The etiology of endemic goitre : being the Milroy lectures delivered at the Royal College of Physicians in January, 1913 / by Robert McCarrison.

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McCARRISON

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Being the Milroy Lectures delivered at the Royal College of Physicians of London in January, 1913

BY

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PREFACE.

I DESIRE to express my indebtedness to Mr. James Berry, for his helpful and valuable criticisms during the ten years I have been engaged in this research; to Sir Ronald Ross, K.C.B., F.R.S., for the encouragement which he has at all times extended to me, and for permission to use figs. 13-17, 24, 25, 52, 54-56, and 58, which originally appeared in certain of my papers published in the *Annals of Tropical Medicine and Hygiene* between the years 1909 and 1911; to Mr. C. C. Garbett, I.C.S., for his assistance while I was carrying out my Continental investigations; to Professors T. Kocher, Kolle, Langhans, and the other members of the Swiss National Commission on Goitre for their courtesy and readiness to place their material at my disposal, and for their help in the course of my researches in Switzerland; to Dr. Eugene Bircher, of Aarau, for so kindly permitting me to examine his specimens and to see the conditions under which his experiments were carried out, and for the use of figs. 18 and 57; to Dr. Répin, of the Pasteur Institute of Paris, for the use of fig. 4; to Drs. Marine and Lenhart for the use

of figs. 7, 8, 22, 23, 29, and 53; to Mr. Rupert Farrant for the use of figs. 20 and 21; to Dr. Carlos Chagas for the use of fig. 19; and to His Majesty's Secretary of State for India in Council, and the Science Committee of the British Medical Association for grants in aid of my researches in Europe. But especially am I indebted to my wife for her untiring help during the past six years, not only in the laboratory but in the remote regions where the main part of my researches have been carried out.

It is my hope that by publishing these Lectures in a considerably amplified form I may have provided a readily accessible record of the extent of our present knowledge of the causation of endemic goitre, and that the bibliography may prove of assistance to those who desire to undertake further researches on this subject.

R. McCarrison.

London,
December, 1912.

LECTURE I.

MR. PRESIDENT AND GENTLEMEN: Before I enter upon a consideration of the etiology of endemic goitre, permit me to thank the College for the honour conferred in electing me to address you on this subject.

Having had the good fortune to reside for some ten years in a part of India where goitre and cretinism prevail with great intensity, and which is probably one of the purest regions of endemic goitre in the world, I have had exceptional opportunities for carrying out extensive observations and experiments not only on animals but on man also. Though my official duties as an officer of the Indian Medical Service have often compelled me to interrupt my researches, and the prejudices of the people in some of the more backward villages have not always been easy to overcome, I have been able, with the help of the civil and military officers, and the native chiefs and rajahs of the district, to carry to a successful issue many observations and experiments which I venture to think would not have been possible in any other part of the world. Especially am I grateful to those men

who came forward in response to my request and offered themselves as subjects for experiment. They have performed a service to humanity of which there are parallel instances in the field of medical research, but none more commendable.

The tract of country where my researches have been mainly conducted comprises the districts of Chitral and Gilgit, and is situated at the extreme northern point of British India, in that part of the Western Himalayas known as the Hindu Khush. It lies between the parallel of latitude 35° and 37° and meridians of longitude 72° and 76°. The main valleys of this district, through which the Chitral and Gilgit rivers flow, are narrow, being rarely more than one mile broad at any part. They are bounded on either side by high hills ranging between 10,000 and 15,000 ft. The ranges bounding the valleys are intersected at intervals by narrow nullahs or valleys, each with its mountain stream derived mainly from the melting of the snows on the hills above. At the mouths of these nullahs, alluvial fans stretch with a gentle slope towards the river. These alluvial formations, composed as they are of a porous soil, are the only habitable portions of this mountainous country : on them we find villages and a considerable amount of cultivation.

The climate is a temperate one, never excessively cold nor excessively hot, except for a few months of summer. Snow covers the ground in some parts during the winter months, usually up to the end of February. The rainfall is small.

