion of all vessels with a loss of their tonicity. The expansion of the vessels with loss of tonicity is observed at the beginning of the disease, localized at the origin of the aortic arch. Later on it spreads to the aorta of the chest and abdomen, to the arteries of the neck and head and upon the other vessels of any particular size (see here my observations made to the Académie des Sciences of February 11 and 18 and May 21, 1918). All of the vessels, in all of the vascular systems get out of orders, as e. g. enlarged section, diminished tonicity, abnormal constriction etc., no matter, whether it be here a question of large or small caliber, the capillary vessels included. Distinct from the classic doctrine of the symptoms there is accordingly present with the Basedow disease as an essential feature a general vascular expansion and a far-reaching disturbance throughout the entire circulation of the blood. This vascular expansion becomes strongly manifest in the orbital cavities of the eyes through exophthalmia, in the region of the thyroid gland through its enlargement and through an excessive or diminished secretion, in the region of the pancreas through increased secreting operations and as pancreatic diarrhoea, in the region of the sweat-producing glands through very abundant and strong secretion of sweat etc., etc.

This telangiectasis and the changes that originate from it are preceded by other symptoms, among which I shall merely mention the ptosis of all abdominal parts of the digestive apparatus. This ptosis is strongly marked and appears to be in a certain way disproportional to the condition of the abdominal muscles, which to all appearances can be normal.

This ptosis has been drawing our attention for a long time through its early manifestation and its gravity, and I believe, that it may be responsible for a part of the symptoms of the exophthalmic goiter. All individuals that are afflicted with this disease are sufferers of temporary or chronic infections of the lungs and of the urinary passages. These infections stand in relation with disease conditions of the intestines. These enteropulmonary and enterorenal infections are, in my opinion, characteristic for the « spirillose » ones. (See below in the Chapter on Endemic Goiter.)

The general telangiectasis, the ptosis of the digestive organs, the infections of the kidneys as of the lungs are very conspicuous and even continue after the treatment causes the goiter and the exophthalmia to disappear.

For many years I have been observing such, who were suffering from Basedow disease, whose condition had been very much improved through Rœntgen-ray treatment or through surgical intervention, so that they could be considered healed. Nevertheless the improvement seemed to be a recovery only in name only as it was simply the contrast with the previous aspect, which the fear-inspiring Basedow disease had called forth. All diseased individuals, whom I was able to observe, have nevertheless fallen into a state of deterioration in the end, similar to certain varieties of syphilis, without goiter and without the exophthalmic condition. They died having such a complex of symptoms, that I was brought to the thought, that the Basedow disease was called forth through an infection, the germ of which is still unknown.

My attempts to reproduce the disease in an experimental manner, have served to confirm my opinion. In a great number of abortive experiments, for which I made use of extracts, medullary substance, inoculation of entire organs, thyroid gland, mammary gland, I took pains to call forth through animal experiments the abdominal ptosis, which my clinical observations in regard to the diseased individuals had demonstrated to me. I have seen a number of Basedow disturbances break out, which, however, rapidly disappeared again. In a recent number of experiments I employed material, which I had taken from Basedow patients, who were suffering from an acute and malignant variety of the disease. In their blood and in their urine I determined the presence of moving micro-organisms, which resembled the spirochaetas, but which could be distinguished from these in that they did not admit of being cultivated in the same nutrient mediums. After I had inoculated a number of full-grown mice with the blood and the sediment of the centrifugated urine, the animals experimented upon displayed an enormous exophthalmia, a large goiter and a characteristic trembling; after a while they perished and, as the case with the sufferers of exophthalmic goiter, their dead bodies did not show the indications of goiter nor of the exophthalmic condition any longer. At the autopsy I noticed the resuscitation of the thymus, which took up a considerable part of the thorax. I made endeavors in vain to transmit the infection upon other mice and for that purpose took the material from the dead mice.

then did he grow the "bits" in mice?

The experiments of cultivating the micro-organism, which I discovered as present in the diseased individuals and in the mice that had perished in consequence of the inoculation, were without success.

Endemic Goiter.

Before I proceed to the investigations of the endemic goiter I must make a little more clear what I understand under the term « spirilloid ». Certain spirillae or spirochaetas appear in the pure cultivations only in two varieties: the granulated variety, which is capable of resistance and resembles the spores of bacteria, and the spiral form. The spirilloids are micro-organisms, which I shall describe later and which exist in the form of spirillae only during one phase of their evolution, in the course of which they are able to assume the most varied aspects. These spirilloids likewise manifest granular forms, which behave similarly to the spores of the bacteria, in regard to their power of offering resistance. These granules of the spirillae, the spirochaetas and spirilloids are ultra-microscopical and can be filtered, whereas the remaining evolutionary varieties do not pass through the filter. The majority of the parasites are living in the interior of the cells of the animal, that is the host; as a result of this intracellular habitation, they also resemble one another in their action; with a like quantity of definite cells infected with parasites of different kinds the diseased person almost always shows the same symptoms. There are certain ones of these micro-parasites, which live only in a single species of cells, whereas there are others, which are found only at the beginning of the infection in one or in several species of cells, but then pass over also into every imaginable other cell of the host. A haematospirilla has its existence only in the red blood corpuscles as a little ball, on the other hand the spirochaete pallida can in course of time spread out over almost all possible kinds of the cells of a human being.

The spirochaetae, spirillae, spirilloids are the causes of a group of chronic diseases, the symptoms of which are very much alike and which I desire for the present to designate with the name of « spirillose », which term to be sure does not entirely apply. These « spirillose », which are called forth by intra-cellular parasites that can frequently be borne well and act only by means of their great numbers, manifest especially as characteristic features:

1. Distrophias; anomalies, due to development, of organs or of

entire groups of organs; metamorphoses in organs that are already fully developed.

2. Infections of the lungs, the cause of which lies in the intestines.
3. Infections of the urinary passages, the causes of which likewise lie in the intestines.

In the following very brief outline, I shall confine myself to these clinical characteristics.

The « spirilloses » can be of an endogenous or an exogenous variéty. They are of an endogenous nature, e. g., if an inherited non-malignant syphilis is intensified through the complication of common infections or if a haemato-spirochaetosis becomes malignant through the action of influenza etc. We call them exogenous, if a strong infection can be attributed to the taking up of granules (spores) of spirillae, spirochaetas or spirilloids in the water. Water, milk and vegetables can be bearers of infection. For producing the symptoms of the « spirillose », the number of the parasites comes into consideration, but also the behavior of the infected organism. The organism, that is attacked by the disease, may manifest rather great disturbances, it depending upon the climatic, hygienic and alimentary conditions, although the number of micro-parasites may not have been changed or only so to a small extent.

Now that we have established this fact, let us pass over to the biological investigation of those afflicted with goiter, which will be pursued in two directions: Researches on the organisms afflicted with goiter and researches made on the goiter itself.

All afflicted with goiter showed dystrophias, which resemble those that medical treatises have described as occurring among those suffering from heredetary syphilis.

All afflicted with goiter manifest indications of infections of the urinary passages, which regularly accompany diseased conditions of the intestines. The urinary infection is permanent or intermittent; numerous varieties of bacteria can occur with it. In the region of the intestine an abnormal absorption of dissolved chemical and developed substances takes place. The organic sieve, which permits the products of digestion to pass over into the circulation of the blood, does not act in a proper manner any longer, and allows a quantity of substances to pass through, which normally ought to remain in the intestines. The bacteriuria characterizes a pathological condition, which is called forth by a very intensive « spirillose » one. This disease is nothing else than the

proof of the disorganized condition of the filtering system of the intestines.

All afflicted with goiter show permanent or intermittent infections of the lungs, which stand in connection with the bad functioning of the intestines. In the lungs it is possible to find all possible bacteria, worm embryos in different stages of development etc. The coincidence of the intestinal and pulmonary infection marks important « spirilloses » ones in the same way as the intestinal and renal infection.

All goitrous invalids are afflicted with different kinds of spirillae, spirochaetas and spirilloids. The number of these minute parasites in a cubic millimeter of blood or tissue is always very great, it frequently is as high as many millions or even billions and sometimes reaches figures so high that « font penser à l'éternité », as Eggenberger has so beautifully said.

To the intensive « spirillose » condition of the individuals afflicted with goiter, which is defined as well clinically as bacteriologically, there is always present a serious worm infection of the intestines. All goitrous invalids house within their intestines numerous varieties of worms, of which each variety is represented by a considerable number of separate individuals. The varieties, which are most frequently met with, are the ascarides, the oxyures and the trichocephales. They are here mentioned in the order of their frequency. The ascarides and the trichocephales of themselves exert an effect upon the origin of goiter, which can certainly be determined. These varieties can occur each by itself or both together. It appears that a greater importance is to be attributed to the trichocephales than to the ascarides in the production of the toxic phenomena that are embraced in the designation hyperthyroidism.

The biological researches of goiter have placed me into the position of determining the intensity of the « spirillose » in the region of the thyroid gland. The investigation of the contents of the cysts has made clear that the cysts are at one and the same time both botanical and zoological gardens. We find therein bacteria, that can be cultivated and those that can not be cultivated, mould fungi, yeast, spirillae, spirilloids, spirochaetas, worm embryos, gregarines, coccidias. In the region of the goiter and in the cysts we do not find any permanent flora and fauna, a fact, which contrasts with the « spirillose » and the intestinal worm infection, as we constantly meet with in the organism of the goitrous invalids.

Proceeding from these experimental ascertainments, I have believed that goiter would be caused to disappear if it would prove successful in making the « spirillose » and worm infection to disappear. The results, which were obtained by my colleagues, who followed my instructions, as also by myself, have absolutely confirmed this hypothesis. The treatment is performed in two stages:

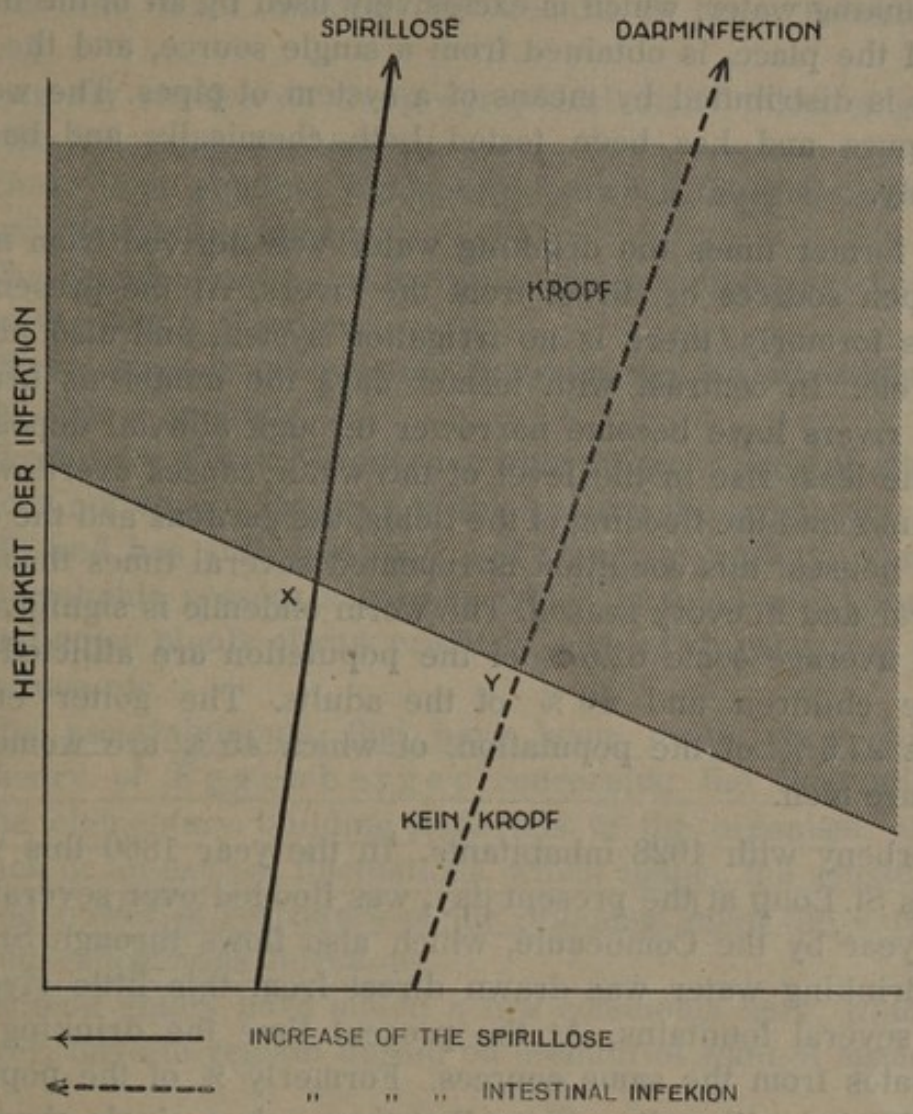
I. Treatment of the worm disease with Oleum Chenopodii, in the evening on retiring five glutoid capsules each with 10 drops and in the morning on awakening five gelatine capsules each with 10 drops are to be taken and three hours later a purgative remedy with Jalapa, Scammonium or Rhamnus in such a way that in the course of the forenoon at least four evacuations of the bowels will take place.

This treatment applies to adults; the evacuation of the intestines must be watched over in order to avoid any accidents. With this treatment the ascarides disappear entirely, whereas for the trichocephales the complete removal could never be established. The other worm remedies, which I have at times prescribed, have never given me such satisfactory results as the chenopodium oil.

II. The treatment of the « spirillose » is easily accomplished by means of remedies containing arsenic, similar to sulfarsenol, and mercurial products that are to be taken through the mouth. The sulfarsenol, e. g., is injected subcutaneously in a dose of 24 centigrams (3.7 grains) every three days, up to a total dose of 4 grams (61.7 grains). The parenchymatous goiters become greatly reduced through the action of the first gram and disappear completely before the total dose of 4 grams has been injected. The cysts are generally not influenced. Notwithstanding that the goiter has disappeared, I have shown that the result of this method of treatment achieves mostly a mere attenuation of the intestinal infection and of the « spirillose », which is more or less recognizable.

The arsenical-mercurial treatment occasions an improvement of the « spirillose », but it cures them just as little as a change of the habits of life, of the climate, of hygiene or of alimentation does. The vaccinal therapeutics alone have permitted me to undertake an organic disinfection, which is much more complete and consequently gives better results.

The results of my researches and of my methods of treatment admit of being represented graphically.



If with any invaiid the spirillose exceed the value of X and likewise the intestinal infection that of the value of Y, then there is *goiter.*

If one or both of these infections is kept below the critical values of X, respectively of Y, then there originates *no goiter.*

Geographical Observations.

Dr. Chagnot, who is kept informed regarding my scientific labors, has thoroughly studied the region of St. Loup, where he has been practicing for several years; the statements, which follow, originate from this colleague, whom I have the honor to count among my friends and students.

St. Loup, a town of 3000 inhabitants, lies in an extensive and swampy plain, which is traversed by numerous little rivers formed by the last streamlets coming from the torrential brooks, that originate in the Vosges Mountains. In this village the number of goiter invalids has been increasing for some 30 years while typhus has completely disappeared during this time. Since the year 1897

the drinking water, which is exclusively used by all of the inhabitants of the place, is obtained from a single source, and the water of this is distributed by means of a system of pipes. The water is very pure and has been tested both chemically and bacteriologically.

In former times the drinking water was derived from numerous open sources or direct from the rivers. At the present day, just as formerly, there is no irrigation system and also no cesspools etc. In contrast with former days the numerous branches of the rivers have become narrower through alluvial deposits, so that the least rise in the level of the water causes overflowing of the banks and the flooding of the fields, the gardens and the cellars of the houses; this condition is repeated several times throughout the year and in every season. The worm endemic is significant, for on an average some 62.5 % of the population are afflicted: 95 % of the children and 40 % of the adults. The goiter endemic afflicts 27.5 % of the population, of which 45 % are women and 10 % are men.

Corbeny with 1028 inhabitants. In the year 1860 this village, just as St. Loup at the present day, was flooded over several times each year by the Combeauté, which also flows through St. Loup. The drinking water was drawn direct from this little river and from several fountains. At the present time the drinking water originates from the same sources. Formerly ⅓ of the population was afflicted with goiter. Since that time only a single change has been made, viz., the little river has been held back through a dam and there is no longer any swamp there. 12.45 % of the population, of which 20 % are children and only 5 % adults, are afflicted with intestinal worms. The goiter is of rare occurrence and there are only 7 cases in the village.

Fougerolles with 5000 inhabitants lies also on the Combeauté, up the river from Corbenay and about 7⅓ miles distant from this village. As in St. Loup there are no irrigating canals, no hygiene and no street police service in this village. The drinking water is drawn exclusively from open fountains, which lie scattered about in the village. The little river overflows its banks repeatedly every year. Typhus prevails endemically in the village and the inhabitants are very numerous, who are afflicted with intestinal worms, averaging 50%. We find there about 12.5% afflicted with goiter, of which 20% are women and 5% are men. (Research work was also extended over other villages, but the want of space

prevents me from making the results of these investigations known.)

From my studies on the geographical distribution of goiter I draw the following conclusions:

I. There is no relation whatsoever between the goiter endemics and the typhus endemics.

II. The chemical nature of the water has no influence whatsoever on the origin of goiter.

III. There exists some relation between the worm endemic and the goiter endemic. Worm

IV. The theory of insufficient nourishment and a lack of vitamines does not appear to apply to this region; the population is well off, and has sufficient food and abundant variety. Almost all households possess a garden, which is frequently submerged and enjoy plenty of raw products, such as strawberries, garden lettuce etc.

V. The ascertainments, that have been made, agree with the theory of Eggenberger concerning the fluctuations of the elementary building materials in the organism, either a lack or an excess; fluctuations, which change the sensitiveness and power of resistance of the organism upon the exogenous and endogenous infections.

I should gladly have added a few comments here, which will, however, have to remain unsaid on account of want of space.

Conclusions.

I. The disease, named after Basedow, is obviously only an episode in a general infection, that is as yet but little known.

II. The Basedow disease (exophthalmic goiter) is in mild cases mistaken for symptoms of worm poisoning, of the inability to stand iodine, of hyperthyroidism etc., that are present with the goitrously afflicted.

III. The goiter endemic originates through the simultaneous action of « spirillose » and of intestinal infections.

IV. The chemical character of the water has no influence upon the origin of goiter. (Example of Corbenay).

V. There is no relation whatsoever between the goiter endemic and the typhus endemic. (Example of St. Loup and of Fougerolles).

VI. The theory of the requirement of iodine can not be reconciled with the results of the investigations of Chagnot. Our ascertainments in common relative to the action of iodine upon goiter have led us to the recognition of this remedy as being iodine — deficiency

unable to drive away the goiter completely and as very dangerous, if we take into consideration the nervous disturbances which it brings forth with those, who suffer from goiter. We have, therefore, given up entirely the iodine therapeutics, whether with iodine alone or with iodine in combination wth other remedies.

VII. The theories, which lay great stress upon the insufficiency of nourishment and the lack of vitamines, are apparently refuted through St. Loup, as observed by Chagnot. It is, however, not improbable, that it plays an important rôle in other regions in the question of origin of goiter.

VIII. These few observations, briefly stated, show that a simple forcing down of the « spirillose » and the intestinal infection suffices to cause the goiter to disappear. This checking can be obtained just as well with the treatment, which I have mentioned as through a modification of the mode of life, through a change of climate, through hygiene etc.

Observation made at the time of writing:

Not until a short time ago did I by chance learn of the publication of Stiner's work. This author has among other things expressed views of remarkably sharp clearsightedness upon the relations of goiter, dental caries and cancer. I am convinced that in the days to come the theories and experiments of Stiner will bear a most decisive influence upon our knowledge and views concerning the stated diseases.

Researches on the Aetiology of Goiter.

By Dr. Achilles Marchesa Monneret, Armeno (Italy).

Preceeding orators have pointed to the great variation of size in which the thyroid presents itself in the human organism, and it may indeed be asserted that no part of our body exhibits such a striking diversity in its volume, according to the region in which we are borne and brought up. The Italian proverb « Countries you travel, customs you meet » might with reason be paraphrased as applying to the thyroid.

To this hypertrophy — taking the term in a wider sense — quite a series of morbose entities corresponds, ranging from the

goiter (in its specific varieties) to cretinism, to deaf-mutism, stammering, to dwarfishness, to mixoedema, the Basedow (exophtalmic) goiter, etc.

But, if the ponderous works of accurate investigation, put before this conference by savants of renown, have thrown ample light upon the anatomy, physiology and the pathology of the thyroid, we cannot say as much, nor with equal conviction, in regard to the aetiology of the goitrous endemic.

And I fully concur in the observation already made by Dr. Muggia: that this uncertainty is mainly to be ascribed to the absence of a common agreement as to the lines to be followed in the conduct of research work.

Lines of Research

We would require:

1. To prepare statistics dealing with the extension and gravity of the endemic as accurately as a uniform criterium on which they are to be based would allow. It is only in this manner that the results obtained by different observators in various regions can be compared; and from such an examination — the personality of the investigator (which allows too often, though involuntarily, a preconceived conviction to transpire) having, so to say, been eliminated from it — some exact and positive definition might be derived. Thus, it would appear that the classification evolved by the Swiss Goiter Commission cannot be applied to those countries where goitrous endemics, though notably in existence, are not presenting — especially as regards thyroid hypertrophy — the same gravity as in Switzerland itself. Therefore, an evaluation based on the conformation of the cervic front line, i. e., according to the same being shaped concavely, as in the normal state, or either straight or convex, should — as held by Muggia — certainly be preferred.

Muggia's method.

2. When the characteristics of an endemic in any given region, i. e., its entity and extension, have been ascertained, to put it into relation with all the conditions of the surroundings, as had been proposed already by Cerletti at the Conference of 1909 in Milan.

Adhering, with some modifications and amplifications, to the plans laid down by Cerletti, I have carried out investigations in some of the rural districts situated on the western slopes of the Mottarone (a mountain group between the lake Maggiore and the lake of Orta, and which districts have notable percentages of thyroid hypertrophy. Of every parish, or fraction of parish, I have noted in the first place, and besides the number of its agglomerated and dispersed populations, the altitude, the position, the climatic

conditions, the geological qualities of the territory, the data concerning the aqueous stratum, the water courses with their origin and their distance from inhabited parts, the nature of existing vegetation, the conditions of cultivation and irrigation of the soil, and the produces of the latter.

I have computed the percentages of general mortality, the infant mortality up to two years, the rates of birth and of morbidity, the principal causes of death — all these data comprising the years of 1910 to 1927.

From the mustering records covering the years of birth from 1830 to 1906, I have extracted all the percentages of rejected recruits with special regard to those exempted on account of goiter, cretinism, deaf-mutism, deficient height, and in listing the names and district of residence of all those rejected for goiter and cretinism.

As regards populations in general, I have recorded the economical conditions, the chief professional activities, tendencies to emigration, if any, and the countries it is mainly directed to.

Passing to the study of housing conditions, attention was given to every particular of disposition of the interior, of the stables and dung-heaps, all in relation to hygiene. Further records bear on the circumstances of the hydric alimentation, of the habitual general alimentation, of the prevalence of any particular substance in the latter; finally, on the manner of living and in considering whether there be a living in community, or one merely in contact, with animals.

Descending to scholastic statistics, I have established an individual docket for every pupil, wherein are registered — besides the name, sex, parentage (on either side) date of birth, the class frequented — details of anamnesis, such as for instance, hereditary affections, infant nourishment: whether natural (maternel or mercenary) or artificial, the epochs of the first steps, of first speech, of dentition, previous maladies, the dwelling and feeding conditions, all in conformity with the criteria followed in respect to the general population. A constitutional outline having thus been obtained, I recorded trimestrially the modifications in stature, weight, the dental conditions and, particularly, the anteposterior diameter, together with the circumference, of the neck, as, also, the dimension of the thyroid (transversal diameter and height of lobes). The teaching staff, on their part, supplied me with trimestrial reports regarding their pupils individually and in which these were divided into categories of « sufficient » and « insufficient » scholars.

Differently from the majority of other research workers, I have, in my statistical tables, classified the scholars according to their number of years, instead of according to classes frequented. In this manner I was able to form an ultimate table showing the class frequented by pupils with hypertrophical thyroid, in confrontation with those possessing a normal gland.

I beg here to put on record the principal data contained in my tables:

Medical Group

of

Armeno - Agrano - Miasino - Coiromonte - Sovazza

Total of population: 4984.

Parish	Inhabitants	Altitude above sea	Mortality	Infant Mortality up to 2 years	Birth-rate	Number of Exam. from 1898 1906	Exemptions	Percentages among recruits examd				No. of pupils	Pupils with hypertr. tyroid	Percent. of pup. with hypertr. tyr.	Percent. of bovines in relation to population
								Exemptions	Goiter	Goitrous cret. etc.	Deflct. stature				
			‰	%	‰			%	‰	‰	‰			%	%
Armeno	1987	523	16.38	12.50	20.57	1538	358	23.20	23.40	37.70	39.50	242	172	71.00	40.41
Agrano	737	459	16,28	11.96	19.84	560	113	20 00	23.20	25.00	64.28	93	53	54.10	13.24
Miasino	1120	485	16.65	14.72	18.52	1032	225	21.80	8.84	14.53	42 40	93	50	53.76	11.60
Coiromonte	421	810	17.22	14.05	17.96	351	84	21.08	17.09	25.64	82.62	37	17	46.00	65.32
Sovazza	719	626	14.25	14.45	31.29	595	113	19.00	8.38	11.76	47.05	116	47	40.50	76.50

There having moreover resulted in the section of Bassola a percentage of 86 % of school pupils with pronounced hypertrophy of the thyroid and the very high rate of 170 ‰ of recruits exempted on account of goiter, I proceeded to work out a detailed enumeration of this latter category:

I made up a special card for every family and formed groups of such as were found to be connected by kinship, establishing for some of them a genealogical tree. Particular attention was given to the place of birth, both of individuals and parents, as also to the question whether an individual was an immigrant, or whether he had emigrated (and whereto):

Parish of Armeno — Section of Bassola.