In many parts of these valleys the hills are poorly wooded, and in consequence fuel is scarce. During the winter months the people live crowded in small stone-built huts, of which the only ventilation is a hole in the roof. The average cubic space per individual is 200 to 250 cubic ft. In summer the people live for the most part out of doors. The natives of this region are, as a rule, poor. Food is plentiful, comparatively speaking, from July to February, after which the people are often obliged to live on the poorest grains, dried fruits, and the greenstuffs of the spring. Their food is almost entirely vegetable. Flesh meat is an article of diet far beyond their means, while in Chitral especially salt is a luxury to all except the richest families.

There are certain local beliefs as to the causation of the enlargement of the neck which are not without interest. Some of the people say that their necks increase in size when food is scarce, that is, in the spring months after February; others that the increase takes place in the mulberry season (May, June, and July), or when the water turns grey from the presence of fine sediment, or when the snows begin to melt (May, June, and July). All local authorities agree as to an observed increase in May, June, and July. Curiously enough, it is only in certain villages that water is believed to cause the disease. The water of the village of Awi, in Chitral, for example, has a goitre producing reputation, while it is affirmed that the water

of Sanoghar, where the disease is equally common, does not cause goitre. There is a belief in the district that goitre is not so prevalent as it was.

But my observations have not been wholly confined to this region. During my periodic visits to Europe, and especially during the last year, I have employed myself in studying the disease as it prevails in the British Isles, Germany, Austria, Bavaria, Tyrol, and Switzerland. I have had an opportunity, through the courtesy of Dr. Eugene Bircher, of Aarau, and of Professors Kocher and Kolle, and other members of the Swiss Goitre Commission, which is at present sitting, of acquainting myself with the conditions under which their experiments have been conducted and of examining their results. In consequence of this unusual experience of the disease, I am in a position to assure you that the endemic goitre of Europe is the same disease as the endemic goitre of Himalayan India.

Before proceeding to an account of my own work, which comprises the major part of these lectures, it will be necessary for me to go over ground with which most of you are doubtless familiar. I must, therefore, crave your indulgence during part of to-day's lecture, while I present to you facts, which though somewhat dull in their narration, are essential to my argument.

The problem of the causation of goitre is one which has exercised the minds of observers since

the earliest days of medical history. There are, indeed, few diseases about which so much has been written and so many diverse views propounded. For a student of the subject, perhaps one of the most onerous tasks is the sifting of the enormous mass of evidence which has been brought forward by the supporters of these different theories. He finds early in his study that the greater part of the evidence is purely circumstantial, and that the literature of the subject consists, to a great extent, rather in records of impressions and opinions of observers than in scientifically proven facts. The separation of the wheat of fact from the chaff of fancy is consequently a matter of considerable difficulty.

My plan in these lectures is to bring to your notice both such facts and deductions from the literature of goitre as I believe to merit credence, and also the experimental and other observations I myself have made, as a result of which I am convinced that endemic goitre is due to a living excitant of disease.

The Distribution of Endemic Goitre.

Endemic goitre is widely distributed over the whole world. Few countries appear to be entirely free from it. The disease is so common in certain parts of England and Scotland as to be distinguished by the names, "Derbyshire neck" and

"Nithsdale neck"; but the extent to which it prevails in European countries generally and in the East is seldom appreciated. Baillarger estimated that about the year 1874 there were in France alone no less than 500,000 goitrous individuals and 122,700 cretins and cretinous idiots. In Switzerland, during the six years between 1875 and 1881, 12,227 young men were exempted from military service on account of goitre. In Italy, 3 per cent. of the conscripts were rejected for the same reason between the years 1859 and 1864. In the provinces of Piedmont, Lombardy, and Venice, there were, in the year 1883, 128,730 goitrous, and 12,882 cretinous individuals amongst a population of nine and a half millions. In other words, one in every sixty-seven of the inhabitants was either goitrous or a cretin. In some of the villages of that part of the Himalayas where my own researches have been carried out, goitre is so common that it is difficult to find a man, woman, or child not suffering from the deformity. I estimate that not less than 20 per cent. of the total population of Gilgit suffer from goitre; and I found amongst a population of about 70,000 over 200 cretins. In European countries the proportion of cretins to goitrous individuals is still higher, so that when we consider the vast number of sufferers from goitre in Himalayan India and Europe alone—a number which cannot fall far short of 5,000,000—and that the disease is capable of giving rise in the children

of these sufferers to the grossest forms of physical and mental degeneration, we are in a position to realize the immense amount of disability and race degeneration for which goitre is responsible, and to appreciate the necessity for its extermination.