	Totals	Males	Females
Population	127	61	66
With thyroid hypertrophy . .	86 (68,5 %)	40 (32,3 %)	46 (36 2 %)
School pupils	15	8	7
With thyroid hypertrophy . .	13 (86,66 %)	7 (46,66 %)	6 (40,00 %)

The Family: Romagnoli (Bassola).

Romagnoli Leandro (Bassola) goiter-affect.	Filomena in Bogianchini (Agrano) goiter-affected	2 sons service-exempt. f. goiter
	Teresa in Andreini (Agrano) goiter-affected	1 „ „ „ „ „
	Giovanni (Pescone di Agrano) goiter-affected	1 „ „ „ f. stammering
Meazza Carolina (Agrano)		4 „ with hypertroph. thyroid
		2 „ exempted for goiter
	Antonio (Bassola) goiter-affected	1 „ „ „ epilepsy
		6 „ with hypertroph. thyroid
		1 „ „ normal thyroid

Now, as to conclusions? — I do not pretend my work to have — nor could it possibly have — as it were, a conclusive bearing whatever, since there must be linked up with it all those other investigations of chemical and bacteriological import, which are indispensable in the adequate valuation of the causes of the endemic.

From the investigations carried out in the five parishes of my medical province — upon a population of about 5000 inhabitants, these living at altitudes from 300 up to onethousand meters above sea-level and in conditions radically differing as to nature of ground, vegetation, cultivation, economical status, habits of life, alimentation, housing etc. — and confronting particularly the various topographical charts made, I arrive at the following deductions:

Life in contact or in community with animals has no influence of any kind upon the goitrous endemics in surroundings, that is to say, where satisfactory or, at least, tolerable hygienical conditions prevail. (In Sovazza, where cattle breeding reaches the importance of a veritable industry and where the tenets of cleanliness are in consequence more strictly adhered to, bovine animals are represented in a maximum percentage, while that of persons affected with goiter is lowest).

The quality and amount of the water consumed in the alimentation (as resulting from the usual chemical and bacteriological analyses) shows no notable influence: we find, in fact, inhabited places, very little distant from each other, making use of the same water and presenting nevertheless enormous differences in the proportion of goitrous individuals. The same may be said regarding the nature of the ground, the cultivation, vegetation etc.

Manifest, on the contrary, is the influence exerced by the conditions of fortune, of dwellings and the quality of alimentation. Hygiene

Surroundings, however, with improved hygienical conditions and a more wholesome and abundant alimentation are of importance only in respect to the degree of thyroid hypertrophy. In recent times, goiters have noticeably diminished in volume, while their number has inversely increased. Food

Among the factors to be encountered with most constant frequency we must mention that of heredity, and which heredity does not cease to manifest itself (increased susceptibility of the individual) even when some descendent emigrates from a part were goiter is endemical to others where is exists sporadically only. Heredity

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Concluding Remarks.

Prof. Galli-Valerio:

From the ensemble of the reports and communications on the aetiology and prophylaxis of the thyroid endemic we gather that the majority are pronouncing in favor of hydrical aetiology. No agreement has so far been reached regarding the manner in which the water performs its action in the development of the endemic; for, if some have in view specific, or non-specific, germs assumed to be contained in the water, others, instead, contemplate the existence of especial substances in certain subsoils passed through by the goitrigenous waters, or a particular chemical composition of the latter. As to the innumerable and great variety of germs which some observers affirm to have encountered in goiters, I confess to a good amount of scepticism, for, as far as I am concerned, I was never able to see them. — Be this as it may, this agreement of the majority of reporters and debaters, concerning the share of the water in the development of the thyroid endemic, is certainly of very great importance in regard to the prophylaxis of the endemic, since it directs our attention to the amelioration of the potable waters in the affected zones. This striving for the improvement of potable waters in the areas visited by the thyroid endemic will undoubtedly find the support of those, even, who declare to ignore the cause of goiter, but are recognizing that an existing goiter may become worse through the use of infected water.

Prophylaxis of Endemic Struma.

Prophylaxis of Endemic Struma.

By Prof. Wagner-Jauregg.

The prophylaxis of a disease must become effective before the endangerment through the disease sets in. Applying this thought to the endemic goiter it means, that the prophylaxis must begin to have effect upon the child even before birth, perhaps even upon the germ-cells; for in those regions, where goiter is endemic, it is not a rare occurrence to find it already existing in the new-born babe. In common with Dr. Diviak, e. g., I investigated at a place in a pronounced goiter district all newly born children during a period of several years and we discovered in 25 % of the same. This was a locality in which at the examination of a girls' department of the elementary school with girls of 11 to 12 years of age, there were found to be 80 % of the children afflicted with goiter No. II and No. III of the Swiss scale. And that the goiter of the mother is of great influence upon the development of the goiter in the children can not be doubted.

The prophylaxis of a disease, if it is really to be efficacious, must furthermore extend over all that are endangered by the disease. That is to say, over the entire population in such places where the goiter is endemic; for, the individual, who has no goiter at present, can not tell but that he will have one in time to come. I refer here to the fact that, in the numerous goiter examinations that have been made in the schools, it was found without exception that the frequency of goiter increases from the lower to the higher classes.

The prophylaxis of a disease ought finally to be removed as far as possible from any initiative on the part of the individual; for how difficult a thing it is to carry out a hygienic measure against the want of intelligence of mankind, can be understood from the difficulties, against which, e. g., vaccination has at the present day to combat in many places.

Looked at from these three points of view the goiter prophylaxis, as it was first of all introduced in Switzerland, is an ideal prophylaxis, or rather it can become such, if it happens that certain hypotheses come true.

After we had become familiar with the curative effect, which iodine develops in the case of goiter, the idea of making use of this remedy prophylactically seemed so obvious that it was time and again spoken of, and even as long ago as the beginning of the fifties in the past century it had been brought into realization. This was, however an experiment which at that time, to be sure, had to come to naught, because not sufficient preliminary work had preceded it.

The difficulty of carrying out this idea lay at that time in the fact that soon after the proof of the curative effect of iodine in the case of goiter had been given, the experience was likewise gained that the intake of iodine was acting in an injurious manner on some individuals and especially on many who were afflicted with goiter, inasmuch as diseased conditions were developed through it, which were later on recognized as hyperthyroidism.

It therefore was a question of determining whether it is possible to find a dose of iodine, which is nevertheless large enough in order to have prophylactic effect and at the same time small enough so as to develop no injurious effects.

We accordingly have as the first fundamental question, whether the quantity of iodine that is contained in the Swiss complete salt is great enough so as to develop a satisfactory prophylactic effect. In other words: Is the dose of 0.005 gram potassium iodide in one kilogram (2.2 English pounds) of kitchen-salt, which is the amount in the complete salt of Switzerland, sufficient to prevent the formation of goiters? Iodized salt

There is not as yet any research matter on hand so that this question can receive a proper answer, nor can we expect to have it at the present time. That can not be the case until the classes of children of certain ages will have entered the school, who have already grown up under the action of complete salt, for an examination of the entire population is not possible until the children are at school. But quite naturally that will not be the case with reference to the lowest school classes, in which the children are from 6 to 7 years of age, until the prophylaxis with complete salt has been carried on some 7 to 8 years; for, according

to what has just been said, the prophylaxis must have already acted upon the parents, especially on the mothers.

This condition will not be fulfilled in Switzerland until the school-year of 1929 to 1930, not even in the Canton of Appenzell where the complete salt was introduced as long ago as 1922. In Austria it will not be until 1930 to 1931.

Moreover, telling figures can, however, only be obtained in such places, where the complete salt prophylaxis has been applied to the entire population, for otherwise it will be a difficult matter always to determine in any individual case with the necessary positiveness whether an existing goiter can be explained through the inefficacy or through the absence of the prophylaxis, all the more so, since the parents likewise come under consideration.

This general prophylaxis has, however, been put into force in Switzerland only in six cantons, namely, in Vaud and Nidwalden in 1924, and since that date, as I have learned, in Neuchâtel, Schaffhausen, Schwyz and Zug. Attention will accordingly have to be directed in the next few years to the experience gained in these cantons. In addition to these there are, as has lately been told to me, the districts of Kempten and Sonthofen in Allgäu, where likewise the use of complete salt has become generally adopted.

Individual observations, however, are already at our disposition, which present to us the prophylactic effects of the complete salt in a favorable light.

Zeller in 1925 reported from Appenzell that 22 women in labor, who consumed only iodized salt during the entire time of pregnancy, gave birth without exception to children, who had non-palpable lateral lobes of the thyroid gland and an isthmus, that could be felt just a little or not at all, while of nine suckling infants, whose mothers did not come under the prophylactic treatment, only two demonstrated such conditions.

Still more important is the fact, that was laid down by Wegelin, concerning which de Quervain made reference in his Düsseldorf address. Wegelin discovered that the thyroid glands of newly born children, after the complete salt treatment on the part of their mothers, were not only of smaller dimensions than those where ordinary kitchen-salt had been employed but that they had a normal histological structure with vesicles containing colloid, which was in contrast with the usual Bernese neonat-struma.

Until we, moreover, have more extensive records of observations on the prophylactic action of complete salt to judge

from, we must depend on drawing our conclusions as to the prophylactic action, that is being looked for, from the therapeutic action of the same.

The determination of the amount of iodine to be administered in the complete salt has been determined on the basis of therapeutical experiments. After Hunziker had determined in experiments, which extended over many years, that $^1/_{10}$ of a milligram of potassium iodide, given as a daily dose, is in a position of making goiters in schoolchildren disappear, and after Bayard had demonstrated, first with the results obtained from the study of only five families and later on of the population of two villages, that it is possible to cause goiters to disappear with even a smaller dose, we had approached quite closely to the lowest limits of the dose, with which we could still expect to obtain effect. We were actually approaching that dose of iodine which the individual person, even in goitrously infected regions, as the experiments of von Fellenberg have shown, takes in daily on the one hand in the line of food, water and air, and on the other hand secretes.

That goiters can be made to disappear through the iodine dose contained in complete salt, both in the case of youthful individuals and also with many adults, has been proved through the experiments of Bayard in Switzerland and Kaspar in Vienna.

But, on the other hand, it has also been shown through experiments on schoolchildren, that not all of the goiters of schoolchildren can be made to disappear through these doses nor even through much larger doses.

Tschamler in Innsbruck had, e. g., after an almost two year treatment of schoolchildren with iodo-starin tablets (with 0.005 gr. iodine per week, which signifies a quantity of iodine considerably in excess of that in a complete salt dose), still some 2.1 %, respectively 0.04%, of No. III and No. IV with boys and 4.9%, respectively 0.2 %, with girls. The data before the treatment were 8.8 % and 1 % with the boys and 15.7 % and 2.2 % with the girls. Nevertheless, these data approach so closely to an absence of goiter, that we could perhaps expect even complete success if the treatment will have been undertaken much earlier. But our experiences are not seen to be as favorable in all of the information reported on school treatment of goiter.

As we see, it is not yet possible to draw any positive conclusion on a presumably marked effect of the complete salt prophylaxis from the success obtained in school treatment.

The second fundamental question, whether the

iodine dose contained in the complete salt is small enough so that no injurious consequences are brought about can not be answered in a positively affirmative manner.

De Quervain has emphasized the possibility, even before the introduction of complete salt, that there are some individuals who are not able to endure even this dose, and such cases were actually discovered later by observers whose reliability can not be questioned. The number of such cases has been greatly exaggerated, however, by many parties, who on principle take a negative stand over-against prophylaxis with complete salt. Above all we find that a great many cases of iodine injuries have been attributed to the complete salt, which stand in no relation whatsoever with the use of the same but in part with the introduction of it. The introduction of the complete salt came about after a certain style of propaganda; popular lectures were held and many articles on iodine prophylaxis were published in both medical and non-medical periodicals. Immediately thereupon the pharmaceutical industry took hold of this question, which constitutes a chapter that Mr. Hunziker worked up dramatically in a very interesting treatise, which has unfortunately not as yet been published.

In consequence of this movement many people suddenly remembered that they had goiters and procured for themselves any and every kind of iodine preparation, mostly without consultation of their physicians, and had no idea of the proper dose. These are the injuries due to the so-called "wild goiter treatment." It is accordingly, in the sense as represented, a consequence of the introduction of the prophylaxis of iodine salt. But it constitutes a bridge, over which the iodine salt prophylaxis can not avoid passing, especially as long as we stick to the principle of perfect freedom in obtaining complete salt.

Attempts have been made to find ways to put a check on this wild goiter treatment and it has been demanded that the traffic with remedies containing iodine and the prescription of such should be regulated by law.

I feel skeptical towards such measures. The best method of doing away with the wild goiter treatment would be the compulsory introduction of complete salt, as it is already the case in Switzerland in the stated six cantons, for then there need be no longer so much talk about the matter and to the extent, in which

the goiters disappear, the wild method of treating goiter will no longer have any foundation.

But it is nevertheless a fact that individual authenticated iodine injuries have occurred through the use of complete salt only. In Switzerland official enquiries have been conducted for the purpose of determining the number of such injuries, on which investigations de Quervain reported in his address at the Düsseldorf conference of the Scientific Association. We can learn from these Swiss official enquiries that such iodine injuries, which have been occasioned simply through the complete salt, could be established only in rare instances and that with the consumers of complete salt they appear spontaneously only very slightly more frequently than such so-called thyrotoxicoses occur with the population that does not consume complete salt.

It will be all the less possible to make use of the rare cases of iodine injuries as an argument against the introduction of complete salt, since it can never occur to anyone to demand limitations in the sale of our daily bread or of the kitchen-salt, whether the latter be iodized or non-iodized, simply because the one acts injuriously with the subjects of diabetes and the other with the nephritic patients.

It is probable, however, that the general introduction of complete salt will later on be found to be the best remedy for the prevention of such injuries, which are due to the use of complete salt, in so far as these occur mostly with people of advancing age, who had been afflicted with goiter.

To the question of the introduction of complete salt, there comes up immediately a series of further fundamental questions. How long ought the complete salt prophylaxis to be kept up? To this question Hunziker has already given the correct answer: « Just as long as human beings are living in a dangerous region, that means, with the resident population for all times. » Here comes naturally the second question, namely, to what extent the principle of free will ought to be maintained in the obtaining of the complete salt.

In the beginning it was a perfectly voluntary matter in Switzerland to obtain the complete salt and the hope was cherished that by carrying on a very intensive propaganda it would be possible to persuade the greater part of the population to make use of complete salt. This expectation, however, does not become realized, for even in the Canton of Appenzell itself, which was the first to introduce the complete salt prophylaxis and in which Eggen-

berger is at work with exemplary indefatigability for extending the use of the same, we are nevertheless still rather far distant from the 100 % consumption of complete salt.

But according to my opinion we can not found upon propaganda alone, however, any system or method, which is intended to be a permanent one. To bring it to pass there is nevertheless a certain degree of compulsion required. The principle of letting it be a voluntary matter can be here maintained in the manner of having everyone, who does not desire iodized salt, specially state that fact when making the purchase and, besides, perhaps not having such salt on sale at every retail store, but only at special stores. This exception is in fact necessary because of the really extremely rare cases of consumers of salt, who can not stand the iodized variety.

It would accordingly be not the question of free will in obtaining but only that of refusing the iodized salt, that would be maintained.

This system has been followed in Switzerland, as far as I have been informed, up to the present time in the already mentioned six cantons of Vaud, Nidwalden, Neuchâtel, Schaffhausen, Schwyz and Zug, and furthermore in two districts of Allgäu. Unfortunately the principle of introducing complete salt has yet been nowhere accepted in Austria, notwithstanding that many Alpine districts are quite abundantly afflicted not only with goiter but also with cretinism and deaf-mutism, so that such a measure would seem justified.

Such an introduction of the use of complete salt, especially as a permanent system, even if it is compulsory to a certain degree, is, however, a very decided measure. It is only to be justified in such a locality, where goiter is a prevailing scourge to the population in the truest sense of the word; that is to say, where not only goiter exists among a very considerable part of the population, but where also the accompanying ailments of goitrous endemic, the cretinic degeneration in its different degrees of development and the endemic deaf-mutism play an important rôle.

It will be all the more necessary for us to consider whether in any particular region the goiter endemic is spread to such a great extent that, because of this, the compulsory introduction of complete salt is justifiable, for, of course, the goiter prophylaxis, as it is continually being claimed by its advocates, is an experiment on an extensive scale, the success of

which is being expected on the basis of scientific hypotheses, and is being made highly probable through the experiences thus far gained; the full incontrovertible proof for the anticipated action of the complete salt can not be realized until after many years, even, as de Quervain believes, perhaps not until after the time of a human generation.

If this evidence will have been given, then it will be an easier thing to make up our minds to introduce the complete salt into such regions, where up to this time only goiter played an important rôle, but not the accompanying ailments, the endemic cretinism and the endemic deaf-mutism.

The optional introduction of complete salt is, however, even now justified in these regions. But here also the so-called school prophylaxis will play an important rôle, though this is, in reality, no prophylaxis, but only a goiter treatment.

Prophylaxis v. Treatment

This school treatment can further the complete salt prophylaxis in various directions. In the first place it prepares the population for the introduction of the complete salt prophylaxis and makes it acquainted with the same. Secondly, it offers the opportunity to recommend the complete salt to those families, which are in danger of getting goiter. These propagandistic efforts in favour of the complete salt prophylaxis ought never at any place to be neglected at the time of the school treatment of goiter. And thirdly, through its undeniable success it develops a general inclination towards the adoption of complete salt.

But the school treatment of goiter has one disadvantage, namely, it has too little automatic action. The carrying it out continuously is too greatly dependent upon the zeal, that will not abate, on the conscientiousness of a great number of individual persons and on the intelligent co-operation of the population. It is a fire, which does not of its own accord continue to burn but which must again and again be revived and stirred up.

In the proceedings, which took place in the Prussian Board of Health in June, 1926, regarding the goiter question, there was one subject which took up considerable time and attention in connection with the school treatment of goiter and this subject I should like to speak of briefly on this occasion.

We are aware that Walter Jaensch discovered peculiar changes in the cutaneous capillary system in several hypothyrotic cretins by means of the use of the capillary microscope, as is employed in the Tübingen clinics. These changes he looks upon as

Capillary microscope

the manifestation of an arrest of development and saw that they showed improvement when the thyroid gland was fed.

By continuing to follow up these discoveries Jaensch found in goitrous regions similar defects of development in the cutaneous capillary system with assisting pupils, who had no external indications of cretinism and he was able by means of the feeding of the thyroid or of iodine to achieve an improvement of the mental condition as also of the capillary state.

To what extent the frequent occurrence of such pathological capillary states in weak-minded or imbecile children in endemic regions, as has been established by Jaensch and his collaborator Wittneben, may be an indication of a defection of the thyroid gland function, even without any demonstrable goiter, that can not be brought out by means of other methods, researches of a comparative nature will have to show, which are made in other regions, both those afflicted with and those free from goitrous endemic.

It must be considered as rather premature if we lay down as manifestation of a goiter noxa, that does not yet admit of being perfectly defined, any capillary changes, of which we can not as yet give any conception as definitely established, and then desire to introduce in lieu of the usual school goiter treatment, or even of the complete salt prophylaxis, a system of treatment, that is to be carried out in the schools, and, moreover, an individualizing one.

For the general introduction in the schools, as Höpfner recommends in his address at the above-stated proceedings, this method of investigation of scholars, who are to be subjected to the iodine treatment, is not suitable even for the reason that it would require on the one hand a very considerable expenditure of labor, that will have to be performed, such as the taking up of the capillary-microscopic findings and the test of intelligence, and since, on the other hand the greatest possible elimination of subjective conceptions here is still less to be reached than with the determination of the fact as to whether in an individual case goiter may be present and to what degree, which is quite simple and easily demonstrable.

The complete salt prophylaxis develops certain curative effects not only with the schoolchildren but also in persons of older age, of whom, to be sure, it is difficult to give any numerical data, because it is not possible to carry out any exhaustive examination of the individuals of greater age.

An interesting bit of information, that must be given here, Dr. Hans Sepp of Dietmannsried gathered in Allgäu, where according to the declarations of this author, the complete salt has been introduced obligatorily into two regions, Kempten and Sonthofen, so that since the beginning of July, 1924, there was no other salt at all to be obtained anyhow, not only for the household, but also for industrial purposes and in part even for feeding cattle.

Dr. Hans Sepp made the observation that, since the introduction of the complete salt in his sick fund consultation practise, where he is also consulted by persons beyond the school age, there were always fewer persons coming to the consultation on account of goiter. Whereas in the six quarters that preceded the introduction of complete salt some 15.4 to 22.6 % of the invalids insured against illness applied because of goiter, the number fell and was continually reduced during the following eight quarters from 13.7 % to 3 % with approximately the same degree of frequency of visits of those insured against illness.

I feel also grateful to Mr. Eggenberger for some data on the size of the thyroid glands of the schoolchildren of these two regions of Allgäu.

The system of measurement is that mentioned by Eggenberger and made use of by Zeller in his report. The figures signify the area of the surface of the thyroid gland. It is seen that the surface of the thyroid glands in the boys and girls, who are just entering school, was in the district of Kempten in 1924 before the introduction of complete salt 23.8 and 22.1 square centimeters respectively. The boys and girls, who made their first visit to the school after the introduction of the complete salt had been in force for two years, had swellings of 9.5 and 11.7 sq. cm. respectively, that is to say a decrease to the one half and even further. In Sonthofen the comparison of the two data gave us 26.9 and 11.7 sq. cm.

Still more favorable results are recognized from the measurements, which as far as I am aware have not yet been published, that the school medical officer, Dr. Schell, had made on the schoolchildren in Kempten in the Allgäu district after a three year consumption of complete salt.

Another observation, which has repeatedly been made is that, where complete salt has been introduced, the goiter operations are of less frequency.

It must be admitted that the operations to remove goiters must nearly cease, with the exception of the Basedow goiters, owing to the complete salt prophylaxis, if it has become effective with

the entire population and fulfills all that is expected of it. But until this condition of a general absence of goiter can be attained a full generation and even a longer time must have elapsed. But the curative action of the complete salt is already felt from the beginning with many individuals in all stages of life. If this effect is most especially noticeable only in the case of young persons to that extent that the goiters disappear entirely, nevertheless such cases are found to occur also in adult individuals of various ages, even if only rarely, and still more frequently the goiters at least become reduced in size. And in this way the goiter complaints are diminished and with that the necessity or at least the inclination of being operated upon is likewise diminished.

I instituted inquiries at the different surgical clinics and the surgical hospital departments and the sanatoria to ascertain the number of operations for goiter in Vienna and Lower Austria in the years from 1922 to 1926.

The data collected are here given in table I:

Table I.

Goiter operations in Vienna and Lower-Austria					
	1922	1923	1924	1925	1926
Goiter operations in Vienna	1308	1342	867	803	806
%; Number for 1922 = 100 %	*100*	*103*	*66,3*	*61,4*	*61,6*
Goiter operations in Lower-Austria	152	212	118	131	123
%; Number for 1922 = 100 %	*100*	*139*	*77,6*	*86,2*	*80,9*

It must here be explained that the propaganda for the introduction of complete salt into Austria began in January, 1923, so that the year 1923 came already under the influence of this propaganda. The introduction of the complete salt did not, however, follow until the end of 1923, so that it did not come into the general trade in very marked quantities before the beginning of 1924.

As you can understand from the above data the propaganda for the complete salt really was responsible for an increase in the number of goiter operations, which was still more plainly to be recognized in Lower Austria than in Vienna.

With the introduction of the complete salt the number of goiter operations fell off most significantly very rapidly to a much higher degree in Vienna, where the complete salt came into use more quickly and more generally than in the country districts.

It would certainly be a mistaken notion to connect the falling off in the number of goiter operations exclusively with the action of the complete salt. One thing, that might have played a rôle here, is the rational iodine treatment of many goiters, which was incited through the propaganda. Furthermore, the making of a goiter operation is an event, which also depends upon the psychological constitution of the goitrous patient. It probably has also frequently happened, that a person afflicted with goiter kept on putting off his resolution to be operated on, because his attention was drawn through the propaganda movement to the iodine treatment, so that he cherished the hope of getting in this way out of the necessity of an operation. But the really urgent goiter operations do not admit of indefinite postponement and the falling off in the number of goiter operations has now for the past three years been in about the same proportion.

In conclusion, I should like to give you some data on the frequency of goiter in Austria, from which some essential points as to the action of complete salt can be gained and, as a matter of fact, in correspondence with the present stand of the question, they are not prophylactic on the whole, but curative.

In Austria the sanitary authorities made arrangements in the Autumn of 1923, at the very time when the complete salt was introduced into Austria, for an ascertainment regarding goiter among schoolchildren, and decided to follow the same plan, that had been employed in Switzerland, making a classification of four grades, namely, No. I, no goiter; No. II and No. III, the initial stage and slight but marked enlargement of the thyroid gland; No. IV, prominent goitrous structure.

Surveys: Grades of Go

The results of this enumeration were made known by Dr. Hermann Schroetter in the official bulletin of the Municipal Health Department in Vienna.