In the map which I now show (*vide* map), I have indicated roughly in colour those parts of the world where endemic goitre is known to prevail. It doubtless occurs in many other places of which there are no records. It has lately been found, for example, in great abundance in the Abor country by the medical officers with the expedition directed against the people of that region. The map is intended to do no more than represent graphically the very wide distribution of the malady, as known at present.

Two main facts emerge from a study of this map; the first, the very marked association of goitre with regions of high mountains; the second, the comparative limitation of the disease to temperate and sub-tropical zones.

The association of the endemic with mountainous regions is perhaps the most striking peculiarity of the disease. The Alps, the Pyrenees, the Himalayas, the Carpathians, the Caucasus, the Andes, the Cordilleras, the Ural and Altai Mountains, and in our own country the valleys of the Pennine range, the Cotswolds and the Mendips, are all noted haunts of goitre. But while it is true that the disease has its home in the mountain ranges of the

world, it is not confined to them. St. Lager has assured us that it is met with far away from the hills, in the plains of Lombardy, of Piedmont, of Alsace; in the plains of the Danube, in Upper and Lower Austria; in the plains of the Lena and Obi, in Russia; of the St. Lawrence, in Canada; and in some of the oases of the Desert of the Sahara. Macnamara records its occurrence in the plains of the Ganges and the Bramapoutra, and of the Chenab and Sutlej, in India. St. Lager enumerates many other localities where the endemic is met with outside mountainous regions, but those I have quoted are sufficient exceptions to a very striking rule.

Some mountainous countries, on the other hand, are almost exempt from goitre, as for example certain parts of Norway, and in the Highlands of Scotland, where it appears to be almost unknown. The hilly nature of a country, therefore, cannot be regarded as a necessary factor for the development of goitre.

Goitre is found at all heights above sea-level where man can live and cultivate the ground. I have met with it at as great an altitude as 10,000 ft. On the other hand it is not absent from the sea-coast, as is often erroneously stated. It occurs, for example, in the delta of the Ganges, on the coast near Manilla Bay, where Duncan has found, at Macabebe, as many as twenty per thousand of the inhabitants are goitrous. It occurs in the Island

of Arran, and on the coast of Ceylon. Berry has met with it amongst people who live and have always lived close to the shore of the Burry Estuary, in Glamorganshire. It occurs also in Algeria, on the shores of the Mediterranean Sea.

Our map also shows us that goitre is most prevalent in temperate and sub-tropical zones. It is found, however, in regions of great cold, as in parts of Siberia, in Finland, and in the Hudson Bay Territory of North America. It occurs also in regions of great heat, as in Tropical South America, Borneo, Sumatra, Java, and India. While, therefore, temperate and sub-tropical climates are more favourable to its development, neither great heat nor great cold excludes its occurrence. In short, though the disease shows a marked preference for mountainous localities and prevails with the greatest intensity in the deep-cut, narrow valleys which intersect the mountain ranges of temperate and sub-tropical zones, it can and does prevail in all countries, flat or hilly, hot or cold, dark and dismal, or bright and sunny, where man dwells and cultivates the soil.

The association of endemic goitre with mountains has led to the promulgation of the most diverse views as to its causation. A causal influence has been attributed to configuration of the soil, to altitude, to the rarity of the atmosphere, to cold and dry air, to air holding too little oxygen, and to air holding too much, to the action of cold air on the

neck, to air laden with sulphurous vapours, to a want of iodine in the air, to air charged with electricity, and many other such-like causes; the evidence, however, now before us is sufficient to demonstrate finally the error of all such hypotheses.

Race, Predisposition, Occupation, Social States.

All races suffer from goitre; there appears to be no such thing as race immunity to the disease.

It is stated by Bauer that persons of a lymphatic temperament and those of a neuropathic constitution are especially prone to develop goitre.

There appears to be a family *predisposition* or *heredary tendency* to the disease; the children of goitrous parents are more usually goitrous than those whose parents or grandparents are goitre-free. It is to be remembered, however, that this may be in part accounted for by a greater liability to infection on the part of those living in houses where the disease occurs.

Occupation plays a part of considerable importance in the development of the disease. Mackenzie, writing of an endemic centre of goitre in Lanarkshire in 1898, found that 98 per cent. of the cases occurred in the labouring and mining classes. In Gilgit and Chitral it is very noticeable that those whose occupation brings them into contact with the soil suffer to a much greater extent than those who

employ themselves otherwise. It is comparatively rare to find goitre in the families of any of the ruling chiefs of the district, or of their relatives; these by virtue of their birth do no agricultural work of any kind. The numerous clerks, shop-keepers and merchants who come from various parts of India and reside with their wives and families for many years in Gilgit, suffer to a much lesser extent than the indigenous inhabitants. The fact of the much greater incidence of the disease amongst cultivators of the soil and the labouring classes generally is one of considerable importance to the etiologist.

The hygienic conditions of life of all classes of the native population in Gilgit differ in no essential. Their houses are all insanitary, and are infested by the same biting insects. Their water supply is the same, and they suffer to an equal extent from endemic diseases other than goitre. It is true that the labouring classes are poorer than other classes of the community, and that their food is almost wholly vegetarian, but this difference in food-supply, though it may contribute to the result, cannot be considered sufficient to account for the greater prevalence of the disease amongst those who handle the soil. The difference is due to the greater liability to infection of the poorer and labouring classes generally.

The Chitralis have an interesting belief that the greater prevalence of goitre amongst the poorer

classes is due to the fact that the poor are unable to afford themselves the luxury of salt with their food.

Behaviour of the Endemic.

The endemic of goitre prevails with different degrees of intensity, in different countries, and in different parts of the same country.—In France, according to Baillarger, the endemicity reaches a very high degree in certain departments, especially those situated in mountainous tracts, whilst in others the endemicity is so slight that the disease appears to occur in the form of sporadic cases only. Similarly in England, goitre is well marked in certain counties, while others are comparatively free from it, and some are said to be wholly so.

It is highly probable, as has been stated by James Berry, that "most goitres may fairly be considered to belong to the endemic class, but the endemicity is so widely spread over the whole country, while at the same time it is so slight, that it easily escapes notice, and cases of goitre are often considered to be sporadic, which should more correctly be classed as endemic." Thus, while the degree of endemicity varies, it would be difficult to declare any area to be wholly goitre-free.

In any locality in which goitre is well marked, as in the Alps and Himalayas, it will be found that the disease prevails with widely *different degrees of intensity in villages situated adjacent to one another.*

In one village there may scarcely be found a woman who is not goitrous, while in another, within pistol shot of the first, it may be difficult to find a woman who has goitre. Macnamara noted that "in villages situated along the banks of the Ravi, which are subject to the same telluric, atmospheric and hygienic conditions the difference in the endemicity of goitre in villages quite close together was remarkable." Even in a goitrous village, occupants of certain houses, groups of houses, or institutions may escape the disease or suffer from it in such slight degree that it is not noticeable.

Moreover, in an endemic area, *the disease may fluctuate.* It is subject to periods of increase and decline. Baillarger studied the variations of the endemic in sixty departments of France on the basis of figures afforded by the tables of recruiting for the years 1816-1865. He divided these fifty years into periods of ten years each, and in comparing the five periods he was able to arrive at the definite result that the endemic had increased in twenty-six departments, diminished in seventeen, and remained stationary in the remainder. The augmentation of the disease in the twenty-six departments was seldom uniformly progressive throughout the whole fifty years, but took place mostly during the last three or four decades. He also noted the increase of goitre in some departments which had previously been almost wholly spared. Fifteen of the seventeen departments in which goitre was found

to have diminished were amongst the most goitrous in the whole of France. In these the intensity of the endemic diminished by about one-third in the fifty years under review. I consider this investigation of Baillarger to be highly important, and that the results arrived at can most reasonably be explained on the assumption that goitre is due to a living excitant. Progress in hygienic conditions cannot provide a sufficient explanation; for whereas this was uniform throughout the departments, the disease fluctuated.