It is now more than 3½ years since the complete salt was introduced into Austria and, since the consumption of it has been rather extensive, especially in Vienna, it appeared advisable to gather statistics again concerning the present frequency of goiter and to compare the same with those of Autumn, 1923. The Municipal Board of Health complied with this request in a most grateful and appreciative manner and arranged for an ascertainment in Spring,

1927, of the frequency of goiter in the elementary and middle-class schools, which was carried out similar to the investigation of the year 1923.

The tables, which I present to you here, will make the results clear to you.

Table II.

Examinaton of the scholars of all the elementary and middle-class schools of Vienna by the school physicians in April, 1927, and Autumn, 1923

1927: 51,853 boys, 53,275 girls; 1923: 65,766 boys, 66,724 girls

Of every 100 examined there were found

	Elementary schools						Middle-class schools					
	Total		Boys		Girls		Total		Boys		Girls	
	1927	1923	1927	1923	1927	1923	1927	1923	1927	1923	1927	1923
Without goiter	69,5	*57,8*	73,0	*59,8*	66,2	*55,9*	56,6	*55,9*	61,9	*58,3*	55,5	*49,6*
With goiter	31,7	*42,1*	27,0	*39,9*	33,8	*43,9*	43,2	*47,8*	38,2	*44,2*	44,3	*50,5*
Goiter I Grade	27,1	*30,1*	24,6	*28,6*	30,0	*31,6*	35,1	*32,2*	31,6	*30,1*	35,6	*33,7*
Goiter II Grade	2,9	*10,4*	2,3	*9,7*	3,6	*10,8*	7,5	*13,1*	6,1	*11,8*	8,1	*14,7*
Goiter III Grade	0,16	*1,6*	0,09	*1,6*	0,24	*1,5*	0,57	*2.5*	0,43	*2,5*	0,69	*2,6*

From the first table you can see that the number of children afflicted with the formation of goiter had fallen off in 1927 from the number in 1923: in the elementary schools from 42.1 % to 31.7 % and in the middle-class schools from 47.8 % to 43.2 %. This falling off is seen to be more strongly with the boys than with the girls.

The degree of improvement, however, becomes more apparent, if we make a comparison of the three grades of goiter. For example, we find in the III grade, that of strongly marked goiter, a falling off from 1.6 % to 0.16 %, i. e., down to the one tenth in the elementary schools and from 2.5 % to 0.57 % or to about one fourth in the middle class schools.

The data for the II grade, the marked enlargement of the thyroid gland, likewise indicate a strong falling off: in the elementary schools from 10.4 % to 2.9 % or approximately one third and in the middle-class schools from 13.1 % down to 7.5 %, which is about one half.

To a considerably less extent do we find the diminution in the cases of goiter in the I grade, the initial stage of enlargement, namely, from 30.1 % to 27.1 % in the elementary schools and even a slight increase in the middle-class schools, namely, from 32.2 % up to 35.1 %. This increase is, to be sure, only an apparent one; it is the result of a shifting, since manifestly many cases of goiter of the second and third grade of the year 1923 have now become goiters of the first grade.

compare the figures in which there is an actual increase

Table III.

Of every 100 examined there were found:						
With Goiter Formation II. III. IV.	Boys			Girls		
	1927	1923	Difference	1927	1923	Difference
1. degree, age 6—7 years	20,6	*34,0*	**13,4**	25,2	*35,5*	**10,3**
2. degree, age 7—8 years	23,1	*37,0*	**13,9**	29,2	*40,6*	**11,4**
3. degree, age 8—9 years	27,3	*39,4*	**12,1**	34,6	*43,5*	**8,9**
4. degree, age 9—10 years	32,1	*42,7*	**10,6**	39,0	*46,0*	**7,0**
5. degree, age 10—11 years	36,9	*43,7*	**6,8**	45,1	*49,7*	**4,6**
6. degree, age 11—12 years	37,2	*44,0*	**6,8**	43,6	*49,3*	**5,7**
7. degree, age 12—13 years	39,0	*47,0*	**8,0**	49,5	*50,4*	**0,9**
8. eegree, age 13—14 years	38,6	*43,7*	**5,1**	51,5	*52,2*	**0,7**
9. degree, age 14—15 years	36,6	*42,0*	**5,4**	50,7	*51,5*	**0,8**

Looked upon in age divisions, in Table III, we see that the frequency of goiter increases continuously from the lowest division on, up to the seventh with the boys and up to the eighth with the girls, and that it shows a slight diminution in the last two divisions with the boys and in the last division with the girls.

This relation of the age divisions was just the same in 1923 as in 1927.

The falling of in the frequency of goiter in 1927 as compared with 1923 is seen to have been strongest in the lowest years and fell rapidly down in the highest years, with the boys from 13.9 % to 5.1 % and with the girls from 11.4 % to 0.7 %.

It was unfortunately impossible to ascertain which children had come under the influence of complete salt and which had not.

It therefore can not be determined, whether the falling off in the frequency of goiter is exclusively an action due to the consumption of complete salt or whether there might also have been here

an abatement of the wave of goiter, of which I made mention in my Düsseldorf address and even in previous published articles.

The really stronger falling off in the frequency of goiter in the lowest four age divisions which have already in part been under the influence of complete salt, as compared with the later age divisions, admits perhaps of drawing the conclusion that the new generation of goitrous children in these years has already become diminished. This appears accordingly to me to confirm the fact of an action of complete salt.

But more plainly still does the circumstance seem to deny the assumption that an abatement of the wave of goiter has played a rôle in the falling off in the frequency of goiter, that this falling off is of quite different degrees in the individual municipalities and that in some parishes the frequency of goiter in the year 1927 was even greater than it was in the year 1923, an event, which admits much more easily of being explained through the fact of a different method of delivery of complete salt in the different parishes than through a different action of the noxiousness of goiter by districts.

In order to be able to judge the described changes in the frequency of goiter among the Viennese schoolchildren, it will also be necessary to get an idea as to how great the consumption of complete salt really was among the inhabitants of Vienna. From evidence, which was placed at my disposition by the salt administration, I was able to make the estimate that approximately 47 % of the common salt consumed in Vienna was complete salt. We must admit that the average contents of iodine must be considered to be lower than 5 milligrams (0.077 grains) of potassium iodide per kilogram (2.2 lbs.) of salt, for the difficulties connected with the preparation of a complete salt having a percentage of iodine, that is constant, have not as yet been overcome.

* * *

Conclusion :

The method which has originated in Switzerland for general (not individual) anti-goitrous prophylaxis through complete salt (iodized cooking salt) fulfils all the requirements which can be demanded of such a prophylaxis.

A final judgment on the scope of the prophylactic action of this salt can only be obtained after some years. Individual observations even now show a complete success of this prophylaxis to be probable.

A final judgment can only be obtained in regions where the salt is (approximately) the only remedy used. At present this can only by in districts where endemic goiter is very severe.

In districts where endemic goiter exists to a less degree, besides the optional introduction of the complete salt treatment, individual treatment of goiter should be given in the schools.

The remedial action of the complete salt and of the individual treatment in schools is already a matter of proof, but is still not sufficient to cure an entire populace of the goiter.

Harm done in isolated cases by the use of the complete salt is too exceptional to constitute an argument against its general introduction. These cases should be considered individually.

The employment of the capillary microscope, recommended by Jaensch, Wittneben, Hoepfner and others, for the detection of goitrous individuals may shortly be tentatively introduced in isolated neighbourhoods as the basis for individual treatment in schools. It is impracticable as a basis for general antigoitrous prophylaxis.

In districts where the salt monopoly is in existence, the complete salt shall, as a matter of principle, be obtainable at the same price as non-iodized salt.

The curative action of the complete salt was shown by a comparison of the incidence of goiter in the Viennese schools in 1927 as against that of 1923, and by the decrease of operations for goiter performed in Vienna.

The Prophylaxis of Endemic Goiter.

By Dr. Muggia.

The position we hold in regard of the prophylaxis of endemic goiter is, in appearance at least, contradictory: Conscious as we all are of having to remain within the bounds of the purest empirism so long as we do not succed to account accurately for the cause, or causes, of goiter, and while there exists on this point a profound disparateness of views we are all agreed as to the prophylactic-curative efficacity of iodine — short of interpreting from our respective standpoints the mechanism of its action, and short also of the reserves concerning the mode of its administration.

In Italy, even the most fervent upholders of the toxico-infective theory (Balp) and of the hydro-geological theory (Pighini) have not neglected iodine as a recourse, though pursuing, each, those other hygienic measures to which in their convictions, they attribute greatest efficacity. Pighini, who has made use of it for years, owns to its advantages, and Balp expressly acknowledges the utility of the use of « iodized salt » in regions afflicted with the endemic, while yet declining to recognize « iodic deficiency » — which, all appearances notwithstanding, requires to be more authentically demonstrated — as the cause of goiter. The binomial « goiter-iodine » may therefore be considered, concordantly with the general persuasion, as an equivalent to that other one of very ancient date and no less vigorous resistance to all attacks, viz. « malaria-quinine », and as an equivalent to yet another, which has lost ground only in recent years (though, perhaps, in a lesser degree than some may believe): the binomial, namely, of « syphilis-mercury ».

But the contradiction resides perhaps wholly in the fact that, here, like, or perhaps more than with any other disease, it is difficult to distinguish the prophylaxis from the cure. No one will deny that in healing a potential mother we are extending prophylaxis to the future child; on the other hand, it has to be admitted that the treatment which school-children above the age of 6 or 7 years are made to undergo, takes, if not wholly, at least predominantly, a curative character, even though such treatment may, for particular reasons, be applied to all the pupils without exception. It is agreed on all hands that, in endemic regions, the thyroid is assuming from the first years of life, if not congenitally, those structural characteristics which (apart from weight and volume) appertain to what I call the « mountain thyroid » and constitute the first stage of the ulterior morbid evolution that concludes with the manifestation known, even to the profane, as « goiter ».

Prophylactic efficacity, however, in the fullest meaning of the term, must be conceded to the « iodized salt », so far, at least, as thyroid hypertrophy and the degenerative processes usually accompanying it are concerned.

Italy, to which belongs the credit of having well fought, and gained, another battle — I am alluding to pellagra, that ferocious and insidious ravager of our peasantry, who sacrificed their very lives in the fecundation of the soil — Italy has, long before now, awaken to the necessity of initiating the struggle against the endemic of goitrous cretinism. This, the more so, as pellagra —

which was overcome before its cause became known — shows some curious affinities with the goitrous endemic (affinities certainly not of a symptomatological, but of an epidemiological character) and amongst which we may note the decrease of both endemics in the presence, I do not venture to say in dependency, of an improvement in the conditions of living; so much so that I am greatly tempted to relate both to a common origin of deficiency in elements, may be diverse in their nature, but equally indispensable to the development and the normal functionality of the organism.

Investigating and combating centers have been instituted in Italy in the provinces of Novara, Genova, Trento, Belluno, while actions on a larger scale have been organized in the province of Turin under the guidance of Prof. Lugaro, in the province of Reggio-Emilia through the care of Prof. Pighini, in Sardinia by Prof. Riquier and Dr. Ottonello, in Sicily on the initiative of Prof. Coppola, in Valtellina on the part of a Provinial Committee constituted in 1921.

Recourse was taken, in turn, to opotherapeutic and iodic (organic and anorganic) preparations; sometimes, both have been combined.

In Valtellina, treatment had primarily been restricted to pupils with a visibly enlarged thyroid, successively to be extended to the generality of the pupils of elementary schools. In the years 1924 and 1925 about 16'000 school-children were treated. In resorting to this generalisation of our measures we have been guided less by hygienical than by psychological considerations: From the day when the distribution of medicated chocolates was started, the natural desire of all the children to have part in it became evident and lead in many cases to the sharing in private of the chocolate tablet with a playmate who had been excluded in the distribution; or to an attitude of hostility, inspired by jealousy, on the part of the latter towards the favoured ones, culminating at last in a gibe: « You have a goiter! »

The results, as defined at the end of each scholastic year by the mensuration of the circumference and the ante-posterior diameter of the neck, were everywhere found to be of an absolutely positive character and such as to impress even the most diffident.

But, notwithstanding the apparent identity of the conditions under which the experiment was conducted, the results have, from year to year and from one place to another, shown such a different and often contradictory complexion that we have not felt authoriz-

ed to attribute greater efficacity to the one or the other of the medicaments employed.

The rate of improved cases in the triennium 1922—1925 has indeed oscillated between 34,8 and 70 % of the individuals with a visibly enlarged thyroid. No plausible explanation of such large differences in the rates of improvement having been found, we were induced to doubt our own measurements, which, although taken by myself personally (therefore in following constantly the same line, technically, and with the same criteria of valutation according to which only such individuals were considered to have improved as were presenting a reduction of at least 3 millimeters) appeared to us succeptible to error so frequently as to cause perplexity each time when, at the control, circumference and diameter showed a discordance of data between them.

From the result of our examinations concerning over 12'000 pupils in Valtellina during a triennium, we found ourselves entitled to draw, without misgiving, but the following two conclusions:

1) that the reaction of the curative treatment is the more rapid and the more manifest according to the original gravity of the hypertrophy of the thyroid (provided always that no nodular forms be in question) and, in those conditions, quite a minute dosis of either a iodic or an opotherapeutic medicament suffices mostly to bring about very notable results: thus, indeed, can we explain that in the second and successive years of treatment the effects had each time become less evident;

2) that a weekly dose of 2 centigrams of iodide, administered during the whole of the scholastic year (to be reckoned as a period of seven months) has never been found to have caused any sort of inconvenience.

This favourable outcome of our observations, together with the experiences previously obtained by many of the Swiss Cantons, encouraged us to recommand to our Board of Hygiene the introduction of the « iodized salt », which — as had already been done in a way of experiment, in 1922, under the auspices of Professor Roux — was tacitly substituted in Valtellina to the common salt, in April 1925, thus extending the prophylactic-curative intervention at once to the entire population. It must be recognized, at any rate, that, the treatment having already been in practice in the schools among all the pupils without exception, the leap was not of such an acrobatic kind as might appear: it was a comparatively easy transition from the scholastic to a generalized prophylaxis.

In 1925, the distribution of iodized salt amounted to 874,405 kilograms, and to 1,183,846 kgms in 1926 (a proportion of about 9 kilograms per inhabitant and inclusive of the quantity employed in bakery, sausage manufacture and dairy-products) the prepared salt being sold at the same price at which common salt had previously been, and is still being, sold in that province as in all the others.

Those who are aware that in Italy marine salt is almost exclusively in use might be tempted to assume that a certain amount of iodine was already contained in it naturally. An inquiry, however, carried out among the salines, and an explicit declaration issued by the Board of Revenue have assured me of the contrary. Such traces of iodine as may be remaining during the process of crystallization are dispersed in the course of the maturation which the salt, before being stored, is submitted to in being left exposed in cumuli for more or less prolungated periods of time, open to the influence of every kind of weather. The only salt found to contain iodic traces at the moment of reaching the consumer is that originating from the salt-pits of Salsomaggiore, which, however, hardly suffices to the needs of that local population, who, by the way, are very jealous of its possession.

Thus, things being as they are, we cannot a priori consider as superfluous, and, less even, as harmful, the adjunction of a modicum of iodine: the distribution of « iodized salt », moreover, has been practized for over two years without having given rise to any ill effect whatever.

The iodization itself is accomplished at the rate of one gram of potassium iodide per 100 kilograms of salt. This dose might be deemed a strong one, but it must be called to mind that, the question being of sea-salt — rather often of little purity and therefore deliquescent — a part of the added iodine readily disappears. Dr. von Fellenberg, in fact, has ascertained the presence of only 8,6 milligrams per kilogram. Such a reduction, as confronted with the original adjunction, can be imputed neither to a lenghtened storage, nor to transport conditions, inasmuch as the preparation takes place at Milan (distant 131 kilometers from Sondrio, Chief town of Valtellina) hardly a few days previously to the supposed arrival of requisitions from distributing depots, oftenly even on the very same day; the storage of « iodized salt », therefore, is seldom of a duration greater than 3 or 4 days.

The fact of the aforesaid reduction notwithstanding, which, it is not to be excluded, may yet become accentuated during the sub-

sequent stay in the district stores and retailing shops, i. e., previously to the salt actually reaching the consumer (although the prevalently dry climate of this province might favor its preservation) I anticipate the objection of some of my colleagues: « You are dosing too high! » I have already heard it being remarked that 2 centigrams, or even 1, of iodide per week be excessive, seeing that in the long experience of Switzerland one milligram has proved to be adequate. We must not however lose out of sight how different the conditions are from one place to another. My colleague Eggenberger, when present at Sondrio in September 1924, to assist at our conference, has explicitly recognized, in agreement with myself and on the basis of a summary examination of the immates of the Ospedale Psichiatrico and of the Male Orphan Asylum, how much the lesions encountered in Valtelline thyroids are in their great majority wanting in gravity, as compared with those of some of the Swiss cantons. In fact, thyroids comparable to those comprised in the 4th category, as set up by the Swiss Goiter Commission, constitute in our country a rare exception among the scholastic age, and even such as aspects as would correspond to category No. 2 are by no means frequent.

Lord Goitre of the small [illegible] in Italy.

An experience, now more than quinquennial has demonstrated not only the perfect tolerableness on the part of our subjects, but also the necessity of the relatively elevated medicinal doses employed by us, if appreciable results be desired.

This tolerableness finds an illustration in a circumstance which is undiscutably proved: viz. the absolute rareness of exophthalmic goiter in Valtellina, even concerning those thwarted forms which Plummer has comprised in the term « toxical adenoma ». We may assume both these circumstances: tolerance of relatively high doses of iodine and the rarity of exophthalmic (Basedow) goiter, to be an expression of the same fundamental, i. e. anatomo-fundamental, condition of the thyroid. In the hospital directed by me and which receives over 250 mental patients — about 50 new subjects passing through it every year — I do not recall having observed a single complete Basedow case during 15 years (though the goitrous be still in goodly number) and the subjects in which one or other of the characteristic symptoms have been encountered, even singly, may be counted at one's finger-ends. I have to add, however, that this judgment rests solely upon manifestations of an external kind, as we could not proceed to the investigation of the basal metabolism.

Many of my colleagues with whom I inquired in reference to conditions obtaining within the territories of their competency have arrived at analogous conclusions. The dates collected are not sufficiently complete to permit of even an approximative computation of the totality of cases existing in Valtellina; in some instances, however, the notes furnished have been precise enough to elucidate the fact that, in a population of 25,000 inhabitants belonging to 15 parishes, situated in different regions and at most varying altitudes (from 250 to 1000 meters) only 9 individuals were presenting symptoms of more or less gravity related to exophthalmic (Basedow) goiter. And, not only is this affection occurring less frequently in Valtellina than elsewhere, but it assumes in this province a more moderate character and a course more benign; this would perhaps account for the fact that none of the cases observed has grown worse through the habitual use of iodized salt. Besides our experience has definitely proved that the intolerance of iodine is by no means absolute with these patients.

Such an array of favorable circumstances fully warrants our going onward, without preoccupation, with the prophylactic work so auspicuously begun and which we have carried on now for more than two years. Nevertheless, to do full justice to its efficacity without the likely risk of crediting it with virtuess not belonging to it, I deem it necessary to allow a longer period of time to pass. Truly, Eggenberger, already after one year, has observed that in none of the infants born from mothers who had made use of iodized salt during pregnancy did a thickened thyroid occur, whereas of those born from mothers who had given preference to common salt 50 % presented a palpable thyroid. On our own part, however, we are lacking such a demonstrative term of confrontation either because lesions of such conspicuousness in the newly born were met by us only exceptionally, or else because minor lesions — as alluded to before — be concomitant with effects more tardy and less pronounced.

At any rate, having examined, towards the end of May last, a few hundreds of pupils in the Malenco valley (to be more precise: of the parishes of Spriana, Torre Santa Maria, Chiesa, Lanzada) in order to confront the conditions then obtaining with those of the scholar populations untouched by any treatment, and whom I had visited in those same parts from 1921 to 1924, I found the average percentage of hypertrophic thyroids reduced by about one half, it having receded from 61 to 33 %; elsewhere (at Sondrio)

the improvement appeared to be even more sensible, but, far milder degrees of hypertrophy having been in question there, I regarded these latter findings with some scepticism, since they were the outcome of observations rather hastily conducted.

At this juncture, the question ought to be considered as to whether the aforesaid improvement be attribuable wholly to the use of iodized salt, or if other conditions might not have contributed to it.

Distrophic endemic (I have pleasure to make use of the comprehensive and happy term employed by Kutschera), is, by a conviction diffused among our population, diminishing progressively in gravity and this independently of any systematic treatment whatever; circumstantial facts are being cited in proof on all sides, and physicians themselves are bearing testimony in strength of this conviction.

Mustering statistics — to which the revisals effected during the recent war have lent a uniformity of criteria which previously we could not have relied upon — while revealing Valtellina to be the province most gravely affected in Italy (though it is not to be excluded that Aosta, now constituting an autonomous province, may eventually surpass it) mustering statistics are documenting the improvement by such figures as may be cited here in reference to the following septennaries of birth dates:

	Subjects rejected on account of goiter:
1880—1886	1,49—2,41 %
1887—1893	1,35—1,89 %
1894—1900	1,19 %
1901—1907	0,81 %

(I have to point out that, in order to arrive at a more uniform and precise valuation of data, I have undertaken a re-examination of the muster-registers on my own, instead of taking advantage of the resumptive reports).

The first of the two figures indicated above with those of the two initial septennary periods refers to the number of rejections on account of goiter as reconfirmed on the occasion of the many successive revisions, while the second figure corresponds to that number as increased by the calculation of a quota of individuals previously rejected for goiter, but refused subsequently on account of other pre-existing, or intervenient, infirmities, or of deceased, or renitent, subjects: a quota which has been computed

proportionally to the number of subjects whose rejection was confirmed and of those who were retained, instead, as being, conditionally or unconditionally, apt for military service.

The existence of an improvement is certainly not to be denied, seeing that within 28 years the percentage has receded to one third or, if the most severe hypothesis be admitted, to one half of its former amount.

In the above computation, account has been taken of cystic, nodular and visibly monstruous goiters, as well as of those which — without any of these appellations applying to them — were gravely interferring with the functions of the circulatory or respiratory systems and, finally, of the not infrequent cases of pure hypertrophy of the thyroid which, besides causing equally grave disorders, had proved irreductible during a protracted period of time. On the other hand, we have excluded altogether the great bulk of « thick-throats »: as to the relations, however, existing between the former and latter kind of cases, it may logically be held that to the numerical reduction of the graver forms an attenuation of the others may be found to correspond.

In the presence of the acquired fact that, among those who passed muster, not even the recruits belonging to the most juvenile classes had been put to the benefit of any prophylactic treatment other than the use of iodized salt — which latter is not credited, even by its most enthusiastic champions, with the faculty of causing nodose and cystic goiters to disappear — we are lead to admit the existence of circumstances that must have contributed to prevent those graver manifestations.

In our opinion, great influence is to be ascribed to improved conditions of life as considered in their essential part, namely alimentation. Our mountaineers, formerly so parsimonious, have emerged from the war undoubtedly with notions of better feeding, and this after the improvement which the opening of always more ways of communication, in the previous decenniums, had already brought about in the variety of their modest fare, the latter comprising thus a good part of victuals originating from non-endemical regions. Nor should the enormous diffusion be overlooked, which iodic preparations have gained in the course of time, as an element which probably has furnished its contribution to the abatement in question.

Better nutrition

Unfortunately, we cannot speak to a simultaneous improvement

in the pursuance of personal and domestic hygiene, even though a tendency also in this direction, and however faint, cannot be denied.

The influence which the general conditions of living are exercising upon the degree of the endemic appears to me as having found a corroboration in the aggravation ascertained in recent years in the whole of the Austrian territories, the privations which those populations have had to endure being ignored by none; and their sanitary authorities are justly manifesting concern in that regard.

In the perusal of the mustering records, we also have discerned oscillations from year to year, partly of great extent; but we presume these to be of an accidental nature, as — while we were unable to connect them with any particular circumstance (unless we meant to explain them in reference to the questionable epidemics assumed by Balp) — they are fully compensated in the data of either the preceeding or the following year.

Now, this improvement, which in Valtellina undoubtedly prevails, has also been noticed recently in Liguria, and, from observations supplied by Raseri, Cavatorti, Castaldi, we may conclude on its ascendent generality in all the regions of Italy. But, when we consider the primal cause of the endemic as being intimately related to circumstances of environment, we may not anticipate the improvement to remain indefinitely progressive; and does it obtain in all the territories where the endemic be known? In the affirmative, what attitude ought we to take in respect of the question of what I should call the medicinal prophylaxis? Are we to disinterest ourselves from it altogether, or return to practising it individually, or shall we rather employ ourselves in propagating the use of iodized salt and extend it to all the affected zones?

It is here that the proplem resides. —

General prophylaxis in its tacit application, as carried out in Valtellina, if it has permitted the easy avoidance of mistrust and apprehension such as experience is indeed proving — at least with us — to be entirely unjustified, presents the disadvantage of hindering the enlistment of support and assistance on the part of those interested in this real work of social redemption and of being thus deprived of the propagandistic function so requisite among that vast circle of populations who, in many places, refuse, from time-worn prejudice, to recognize the existence of the evil.

Nevertheless, all the pros and cons considered, I am still deciding in favour of this system, convinced as I am that the advantages

outweigh its drawbacks. And, we Italians whatever our views concerning the pathogenesis or aetiology of goiter, are all at one in anticipating our Board of Hygiene, without waiting for the exhaustive completion of investigation on the side of organic criteria — however indispensable these be — as to distribution and gravity of the endemic, nor for more precise data on the efficacity of the iodized salt, to decree its use in all the regions more seriously affected and which we have reasons to look for, pertinently, among those of the Alpine circuit.

In fact, if we compute the annual outlay as it has resulted in 1926, viz. 9 centesimi di lira per inhabitant, upon the total number of the population of the regions where the endemic is to be found more or less prevalent, we see the expense reach an amount by no means indifferent in view of the many other requirements in the interests of hygiene and, even, perhaps of a more impellent nature. Thus, we can understand and account for the hesitation of our Board of Hygiene, who are not, meanwhile, finding themselves between conflicting currents of opinion, as is the case elsewhere.

If therefore a cautious and gradual course should be adhered to, we ought not to lose sight of the fact that two other provinces: those of Turin and Aosta, have been laboriously worked, through the unremitting efforts of Professor Lugaro and his disciples, with the purpose of making them receptive to the measure: and the long experience gained in these districts with school-prophylaxis, most variedly applied, may indeed be looked to as the most dependable demonstration of the perfect safety with which the administration of the iodized salt could be extended to the zones proving to be most afflicted.

Even, if we consider — accordingly to the views recently exposed by Kutschera — the distrophic endemic to be the expression of a primitive lesion of the nervous system, and the goiter to be but one of its symptoms and, maybe, the ultimate outcome of the struggle engaged between the morbigenous agent and the organism, no one will, for the matter of that, dare to dispute the expediency of our attempting to modify, once the means be known, the anatomo-functional conditions of the thyroid, in view of the presumptive possibility that we may thereby attenuate the repercussions of its insufficient and abnormal function upon the ulterior evolution and activity of the whole organism.

* * *

Conclusions:

1. The administration of iodine, by whatsoever method, as a prophylactic against goiter must in the present state of our knowledge be considered as a purely empirical measure. As such it is regarded by the great majority of the medical profession in Italy, no matter what views they take as to the aetiology and pathogenesis of goiter.

2. If iodine is given carefully and after accurate investigation of local conditions, i. e. the gravity and type of the endemic in a given district, it can be regarded as absolutely harmless, while any resulting benefit is speedily evident.

3. It is under such conditions at once of harmlessness and of efficacity that the prophylactic treatment of the general public with iodized salt is carried out in the Valtelline, by the simple method of replacing common salt by the new variety. This « surreptitious » form of prophylaxis seems indicated wherever stubborn prejudice renders the people unwilling to grant the existence of the evil or to submit voluntarily to a treatment howsoever innocuous.

4. No one in Italy has failed to notice the marked tendency toward improvement of the endemic which has proceeded pari passu with the rise in the standard of living of the people at large. If however the risk of a fresh outburst is to be avoided and the present abatement, which cannot be relied upon to continue, to be possibly forwarded, then the imperative necessity must be realized of insisting on the continuance of iodine prophylaxis wherever it has already been introduced with manifest benefit and of extending it to all districts where the endemic shows a certain incidence and intensity.

The Prophylaxis of Endemic Goiter*.

By Prof. Dr. W. Silberschmidt, Zurich.

In the following address we shall endeavour to show the present status of the prophylaxis of endemic goiter, taking our Swiss conditions into particular account. There can be no question of a complete solution having been reached. Since the last few years, this problem has been attacked from various points of view and we can see, that valuable results have been obtained. In the field of prophylaxis, many promising combative methods have been brought to our notice, however, I wish to emphasise the fact that we are still in a stage of experimentation.

School and military statistics have furnished us with information, concerning the distribution and occurrence of goiter. The first examinations in Swiss schools were started by our two eminent surgeons and research-workers, Theodor Kocher and Heinrich Bircher. Bircher's examinations covered 3144 school children, of whom 804 or 25,4 % had goiter, viz. 22,7 % boys and 27,9 % girls. From 1883—84, Theodor Kocher, with several collaborators, examined 76.606 pupils, ranging in age from 7 to 16 years, and coming from different districts in the Canton of Berne. The number of those afflicted with goiter varied. In the City of Berne it amounted to 54 % with fluctuations between 29 and 78 %. In 1908 Kocher jr., de Mestral and Vannod undertook a new series of investigations which showed the same results.

Of the more recent examinations on school children, I wish to mention only a few, which were made before the adoption of school prophylaxis. At the same time the fact must be stressed, that the data given by several of these investigators do not coincide, and that the terms «normal», «palpably enlarged», «distinct goiter» «nodulous goiter» and «large goiter» have not one and the same meaning, when applied by different investigators. The Swiss goiter commission published a schedule which now makes a uniform examination possible.

Klinger found that in different small communities in the Canton of Zurich, from 72 to 100 % of the school children, ranging

*) I wish to acknowledge my obligation to Mrs. D. Bloch-Sulzberger for the translation of the present article.

from 6 to 14 years, were afflicted with struma. According to a summary of investigations (1922—1926) made by Dr. Kraft, the school physician of Zurich, it is seen that out of 4689 boys of the first class, 14,3 % were normal, 51,7 % hat a palpably enlarged thyroid gland and 34 % a visible goiter. The examination of 4740 girls showed similar results (12,8 % normal, 51,6 % palpatorily enlarged glands, and 35,6 % visible large goiters). In 1921 an examination was made on 12 years old scholars in the 6th class. 50,3 % of the boys and 56,4 % of the girls showed noticeable goiters, of which 4,7 — respectively 6,5 % — were recorded as having large strumas. Lauener found that in the City of Berne 82 % of the school children had enlarged thyroid glands. In the Canton of St. Gall, where 44.000 scholars were examined, the statistics compiled by Steinlin, showed 61 to 68 % to be suffering from goiter, and in the City of St. Gall, the number of those having goiter in the 5th and 6th classes, was respectively 83 % and 75 %. In Glarus, Fritzsche found 12,6 % normal, 51,2 % with slightly enlarged thyroid glands and 36,2 % with goiters. The conditions in Geneva are more favourable; in 1923 according to information kindly given by Rilliet, 68 to 79 % showed normal thyroid glands, and 7 to 10 % distinct goiters. Girls show a somewhat larger percentage than boys. During school years, it has been observed that with the increasing age of the pupils, the thyroid gland increases in size. Until the introduction of goiter prophylaxis, more and larger goiters were to be noticed in the older scholars, than in those in the elementary classes. According to Kocher, the greatest number was found in children between the ages of 10 to 14 years.

The figures supplied by Wagner v. Jauregg, concerning Austria, and by different German authors, v. Schittenhelm and Weichardt for instance, for Bavaria all show, to what great extent school children are affected in districts, suffering from endemic goiter.

At an early date, medical examination of recruits afforded the opportunity to observe how common goiter is in men between 19 and 21 years of age. In Switzerland, it was chiefly the statistics for the years 1875—1880 (published in 1883 by Bircher), concerning the number of men released from military service because of goiter, which drew general attention to the significance of goiter, as a cause for military exemption. This led to the making of the goiter map of Switzerland, which has since become famous. Cretinism also came within the scope of these examinations.

When we consider the vital meaning of goiter, it is comprehensible, that the work begun by H. Bircher has been continued. H. Hunziker, and later Stiner, have given us valuable contributions. Stiner's summary covers the years 1921—1922; men, who — because suffering from goiter — were declared unfit for military service, were entered on one card, while on another card were inscribed those, who despite enlarged thyroid glands were found fit.

In Switzerland, the number of 21 year old men afflicted with goiter varies in different districts; in the north western part of the Jura 0 to 2 %, while in certain parts of central Switzerland over 30 % of the male population is thus affected. In only 2 districts, does the number of men declared unfit for military service, on account of goiter, exceed 20 %; on the other hand, in a great part of Switzerland it is from 5 to 15 %. The average of those exempt from military duty because of goiter amounts to approximately 7 % of those recruited.

A comparison of investigations, made in schools and in the army, shows the number of enlarged thyroid glands in children to greatly exceed those found in 20 year old men.

The results obtained by Bircher, Hunziker and Stiner do not entirely agree. The examinations were made by various physicians, and at different times. During the last few years more attention has been paid to goiter at the recruiting of soldiers. We must bear in mind the possibility of the occurrence in Switzerland of a «goiter wave»' as mentioned by Wagner v. Jauregg. The aetiology of goiter is not yet entirely clear; the chronological fluctuations in the spread of goiter lead us to believe that various factors must be taken into consideration. Klinger and his cooperators point out that these chronological fluctuations in normal and pathological conditions are often found in young individuals. This observation leads us to the conclusion that not every soft enlarged thyroid gland seen in a school child is to be diagnosed as goiter, and that some goiters observed in childhood later recede completely. A valuable addition to the results obtained through school and army investigations, is the examination of entire communities; such work was carried on by Dieterle, Hirschfeld and Klinger. These research workers investigated 14 different communities, examining all in all 5549 inhabittants (of whom 4616 were suffering from goiter), in order to determine at what age and in which sex goiter most often occurs. These communities differed in regard to situation, as well as in

other respects. In certain communities only 1 %, in others 7, 12, 24, 40 and up to 77 % had goiters; however, in places where it was most prevalent, a number of goiterless persons were also found. All investigators agreed that goiter is decidedly more prevalent among females than males. The maximum were found to be afflicted between the ages of 14 to 17. From this age on, there is a decrease in the case of men, whereas the curve in women remains practically unchanged from puberty to the beginning of the climateric period.

Economic losses caused by goiter cannot be calculated in exact figures. Before the war 5 to 7 % of the men who came to be recruited were found unfit for service, owing to goiter. To these must be added a number of men who are debarred, owing to the fact that they are either undersize, deaf mutes, idiots or cretins. The so called cretinoid conditions cannot be exactly differentiated. Oswald figures that in Switzerland (which has a population of approximately 4.000.000) the number of persons afflicted with cretinous degeneration, in the widest sense of the word, is 50.0000. In addition to these come the heart disturbances (goiter heart), nervous conditions etc. which we attribute to the harmful influence of goiter.

Dr. Lauener, the school physician of Berne, states that as the result of goiter, 2 % of the public school children is mentally deficient. We will not try to express in figures the injury to the public and public wealth. Anyone who has carefully considered the goiter problem will appreciate how deep-seated and how varied these injuries are.

That it is an urgent hygienic necessity to combat goitre in all the districts where the inhabitants are afflicted with it, has been made clear by the above statements. We must remember that iodine prophylaxis, introduced during the last few years, is merely a resumption of experiments, begun in the goiter districts of France and Switzerland, some hundred years ago. In 1819, shortly after the discovery of iodine (1812) by Courtois, Straub, a Berne physician, applied sponge ashes containing iodine, as a goiter preventive, and in 1820, Coindet of Geneva, recommended iodine treatment. It is sufficient to mention the names of Chatin, Baillarger, Grange, Boussingault and Morel, who introduced goiter treatment in France, both with iodine common salt and with iodine vapors. The lack of iodine theory (Prévost and Chatin) and iodine hyperthyreoidism were likewise already known in the middle of the last century.

In 1859, Rilliet, a Geneva physician, described constitutional iodism. It was due to the serious injuries caused by iodine that iodine prophylaxis was dropped for many decades. As early as the year 1868 Rudolf Virchow made an autopsy on a case of marasm, due to iodine poisoning.

The fundamental investigations, concerning the amount of iodine contained in the thyroid gland, made by Baumann in the middle of the nineties, mark a decided step forward.

Clinical and experimental investigations were now started. Kostl, Wagner v. Jauregg. Kutschera in Austria, Marine, Leonhart, Kimball, Rogoff and others in the United States, Mc.Carrison in India, deserve mention as pioneers in this field.

Our Swiss surgeons H. Bircher, Th. Kocher, Roux, de Quervain and Hotz, among others, called the attention of the medical world to the absolute necessity, and urgent need of goiter prophylaxis, despite the tremendous results achieved in thyroid surgery.

General practitioners Bayard, Hunziker, Eggenberger and the research workers Galli-Valerio, E. Bircher, Oswald, Klinger, Messerli etc. essentially furthered goiter prophylaxis; through their untiring, self-sacrificing activity they helped to have it introduced and generally adopted.

The recent fundamental investigations of v. Fellenberg, a chemist at the Swiss Departement of health, deserve special mention. This research worker has succeeded in finding a process by means of which it is possible to detect the smallest quantity of iodine, and to determine the existence of, and fluctuations in the quantity of iodine existant in our surroundings, as well as in our foodstuffs and bodies.

Thanks to the efforts of the school physicians Steinlin, Fritzsche, Imbach, Lauener etc. we are to-day able to form an opinion and to judge the aims, and the limitations of goiter prophylaxis in our schools. We also wish to mention the energetic support, which the suggestion of the Swiss goiter commission received from our authorities, at their introduction of common salt prophylaxis.

At present iodine prophylaxis is of dominant interest. Every prophylactic measure must fulfill the following conditions: it must be effective, cheap, easily applied, harmless and furthermore, it must be able to reach every part of the population in need of it.

Combating Goiter in Schools.

Recent attempts to combat goiter, in pupils of school age, were begun by Marine in the United States in 1917. He employed a syrup, containing sodium-iodide, and administrated to each girl 2 grams every 10 days. The goiters disappeared, but in individual cases, symptoms of iodism appeared.

In Switzerland the idea of combating goiter in schools was first adopted by Klinger. In place of syrup, which did not seem to be the most suitable vehicle for giving iodine, in public schools, Klinger suggested chocolate tablets. These tablets contained a precisely weighed amount of iodine. At first an organic iodine preparation, iodostarin, was used, later a mixture consisting of 4 parts iodostarin, and one part sodium-iodide. Originally an organic iodine preparation was employed in the assumption, that iodine becoming free in the intestines, it would be resorbed more slowly than inorganic iodine salt, and therefore a more lasting effect would be obtained. Lauener relates, that in order to make comparisons, some classes in Berne were given iodine once weekly, and others were given correspondingly smaller doses daily. Although investigations have not been completed, it would see that the result achieved with daily doses is more favourable. On the other hand, good results were obtained with inorganic combinations, such as sodium-iodide or potassium-iodide alone. Our experiences during many years have proven the efficacy of school-prophylaxis with iodine.

The first experiments with iodastarin chocolate were published by Klinger in 1921. These examinations were simultaneously made in several goitrous communities in the Canton of Zurich, on children of various ages and in different grades. Decrease in the number of goiters was not immediate, but gradual. Already 1 to 1½ years after iodine treatment had been introduced, the total number of struma sufferers hat decreased from 90 to 28,3 %, and, what is more important, the large and exceptionally large goiters had entirely disappeared. Goiters which did not entirely disappear in this short time, did, however, decrease in size.

These first illuminating experiments served as a basis for the introduction of iodine treatment in a number of Swiss schools.

If we compare the results of individual investigations, we see a great difference in the number of goiter cases reported among school children, and also in the successes reported with iodine treatment. In the City of St. Gall, at the school entries, there were

58,5 respectively 64,8 % reported, a year later, after 30 tablets hat been administered (one tablet per week), the number of goiter cases was reduced to 10,1 %, and two years later, in the second class, after 40 tablets had been taken, 10,6 %. Not only was there a considerable decrease in the enlarged thyroid glands but existing goiters seemed also to diminish. It is true that Steinlin, who made a thorough study of scholars in St. Gall, cites certain cases in which an enlargement of the thyroid glands was seen despite treatment; similar observations have not rarely been made.

Failure? iod in certain c

In 1922—1926, Kraft in Zurich, examined 1429 boys and girls of the first classes and kept these cases under further observation. Among those entering school, he found 13,6 % free of goiter, 51,6 % with palpably enlarged thyroid glands, and 34,8 % with goiters; after four years' treatment with iodostarin tablets, 85,3 % were free from goiter, 14,4 % had palpably enlarged thyroid glands and 0,3 % had goiters.

Contrasting with these really brilliant results come the statistics from Glarus and Berne, which are less favourable.

E. Fritzsche, Glarus, made investigations on 1000 pupils; repeating them after 14 months and again after 3 years. According to an arrangement by Klinger he differentiates as follows:

I = Thyroid glands not palpable,
I-II = Thyroid glands scarcely palpable,
II = Thyroid gland lobules, 1,2 to 2 inches high,
II-III = Smaller goiters,
III = well-developed goiters, 3,2 to 3,6 inches,
III-IV and IV = large and very large goiters.

	I	I-II	II	II-III	III	III-IV	IV
Before treatment	2.3 %	10.3 %	51.2 %	28.3 %	7.2 %	0.7%	0
After 14 months	4.9 %	26 %	45 %	21 %	3.5 %	0 %	0
After 3 years	13.54%	46.53%	30.74%	8.72%	0.47%	0 %	0

To be sure the same children much be examined the years later.

Here also the influence of iodine treatment is quite clearly seen. After 14 months, of the 763 children treated, 269 had improved, 453 remained unchanged, and 41 had become worse. After 3 years, however, marked improvement is noted; large goiters, for the greater part disappeared, and over 60 % of the school children under observation had normal thyroid glands.

Dr. Lauener found in the City of Bern:

In 1920 before iodine treatment in 18% no goiter, in 82% goiter
In 1925 after iodine treatment in 52% no goiter, in 48% goiter
With the 6½ yr. school recruits in 27% no goiter, in 73% goiter
After 1 year iodine treatment in 66% no goiter, in 34% goiter

In 1920—1921, Hunziker and von Wyss made tests with smaller quantities of iodine. They gave chocolate tablets containing 1 mgr. KI (1 mgr. = 0,015432 grains) and had the opportunity to make comparisons between those who had been treated, those who had received no treatment whatever, and those who had only been watched and treated very irregularly. Their figures covered:

339 regularly treated (40 chocolate tablets with 1 mgr. KI.)
223 not treated
99 irregularly treated.

Examinations of treated and not treated thyroid glands, undertaken at the same time and place, showed that the former had been materially reduced in their surface area (to about ½) whereas the thyroid glands of other school children, examined in 1921, had increased in size since 1920.

It was also enlightening to watch the course of the goiter nodules. Of 339 school children who had been treated, 39 had nodules, of which 15 disappeared, 12 became smaller, 11 remained unchanged and 1 increased in size. Despite treatment, 3 new nodules had appeared. In the cases of 19 children who had nodules and underwent no treatment, not one decreased in size; 13 remained unchanged, 6 had increased and 12 new nodules appeared.

It is superfluous to give further figures, for the results of all investigators coincide.

We are struck by the different reaction in the case of each child, and the difference in the results reported by each community. The course of the different goiters is dissimilar. The soft, parenchymatous struma is most easely influenced. The nodulous struma (struma nodosa) is more stubborn. Even though individual nodules disappeared as we have seen, we must not conceal the fact, that in some cases an enlargement of the thyroid gland appeared after iodine treatment.

In the beginning, the tablets contained 10 and more milligrams of iodine. Soon the dose was reduced from 5 to 4 milligrams and even down to 3 and to 1 mgr. It is evident, from observations made in Switzerland and in other countries, that children are not susceptible to iodine. Research workers, who have studied and worked on school prophylaxis with iodine tablets, all declare that no single case of iodism has come up in their experience. Very rarely do cases come under notice, where in girls over 12 years of age, show signs of tachycardia after taking iodine tablets. It is there-

* * *

fore important, that iodine treatment should be started at as early on age as possible.

With the administration of larger doses of iodine, a retrogressive metamorphosis takes place more quickly. For this reason the tests in the schools thus far, were made with from 3 to 5 mgr. of iodine. The Swiss goiter commission recommanded the use of only 1 mgr. pro week. How long iodine treatment will be continued in schools, depends on the succes obtained with this treatment.

Steinlin and others prescribe 40 tablets to be given in the first, 12 in the second, and 8 in the third year, and advise altering the dose, according to each individual case. I would warmly recommend that this «individual treatment» be adopted by all. Even if a child is not susceptible to iodine, I can conceive of no reason why it should be given more iodine than it requires. We must also remember that a recurrence of goiter is at any time possible, — also after the school-years are over.

The prospect for success with this iodine tablet treatment depends not only upon the age of the scholar, but also upon the nature of the enlarged thyroid gland. Several years ago, in a girl's training school, I had the opportunity to make interesting studies on young women, aged from 15 to 22 years. The board of directors instituted a test with iodostarin tablets. The pupils were instructed to stop the tablets at the slightest indication of a disturbance in their general health. The majority took the tablets regularly. Although success was less evident here, than in the case of younger school children, a number of heretofore visible goiters (in girls aged from 15 to 18 years) disappeared. On the other hand, in the teachers' training school, where the young women ranged from 20 to 22 years, no success was achieved after thyroid gland therapeutics had been employed during a year. It is true, that soft goiters receded, but the firm and nodula strumas were no way influenced.

Failure? iodine.

Goiter prophylaxis, through the medium of iodine tablets, given in schools, has within a few years, given most satisfactory results. Through this method of procedure, thousands of children were freed of goiters. This school treatment does not, to be sure, give complete satisfaction in every case. We find, in different vicinities, a greater or lesser number of strumas, which do not recede, or at all events, not entirely, owing to the fact that treatment was begun too tardily. Iodine tablets cannot be given early enough; in Kindergarden this therapy should be started.

Combating goiter in military Service.

Since 1921, treatment with iodostarin tablets has been introduced into Swiss recruiting schools; men suffering from goiter or enlarged thyroid glands, were weekly given two tablets containing 5 mgr. of iodine. During these five years, on an average 4000 recruits were annually given treatment under medical supervision. A recruiting course lasts only two months in Switzerland. Thanks to the kind cooperation of the Sanitary Division, I had the opportunity to examine reports made by army physicians. Not all of these physicians agreed in their opinions concerning the results. Nevertheless one thing is important, i. e. that after the prescribed iodine treatment had been employed for the short period of 8—10 weeks, in 50—60 % of the cases, an improvement could be noted, particularly in the soft parenchymatous strumas. In about 30—35 % of the other cases, no distinct diminution could be observed, although the recruits declared that there was an improvement in their general (subjective) condition. (In 5—10 % of the cases, despite iodine treatment, an increase, if only a slight one, was found in the circonference of the neck.) We will not attribute these favourable results exclusively to iodine treatment. A diminution may be brought about through a changed mode of life. This question could naturally only be answered, if a great number of carefully supervised examinations could be undertaken, on persons afflicted with goiter, and who have undergone no treatment whatsoever.

This test made on a number of young men (who although suffering from struma were otherwise quite healty) showed the susceptibility to iodine at this age, despite the exertions of military service, to be very slight. The recruits were repeatedly weighed, in order to ascertain whether through the taking of iodine, they had decreased in weight. At the end of the session, a large majority of the recruits who had been treated, showed a considerable increase in weight. Great loss of weight was noted only in very rare instances in cases of obesity (adipositas).

Iodized Common Salt.

The experiments begun in 1860, in several departments of France, with the purpose of combating goiter, by means of the addition of iodine to common salt, were discontinued, because of ill effects observed in persons hypersentitive to iodine. Credit is due to two Swiss doctors, Bayard and Heinrich Hunziker, who about 12 years ago, introduced iodized common salt into

Switzerland, and tested its practicability. It is due to their, as well as to Eggenberger's, and Prof. Roux's efforts, that prophylaxis was now begun on a larger scale. The main importance of the new tests was, that they proved the efficacy of minimum «homeopathic» doses of iodine Bayard found that the minutest quantities of iodine, if employed over a long period of time, could prevent the formation of goiter, arrest incipient goiter and in certain cases even bring about an involution. The Swiss Goiter Commission willingly gave its support to this test. After detailed discussions, an agreement was reached, regarding the quantity of iodine to be administered; it was decided to recommend the addition of ½ gr. of potassium iodide to 100 kilograms (1 kilogram = 15,432 troy grains) of common salt. At first a double quantity of iodine was employed in the Canton of Appenzell A. Rh. Eggenberger worked out a simple and easily regulated combination of iodine and common salt; besides, he gave us an excellent method to determine quantitatively the iodine contained in common salt.

According to the exhaustive research work of v. Fellenberg, the quantity of iodine, daily absorbed through our food, amounts in Chaux-de-Fonds, a goiter-free town of the Swiss Jura mountains, to 31,3 millionths of a gram, whereas in Signau (a goiter district) it is only 13,0 millionths of a gram. The further addition of 40 millionths of a gram should suffice to cover this «physiological» lack. This is about the amount of iodine contained in a daily ration of iodized common salt.

If carried out as «silent prophylaxis», the employment of iodized common salt is one of the simplest forms of goiter prophylaxis.

Since 1924, the Cantons of Vaud and Nidwalden have employed iodized common salt almost exclusively. During the past three years the Canton of Vaud for instance annually consumed 2796 tons of common salt, of which only 6 tons were free of iodine. The only possible means to determine, whether the small quantity of 0,5 grams of potassium iodide to 100 kilograms of common salt was sufficient to rid the entire population of goiter, in a district where this ill prevails, was universal prophylaxis; it has been introduced in Lausanne at the instigation of our eminent Prof. Roux. It is quite evident that the question as to whether the process is an effective one, the dose sufficiently large, and whether this treatment produces ill effects, can only be answered after a general introduction of iodized common salt.

According to replies received by Director Marolt of the Salt Departement of Zurich, in answer to a circular letter, since two years the Cantons Schwyz, Zug, Neuchâtel, and since May 1926, also Schaffhausen, have decided to supply only iodized salt.

In the majority of the remaining Cantons, the use of iodized salt was recommended by the authorities; but in each salt depot, besides iodized salt, non-iodized salt is obtainable. The consumer is therefore at liberty to purchase either one or the other. The consumption of iodized salt varies in each town, and as I have personally observed, from salt station to salt station. In Zurich, in some shops, iodized salt is given, if the purchaser does not expressly demand iodine-free salt; in many others, the reverse is the case, and iodized common salt is supplied only on demand. In the last two years, 17 to 18 % of the salt sold in the Canton of Zurich was iodized. Some salt dealers take only 7 to 10 %, while others as high as 30 % of their total requirements, iodized; $^1/_5$ of the salt consumed in the City of Zurich and $^1/_8$ of that consumed in Winterthur, is iodized.