Similarly in parts of Gilgit the disease is believed to be much less common now than formerly, though the conditions of life of the people have not altered. My belief is that there is for each endemic centre of goitre a point of maximum intensity for that centre. Having attained to this point the disease tends to diminish owing possibly to the acquirement, after a number of generations, of a certain degree of natural resistance to it. It was in fifteen out of the seventeen most goitrous departments of France that a diminution in the intensity of the epidemic took place, and not in those which were only moderately severely affected.

Goitre has made its appearance in many places where it was formerly unknown. Baillarger, writing in 1873, quotes the Ardennes and the Haute-Savoie, as departments of France, formerly almost free from the disease, which had become relatively highly affected. South America, especially Brazil, furnishes

many instances of the spread of the disease. It will be interesting to find whether these are examples of the spread of the "parasitic thyroiditis" of Chagas rather than of true endemic goitre.

My own experience has provided one example of the appearance of goitre in a locality previously exempt. As this case is of considerable interest, I may be permitted to refer to it in some detail. Previous to the year 1893, goitre was unknown in the hill State of Nagar. The ruling chief of Nagar, his councillors, priests, and other reputable residents in the State are most emphatic on this point. After the Hunza-Nagar campaign, in 1893, the little State began to enjoy freer intercourse with the outside world. About the year 1898-99, four goitrous individuals came to reside in the village of Nagar, which is the capital of the State of the same name; of these, three were members of a priest's family. This family resided in a house which was close to the head of the spring supplying the village with drinking water. The fourth individual lived in a house in a different part of the village. About six years after these four subjects of goitre were stated to have arrived in Nagar, I examined the villagers for goitre. I found in the priest's family that there were seven goitrous individuals, three being the imported cases, and four children who had developed the disease in Nagar. The fourth imported case was that of a man whose family consisted of himself, his wife, his brother, and his

son, aged two years. Neither he nor his wife, brother, nor child, had been outside Nagar since the date of his arrival, six or seven years previously. This man's brother and son were both found to be goitrous; the child was stated to have developed the disease at the age of one year. He denied that his wife was goitrous. I was not permitted to examine her, owing to religious scruples.

Twelve other children in the village were goitrous. The children were from different houses scattered over the village. They were all under the age of 10 years and none showed any signs of cretinism, myxœdema, or nervous disorders. There were, therefore, in the village, 23 cases of goitre, of whom 5 were imported cases and 18 had developed in the village itself. Of these 18 cases all were in young people, 17 being in children under 16 years; the youngest case was in a child of 2 years of age. All these 18 cases came from a part of the village which was supplied by the spring at the head of which the priest and his goitrous family lived.

Two years subsequently I made a further examination of the people of this village. It was impossible on this occasion, however, to see the whole population as harvesting was in progress. Amongst about two-thirds of the male and child population I found 23 cases of goitre; of these 10 were old cases, that is to say, they had been taken count of in my first examination, while 13 were new cases. Of these 13 cases, 11 were in children,

of whom 7 were boys and 4 girls. The remaining two cases were in adults. All the goitres were small uniform enlargements and there was no evidence that the children were in the slightest degree inconvenienced by the swelling, or that it was accompanied with other symptoms. It is important to note that none of the children had developed myxœdema or showed signs of nervous disorders. The second examination confirmed the finding of the first with respect to the much greater incidence of the disease in children than in adults. It was found from a study of the distribution of the cases over the village that they were scattered here and there amongst the houses. There appeared to be no definite line of spread of the malady, nor were all children in the same house always affected. It was found also that cases occurred almost entirely amongst those who lived all the year round in the village and who did not go out and live in the fields during the hot months of the year as is the custom amongst a certain class of the villagers. It will be noticed that the disease spread very slowly, only 31 new cases amongst the male and child population having arisen in seven or eight years out of a population of approximately 1,500. Here we have an example of the slow and steady spread of goitre amongst susceptible individuals as a result apparently of the importation of cases of the disease into a locality formerly free from it. The difficulty in

the case is that we are compelled to rely on the statement of the elders of the village that the disease was formerly unknown, and that its appearance coincided with the importation of cases of goitre from without. Personally, I regard their evidence as sufficient. However this may be, there is no doubt but that the disease is increasing in Nagar and that this increase is chiefly amongst the children. Whether goitre is spread by soil, water, biting insects or other means, it is impossible to explain such a case as this on any other hypothesis than that which attributes the disease to a living excitant.

The endemic of goitre may disappear almost entirely from a place and only persist in isolated cases. This is usually attributed to changes in the water-supply. We shall subsequently see with what reason. In such localities, however, "sporadic" cases are not uncommonly met with, and actual "epidemics" may occur. The goitrigenous agent clings to certain places in a way which is very remarkable, so that a locality may be goitrous though the endemic may have ceased to be a notable feature of the district.

The endemic prevails especially in rural districts. Although goitre may be comparatively common in many towns, as for example, in Innsbruck, Vienna, Bern, and Bayreuth, it is never found to prevail to such an extent as in country districts.

In concluding our consideration of the behaviour

of the endemic, I would emphasize the fact that a correct criterion of the endemicity of goitre cannot be obtained by a mere reference to the numerical ratio of thyroid enlargements, but regard must also be had to the virulence of the disease as manifested by the presence of cretinism, deaf-mutism and its other sequelæ. A proper index, therefore, will include : (1) The number of cretinous children, deaf mutes, and idiots ; (2) the number of susceptible newcomers who acquire the disease within a fixed time ; (3) the proportion of men and women affected ; and (4) the size and character of individual goitres. In regions where the endemicity of the disease is not high the thyroid swelling is, as a general rule, correspondingly small, and although considerable numbers of the inhabitants may have enlarged thyroids, the large degenerated goitres are comparatively rare or wholly absent. This is very noticeably the case in certain villages of the Gilgit district and in Switzerland and parts of Bavaria.

Cretinism, on the other hand, is usually met with in villages where the endemicity is high ; in such villages the women suffer from large degenerated goitres and the hygienic conditions of life of the people are bad.

Seasonal Prevalence of Goitre.

The disease exhibits a distinct seasonal prevalence. In Gilgit and Chitral new cases of goitre

arise and enlargements of pre-existing goitres take place during the spring and autumn months, that is to say, during the months of moderate heat. I have never known a case of goitre arise during the winter months when the atmospheric temperature sinks to freezing point, while there is a tendency for existing goitres to diminish. Nor do new cases of the disease arise during the hot months of the year from June to September, when the temperature rises as high as 108° to 110° F. in the shade. In Chitral the people of the country affirm that goitre develops during the "mulberry season" only, that is, during the months of May and June, and at a time when the water turns "grey," owing to the large amount of fine silt which is brought down from the hills by the melting snows. In the whole of Himalayan India where goitre is met with, "it is during and after the rains that the disease most commonly begins and most rapidly develops" (Macnamara). It is at this time, when the water-supplies become flooded with the washings from cultivated fields and when the people are usually attacked by other endemic diseases that the goitrigenous influences find the conditions most favourable for their action. St. Lager has quoted Lettinis, who found in villages on the banks of the Argis that goitre developed only during the months of March, April, and May. These observations correspond with the results of recent experiments on rats, as published by

E. Bircher, who appears to have convinced himself that water is more potent to produce goitre during the summer months, the potency being lost during the winter time—the temperature of the summer months of Switzerland corresponds to that of the spring and autumn of the Himalayas. Hence it is that in non-tropical countries the use of such terms as "summer goitre" or "goître aigu" have become frequent, and many examples of these so-called "epidemics" of goitre are to be met with in the literature.

Epidemic Goitre.

The most striking feature of these epidemics is that they occur only in endemic centres, in the neighbourhood of such centres or in localities where the disease has previously been prevalent. An interesting example was brought to my notice some years ago by Colonel Macnab, I.M.S. The epidemic occurred amongst the boys of the Bishop Cotton School, at Simla. Goitre was known to have prevailed formerly in the school buildings but no cases had been observed among the scholars for many years. The epidemic appeared suddenly, attacked a considerable number of the boys, and even some of the masters, without any change having been made in the water-supply and without any appearance of goitre amongst the other residents of Simla, who used the same pipe-supply. The goitres were small uniform enlargements and were

accompanied with no symptoms. They responded readily to treatment or disappeared spontaneously during the vacation when the boys went to their homes.