The consumption of iodized common salt is on the increase in Switzerland. In 1923 30.000 double hundred weights of iodized salt were bought, in 1924, 56.000, in 1925, 77.000 and in 1926 in round figures 88.000. On the other hand, respectively 413.000, 391.000, 380.000 and 359.000 double hundred weights of ordinary, non-iodized salt were demanded.

Heretofore the bakers in many towns had used only iodine-free salt.

It is not yet possible to form an opinion regarding the results of iodized salt prophylaxis. Zeller published the results reached in the first year of voluntary goiter prophylaxis, in Appenzell. The observation is important — in that it is a confirmation of Bayard's experiments, — that in a number of school children (particularly where young children were concerned) the enlarged thyroid glands diminished after only one year's use of iodized salt, containing the insignificant quantity of iodine (1 part of potassium iodide to 100.000 parts common salt); the results obtained with this treatment are by no means as favourable as when larger doses are administered.

Goiter prophylaxis is of paramount importance in earliest childhood, even before birth. This fact was soon recognized. Jodized common salt, taken during pregnancy, suffices to prevent the foetal development of goiter, and to produce new-born children free from this malady, in goitrous districts. This was made clear

through Wegelin's and Eggenberger's experiments, and is most important.

Is the quantity of iodine contained in our iodized common salt sufficient to meet this great need? If we succeed in bringing into the world new-born children without goiters (in hitherto goitrous regions) and they continue to remain free of goiter, then the problem of combating this evil is solved. In a private communication, Eggenberger states that in the Canton of Appenzell, salt, containing a somewhat greater percentage of iodine is dispensed to pregnant women. Continued research will enable us to decide whether these larger doses are still required, when iodized common salt shall have been generally adopted.

Jodine prophylaxis must, however, also be continued during the nursing period, and mothers must be persuaded to use iodized salt during this time.

Only in those parts of the country where iodized salt has been generally introduced, will it be possible after a number of years, to ascertain whether this prophylaxis is efficacious and whether the quantity of iodine given at present is sufficiently large. It is therefore urgently to be desired, that the example, set by the Cantons of Vaud and Nidwalden, be followed and the «silent prophylaxis» be introduced, particularly in those sections of the country where goiter is most prevalent. So long as 5, 10, or 25 % of the population, consumes iodized common salt, while the remainder does not, it is impossible to give a wellfounded estimate.

Since a long time, a particularly salutary action has been ascribed to sea-salt, in goiter prophylaxis. Eggenberger proved that common salt, employed by the large majority of the population of Bordeaux, contained from 7.500 to 15.800 millionths of a gram of KI to the Kilogram, that as about 3,5 times as much as the artificially iodized salt. (1 gram = 15.432 grains. 1 kilogram = 2.2046 lbs.). To deduce from this fact, that all sea-salt contains iodine, would be incorrect. The valuable facts, determined by von Fellenberg have taught us, that sea-salt from various parts of France, as that of Aigues-Mortes, Dax, Béarn, contains only small quantities of iodine, or is even devoid of it. Most of the salt consumed in Bordeaux is not sea-salt, but a secondary product of the Chile saltpeter refineries. The employment of sea-salt in place of the artificially iodized article can scarcely be considered preferable. Are possibly ingredients other than iodine contained in sea-salt, which have the tendency to check the de-

Sea-salt

velopment of goiter? An answer to this query is just now not possible.

Up to the present, cattle-salt, in Switzerland, had not been iodized, due to the fact that the farmers'prejudices against iodized salt, had been supported from certain medical quarters. The fear prevailed that, through an addition of iodine to fodder, the milk supply could be unfavourably affected. At the instigation of the Swiss goiter commission, experiments were made on a large farm in the Canton of Berne and also in the Canton of Ticino during 9 and 13 months respectively. These tests were carried out in the following manner: A part of the live-stock were given iodized salt and others received common salt free from iodine, in other respects the cattle received identical treatment. From an interesting summary made by Stiner, we see that the tests all showed that the secretion of milk was in no way lessened, on the contrary, the quantity of milk, as also the percentage of fat in the milk, was somewhat greater in the case of animals fed with iodized salt. Nor did the cattle become less productive. Let us hope that the iodization of cattle salt will be successfully introduced in goiter regions; this would surely accrue to the benefit of our infants. Since part of the iodine enters the milk, the quantity of iodine received in earliest childhood would be slightly augmented.

Fluctuations in the Percentage of Iodine.

Eggenberger had noticed that the percentage of iodine in artificially iodized common salt varies; von Fellenberg was able to verify this fact. The iodized salt prepared in salt-pits loses some iodine through evaporisation. Furthermore after a short time, considerable fluctuations, due to a disturbance of the mixture, set in. This can occur in a silo as well as in small receptacles. In a silo for instance, after 2½ months, estimates found quantities which fluctuated between 3,7 and 9,9 milligrams (1 mgr. = 0.015432 grains) of KI to the kilogram (2,2 lbs.) of common salt, in the different layers. Von Fellenberg believes the main cause for this disintegration to lie in the water content of the salt. He recommends that an expedient process of drying be employed after the iodization. A homogeneous distribution of iodine must be attempted. For the present a continued quantitative control is advisable.

Drinking-Water containing Iodine.

Beside the iodized common salt, drinking-water containing iodine was also recommended as a prophylaxis against goiter.

Jeger tells us, that school children of Rothenbrunnen, where a mineral spring containing iodine exists, are free from goiter, whereas their schoolfellows, in the same district, (Heinzenberg-Grison), where the drinking-water is devoid of iodine, suffer from this malady. This experiment with natural resources is interesting, in that it shows that iodine may be absorbed through channels other than common salt.

springs containing iodine.

It has been suggested that iodine prophylaxis be carried on by means of artificially iodized water. We can, however, hardly expect this method to be generally introduced. From a technical point of view, it is more complicated, and besides, the disintegration of iodine would be more likely to take place in a reservoir. than in iodized salt.

Iodine in the Air.

The influence of iodine in the air must also be mentioned. Prof. Roux caused crystals of iodine to be set up in open vessels, in Lausanne schools, and observed how favourably these affected the hypertrophied thyroid gland, helping to bring about an involution.

Iodizing the air.

Injuries caused by Iodine.

Iodine, which at the present time, is considered the most efficacious medicament for combating goiter, is no harmless preparation, but a most active one, one which has been responsible for many serious injuries, and in some cases even fatalities. It is therefore the duty of every worker in this field of research, to make a thorough study of the recorded injuries, and to endeavour to arrive at a formula for giving jodine in such doses, that the public shall not be endangered or as slightly as possible.

The method of treating goiter with iodine dates more than one hundred years back. Besides the benefits derived from it, its disadvantages were soon recognized. Physicians were guilty of laxity, until our surgeons, in particular Th. Kocher, pointed out the dangers connected with iodine therapeutics (these had already been recognized by Rilliet of Geneva). It is not for us to dwell upon this question here.

In the following, we shall only consider those injuries which appear in connection with the methods which we have recommended for combating goiter, i. e. iodized salt, and tablets containing iodine, administered in the schools.

Before we recommend that any mode of procedure be generally introduced, we must make sure that such a process is devoid of

danger. The fact must continually be emphasized, that since the public has learnt of the amazing action of iodine preparations upon enlarged thyroid glands, this remedy has been introduced in most of the regions afflicted with goiter. The result was, that treatment of goiter was no longer under medical control, but that iodine preparations could be procured and taken indiscriminately by everyone; in consequence iodine injuries increased perceptibly. Lately, physicians of many different countries, including a great number of Swiss, have raised their voices in warning against the uncontrolled « trade » with iodine, and have even cautioned against a general iodine prophylaxis.

Just what quantities of iodine may act injuriously, is gaged quite differently by various authorities. We are aware, and must not forget, that susceptibility to iodine, varies in each individual and in families (hereditary susceptibility). The fact is of great importance, that iodine tolerance can be lessened through a change in the thyroid gland and that, in general — the rule is not infallible, — one encounters in regions afflicted with goiter more persons hypersensitive to iodine than in goiter-free districts. Furthermore it is important to note how dissimilarly persons of different age and sex react to iodine.

It is a generally recognized fact, and rarely contradicted, that in childhood we are not susceptible to iodine. The serious form of iodine poisoning, called iodine-basedow, is unknown in childhood, never occurring before the 12th year. Our child specialists, as well as school physicians, who had the opportunity, in recent years, of observing tens of thousands of children, who had taken iodine tablets during several years, all emphatically declare, that at this age no signs of iodine poisoning are to be seen. As puberty approaches conditions change. Several cases of iodine-basedow in girls, between the ages of 12 and 15 years have been discribed, and the number of cases increases with the advancing ages.

Jodine tolerance in certain diseases, such as syphilis, must not lead us astray. E. Bircher tells us, he personally observed, that individuals susceptible to iodine can frequently be recognized by their slight, delicate constitution, and that those afflicted with nodulous struma often stand iodine much less well, than patients suffering from parenchymatous goiter. He calls iodism « the disease of banished goiters ».

Susceptibility to iodine is observed more frequently, but not exclusively, in the female sex. The aspect of the disease is varied.

In addition to disturbances of the heart and nervous system, there is a decrease, and occasionally, a decided drop in weight.

That susceptibility to iodine is not universal, even in goitrous regions, is evident from inquiries made in our Swiss recruiting schools. In the past five years, during a period of two months 20.000 recruits were weekly given iodine tablets, containing more than 10 mgr. and no single case of serious injury was noted. Only in extremely rare cases, was it necessary to interrupt this treatment because of the appearance of signs of iodism.

My two years' experience in a school of social science, where girls ranged from 15 to 22 years, showed me, that at this age, women are very rarely susceptible to the ill effects of iodine.

We must conceal the fact, that the introduction of iodine tablets in schools as a goiter prophylaxis, and the wonderful results effected therewith, led many adults to take preparations prescribed for children, and occasionally even larger doses without consulting a physician. It goes without saying, that serious injuries resulted.

Iodine medicaments must be held under control. At an early date, the Swiss goiter commission applied to the authorities, asking them, in the interest of the people, to put an end to the uncontrolled « trade » in goiter remedies containing iodine.

It is furthermore important, that medical men should be placed in a position to properly recognize and diagnose injuries caused by iodine. Most disturbances can be cured with comparative ease; if iodine is immediately left aside, they as a rule completely disappear. In the last few years however, cases have been cited, which, after only a short administration of iodine, showed irreparable lesions, which finally proved fatal. For this reason, I should urgently suggest, that in all countries where iodine prophylaxis has been intruced, students and physicians be throughly trained, in order to be capable of making a correct diagnosis and differential diagnosis on iodine injuries. How difficult this diagnosis is, is evident from the contradictory data given by experienced goiter investigators, where one attributes certain injuries to iodine and another catigorically denies this.

We learn a great deal from the results of the inquiry on iodine damages, made in the years 1922—1924, by the Swiss goiter commission, and arranged by Stiner. Of the 3008 doctors in Switzerland, 1675 participated in it.

The first question pertained to the number of Basedow case; 3625 cases were reported by 904 physicians. The second question, which interested us, was: Were there among these, cases of Base-

dow which could be attributed to the use of iodine preparations? In 1116 cases,i. e. almost ½, the reply was in the affirmative. In 1110 additional cases, other disorders occasioned by iodine were reported. In other words, within three years physicians reported 2226 cases of iodine injuries, half of these pertaining to iodine Basedow.

The fourth question interests us especially: Were there among those patients, who had sustained iodine injuries, any, who had employed no iodine medicaments, only iodized salt? 79 physicians answered this query affirmatively, in 167 cases. In a second inquiry, the attempt was made to supplement these summary investigations, through more precise information concerning each individual case; at this, the number of hyperthyroid conditions, said to have originated through iodized salt alone, decreased to 18. De Quervain undertook the task of personally, exhaustively studing some of these cases in the Canton of St. Gall. He rightly declares, that hyperthyroidism may also occur spontaneously without iodine consumption, and that the number of cases reported remains within the range of spontaneous morbidity in thyrotoxicoses. Regarding disturbances caused by iodized common salt, E. Bircher's cases must be mentioned. These showed an impairment of health, caused by erroneous taking of iodized, instead of plain common salt; in opposition to these, we have the cases reported by Eggenberger, in which common salt is said to have caused thyrotoxicoses; careful investigation showed this to be free of iodine.

It was of personal interest to me to study this question regarding iodine injuries, occasioned by common salt, and with this end in view, I applied to several of my colleagues, whose opinions I shall in brief repeat here.

In the Canton of Vaud, iodized common salt has been employed almost exclusively, during more than three years. Prof. Michaud, director of the medical clinic at Lausanne, informed me in reply to my inquiry, that since the introduction of the «silent» iodized salt prophylaxis, not a single case of iodism, or of iodine-basedow, has come under his notice, either at the cantonal hospital, nor in his private practice.

Dr. Zollikofer, physician in chief of the department of internal medicine in the cantonal hospital of St. Gall, (a canton from which a proportionately very large number of iodine disturbances are reported), is convinced that the advantages derived from iodized salt, infinitely exceed the disadvantages; he declares that

he has never observed any injourious effects, from the use of iodized salt.

Prof. Hotz, the deserving director of the Surgical Clinic, in Basle, who passed away all too soon, gave a particularly large part of his attention to the question of iodine disturbances. His successor, Prof. Henschen, informed me, — and this fact is of great value, — that the two chief physicians, Dr. Merke and Dr. Heusser, during a series of observations, covering a period of more than five years, had seen absolutely no iodine disturbances, such as iodine Basedow, which could be exclusively attributed to the consumption of iodized salt. At closer study, it was always found that the patients, or physicians had been mistaken, and purely nervous disorders, such as thyrotoxic symptoms had been wrongly diagnosed. A functional disturbance of the thyroid gland, (determined by respiratory metabolism) and occasioned exclusively by iodized salt, could not be proved.

Another expert on iodism, Dr.Roth, director of the cantonal hospital, Winterthur, who has repeatedly raised his voice in warning, against too great optimism in regard to iodine, writes, that he has observed far fewer cases of iodine injuries, during the past few years than formerly; however, he still sees isolated cases. As far as iodized salt is concerned, he can report only one case, that of a 36 year old woman, suffering from intense extra-systolic troubles, and nervous complaints. Three months after the iodized salt treatment was interrupted, the symptoms vanished. However, he adds, we were here dealing with a nervous and extremely excitable individual.

What can we infer from these different reports? I must almost believe with de Quervain, that although only minimal quantities of iodine are added to common salt in Switzerland, it is possible, that these small quantities, may cause iodine injuries. They are, however, so rare, that many directors of large hospitals declare that not a single case has come under their observation since many years; this, in spite of the general use of iodized salt. It is important to remember, that in the great majority of these cases. the disorders disappear completely, a short time after iodized salt is left aside, and no lasting bad effects remain.

Persons over 35 years of age, are particularly sensitive to the effects of iodine, but even here, the number is negligible. At this age prophylaxis is no longer necessary, (with the exception of elder pregnant women) for it is also no longer efficacious. The

greatest benefit from iodized salt prophylaxis accrues to the young, and also to pregnant women. If possible, I should recommend administering iodized salt to the young members of a household, and to the older people, salt free of iodine.

Whereas ill effects occasioned by the use of iodized salt, appear in Switzerland only very exceptionally, the American investigators, such as Kimball and Hartstock, only recently described cases of hyperthyroidism, attributed to iodized salt. These cases pertained exclusively to women over 40 years, mostly with nodulous strumas. These important observations may perhaps be attributed to the fact, that in America a larger quantity of iodine is added to common salt than in Switzerland.

General Hygienic Prophylaxis.

Iodized salt prophylaxis must be termed an experiment; up to the present, no definite solution has been reached. Experimental aetiological goiter research has brought us nothing essentially important during the last few years, with the exception of Mac Carrison's new reports which seem to prove, that those who do not attribute goiter exclusively to a lack of iodine, but consider an avitaminous condition, are in the right. Stiner produced goiters in guinea pigs, after giving them food, poor in vitamines, over a length of time. After all, it must strike our attention, that even in goitrous regions, not all the inhabitants, — although living under similar conditions, — suffer from this ill. Not only a hereditary, but also a personal disposition exists. It may also be stated, that social position may influence the development of goiter. Lauener observed in Berne, that after identical treatment had been administered during six years, to the scholars of the Progymnasium, and the scholars of the ordinary public schools, 69,9 % of the former, and only 47,8 % of the latter were free of goiter. Whence this difference?

The observations of Bernhard, of St. Moritz, must also be mentioned, although they have, by no means been generally confirmed. According to Bernhard's statements, goiter are not found among people living on sunny mountain slopes, which fact suggested the question: might not a lack of light cause goiter? Haslebacher noticed that goiters became softer, and even disappeared through the use of the mercurial vapor quartz lamp.

MacCarrison, Galli-Valerio and Messerli recommended continued intestinal disinfection by means of benzo-

naphtol, thymol etc. and were able to recognize a distinct involution in enlarged thyroid glands, after this treatment.

In more than one goitrous region, the endemic was brought to a standstill, through improvement of essential conditions, a new water supply, and through more active intercourse with the outside world.

It is difficult to say which factors here played a part; I should say, that in addition to greater cleanliness and generally improved hygienic condition of dwellings and drinking water, the better, and less monotonous fare, played an important role. Under all circumstances, I should recommend a varied diet (the food being prepared in a cleanly manner), the eating of fresh, uncooked fruits and vegetables, and above all, a diet that is rich in vitamines, as recommended by MacCarrison and Stiner.

Care of the body, and what to-day known as « physical culture », is doubtless of great value; all efforts in this direction should be encouraged.

I do not consider the aim of such conferences as this, to lie solely in the presenting of new ideas, nor yet in the communicating of results of research work, but above all, in an effort to clear up contradictory opinions through discussion and mutual exchange of ideas, and on this basis, to set up a clear plan for future action.

* * *

Summary :

1. The prevention of goiter is for all regions where the endemic goiter is prevalent an urgent hygienic and social problem. The combined observations during late years have shown that it may be successfully combatted.
2. The use of iodised kitchen salt constitutes an experiment which opens a wide range of possibilities of great promise. The dose of 0,5 gr. of potassium iodide for 100 kilogr. admitted in Switzerland seems sufficient; but up till now the results can not be judged of.

   It is necessary that the iodide of potassium be equally distributed amongst the salt.
3. The prophylaxis of goiter in the schools by means of tabloids containing 1 milligr. of iodine (in certain cases 3—5 milligr.) has given excellent results in Switzerland. It is to be recommended wherever iodised kitchen salt is not generally intro-

duced. But this preventive method must be used under medical control and supplemented by an individual treatment of the scholar.

4. Iodine is not a harmless substance and its use ought to be under control. In those countries where the goiter is prevalent the free sale of iodine ought to be prohibited. No symptoms of iodism are observed during childhood, they are rare during puberty, more frequent in adults, above all in women between the ages of 35 to 60 with anomalies of the function of the thyroid gland.

   Jodised kitchen salt containing 0,5 gr. per 100 kilogr. rarely is followed by bad effects; for such individuals as are specially susceptible of the effects of iodine it is better to give them salt without iodine.

5. In those countries where the prevention of goiter by iodine is in use medical men should know how to diagnose and to treat the symptoms of iodism.

6. Besides the specific preventive treatment of goiter it is necessary to pay more attention than has been the case heretofore to a general hygiene: Cleanliness, good drinking water, rational feeding (mixed alimentation rich in vitamines), individual hygiene, sport.

Remarks

in Discussion of Prof. Wagner von Jauregg's report.

By Dr. W. Jaensch, Berlin.

I beg to resume on the matters brought forward yesterday by Mr. Th. Hœpfner on the occasion of Mr. McCarrison's report and to express, relating to the former, the sincere gratification of my collaborators at finding a clinical authority of W. von Jauregg's standing to have incorporated in his conclusive theses the results hitherto obtained by us, as a « basis for an individual treatment in schools » in complement, that is to say, of the general prophylactic measures against the diffusion of goiter proposed by himself, Eggenberger, and others. We are also in entire agreement with W. von Jauregg in his statement that our method of individual treatment controlled by the capillary microscope is unsuitable for

«general prevention of goiter». Still, we must admit, in opposition to those meritorious investigators that, today as formerly, we are adverse to generalization of any prophylaxis of goiter, particularly to the exclusion of individual treatment. The grounds on which this opinion is founded we gave in December 1926, in a few brief statements sent to Eggenberger with the request for collaboration in spite of the differences in our views and conclusions. They ran somewhat as follows: —

It may be conceded as common knowledge that the frequency of cases of Basedow upon iodine-treated subjects who had the complete iodine salt in Switzerland, of which we have recently heard, could by accurate analysis of the separate cases be regarded as reduced to 17, as you estimate, although no further details of these are as yet known to us. In spite of this assumption on our part, we would adduce from our experiences in Hesse the following reasons against a general iodization as a preventive of goiter:

1. It must not be forgotten that again and again there have been individuals with an idiosyncrasy for iodine (also for doses of the complete salt) and that they will continue to crop up. This is a matter of the most ordinary clinical experience and, unfortunately, it is found chiefly in individuals of high biological standard and, according to our conclusions, these persons are always those who show a greater susceptibility to iodine and possess a high degree of capillary development. This of itself would militate against the indiscriminate exhibition of iodine in any shape or form.

The sequelae of hypersusceptibility to iodine do not in our experience show themselves only in the more obvious symptoms of Basedow's disease, but often in symptoms of a nervous or psychic order. The frequency of Basedow's disease, in its usual form, does not suffice as the sole evidence of a measure of the tolerance or intolerance of the people for the salt. — We observed in our adolescent cases even a mental retrogression with iodine, showing itself in part by a definite fall in the standard of school-work. Such occurrences prove very baffling in our routine observations. We found them, it is true, not only with higher doses, as with the full salt, but even with those used for the so-called «school prophylaxis», 3 mgm of potassium iodine weekly. Consequently, later, we categorically refused to employ it in the former non-individualizing way; be means of the capillariscope it is possible, on the basis which we elaborated, and particularly where iodine is at all applicable, to restrict the doses to those that regarded as optimal for school use, having in view in this line of treatment no longer

a reduction in the size of the thyroid, but amelioration of the general state, which is easily recognizable. There are, however, persons for whom the optimum maximum doses are suitable, for others the minimal, while there are yet others who do best when iodine is withheld altogether, and, finally, those who reap no benefit without endocrine preparations. There is no need, however, to regard these as cretins, they have merely a primitive development of capillaries. Further, in our opinion the capillariscope permits a differentiation of these cases, without at the same time neglecting the general clinical condition. In this connection I would refer to the «Clinical Capillary Schedule» as worked out by Th. Hoepfner (Publications of the Department of Medical Administration, 1927, Berlin, W. Schoetz, Wilhelmstrasse 10).

The idea is also erroneous that cretinism or deaf-mutism (a highly complex group!) should be regarded as immediately equivalent in an important percentage to thyroid affection, and be combated somehow with excellent prospects by those means which may, if you like, diminish the prevalence of thyroid enlargement as we grant it to be the case with iodized salt. What holds good for deaf-mutism and cretinism holds good also for very many other serious development disorders of the class of psycho-physical afflictions. It is better to disregard the purely goitrous aspect once for all. It is certainly often the most striking symptom in an individual in other respects apparently healthy; but, and this is particularly the case with adolescents, it is of itself in many cases the most insignificant symptom of a series of deep defects, partly hereditary and unalterable, recognizable in the capillaries as a concomitant stigma, and even when obvious development disturbances, including goiter, are wanting; it is equally so in other cases, among them those with physiological enlargements of the thyroid.

It is not by any means our object, then, merely to get rid of the goiter; much more must we stress the importance of caring for the helpless in whatever direction their mental or physical crippling may take, especially because, in our country, legal provisions would allow us to treat these cases preferentially in a decisive manner. — The majority of them also require individualized treatment, either with very large doses of iodine and other remedies, or at least with endocrine preparations in addition.

Some can only be improved up to a certain limit and that a low one. There are instances of great or average severity of

cretinoid degeneration where we have to deal rather with hereditary conditions in the way of unalterable «Mutations» (see later). — We may say, in brief that all theses, in which what is called general goiter prophylaxis has been recommended hitherto, simply ignore the definite knowledge of the present day on the vast question of heredity. I say this in full consciousness of the undeniable fact, of which we ourselves have become aware, that the science of heredity considers insufficiently the universal constitutional variants (phaenotypical variations) conditioned by environment and regards too many of them as hereditary variants (Mutations), determined by transformations in the germ-plasm. The latter cases, in accordance with the position of present-day ideas on heredity and racial hygiene would, strictly speaking, require sterilization. It is therefore perfectly hopeless to foster the idea that the salt can affect what is already basally present in the body of the mother, whether its origin be considered as definite mutations or as gradually forming hereditary paravariations, which, according to the science of heredity at the present day is not believed to be possible.

Even in the latter case, such hereditary strains would be more than a century old and the hope of effecting a retrogression by means of the salt would at best have to allow for an equal period of time for its action to achieve results.

2. As the outcome of all these considerations, apart from the clinical aspect, we hold it as tactically wrong to speak always of a «goiter-prophylaxis». The question of thyroid enlargement is, we are firmly convinced, only to be cleared up by solving the whole problem of racial hygiene, in which the goiter-question itself plays but a relatively small part.

Nevertheless, we believe that more general prophylactic measures of some kind will play a part in this problem, but that the propaganda of iodine prophylaxis, as it is being ordinarily pushed to-day, must cause a diversion, even in public opinion, from the real problem and its extra-ordinary complexity: Comprehensive and incisive measures of racial hygiene would thereafter meet with a stronger opposition than would otherwise have to be reckoned with.