This is a difficult case to account for. The water-supply could not have been the source of infection, nor is it known by what agency it could have been conveyed; all that can be deduced is that the immediate cause of the epidemic was most probably a living organism.

It is also remarkable that young people are more liable than old to these outbreaks. On a fresh arrival of troops in Gilgit, for example, I have noticed that it is the young soldiers who first develop the malady. In regions of higher endemicity older men might suffer also, but not to the same extent as those who are younger. Many similar instances have been recorded among school children, and it is possible that a contributing cause is to be found in the fact that both troops and school children not uncommonly are housed in buildings in which the air space is inadequate. Under such circumstances, the thyroid gland which is intimately concerned with the regulation of the gaseous exchanges of the body, may be abnormally taxed, and the addition of goitrous influences may by making a further demand on its functional activity result in some cases in its visible enlargement. The collected instances of "epidemics of goitre" confirm the statement which I have already made, that the

disease shows a marked tendency to occur within certain definite seasons.

All this amounts to little more than that susceptible newcomers to a goitrous locality, especially if they are living under non-hygienic conditions, are very prone to develop goitre ; there is no essential difference between epidemic and endemic goitre.

You are possibly familiar with accounts of the epidemic of goitre which appeared in mid-ocean among the followers of Captain Cook in the year 1772. Having run short of fresh water, the crew collected ice from the bergs among which they were then cruising. The ice was melted in iron pots, and in consequence apparently of drinking the resultant water a number of the crew became goitrous. It is stated by Forster, the ship's surgeon, that the disease did not affect those who refrained from drinking this water. Assuming the authenticity of this account and that the melted ice-water was the vehicle for the excitant of the disease, this outbreak indicates only that the excitant is resistant to great cold—a fact already made clear to us by the geographical distribution of the disease.

Course of the Disease.

It is my experience that goitre generally develops in susceptible individuals in a period varying from six weeks to three months after their arrival in a goitrous locality. Cases have been recorded by

Baillarger, St. Lager, Macnamara, and others, in which the swelling made its appearance after an exposure to goitrigenous influences for periods varying from eight days to one month only, and I myself have seen parallel cases, but believe them to be exceptional. The goitre, which is soft in consistency is, as a rule, a uniform enlargement, though occasionally one or other lobe may be the more prominent. In the latter event the more prominent lobe is usually the right. There is not infrequently considerable pulsation in the vessels of the neck. The swelling does not, as a rule, progress in size in a uniform manner but fluctuates considerably from time to time. Very occasionally the gland may return to its normal size without treatment of any kind. The enlargement after it has attained to a certain point usually subsides to a size at which it remains stationary. Incipient goitres almost invariably disappear spontaneously when the patient leaves the goitrous locality, and I have noticed that they may occasionally do so also from such slight alterations in residence and water-supply as is entailed by a transference of the sufferers from the barracks to the regimental hospital. This is a point which it is necessary to bear in mind in gauging the value of treatment. Swellings at this stage are rarely large. Such a train of events is what may be called a "first attack" of goitre. The tendency is for the gland to revert to a condition approaching as nearly to normal as is possible. In some few

cases the reversion may be complete, but in the great majority the "attack" leaves the thyroid larger than it found it. With succeeding springs and autumns, however, recurring attacks of thyroid hyperplasia occur and the gland increases in size by a step-like process which was also described by Lawson Tait in the case of goitre associated with pregnancy. The process is comparable to that which takes place in the spleen, as a result of successive attacks of malaria. If the patient is subjected to goitrous influences for any length of time degenerative processes soon make their appearance and the large cystic and adenomatous goitres which are so common in goitrous localities are the result, while symptoms of slight hypothyroidea are almost constantly present in such cases. Should the subjection to goitrous influences be intermittent the onset of degenerative processes is much longer delayed, and these changes are much less marked than in the case of the indigenous inhabitants.