We allude here only to the question of sterilization, a measure which science and the law will have seriously to discuss also in Europe in a not far distant future.

3. We maintain, then, that where marked or early enlargement of the thyroid is found, the subjects, adolescents and adults, should

be sent to a doctor just as other patients. He alone can determine which of the endocrine glands is responsible for the symptoms, and even in cases of definite goiter it is not always the thyroid which is at fault.

We believe that in a campaign to deal with enlargement of the thyroid at Hesse individual treatment should find the first place provided that the endeavour be made (in conjunction with capillary microscopy) to include the youngest infants and the putative mothers. We are well aware that organization of these measures must progress relatively slow. In districts where goiter is especially rife, we at least concede that a so-called «general goiter-prophylaxis», perhaps with iodized salt has much in its favour; in particular in places where there is an alarmingly increasing prevalence of goiter, and where some immediate, even if not final, effort appears to be unavoidable, so to say «to get something done».

We therefore admit that for certain districts, in spite of much convincing argument, some measure would be applicable that would give promise of improving fairly quickly the most obvious and urgent symptoms in the entire population. It would however, we think, only amount to a systematic reduction of the thyroid enlargement and not in the slightest degree eliminate the necessity for individual treatment, somewhat on our lines, and of other measures of racial hygiene, as already pointed out. The measure would have to be undertaken with the consciousness that a minority of highly developed individuals might be exposed to injury in order to realize for the generality the aforesaid definite purpose, a standpoint which, if consciously acted upon, might appear quite defensible from a purely administrative point of view.

On "The Prophylaxis of Endemic Goiter".

By Dr. Wittneben, Hephata-Treysa.

Now that you have already heard the statements of Dr. W. Jaensch and Dr. Th. Hoepfner on the intimate relations which exist between anomalies of the thyroid gland, changes in

the capillary structure and defects of development, I should like to show you, as briefly as possible, a few examples of further development of capillaries brought about by appropriate treatment, and, as going hand in hand with this, improvement of the general physical and mental well-being of the individual. In treatment we must pay attention to the endocrine factor and it is consequently necessary to determine previously which gland plays the chief part in the morbid condition.

In the Institute at Hephata, Treysa Bez. Kassel, I have investigated from this standpoint 500 mental defectives and found endocrine disturbances in nearly 25 per cent. The majority of cases were examples of thyroid mischief, but among them were also those with a pituitary syndrome or gonad infantilism. My researches are not yet complete. We have to test these first experimentally by the interferometric method (Abderhalden-Hirsch).

Hitherto, the treatment, as adapted to the conditions present, has proved very effective. When we are unable to determine beyond cavil the correlation of the capillary-arrest present with one endocrine factor, I merely give Lipatren, Lipatren with thyreoidin or tablets of pituitary or gonad; with signs of pluriglandular defect the corresponding combination.

I reported last year, in conjunction with W. Jaensch, at the Third Child-Welfare Congress at Munich, the results in 100 children and was able to show that we had succeeded in improving those with 50 percent mental capacity to 75 percent, and in restoring those with three-quarters capacity to normal, in stimulating growth and in improving corporeal defects.

Since then I have treated another 100 children, 60 with Lipatren in combination with preparations of the glands affected, and 40 with Lipatren alone. The results were pretty well the same, but a little better from the combination.

The Lipatren employed was the Behringwerke product, Strengths I, II and III, of which

Strength	I	contains	0.0238	Lipatren,	corresp. to	2.28 mgm Iodine
»	II	»	0.125	»	»	to 12.25 mgm »
»	III	»	0.5	»	»	to 49.00 mgm »

It was given in doses of one tablet two or three times a week and daily 0.64 to 14 mgm of Iodine, according to the tolerance exhibited. The strength of the dose was determined by the degree of arrest. When reaction appeared, evidenced by the sprouting up of neo-capillaries, the dose of the Lipatren was reduced. I have

not observed any untoward symptoms. Ten controls, with normal capillaries, remained practically unaffected.

In my experience those children react best in whom the deepest arrest of capillary development is present, but in whom capillaries of hair-pin shape are already beginning to form, whose, from the point of view of heredity of the conditions present, are good, and where development shows no gross defect in spite of the arrest (birth-injuries, meningitis, etc.), and whose environment is favourable. Further, there must have been no serious acute injury, in particular of the central nervous system, either at birth or in early infancy. In cases of arrest at a somewhat higher stage of development, arising from the so-called intermediate stratum, the results under otherwise similar circumstances were not quite so favourable. Bad results, or may be no effect at all, have I had when pseudo-neocapillaries have formed, that is, where (unsuitable) differentiation of capillaries had already taken place. It would seen that in such cases we are dealing with a morbid condition which has already run its course and can no longer be influenced.

Of the 100 cases 14 reacted badly, and in them the pseudo-neocapillaries mentioned were present; 58 reacted well and 28 excellently. In three children with concomitant epileptiform fits these completely disappeared. The body-growth increased, the general condition and the degree of intelligence improved. Simultaneously, the capillaries underwent differentiation.

I would like to introduce to you a few instructive pictures.

(Demonstration followed).

My explanations will have made it clear that by an individualization of treatment it is possible to obtain a vast degree of improvement in cases of developmental defects, of which affections of the thyroid gland proper constitute but a fraction.

Aetiology and Prophylaxis of Goiter in Norway.

By Professor Nicolaysen, Oslo.

I made the request to have the privilege of saying a few words to you, in order to be able to tell you about the occurrence of goiter in Norway and about the success, which we have had in

our goitrous districts with the prophylactic and therapeutic treatment of schoolchildren with iodine.

Whereas the investigators, who were the first to study struma in Norway, could establish only isolated cases of Morbus Basedowii among the inhabitants of our goitrous regions, though as a fact it is of frequent occurrence with us, Dedichen, who had for 17 years been practising in a struma region, discovered that about 60 % of his 335 goitrous patients manifested thyrotoxic symptoms.

It is a self-evident fact that this result can not be brought into comparison with any statistical study of the population in one of our goitrous regions, which would have been made for a short time. But nevertheless this work has given the impression as if individuals, suffering from goiter, are exposed to a considerable extent throughout the whole of Norway to secondary Basedow.

After Th. Kocher had proved the existence of iodine-Basedow in 1910, it was thought that the cause with us must be looked for in a theoretically high percentage of iodine in the soil and in the drinking water, occasioned on the one hand through the proximity of the sea in our country, which has so great a coast line, and on the other hand through the fact that the soil in some of our goitrous regions consists of post-glacial submarine deposits.

From this it can be well understood, why a suggestion, which was made by Dr. Danelius in 1925, that we ought to introduce into our schools the prophylactic iodine treatment according to the methods employed in Switzerland, was immediately met with the caution, that such treatment would necessarily be a dangerous procedure with us.

Nevertheless we already at this time had at our disposition the results of the researches of McClendon and of von Fellenberg. I thereupon decided on making a closer study of the conditions in one of our struma regions and more particularly determine the percentage of iodine in the drinking water as also the amount of excretion of iodine in the urine of a number of adult men. In the event that the percentage of iodine in the drinking water and the food was not great, the prophylactic treatment for goiter with small doses of potassium iodide in the case of schoolchildren could also with us give occasion for no misgivings whatsoever.

I therefore put myself into communication with Dr. Fölling, the Chemist of our University Clinic, and persuaded him to analyze samples of the drinking waters used in 29 farm-houses in Modum and Sandsvear, where there are many cases of goiter occurring,

and at the same time four samples of the drinking water used in Oslo, where there is no struma at all to be found, such samples to be drawn at different seasons of the year. Dr. Fölling came to the conclusion that the samples which came from the goitrous regions contained on an average 129 milligrams to 100 liters of water and the water of Oslo 309 milligrams to 100 liters of water *. After the results of these analyses were made known the iodine treatment was introduced into the schools. Some time later Dr. Gulbrand Lunde of the Mineralogical Institute of the University determined the amount of iodine excreted in the urine of 52 adult men, residing in the stated district of Sandsvaer, who had been selected by the medical officer of the district, Dr. Eriksen and by Dr. Thorrud, while at the same time I was kept informed by the individuals under investigation as to what food they had partaken of during the particular week, in which the samples were analyzed.

The goitrous region, which comes here into question, is a typical inland district, the population of which, however, during the last few years has been well provided with an abundance of sea-fish, supplied by the «fish-autos», which call at each farm-house.

The great percentage of iodine in sea-fish is well-known from the investigations of von Fellenberg and Lunde, as also the fact of an abundance of iodine excretion in the urine of persons, who have eaten sea-fish.

After I had been in receipt of these «bills of fare», the persons under investigation were divided into two classes, namely, the one class comprising those, who had partaken of sea-fish from one to three times per week, and the other one those who had eaten no sea-fish at all.

It was seen as a fact that Dr. Lunde had ascertained that there was in 21 fish-eaters an average excretion of iodine in the urine of 75 milligrams in 24 hours and in the 31 men, who had consumed no fish, there was an average of 43 milligrams in 24 hours determined.

According to von Fellenberg, the normal excretion of iodine in the regions, that are free from struma, is from 60 to 150 milligrams in 24 hours.

In respect to fish alimentation, the fact must be emphasized that children do not as a rule care anything for this fish brought to them from the coast, for according to what the parents declare «if the

* 1 milligram = 0.001 gram = 0.015432 grains. 1 liter = 2.113 American pints = 1.76 English pints.

children eat fish at noon, they have lost their appetite for the evening meal.»

Of the entire number of schoolchildren in Sandsvaer, 931 alltold, who had been made a subject of investigation by Dr. Eriksen, Dr. Thorrud and myself, some 422, i. e. 45 %, had goiter. The frequency of it fluctuated between 30 % and 60 % in the different schools. After the children had each been treated weekly with 0.001 grams of potassium iodide for a period of 55 weeks, a subsequent investigation could be made in the case of 839 children. It was then ascertained that 695 or 83 % were free from struma and 115 or 13.5 % gave evidence of only traces (Category I of the Swiss Goiter Commission). With 29 or 3.5 %, struma of Category II could still be detected but in none of the children could struma of Category III be any longer determined.

curative effect.

In order to have a general survey over the occurrence of Morbus Basedowii in this goitrous region, I first of all instituted enquiries among the different medical officers.

Taken all in allthere was only one case known to them.

I thereupon examined the parents and the grown-up brothers and sisters of the children afflicted with goiter, in all 484 adult individuals; of this number some 163 or 34 %, almost exclusively the women folks, had struma and of these in turn 2 individuals showed manifestations of Basedow.

I was also informed that a grandmother on the mother's side and one of the fathers had died of a heart trouble, which was declared to have been in combination with a struma, and that three more distant relatives of the parents had been operated for Basedow. (In the case of a suckling babe inherited myxoedema was proved).

The result of these investigations can be summed up in these words: Goiter prevails endemically in some inland regions in Southern and Eastern Norway. In the regions investigated by me the percentage of iodine in the drinking water and the nourishment is insignificant, judging from the amount of iodine excreted in the urine of those, who have not partaken of sea-fish.

This is not a fact. There is ample iodine as our figures show.

As was the case with those who were the first to investigate struma with us, so likewise with myself in my research work, only a few cases of thyrotoxicosis could be proved in the particular goitrous region. It is therefore evident that cases of thyrotoxicosis occur in varied frequency in the different goitrous regions in Norway just as elsewhere. The prophylactic iodine treatment in the schools has been carried on with success. Parents and children,

teachers of both sexes, have taken the deepest interest in it, so that this treatment is being continued and has been adopted in the neighboring districts. To obtain a more extensive prophylactic treatment of adults with iodine an uninterrupted work for extensive consumption of sea-fish in our goitrous regions would be of great significance, because, as we see, it has been ascertained that those, who like to consume fish, excrete through the urine some 75 milligrams of iodine in 24 hours.

000γ !!!!

The Excretion of Iodine through the Urine and the Goiter Prophylaxis with Sea-Fish.

By Gulbrand Lunde, Oslo.

The extensive research work, which was done especially by Th. von Fellenberg in Switzerland, J. F. McClendon in the United States of America and several other investigators, has shown distinctly that the goiter endemics break out particularly in those regions, in which the quantities of iodine are too small, that could be turned to account by the organisms.

The iodine that stands at the disposition of the organisms occurs in the biosphere in a very active state of circulation and it is just the concentration of the iodine in the biosphere, that is such a slight one in the goiter regions. But it is very easily possible that there may be great quantities of iodine present in the same regions, and these are chemically combined in the rocks, but in such a form or compound that with the transition into the biosphere they can not be made use of by the organisms.

At the request of Professor Johan Nicolaysen I made investigations to ascertain what quantities of iodine are daily excreted by the inhabitants of a Norwegian goiter region through the urine. This research work on the excretion of iodine through the urine was undertaken for the reason that we can the more readily get an idea about the iodine metabolism than through the tedious investigation of all the food materials.

good! to remember correlation.

Th. von Fellenberg has already published a series of articles on the excretion of iodine through the urine, concerning which I shall later touch upon more in detail when commenting on my own results.

Von Fellenberg has demonstrated that those quantities of iodine, which we excreted through the urine, always are approxim-

ately the same percentage rate of the total amount of iodine excreted. For this reason the values for the excretion of iodine are always directly comparable. He has further shown that the quantity of iodine, that is excreted per hour, is approximatively constant with an «equilibrium of iodine». We can therefore reason a posteriori as to the quantity that is excreted within a definite period of time.

Both the statements are of vu doubtful accuracy

The determination of iodine was accomplished according to the method of von Fellenberg.

The persons, upon whom research work was done, are all residents of the goiter region Sandsvaer to the south-east of Kongsberg, with a light endemic if compared with Swiss coiditions.

The persons, thus examined, were all healthy, full-grown men, who had no goiter. They were selected by Professor Nicolaysen with the assistance of the local physician, and the fact was especially made important that these individuals should continue to live exactly as was the general custom in the district.

The following tables show the results of our research work. Besides the name of the village or town there is each time mentioned the percentage of goiter among the schoolchildren according to the enumeration of Nicolaysen.

Meheia, 53,6 %

No.	γ Iodine in 24 hours	Sea-Fish used as food
1	42	
2	57	
3	62	
4	25	
5	10	
Average	39	

Ljöterud, 54 %.

No.	γ Jod in 24 hours	Sea-Fish used as food
6	41	
7	19	+
8	22	
9	28	
10	36	
Average	29	

Vittingfoss, 55 %.

No.	γ Iodine in 24 hours	Sea-Fish used as food
21	38	++
22	55	++
23	50	
24	105	+++
25	(212)	Kl.
26	14	+
27	67	+++
28	(118)	++++
29	39	+
30	20	+
Average	48	

Saggrenda, 43 %.

No.	γ Iodine in 24 hours	Sea-Fish used as food
31	83	++
32	11	
33	(214)	+, Kl.
34	59	+
35	101	+
Average	64	

Hedenstad, 38,6 %.

No.	γ Iodine in 24 hours	Sea-Fish used as food
36	128	++
37	36	+
38	6	
39	52	+
Average	56	

Verp, 36 %.

No.	γ Iodine in 24 hours	Sea-Fish used as food
41	101	?
42	108	++
43	35	+
44	140	++
45	50	
Average	87	

Hostvedt, 59,7 %.

No.	γ Iodine in 24 hours	Sea-Fish used as food
46	37	
47	69	+
48	23	
49	31	
Average	40	

Ruud, 30 %.

No.	γ Iodine in 24 hours	Sea-Fish used as food
51	79	?
52	56	
53	49	+
54	73	+
55	49	
Average	61	

Komnes, 39,7 %.

No.	γ Iodine in 24 hours	Sea-Fish used as food
56	86	+
57	43	++
58	27	
59	13	
60	73	++
Average	48	

Eftelöt, 36,6 %.

No.	γ Iodine in 24 hours	Sea-Fish used as food
61	137	No data
62	40	
63	41	
64	88	
65	20	
Average	65	

We can see at a glance that the quantity of the excreted iodine varies within wide limits, and that there are some particularly high values noticeable. It also became manifest, as Nicolaysen made clear, that this typical inland region had been for some time supplied with sea-fish and that those individuals, who gave indications of especially high values, were almost without exception consumers of particularly considerable fish. In this connection it may be said, that in the majority of the cases care was taken to have the persons eat no fish on the day immediately preceding the day of the urinary test. It is a question, therefore, not of an accidental increase of the quantities of iodine, excreted, but especially of an increased iodine metabolism due to the abundant use of fish as food. Thus we find for the villages of Meheia, Ljöterud and Hostvedt the lowest average values, since in these places fish is consumed only exceptionally or not at all. (In the compilations given above the plus sign, +, signifies « fish once per week », 2 plus signs mean twice per week and three plus signs three times per week). As was ascertained later, two persons had also taken potassium iodide; in the estimation of the average they have not been taken into consideration. No. 28 was likewise not counted in, since this person had eaten considerably more fish than is the custom in this region and this value would therefore no longer present any true aspect of the average iodine excretion.

In making comparisons of the values for the excretion of iodine with the data giving the number of goiter cases among schoolchildren, as it has been compiled in the following table, it must also be observed that the excretion of iodine pertains to males and that the data for the children would be lower, not only on account of their smaller quantity of articles of food consumed, but also because the children as a rule do not like to eat fish.

Village	Goiter expressed in %	γ Iodine in 24 hours
Hostvedt	59,7 %	40
Vittingfoss	55 %	48
Ljöterud	54 %	29
Meheia	53,6 %	39
Saggrenda	43 %	64
Komnes	39,7 %	48
Berg	38,6 %	56
Eftelot	36,6 %	65
Verp	36 %	87
Ruud	30 %	61
Vik i Sogn	0 %	173

The table makes it clear to us that the figures for the excretion of iodine are higher with a falling percentage of goiter, although not entirely regularly. For purposes of comparison I have mentioned the figures also for the village of Vik i Sogn, which is free from goiter, a number, which von Fellenberg determined from the investigation of samples of urine, which Dr. J. C. Holst had at my request sent him last year.

It may be stated here, that in Vik i Sogn there is not at all particularly much fish being consumed, certainly not more than in Vittingfoss, from which we must necessarily conclude that the more active iodine metabolism is especially brought about here through the increased percentage of iodine in the articles of food and the surrounding country.

The persons of Vik i Sogn, who were taken for this research work, were also peasants, who were not living directly at the fiord.

For the purposes of making a comparison with the data given in this last table, I present here likewise the data, which von Fellenberg discovered for Switzerland and at the Ligurian coast:

Village:	Goiter in %	Millionths of grams of iodine in 24 hours
Effingen	1	70
Kaisten	61.6	17
Hunzenschwil	56.2	18
Forte del Marmi	0	112

In comparing these data of von Fellenberg with those for Norway we notice that the percentage data of goiter for the three Swiss villages apply to the entire population, whereas for the Norwegian villages only the school goiters are referred to.

Furthermore the data regarding the excretion of iodine as given for Kaisten and Hunzenschwil pertain to individuals afflicted with goiter, whereas the data for Norway refer only to normal persons, who are in health.

In summarizing, it can be said that von Fellenberg's findings, that the excretion of iodine through the urine is less with the inhabitants of goitrous regions than it is in the non-goitrous regions, has also been positively confirmed for the Norwegian conditions.

* * *

It is a well-known fact, that the sea-fish are very rich in iodine. I have in mind just now the work of P. Bourcet. Less known is probably the work of the two Americans, Tressler and Wells,

who studied a number of sea-fish as to the amount of iodine contained in them. They do not find as high a percentage of iodine as Bourcet, but nevertheless of the same order as to the quantity. Jarvis, Clough and Clark analyzed different varieties of salmon that abound in the Pacific ocean for their iodine contents. Likewise Th. von Fellenberg, in making his extensive investigations relative to articles of food, included several varieties of fish.

Although the estimates determined by different authors vary greatly one from the other, nevertheless all data are not much greater than those for other articles of food, but they are even of another quantitative order. We find present from several tenth-milligrams up to 2—3 milligrams of iodine per kilogram of fish.

It can therefore be understood, that we shall find the iodine metabolism considerably increased with the consumption of sea-fish as food.

The concordance of our results from the goitrous district of Sandsvaer and of the increased metabolism through the use of fish as food with the great quantities of iodine of the sea-fish points out to us really the simplest and most natural way of prophylaxis, at any rate for the Norwegian conditions.

We must aim for an increased consumption of fish in the goitrous regions and render more easy the supplying of fish to the inland districts.

It appeared of particular interest to me to look into the question as to whether the canned fish products or such treated in any other manner still retained their full iodine contents. Such investigations have now been made possible through the ready accommodation given me on the part of the manager of the fishery department.

It became possible for us to establish as a fact that the Norwegian clipp-fish and stock-fish (dry cod) are very especially rich in iodine. Several previous investigations on stock-fish were undertaken by Th. von Fellenberg. They have already been referred to in the Monograph of H. Eggenberger, Goiter and Cretinism, in the Manual of Inner Secretion.

In the table here presented there are a few of the results of my investigations mentioned:

Variety of Fish	mg of Iodine per kg	
	moist	dry
Clipp-fish	1.2— 2.1	2.0— 3.6
Stock-fish, cod variety	7.0—10.8	8.6—13.2
Stock-fish, perch variety	2.4— 4.1	2.9— 4.9
Stock-fish, haddock variety	12.4—19.3	15.5—24.2

The data as found are much greater than those of previous authors, but they are in quite perfect agreement with those, which von Fellenberg has published.

Inasmuch as these fish must, however, be soaked before being used as food, it was a matter of importance to ascertain the quantities of iodine, which become lost in the watering, and above all how great the quantities may be which still remain in the watered fish.

The fish was lixiviated with cold water for a time of 48 hours. The following table shows the results obtained:

Variety of Fish	γ Iodine per kg					
	Lixiviated with cold water	in the residue		in the residue in % of the entire iodine	Tot. contents	
		moist	dry		moist	dry
Clipp-fish:						
from Lofoten	840	370	600	31 %	1210	1960
„ Sunnmöre	1480	600	1040	29 %	2080	3600
Stock-fish: „Cod“	9640	1160	1420	11 %	10800	13180
„ „Perch“	1810	610	730	25 %	2420	2900

Sufficient investigations have not as yet been made, so as to enable us to draw any very definite conclusions from the results obtained. The quantities of iodine which remained in the residue appear, however, to be more constant than the total quantity of iodine. In other words it seems as if the quantity of iodine, which has remained in the residue, becomes smaller absolutely, when the total iodine contents were great.

Furthermore the quantity of iodine, which has remained in the lixiviated fish, is always very great and by all means sufficient to counteract strongly the action due to the absence of iodine in a goitrous region, where the articles of food are very poor in iodine.

The following table will show the results obtained in the examination of canned fish:

Iodine Contents of Norwegian canned fish	γ Iodine per kg (2,2 lbs.)	
	moist	dry
„Brisling“ (Norwegian sardines) in oil	210	450
„ . . .	190	430
„ . . .	160	360
„ with tomatoes	310	940
„ „	280	850
„Kippers“ (Herrings)	510	1430
„	330	930
„Kipper-Snacks“ (without skin and bones) . . .	220	620
„Fiskeboller“ Fish balls . . . . . 1 Kg	1060	6600
„ Fish strength . . . . . 1 „	420	
„ Fish balls . . . . . } 1 „	670	
„ Fish strength . . . . . }	150	
„ Total contents	820	7740

Here also great quantities of iodine are found to be contained.

These results are especially of great importance for the reason that we now know, that it is not only the fresh fish but also the canned fish, which can be transported so much more easily into the inland districts, that can be made use of with advantage in the prophylaxis for goiter.

In conclusion permit me to still call attention to the fact, which Th. von Fellenberg was able to establish, that the iodine, that was present in fish and especially in fish fats, is retained better by the organism and for that reason is more fitted for the storing up of an iodine reserve than the ionogenically combined iodine.

Concerning the great quantities of iodine, which, e. g., can be borne by the population at the sea-shore without any bad consequences whatsoever, F. de Quervain gives his views also in his address on the Basedow research of the Swiss Goiter Commission:

« We therefore are placed before the question, whether it is not perhaps probable that the form of the iodine plays a rôle. In our foods the iodine is conveyed to us to by far the greatest extent in organic combinations, whereas we in the iodized table salt partake of it in an active ionized form. The thought therefore suggests itself that this more active form may, to be sure, accomplish more in regard to the prophylaxis of goiter, but, in spite of the physiological quantity in a population, which has been made sensitive in this respect through the previously existing goiter, it can also lead to toxic results »

Prophylaxis of Goiter in Bavaria.

By Prof. Dr. A. Dieudonné, Munich.

Goiter is of very frequent occurrence in the Bavarian Allgäu district. For this reason the complete salt was introduced in an experimental manner, on the advice and suggestion of experts, in the year 1924 after a lecture given by Dr. Eggenberger. The consumption of it varies in the different districts, but in the jurisdictional district of Kempten it is used to the greatest extent, namely, 88 %, and here it is also fed to the cattle giving milk.

The period of time, which has elapsed since the introduction of complete salt, is naturally by far too short a time, in order to enable us to make a perfectly reliable judgment. However, all experiences,

that have thus far been made and reported, confirm the thought that in course of time favorable results can be reckoned with and that more especially the younger generation will be more and more free from goiter and its consequences. A specialist in pediatrics in Lindau has informed us that the cases of goiter in suckling babes and small children, which were formerly of such frequent occurrence, have no longer been observed since complete salt has been introduced.

No cases became known in any regions, that might indicate injuries to health through the use of complete salt.

The most important idea in this goiter prophylaxis is, that the mother absorbs the iodine with the complete salt and thus conveys the iodine to the unborn child and later through the milk.

The complete salt is prepared in the governmental Reichenhall salt-works according to the Swiss formula for complete salt, namely, 0.5 grams of KI to 100 kilograms of table salt.

The most exhaustive official reports were made by the medical officers in Sonthofen and Kempten. The researches made by school medical officers have shown that the enlargement of the thyroid gland with children is of considerably less occurrence than it was in former years.

In the elementary school of Immenstadt there were measurements of goiter undertaken according to Hunziker's method. By making a comparison of these measurements with those made on September 9, 1924, immediately after the introduction of complete salt, we find that the average surface of the thyroid gland of the first course of the year 1927 is about one third smaller than with the corresponding course of September 1924 and that of the fourth course of this year about one quarter smaller. With children whose thyroid gland did not admit of being measured the surface was put at 8 square centimeters.

	Day of measurement	Average surface in square cm	Boys alone	Girls alone
1st Course: School year 1924/25 (54 scholars)	9. IX. 24	17.80	16.99	18.69
1st Course: School year 1927/28 (100 scholars)	27 et 28 VI. 27	11.52	10.36	12.43
4th Course: School year 1924/25 (42 scholars)	9. IX. 24	20.55	17.86	23.50
4th Course: School year 1927/28 (35 scholars)	12. VII. 27	15.73	12.65	18.09

The fourth course of the school year 1927/28 was the first course of the school year 1924/1925. If we make a comparison of

the measurement results on these children of September 9, 1924, with the measurement data of February 9, 1926, and of July, 12, 1927, we find that the average thyroid gland surface had fallen off in the time from September, 1924, till February, 1926, a period of exactly 1½ years, but had increased again in the time from February, 1926, till July 12, 1927, when it had almost reached again the previous dimensions. However, the number of scholars had gone down from 54 in the year 1924 to 48 in the year 1926 and to 35 in the year 1927, which was in part due to removal from town and in part to entry into the intermediate schools, and it stands to reason that the last measurements data would have been more favorable, if all of the scholars could still have been reached. As a fact the children, who had left the school, are from the more well-to-do and more intelligent strata of the population, of whom it can be expected that they will take deeper interest in the prophylaxis of goiter and the use of complete salt, than the laboring classes would do.

Course of the School year 1927/28	Average surface of the thyroid gland in square cm	Boys alone	Girls alo ne
Measurement on 9. IX. 24	17.87	16.99	18.69
Measurement on 9. II. 26	12.76	11.08	14.32
Measurement on 12. VII. 27	15.73	12.65	18.09

In the school at Sonthofen the following data were determined:

1st course: School year 1924/25, 3. VII. 1924 (Eggenberger) 26.9 sq. cm.

3rd course: School year 1926/27, 13. VII. 1926 (Eggenberger) 14.9 sq. cm.

4th course: School year 1927/28, 18. IX. 1927 (Minderlein) 14.09 sq. cm.

1st course: School year 1926/27, 13. VII. 1926 (Eggenberger) 11.7 sq. cm.

2nd course: School year 1927/28, 18. VII. 1927 (Minderlein) 13.02 sq. cm.

1st course: School year 1927/28, 19. VII. 1927 (Minderlein) 11.72 sq. cm.

4th course: School year 1924/25, 13. VII. 1924 (Eggenberger) 32.6 sq. cm.

4th course: School year 1927/28, 18. VII. 1927 (Minderlein) 14.09 sq. cm.

In Kempten the results were as follows:

6-year old girls (33), measured July, 1924, before complete salt: thyroid gland surface, 22.8 sq. cm.

the same girls (25), measured July, 1926, after 2 years of complete salt: thyroid gland surface, 9.4 sq. cm.

the same girls (25), measured July, 1927, after 3 years of complete salt: thyroid gland, surface, 7.9 sq. cm.

In the year 1924, all thyroid glands could be easily measured.

In the year 1926, 2 thyroid glands could no longer be measured.

In the year 1927, 10 thyroid glands could no longer be measured.

6-year old boys (29), measured in 1924, before complete salt: thyroid gland surface, 23.8 sq. cm.

the same boys (25), measured in 1926, after 2 years of complete salt: thyroid gland surface, 11.3 sq. cm.

the same boys (25), measured in 1927, after 3 years of complete salt: thyroid gland surface, 10.5 sq. cm.

In the year 1924, all thyroid glands could be easily measured.

In the year 1926, 2 thyroid glands could no longer be measured.

In the year 1927, 5 thyroid glands could no longer be measured; there were also thyroid glands with a surface of from 6 to 10 sq. cm. in the year 1926. The girls of six years of age, measured in the year 1927 after a three year use of complete salt, had an average thyroid gland surface of 5 sq. cm., and the boys of 6 sq. cm., whereas the six year old girls and boys, who had been measured in the year 1924, i. e. before the introduction of complete salt, showed a thyroid gland surface of 22.8 and 23.8 sq. cm. respectively.

In the case of the 13 year old girls and boys there was found in 1927 after 3 years of complete salt a thyroid gland surface of 12 and 12.1 sq. cm. respectively, whereas in the year 1924, before the complete salt was used, the 13 year old girls and boys showed a surface area of 28.7 and 27 sq. cm. respectively.

Comparing the measurements, taken in the year 1924, of the girls and boys, who were at the time 6 years old, with the measurements of the same children in the year 1927, when they were 9 years old, we find a reduction in the surface area of the girls of 65.4 % and of the boys 55.9 %, while in the preceding year the reduction found was 58.7 % and 52.5 % respectively.

Dr. Sepp in Ditmannsried reported regarding the members of the benefit associations, who were afflicted with goiter::

In the 7 quarters, beginning with the first quarter of 1923 to the third quarter of 1924, which time was prior to the introduction of complete salt, there were 1798 patients under treatment, among which number there were 320 afflicted with goiter, and in the 7 quarters from the fourth quarter of 1924 till the second quarter of

1926, which time falls within the time of complete salt, there were 1743 patients, including 87 afflicted with goiter.

Experiments made in the Research Institution for Dairy Farming in Weihenstephan in feeding complete salt to cattle giving milk resulted in having a very favorable influence on the excretion of milk which is richer in iodine, a matter that can also be considered of significance for the treatment of goiter in juveniles.

Very instructive lectures were held by the district medical officers. Furthermore a leaflet was distributed that bore the title: «Goiter, Cretinism and Complete Salt», and likewise there was distributed among agricultural circles the treatise by Dr. Kieferle, of Weihenstephan, on «Why ought the Farmer of the Allgäu District feed Iodized Salt, the so-called Complete Salt, to his milking cattle?»

Discussion on Goiter Prophylaxis.

By H. Eggenberger, M. D., Herisau (Switzerland).

Eggenberger (Herisau) expresses his gratitude to Messrs Wagner von Jauregg (Vienna), Dieudonné and von Romberg (Munich), Muggia and Ambrosi (Italy) for their successful efforts in introducing the iodized salt («full salt») in Austria, Bavaria, and northern Italy and he hopes that other goiter-countries will follow their example quite soon. — The results of 5 years prophylaxis with «full salt» in the Canton of Appenzell (Switzerland) are quite encouraging:

1. Operations for goiter diminished by 75 % since 1923.
2. Total disappearance of congenital goiter.
3. Diminished number of stillbirths and death of infants due to thyreogenous debility.
4. Increase of average weight at birth, by 100 grammes.
5. Disappearance of goiter in the young school-children.
6. Diminishing goiters in many adults.
7. Iodism due to the use of «full salt» could not be found.

These results have been demonstrated in extenso and documented in Vol. III d. «Handbuch der inneren Sekretion by M. Hirsch». At the same time lack of Iodine as aetiology of goiter has been pointed out and documented by the microchemical examinations of von Fellenberg, Mac Clendon, Hercus and others. This aetiology can evidently only be accepted if Iodine is recognized as

an essential part of the Hormone of the Thyroid gland, as a normal part of its constitution, as an indispensable «nutriment». This knowledge will soon be generally accepted since the chemical constitution of the hormone-molecule has been established, and since recently the Thyroxin has been synthetized. The body of the hormone contains 66 % of Iodine. — It has been proved, that there are huge territories affording scarcely enough Iodine for building up the Thyroxin. Evidently the Thyroid gland must show compensatory hypertrophy under such conditions, as Marine and Aschoff have demonstrated.

Followed: demonstration of the very simple process of iodizing salt.

Nourishment and Thyroid Gland Function.

By J. Abelin, Berne.

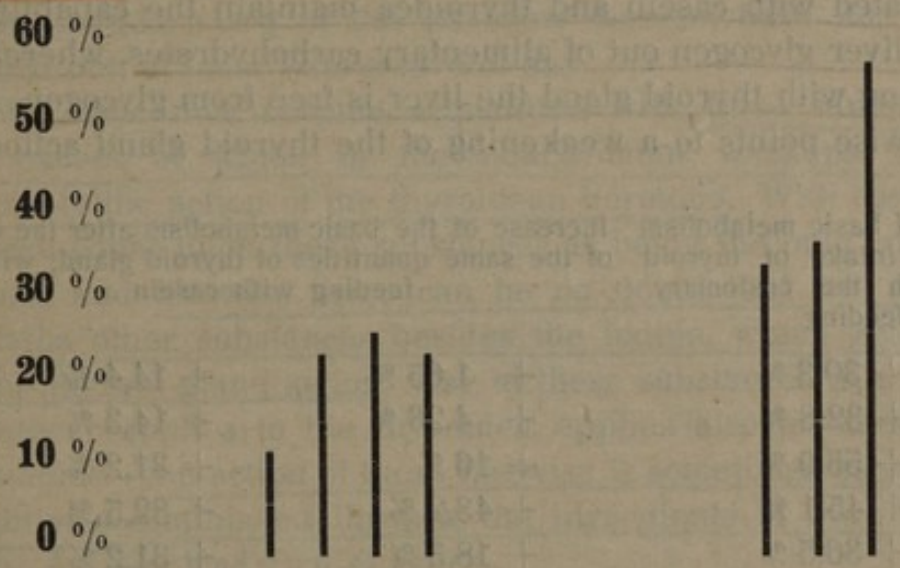
To the fundamental conception of an internal secretion there belongs the idea, that it is a question of a substance, which is formed at one definite place and fulfills its function at another more or less distant place. With this statement it is also implied that the mechanism of acting is a bipartite one and that a derangement of the inner secretory system can be occasioned through an abnormal function of the hormone-producing organ, as also through a modified capability of reaction on the part of the peripheral place where the action is effectuated. A combined derangement of both processes is also possible. The doctrine of internal secretions first of all occupied itself mainly with one of these two factors, namely, with the action of the glands, that secrete internally, and the attempt was made to ascribe the deviation from normalcy to a hypersecretion or to a hyposecretion. Then came the conception of dysfunction, i. e., of a derangement not along quantitative lines but along qualitative ones. But we began to look into the condition of the peripheral place of action more and more, and from the material that has thus far been gathered, though as yet it is not very numerous, we are justified in believing that along this line there are to be found very determinative factors of inner secretory action. The number of factors, which the peripheral action of an inner secretory product may modify, is extremely great and it is the problem of the research work of to-day to make the main factors clear. There exists a physiological condition, that can not be evaded, which at every moment has an effect upon the action of internal secretions,

namely, the kind and manner of nourishment. It is just the thyroid gland, that is representative of an organ with which the relationship between food and function were recognized the very first of all. There can be no question that the distribution of goiter has done much to promote this. There are accounts of former experiences on hand, according to which the animals after thyroidectomy must not be fed with much albumen and quite especially not with meat. Furthermore we have learned empirically that in the case of hyperthyrotic conditions the albumen-meat alimentation acts detrimentally and that we shall meet with better satisfaction with a lacto-vegetable diet. By means of different feeding methods it is furthermore said to be possible to bring about histological modifications in the thyroid gland either of the nature of goiter or of Basedow (Mellanby, McCarrison). For the study of the entire problem it is also of great value to carry on alimentation experiments with animals, that have been hyperthyroidized artificially. The very variable and scarcely controllable factor of the individual function of the thyroidea will in this case be eliminated to a great extent, and we obtain very impressive representations as to how, through the one or the other alimentation factor the development of the hormone, present in the surplusage, is at one time increased and at another time diminished.

Some 4 years ago it occurred to me that we can diminish the substance of the thyroid gland by means of an abundant addition of fat to the customary nourishment. In pursuance of this observation it was ascertained that the administering of fat also protects the glycogen metabolism of the liver from injurious thyroidean action. (Biochemische Zeitschrift, vol. 149, page 109, 1924, and vol. 174, page 232, 1926). It could be simultaneously determined that through the intake of an inorganic phosphate the effect of the thyroidean medication is very considerably intensified. In the course of the further researches it became evident that there are a great number of individual substances, the presence of which in the food influences the action of the thyroid gland in the one or the other sense. Nevertheless it would take up too much time and space, if we desired to make mention here of all of these experimental results. We shall single out only a few substances that have particular characteristic action.

I. In the very first place we must think of the action of the salts of calcium. The frequently described antagonism between the phosphate-anion and the calcium-cation finds also very good acceptance in case of the thyroid substance. If now the

intake of phosphate calls forth an intensification, then the administration of calcium, vice versa, occasions a weakening of the thyroidean action. We must emphasize here that the antagonistic calcium effect is more intensive than the synergistical effect of the phosphate addition. If we add calcium to the customary food it renders it possible for the animals (rats) to put up with very considerable quantities of thyroid gland substance without having it come to any excessive increase of metabolism. At the same time the other symptoms of hyperthyroidization, such as nervous hyperexcitability, strong perspiration, disturbances of respiration are also marked in considerably lighter form, than with the intake of thyroidea alone. It sometimes happens, that the behavior of animals treated with calcium and thyroid gland or with calcium and thyroxine is scarcely to be distinguished from that of the normal animal. The mitigating influence of the calcium salts upon the metabolic action of the thyroidean substances is to be seen from the following comparison:



a. %-increase of the basic metabolism after the intake of dried thyroid gland substance and calcium salts.

b. %-increase of the basic metabolism after the intake of the same quantities of dried thyroid gland substance (without calcium additions).

The not rare favorable effects of the calcium salts in the case of Basedow, as also the experiences gained from experiments on animals, make it very probable that there is not only an exceedingly close relationship between parathyroidea and the calcium metabolism, but also between the thyroidea and the calcium requirement. It can be supposed that the general soothing effect of the calcium salts also follows at least in part via the thyroid gland.

2. Another substance, which likewise acts in an obstructive manner upon the metabolic mechanism of the hyperthyroidization, does not belong to the sphere of the inorganic but to that of the organic nutriments. It becomes a question here of Casein. If rats are fed with freshly prepared and well purified casein, some bread and milk, then they become quite resistant against the thyroid gland action and first become more and more emaciated but after a while reach a body-weight, which remains quite constant, notwithstanding the intake of thyroid gland substance. The metabolic increase has become hereby considerably lessened and parallel with it the nervous symptoms are not so strongly marked as with the animals, which are fed in a normal way and which received the like quantities of thyroid gland substance. This casein action occurs rather regularly, I have thus far seen only sporadic and simply partial exceptions. The counter-action of the casein is especially marked in the initial stages of the treatment of the thyroid gland. We may state further, that such animals, which have been treated with casein and thyroidea maintain the capability of forming liver glycogen out of alimentary carbohydrates, whereas in the feeding with thyroid gland the liver is free from glycogen. This fact likewise points to a weakening of the thyroid gland action.

Increase of basic metabolism after the intake of thyroid gland with the costomary feeding.	Increase of the basic metabolism after the intake of the same quantities of thyroid gland, with the feeding with casein.	
+ 30,3 %	+ 1,65 %	+ 14,4 %
+ 32,8 %	+ 4,26 %	+ 14,3 %
+ 55,9 %	+ 16 %	+ 31,2 %
+ 45,1 %	+ 43,2 %	+ 32,5 %
+ 36,5 %	+ 18,3 %	+ 31,2 %
+ 62,5 %	—	+ 31,2 %

Memoir. Prof. of.

It is accordingly not consistent with the facts, if it is claimed that an abundance of albumen in the nourishment is favorable to the thyroid gland action. It is likewise not possible to assert that with hyperthyreoses animal albumen is more injurious than vegetable albumen. As in many other cases it depends here entirely upon the nature of the particular albuminous body: out of the same group of animal albumens the meat acts in an intensifying manner and the casein in a weakening way upon the increase of metabolism. Concerning the action of other albuminous bodies a report will be made later on.

3. The fat also deserves special interest. Its action has been in short already referred to. The influence of fat upon the metabolism depends entirely upon the phase of hyperthyroidization. In the initial stages of the intake of thyroid gland, just as long as the cells have lost only in part the capability of using up the fat or of depositing the fat, just so long does the supply of fat act favorably, i. e., in a checking manner upon the decomposition of substance. In this stage the thyroid gland action with very obvious success can be overcome through fat as food. If, however, we do not begin with the supply of fat until a later period of time, where the metabolism is already abnormally high and where the injury of the cell has strongly progressed, then the fat can be retained by the cell only to an unsatisfactory degree, it suffers oxidation and acts metabolically still more strongly. There are also data on hand where, in the case of Basedow of more serious nature, the supply of fat increases the basic metabolism to a higher degree (Mellanby, Zondek). Experiments with fat, made on human beings in the beginning of the Basedow disease, have not yet been carried out, at least I am aware of any.

Fats

dual effec of

We have now become acquainted with three kinds of food, the excess of which in the nourishment weakens very considerably the action of the thyroidean hormone. With certainty we can not count upon these substances as being the only ones of this nature, and likewise there can be no doubt that our daily food contains other substances besides the iodine, which give support to the thyroid gland action. One of these substances is, e. g., meat. Whatever applies to the thyroidea, applies also to other internal secretions. The action of these likewise is sometimes increased and sometimes diminished through the ingredients of the foods (Gigon, Abderhalden et al.).

[McCarrison Prob. pte

It can be noted with interest, that all three of these obstructive substances, the calcium, the casein and the fat are present in very considerable quantities in the nourishment of the population of Switzerland, in quantities which frequently exceed the corresponding food quantities of other countries. It is not out of question from a biological point of view, that a constant obstruction of the peripheral action of the thyroidean hormone finally of its own accord exerts an unfavorable reaction upon the function of the thyroid gland, and that, besides other deciding factors, promotes a chronic subduing of the thyroidean action of the diseased condition of the thyroid gland.

Food in Switzerland

Frequent Outbreak of the Basedow Disease in Persons, afflicted with Goiter, in goitrous Regions containing Iodine Springs.

By Dr. Michel Guhr, Tatranska-Polianka.

In the mountainous region of the Northern Carpathian Mountain Range, in the immediate vicinity of the health resort Polhora, where there is a spring containing iodine, we find a goitrous region, in which, besides goiter, cretinism, deaf-mutism and other maladies of the glands with internal secretion are to be met with, nevertheless among juvenile persons especially Morbus Basedowii.

The iodine spring is made use of neither for internal nor for external use as a curative remedy by the population, afflicted with goiter, and has thus far not been recognized as a prophylactic against goiter. Whether the subterraneous water in the vicinity, the fountains or brooks, contain iodine is not known. Only the numerous cases, in which we find a non-malignant Basedow with all of the symptoms, indicate the presence of iodine injuries, such as have been reported from other places since the introduction of complete salt.

The observation, made by the physicians of that locality, is worthy of note, namely, that individuals of the younger age-groups, who are afflicted with goiter, have experienced a diminution in the dimensions of the goiter when they had improved their nourishment and their general manner of living.

* * *

Injuries received in Winter as Causes of the increased Outbreak of the Basedow Disease:

Morbus Basedowii an Avitaminosis.

Since the individuals suffering from Morbus Basedowii, whether this is a genuine Basedow or is simply an accompaniment of an iodine injury, are almost always afflicted with goiter, I am induced to present here a few statistics, which throw some light upon the temporal outbreak of the Basedow disease in the different months of the year.

There were 229 cases of genuine Basedow selected. Those manifestations of disease were excluded, which were the results of particular or occasional injuries, such as lactation, influenza or iodine.

To the separate months, there came:

January	February	March	April	May	June	July
17	31	34	31	28	34	5

August	September	October	November	December
6	1	6	8	8

It strikes our attention to notice the accumulation in the spring months. Upon investigating the manner of living and that of alimentation of the Central European groups of human beings, to which my medical material pertains, we find numerous cases of injuries due to the winter season, especially such due to the deprivation of air and light, i. e., the passing the Winter in closed rooms, and particularly the lack of vitamines in the nourishment.

Season

Vitamins

The A - vitamines are kept from the body through the heating of the milk, butter and fats, the B - vitamines through the grinding the grain with the removal of the silver-colored husks, the C - vitamines through the lack of green vegetables, turnips, onions and cabbage in Winter.

An unilaterally disposed tendency in the tastes and desires especially of juveniles often leads to the detrimental elimination of important vitamines.

Just as we, ex nocentibus, can get a view into the establishment of the hormonal dysfunction of the glands of internal secretion, so the hygienic-dietetical guidance of Basedow invalids in the relation: air - light - vitamine plus optimal manner of living, plus favorable climate, i. e. a mountainous climate free from the south and sirocco winds, sparing the overtaxed sympathetic nervous system, can give us, ex juvantibus, an insight into the internal accessibility, the prophylaxis and therapy of this goitrous trouble.

It is well known to us all that there is an individual predisposition to the Basedow disease through heredity, a Habitus basedowianus hereditarius, as also a predisposition to derangements, which become manifest in the form of sympathicotonic or vagotonic diseases.

We have come a step nearer to the keeping away of the changes for the worse, which occasion diseases.

Here, as with the ordinary goiter, air, light and nourishment play a rôle and in the case of goiter the purity of the water plays an important rôle.

Prophylaxis of the Endemic Struma.

By Dr. K. Scharrer, Weihenstephan near Munich.

Kindly permit me to make a few short observations respecting the relations existing between the iodine problem, goiter prophylaxis and agricultural chemistry.

Since the year 1925 a number of institutes in Weihenstephan and Munich have been working in a systematic manner at the iodine problem, and as a matter of fact the Institute of Agricultural Chemistry with Professor Niklas at the head, the Chemical Institute under Professor Bleyer, the South German Research Institute for Milk and Dairy Products under Minister Fehr and the Polyclinic for Children of the Munich University with Professor Seitz at the head.

The programm of these labors in common has been so planned that each of these institutes remains completely independent within its own sphere of action, but when studying into the border regions it will lay out its respective lines of work by keeping in the closest touch with the neighboring institute concerned.

First of all it is the intention that the problem of these labors in common is to be to study quite generally into the biochemistry of iodine. It was natural that the obligation fell to the Agricultural Chemical Institute at Weihenstephan to solve the problem as to how the circulation of the iodine from the soil via plant and animal to the human being and back takes place, whereby the last phase of this circulation really represents a border territory, which is to be ploughed and cultivated in common with regular medical men. With the importance of the iodine question right in Bavaria, which has particularly many goitrous districts, especially in its southern parts, it was perfectly clear from the outset that the relations of iodine to the goiter problem and particularly the goiter prophylaxis were necessarily to constitute an integrant part of our sphere of labor.

Instead of dispensing the iodine in an artificial purely inorganic manner in the form of the iodized kitchen salt (complete salt) to the individual prophylactically to combat the disease of goiter, we could eventually also consider the dispensing of iodine in a natural combination, because it is perhaps preponderatingly organic at least in a form which has been, as it were, made «physiologically of a higher value» through the vegetative and animal vital functions by enrichment with iodine of the foods, derived from the animal and

plant kingdoms. This way, here suggested, is not without importance also for the reason that the goiter prophylaxis through the direct dispensing of iodized kitchen salt, as it is being done at the present day in Switzerland, Bavaria and Austria, can naturally not come into consideration for the suckling babe, although the necessity might exist, in any particular case, to even protect the infant through an increased intake of iodine against the injuries due to the absence of iodine. One possibility of accomplishing this would be to feed the nursing babe with milk, that has been enriched with iodine through iodine feeding.

In order to give you here a short outline of the labors, which we have thus far been engaged in, and to give you an insight into the methods employed, let me say, that first of all the action of iodine upon milking goats, and in the beginning with iodine doses which must be pronounced «massive doses», given intentionally, was investigated.

Iodine and milk-production

The milk and the blood of these milking goats were tested for iodine. One group of them was fed with containing no iodine and the other group with 60 or 120 or 180 mgs. of iodine which had been added to the main feed as NaI in the form of tablets. With the animals, that had been fed with iodine, there was made manifest, under the action of the high iodine doses, a great increase of the natural iodine contents as well in the milk as also in the blood, which was likewise tested for iodine.

In summing up we may say that the experiments enable us to declare that such iodine, which is in an inorganic combination, if taken in through the mouth, is absorbed quantitively by the intestines in spite of simultaneous feeding. A daily intake of iodine through the mouth of more than 100 milligrams (1.543 grains avoirdupois) with milking goats leads to an iodization of the fluids of the body, particularly of the milk, to an amount which can no longer be laid claim to as being physiological, even if no injurious action upon the state of health can in any way be determined. An iodine intake, beyond all measure, which had been pursued for a rather long time, did not result with either goat or pig in bringing about a greater iodization of the fluids of the body that later on continued as such.

The iodine doses in each case remained without effect upon the conduct and state of health of the animals. The iodine doses of 60 and 120 milligrams per animal and per day were not able to call forth any definite increase in the yield of milk. Moreover, the augmentation of the quantity of milk was only of short duration

through the dose of 60 milligrams. As contrasted with that, the iodine dose of 180 milligrams per animal per day brought forth a (3) considerable increase in the produce of milk. The researches into the fatty contents of the milk demonstrated that, with an iodine dose of 120 mgrs. per animal and per day the absolute quantity of fat was higher, but the percentage of fatty contents, caused through the increase in the quantity of milk, appeared to be lower. If the dose of iodine was 180 milligrams per animal and per day the absolute quantity of fat rose in the beginning and then fell again, whereas the percentage quantity of fat continued to be lower. The weight was in no wise affected through the doses of iodine. It was not possible to determine any action whatsoever of the iodine upon the sexual functions.

In another investigation of the milk of goats, whereby doses of 7.5 and 15 milligrams were given as NaI in the form of tablets, the examination was carried on in such a way that a horizontal manner of observation in the analyses was adopted; namely, at different characteristic points of time of the experimental periods the milk of all of the animals was taken for examination. The result confirmed the previous results with the animals, which had received no iodine in their feed, with reference to the observed normal iodine contents of the milk. With the animals, which were receiving iodine, considerably higher iodine contents than the percentage found in the normal milk were also observed even with these small doses; the investigation of the rapidity of the transition of the iodine, that is taken in through the mouth, into the milk showed that even in the first 30 minutes there had passed over so much iodine into the milk, that in this partial milking the orginal normal iodization had been increased twenty-fold. The point of culmination was attained as soon as after a few hours and the return to normalcy did not take place until after a period of four days. The sinking to the normal condition went on first rapidly and then slowly. The conclusions, which can be drawn from this investigation into the chemism of this second goat experiment, are, accordingly, similar to those, which have been already mentioned for the just goat experiment. An extra feeding with iodine, which had been carried on for a rather long time, did not result in causing a later permanent increased iodization of the fluids of the body.

Upon the basis of these experiences gained in the study of the action of iodine on milking goats, the experiments were now extended to include milking cows. Iodine doses of 1.53 milligrams (= 2 mgs. KI) and 3.82 milligrams of I (= 5 mgs. KI) per animal

and per day could not give rise to any definite increase in the produce of milk. However, the influence of the dose of 3.82 mgs. of iodine became manifest to such a degree that during the progress of the lactation period a decided rather slower lowering of the quantity of milk took place than with the animals without iodine and with 1.53 mgs. of iodine. The action of 76.45 mgs. (= 100 mgs. KI) per animal and per day was to be seen in a considerable augmentation in the quantity of milk, which increase lasted during the entire time of the experiment. The percentage of fatty contents in the milk and the absolute quantity of fatty ingredients were somewhat diminished through the giving of 1.53 mgs. of iodine. Likewise the dose of 3.82 mgs. of iodine caused a slight diminution in the percentage of fatty contents, but the absolute quantity of fat remained the same, due to the greater secretion of milk. The fatty contents experienced an inconsiderable diminution through 76.45 milligrams of iodine, but the absolute quantity of fat showed a remarkable increase through the improved yield of milk. The chemical researches showed that the giving of an iodine dose of 76.45 mgs. of iodine resulted in a significant rise in the iodization of the milk, namely to about the tenfold of the normal state. But the iodine doses of 1.53 and 3.82 mgs. of iodine, respectively, resulted also in a distinct rise of the iodine percentage of the milk, i. e. by about 40 to 100 %.

The milk of those cows, which received 3.82 mgs. of iodine through the mouth per animal and per day when being fed, was forwarded to the polyclinic for children at the University of Munich. Dr. Maurer, Munich, Physician in Chief, carried out experiments on suckling babes with it, concerning which he reported in the Journal for Pediatrics to the effect that the nursing infants can stand perfectly well such milk, which has been enriched through a moderate feeding with iodine.

The result of these experiments, accordingly showed that it is possible to obtain an iodization of the milk through the addition of suitable quantities of iodine to the feed of milking cows, which does not exceed the limits of the intake of iodine, that is as yet free from objections from a physiological point of view, both as regards its constancy as also the absolute amount of the percentage of iodine in the milk.

Whether and, if so, to what extent the plants can be improved in iodine through the enrichment of the soil with iodine, was the problem that constituted other investigations, that were instituted by us.

First of all experiments were carried out in the fertilization of uncultivated lands for sugar-beets with treatment of iodine of 0.251 kgs. to 2. 511 kgs. of iodine (0.55 lbs. to 5.5 lbs.) as $NaIO_3$ per hectare (= 2.471 acres) on black clayey soil. In the case of the plots of ground, which were fertilized with iodine, in comparison with the usual fertilization of the soil, there was a great increase of iodine found as well in the roots as especially in the leaves of the sugar-beet. Similar results were also obtained in the case of different cultivated plants with further experiments in iodine fertilization.

From the experiments, that have been carried on by us, there accordingly can be no doubt that through the addition of iodine a considerable enrichment of iodine in the plant will result. Even prior to our experiments similar results had been obtained by von Fellenberg and Stocklasa, whereas Miss M. Wrangell, Professor, of Hohenheim claims that she observed no iodine enrichment in the plants through the treatment with iodine.

Some further experiments will be necessary in order to clear up many an important question or to solve new phases of the problem that may come up. With us there will be again some plant experiments instituted this year, as well on uncultivated land as also in special plant receptacles. Furthermore, a pasture-land experiment is being carried out, which is expected to solve the question as to what extent an iodine enrichment of the grass varieties of the pasture-lands through iodine fertilization can be determined and to what extent an iodine enrichment of the milk of the grazing milking cows is to be observed in these animals in consequence of their feeding on the iodized pasture-grass. Other experiments are expected to serve in helping to solve the exceedingly important questions on the relations existing between iodine and soil. Finally experiments with nourishment containing iodine will be carried out on children in the Children's Convalescent Home at Deisenhofen, near Munich, conjointly with the Polyclinic of Munich. The problem before us, in these experiments is to be to study into the influence of the giving of nourishment to children, which contains iodine, from the standpoint of human medicine and, as a matter of fact, iodized vegetables and iodized milk will here come into question. At the proper time reports will be issued on these various labours.

We may refer here also to the fact that in the Weihenstephan Institute the work is regularly being done according to Th. von Fellenberg's methods of determining iodine. The experiences,

which we have thus for gained, have convinced us that this method is by far the best one among the processes for determining very small quantities of iodine and, as far as accuracy is concerned, it answers any and all requirements, provided, of course, that it is being followed correctly.

Prophylaxis of endemic goiter.

By Dr. Fr. M. Messerli, Lausanne.

The evolution of the goitrous endemic may be resumed in a scheme proper to form the basis of discussion concerning the prophylaxis of endemic goiter:

Resumé of the evolution of the goitrous endemic.

I. **Pre-thyroidic (or preparatory) period**: General action of the determinant cause upon the organism (preparation of a special ground) or invasion of the organism by the determinant cause.

II. **Provocation of hypertrophy in the thyroid**: the determinant cause produces an alteration of the thyroid.

III. **Action of the altered thyroid**: The altered thyroid acts upon the organism, provoking hyperthyroidism (sporadic and endemic myxoedema).

IV. **The combined action of the determinant cause, the altered thyroid, heredity and consanguinity** provoking genuine cretinism, goitrous cretinism and deaf-mutism.

Ever since the Swiss Goiter Commission had begun its labours, Prof. B. Galli-Valerio and myself *) have insisted upon the initiation of prophylactic measures of two different ordres:

a) Measures of a general order, such as the amelioration of the conditions of living and of hygiene, amelioration of the potable waters, calculated to favor the suppression of the goiter agent and its predisposing causes.

b) Measures of a therapeutical order, viz. the utilization of iodized salt, of iodic tabloids, and, in regards to cretinism, of Thyroidine, etc., to act upon the symptoms provoked by the endemic.

According to the reporters and orators we have heard, the

*) Report of the first sitting of the Swiss Goiter Commission of January 21st, 1922; Report of the Swiss Society of Hygiene, 1922.

though certainly a very important one, of the problem, and the success of which must be applauded to; but it does not bring a definitive solution to the problem of prophylaxis against the goitrous endemic.

The iodized salt and the iodic preparations act upon thyroid hypertrophy, that is: upon a symptom, without suppressing the determinant cause, the infection, namely, by which the hypertrophy has been brought about, and without acting upon the different manifestations of degeneration produced by it.

It is therefore imperative — besides the iodic treatment (by the means of iodized salt, iodic tabloids, etc.) — to attack a primordial importance to hygienic meliorations, to the improvement of potable waters, with a view to the suppression of the causes to which the endemic be due and of those favoring the latter, and not to omit, moreover, measures in counteraction to sporadic and endemic myxoedema, and, particularly, to (both genuine and goitrous) cretinism and deaf-mutism.

By a judicious employment of thyroid preparations, such as Thyroidine, we can bring about a diminution in the number of unfortunates and of the social waste for which the goitrous endemic is responsible and upon whom the iodized salt alone is without influence.

The use of iodized salt constitutes, in our opinion, only a partial solution to the prophylaxis against the endemic, of which it fails to eliminate the cause or to combate the degenerative developments.

Conclusion.

Prof. W. Silberschmid:

I merely desire to point to the fact that no voice has been heard in opposition to the general introduction of goiter prophylaxis by the means of iodized kitchen salt, and the agreement of this conference regarding the trial of this method on a large scale in goitrous regions is thereby confirmed.

THE EXPOSITION.

What is endemic goiter? How does it originate and what are the means for its prevention? — These are the questions which the International Goiter Conference found itself confronted with. From the very descriptions furnished by the anatomo-pathologists as referring to goiter, there results in fact a notable dissimilarity in the modifications of the thyroid gland, according to the regions in which they are observed, a dissimilarity which justifies the question as to whether a univocal aetiology can at all be applied to this affection, such as, for instance, that of iodine deficiency, now so prominently recurring in scientific debates. It seems hardly possible to link by a single and so incomplex a formula the goitrous endemic of the sea-coast and the thyroid lesions observed in mountainous regions. And, the multiplicity of aetiological causes once admitted, are we not in consequence obliged to preclude the applicability of uniform preventive measures against goiter to all regions? The purpose, therefore, of our Conference could be no other than the bringing together of the savants of every country, as far as they were known to be interested in the goiter endemic, by affording them occasion for an exchange of ideas and for the conclusion of an entente on points on which this seemed achievable.

With the discussion, however, of questions bearing on the anatomy and the pathogeny of an affection such as goiter, a collection of demonstrative material had indispensably to be connected and the exposition arranged in conjunction with the Conference was the logical result. At the outset, we contemplated the undertaking with some hesitation, having had to discount an inadequate participation. But our apprehensions soon became untenable: the adhesions we received and the preparations and documents put at our disposal were in so great a number that, in order to lodge the exhibits conveniently, four rooms of the University had to be requisitioned, instead of the single one originally set apart. We cannot but tender renewedly our thanks to all those who have accorded us their collaboration.

As to a detailed description of the exhibits, this would have met with considerable difficulties and we had to be content with enumerating them in a list. We have to add that a part of the precious material exhibited has been graciously surrendered to us in favour of the contemplated creation of an international goiter museum and here again, we beg to give expression to our gratefulness towards the donators.

Objects Exhibited.

Switzerland.

AARAU. *Surgical department of the Cantonal Hospital. (Dr. E. Bircher).*

1. Large collection of skulls and bones of the extremities, originating from cretins.
2. Atlas on the distribution of cretin degeneration.
3. Maps showing goiter conditions in Aargau, in Switzerland, Austria and Bavaria.
4. Several geological maps.

BASEL. *Surgical Clinic of the University. (Professor Henschen).*

1. Corrosive preparations of thyroid glands to demonstrate the arteries.
2. Diapositives of injected bloodvessels of the thyroid gland.
3. Rœntgen ray pictures of strumas.
4. Photographs of the Boas cretin family. (Professor Hotz, deceased).

BASEL. *Pathological-anatomical Institute. (Professor Roessli).*

Preparations of strumas of different types.

BERNE. *Surgical Clinic of the University. (Professor de Quervain).*

1. Operative preparations of strumas of different types.
2. Photographs of macroscopic and microscopic thyroid gland preparations, in common with the Pathological-Anatomical Institute of Berne.
3. Charts:

   Synoptic compilation of the relations between shape and function of goiter, compiled according to different authors.

   Table to explain goiter noxa.

   Colloid contents of the thyroid gland.

Function of the normal thyroid gland, and of that in Basedow and in cretinism.

4. Photographs of goitrously afflicted and of cretins.
5. Rœntgen photographs to show the relation between the goiter and the trachea.

BERNE. *Pathological-Anatomical Institute. (Professor Wegelin).*

1. Collection of pathological-anatomical thyroid gland preparations.
2. Skeleton of a cretin; skull and extremity bones of cretins.
3. Charts:

   Frequency of Struma maligna.

   Life curve of the Kiel and the Berne thyroid gland.

   Development of different varieties of goiter.

   Frequency of Struma nodosa in the different stages of age in Berne.

   Weight of thyroid glands: Comparisons made between Kiel, Königsberg, Berlin, Munich, La Chaux-de-Fonds, Freiburg in Breisgau, Göttingen and Berne.

   Ossification conditions in cretins and in Kachexia thyreopriva.
4. Photographs of microscopic and macroscopic thyroid gland preparations, in common with the Surgical Clinic of Berne.
5. Microscopic preparations.

BERNE. *Federal Health Department.*

Charts:

1. The distribution of endemic goiter as learned from the examination of recruits 1921/1922.
2. The distribution of endemic goiter as learned from the examination of recruits 1924/1925.
3. Goiter at the boundary region of the Cantons of Vaud and Freiburg in the year 1924.

BERNE. *Municipal Medical School Officer's Department.*

Charts:

1. Frequency of goiter with schoolchildren of the City of Berne.
2. A comparison of the frequency of goiter in the City of Berne and in the Jura Mountains (Le Locle, La Chaux-de-Fonds, Neuchâtel).
3. Frequency and treatment of goiter in the schools of the City of Berne:

   after a 1 year's treatment with iodine,

   after a 4 years' treatment with iodine,

   after a 4 years' treatment with iodine (a comparison between primary school and classical school).

   after a 5 years' treatment with iodine.

Photographs:

1. Children afflicted with hypothyroidism.
2. Children of the same age with a difference in physical development due to the malady and to hypothyroidism.
3. Twins equally developed and twins unequally developed in consequence of hypothyroidism afflicting one of them.

BERNE. *Institute for Zootechnics. (Professor Dürst).*

Sections of the thyroid glands of healthy cattle of different breeds from the high mountain regions and from the sea.

BERNE. *Veterinary-Pathological Institute of the University. (Professor Huguenin).*

1. Preparations of animal goiters.
2. Charts and diagrams of animal goiters.

BERNE. *Dr. Isenschmid, University Lecturer.*

Photographs of cretins of the Institute for the Relief of the Poor, Riggisberg near Berne.

GENEVA. *Surgical Clinic of the University. (Professor Kummer).*

Collection of photographs of goitrously afflicted, shown in 3 albums.

GENEVA. *Institute of Hygiene. (Professor Cristiani).*

Preparations and microphotographs concerning the transplantation of goitrous tissue in the rat.

HERISAU. *Hospital. (Dr. Eggenberger).*

Charts:

1. The scholar's goiter in Herisau before and after treatment with complete salt.
2. Comparative data on the dimensions of thyroid glands of newborn infants, whose mothers had consumed complete salt during pregnancy, and such, who had not used any complete salt.
3. Iodine contents in 1 kilogram (2.2 lbs.) of soil in regions free from goiter and such containing goiter.
4. Nutritive iodine in goitrously free regions and in goitrously afflicted localities.
5. Iodine metabolism and goiter.
6. Distribution of goiter and cretinism in the civilized world.

7/8. Comparative study of the dimensions of the thyroid glands with and without prophylaxis of complete salt.

LANGNAU near BERNE. *District Hospital. (Dr. Fonio, University Lecturer).*

1. Charts to illustrate the method employed for the investigation of blood coagulation.
2. Tables with the results from investigation of blood coagulation: Strumas with apparent normal somatic behavior.

Strumas with symptoms of hypothyroidism.
Strumas with symptoms of hyperthyroidism.
Strumas with symptoms of myxoedema.
Endemic cretinism.
Basedow.

LAUSANNE. *Institute of Hygiene and of Parasitology of the University. (Prof. Galli-Valerio* and *Dr. Messerli).*

Photographs of Lausanne schoolchildren, afflicted with goiter.
Photographs of goitrous recruits before and after the treatment through intestinal disinfection with benzonaphtol-thymol.
Charts showing the frequency of goiter among the recruits and the schoolchildren of the City of Lausanne.
The goitrous center of Gandria.
Representation of experimental goiter in the rat, provoked through contaminated water.
Photographs and various charts.

ST. GALL. *Department of the Medical School Officer.*

Chart illustrating the investigation and treatment of goiter in St. Gall.

WALCHWIL. *(Dr. Henry Hunziker).*

Maps and charts to demonstrate the connection between goiter, elevation above sea-level and climate.

WINTERTHUR. *Surgical Department of the Cantonal Hospital. (Dr. Looser, University Lecturer).*

1. Photographs, Rœntgen pictures and drawings of athyreosis.
2. Representation of the ossification derangements with cretinism.

ZURICH. *Surgical Clinic. (Professor Clairmont).*

Collection of diapositives and wax models of goitrously afflicted persons.

ZURICH. *Children's Clinic. (Professor Feer* and *Dr. Monnier).*

Photographs of children, afflicted with strumas.
Rœntgen pictures of strumas.

ZURICH. *Institute of Hygiene of the University. (Professor Silberschmidt).*

Charts: Results of the treatment of goiter in Swiss schools (Berne, Glarus, St. Gall, Zurich).
Experimental rat goiters obtained by watering experiments. (Klinger).

Austria.

GRAZ. *National Hospital. (Dr. Orator).*

Chart illustrating the development of thyroid glands. Diapositives.

VIENNA. *Psychiatric Clinic. (Professor Wagner von Jauregg).*

Charts:

Comparative study of the frequency of goiter in all of the elementary and middle class schools of 1923 with those of 1927.

Development of goiter in different stages of age (6 to 15 years, data of 1923 compared with 1927).

Operations on goiter in Vienna and Lower Austria between 1923 and 1926.

Danzig.

DANZIG. *Surgical Clinic. (Professor Klose).*

Diapositives of Strumas.

France.

LYONS. *Medical Faculty. (Professor Bérard).*

« Lumière » microphotographs of goiter preparations.

PARIS. *Medical Faculty. (Professor Roussy).*

Microphotographs and diapositives of goiters.

STRASBURG. *Institute of Hygiene (Dr. Rhein).*

The endemic goiter in Alsace (map).

Germany.

BERLIN. *Governmental Department of Health.*

Map: Distribution of goiter in the former Kingdom of Saxony, based on the military statistics of 1907 to 1909, by Chief Medical Officer Hesse.

FRANKFORT on the Main. *Surgical Clinic of the University. (Professor Schmieden).*

Operating preparations of strumas of the type occurring in the district of the Main river.

FREIBURG IN BREISGAU. *Pathological-Anatomical Institute. (Prof. Aschoff).*

1. Pathological-anatomical preparations:

Comparative study of the thyroid gland of goitrous localities with the thyroid gland of regions free from goiter in different stages of age.

Life (or weight) curve of the normal thyroid gland (Holland, Professor de Josselin de Jong).

Highest degree of development of diffuse goiter.

Average representation of thyroid glands in the different stages of life.

Consequences of goiter.

Basedow thyroid glands.

Cretin thyroid glands.

Animal goiters.

2. Charts and diagrams:

Curve of the weight of thyroid glands (according to Bürkle-de-la-Camp) in so-called goitrous localities and in so-called goiter-free localities.

Illustrations on strumous modifications of the thyroid gland (Bürkle-de-la-Camp).

Geographical distribution of goiter in the former Grand Duchy of Baden, as per recruiting lists of 1868 to 1874 (according to Lücke).

Comparative study of the histological curve of life in the goitrous locality and in a goiter-free district (according to Büchner-May).

Results of the prophylaxis of goiter on the Freiburg school-children. (Municipal Medical Officer Dr. Pflüger).

Age and iodine contents of the thyroid gland of goitrous localities (according to Schmitz and Moormann).

Classification of the modifications of the thyroid gland.

HAMBURG. *Surgical Clinic. (Professor Sudeck).*

Photographs, microphotographs and curves on operative athyreosis and prophylaxis of substitution.

HEIDELBERG. *Surgical Clinic. (Professor Enderlen).*

Operating preparations of strumas.

MUNICH. *Surgical Clinic. (Professor Sauerbruch).*

Operating preparations of strumas.

Rœntgen pictures of strumas.

MUNICH. *German Research Institution for Psychiatry. (Prof. Rüdin).*

Charts showing cretin research work.

WÜRZBURG. *Pathological-Anatomical Institute. (Prof. M. B. Schmidt).*

Collection of thyroid gland preparations from the endemic goitrous locality of Lower Franconia (Bavaria).

Great Britain.

LONDON. *Medical Research Council. (Dr. Scott-Williamson* and *Dr. Innes Pearse).*

Macroscopic preparations of thyroid glands. Diapositives and microphotographs illustrating the secretory process.

COONOOR, British Indies. *Deficiency Diseases Inquiry. Pasteur Institute. (Dr. R. McCarrison).*

Charts of photographs and micro-photographs concerning the experimental study of goiter.

Italy.

REGGIO-EMILIA. *Institute of Psychiatry. (Professor Pighini).*

Goiter among poultry and microscopic preparations.

Netherlands.

UTRECHT. *Pathological-Anatomical Institute. (Professor de Josselin de Jong).*

1. Collection of macroscopic preparations of Dutch goiters.
2. Microscopic preparations of Dutch goiters.
3. Diapositives of Dutch goiters.
4. Charts:

   Research work on enlargement of thyroid glands with schoolchildren in Utrecht, Breda, Leenwarden, Middleburg.

   Distribution as regards strumas in Holland among 451 patients operated on in Utrecht.

   Distribution as regards men afflicted with goiter among 46,976 mobilized soldiers.

   Cases of enlargement of thyroid glands in Uttrecht with 1792 apprentices of an age of 13 to 18 years.

   Comparative study between thyroid glands of Switzerland and Holland.

UTRECHT. *Surgical Clinic. (Professor Laméris).*

Photographs of persons afflicted with goiter.

United States of North America.

Seattle, State of Washington. (Dr. J. C. Moore).

Percentage of goiter by counties (map).

Analysis of 2013 cases of goiter (chart).

Photographs of goitrously afflicted and of cretins.

University of Illinois. Health Service. (Dr. Sloan).

Distribution of thyroidean hypertrophy among the students of the counties of the State of Illinois (map).

Distribution and degree of thyroidean hypertrophy in different parts of the State of Illinois (map).

Wichita, Kansas. St. Francis Hospital. (Dr. Alex. Hellwig).

Charts:

Relative frequency of diffuse and adenomatous goiter in the mountainous districts and the plains.

Relative frequency of the various forms of goiter at Wichita (operative material).

Relations between colloid diffuse goiter and Basedow goiter.

Microscopic preparations.

Yugoslavia.

ZAJECAR. *(Dr. M. Branovacky).*

Preparations of goiter.

* * *

Behring Works, Marburg on the Lahn.

Charts for the demonstration of capillary microscopy with persons in health and such afflicted with thyroid gland troubles (according to Dr. Jaensch, Dr. Wittneben and Dr. Höpfner).

Charts to show the action of lipatren or rather lipatren + thyroidine on the development of the capillaries.

Hoffmann-La Roche, Stock Company, Basel.

Presentation of the action of thyroxine in the tad-pole experiment.

Charts on the results of Jodostarine prophylaxis and treatment.

Tropon Works, Cologne on the Rhine.

Charts showing the action of Jodotropone.

Dr. Wander, Stock Company, Berne.

Charts showing the action of Majowa (potassium iodide in malt tablets) in the prophylaxis and treatment of school goiter in the municipal schools of Berne.

M. Schärer, Stock Company, Sanitary Articles, Berne.

Apparatus for determining the basic metabolism. Stock of instruments for the surgery of goiter according to Th. Kocher and de Quervain.

F. Büchi, Optician, Berne.

Optical apparatus and instruments for purposes of laboratory work and research work on mankind.

United Mineral Water Factories, Berne.

Exhibition of natural waters of Switzerland, containing iodine (Wildegg and Passugg Fortunatus spring).

Book-stores of A. Francke Stock Company, Berne, and *P. Haupt, Berne.*

Treatises on Goiter.

MEDICAL SCHOOL-BOARD BERNE

Dr. med. P. Lauener, School physician

4 Years of Goitre-Prophylaxis

Children treated : 2000

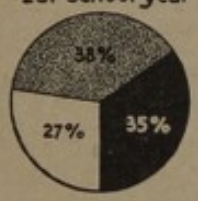
	1st school-year	2nd school-year	3rd school-year	4th school-year
Frequency of goitre in children of different ages — without iodine treatment —				
No goitre	27%	23%	20%	18%
Enlarged thyroid gland	38%	41%	30%	23%
Actual goitre	35%	36%	50%	59%
Influence of iodine treatment. Daily 1 tablet Majowa-Wander 0,0005 sodium iodide				
No goitre	55%	63%	55%	64%
Enlarged thyroid gland	27%	24.5%	35%	33%
Actual goitre	18%	12.5%	10%	3%

The same figures graphically illustrated.

Frequency of goitre in children of different ages.

— without iodine treatment —

1st school-year



2nd school-year

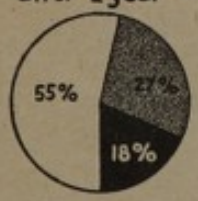
3rd school-year

4th school-year

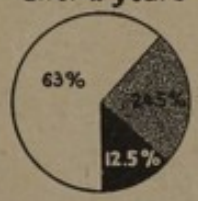
Influence of iodine treatment.

Daily 1 tablet Majowa-Wander 0,0005 sodium iodide

after 1 year



after 2 years



after 3 years

after 4 years

Explanation: ☐ no goitre ▒ enlarged thyroid gland ■ actual goitre