Men who have suffered from goitre in Gilgit often lose all trace of the swelling within as short a time as one month after their departure from the district. But such men on their return invariably suffer again. Ultimately small cysts or adenomata make their appearance in the gland and these are unaltered by a change of residence. The importance of this feature of the malady cannot be overestimated. It emphasizes the markedly place character of the disease, and the fact that

continued subjection to goitrous influences is neces sary to keep the thyroid in a state of enlargement and to produce changes in the gland of a permanent character. It seems clear that the goitre-producing substance resembles in its action that of a poison, which gives rise to the more marked results the longer it is administered and the stronger the dose.

Goitre in Animals.

It is commonly believed that in all endemic localities not only man but animals also suffer from goitre. The disease is said to be most frequently observed in mules, horses and dogs. Goitrous localities, however, appear to differ very considerably in this respect. I, on one occasion, examined all the dogs in a village, where 45 per cent. of the male population were goitrous, without coming across a single animal which showed enlargement of the thyroid gland. I have examined altogether 116 mules, 101 dogs, 150 cows, 100 sheep and goats and 101 ponies belonging to the villagers of Gilgit, but encountered no case of the disease amongst the 567 animals. In the course of ten years I have seen the disease in two dogs, one horse, and one goat, but these animals were recently imported into the district from a non-goitrous locality. In the case of one of the dogs the swelling appeared under experimental conditions, to be subsequently described. In the other dog, the goitre developed within a month of the animal's arrival in the district from

Thibet. The same fluctuations of the swelling were observed in this animal as is the rule in man. The goitre was less marked during the winter months and attained to a great size in the spring. This animal suffered much distress as a result of pressure on the trachea. The horse, an Australian waler, developed, in the autumn of 1909, a swelling of the right lobe as large as a hen's egg, which disappeared very rapidly under treatment by the red iodide of mercury ointment. The animal remained free from goitre all the winter months but developed a swelling of the same lobe the following spring.

It is asserted by some writers that horses, dogs, pigs, goats, cats, and sheep, acquire goitre on being brought into an affected district, but that the swelling often disappears as the animal increases in age.

Marine, in his study of the disease in dogs in Cleveland, has found that 90 per cent. of these animals show some degree of hyperplasia of the gland, and in some cases actual colloid goitre. He regards the hyperplasia as a certain indication of goitrous influences. By this test he also found 90 per cent. of sheep and a lesser number of cattle affected.

This observer has also brought into prominence the most important fact of the occurrence of goitre in fish, in endemic localities, and tells us that carnivorous fish only are affected. Under natural conditions the disease affects pike, for example, but not carp. Trout, bred under artificial conditions,

are peculiarly liable to the malady. Gaylord also has shown that in certain ponds some of the fish are severely affected, while others of the same species are immune.

Epidemics of goitre amongst horses and dogs have been described by Adam. Horses housed in certain stables acquired goitre, whilst others stabled elsewhere escaped the disease. He records also that only a certain percentage of dogs acquired goitre, whilst others living under similar conditions were not affected.

I have never observed any condition in animals bearing the least resemblance to cretinism. In this respect I have been less fortunate than other observers. v. Kutschera in a recent paper gives an interesting account of a puppy which became cretinous under circumstances that suggested to him infection by a medium other than water.

Marine records that in Michigan, fifteen or twenty years ago, "the failure of the sheep industry was a serious consideration on account of the number of cretin lambs." Nowadays, however, this state of affairs is gradually disappearing, owing, it is believed, to acclimatization—or the development of a natural resistance to the disease—aided possibly by the use of iodine-containing salt.

Marine has also found that well-cared-for dogs show a greatly lessened percentage of glandular hyperplasias. The greater incidence of the disease amongst the poor would appear to apply, then, as much to dogs as it does to man.

The conclusion is that goitre which can be recognized by inspection and palpation is not so commonly met with in animals as is generally believed. It, therefore, follows that in experimenting upon these animals a greater power of resistance is to be anticipated than exists in man.

Sex Incidence of Goitre.

Goitre is more common in females than in males. The proportion of the two sexes affected is, however, a very variable one, and differs widely in different endemic centres of the disease. This variability of the sex incidence depends in great part on the degree of intensity of the endemic, the proportion of men to women affected being markedly less in those villages in which the endemicity is low. I have met with a village in which the only sufferers were women, and St. Lager also comments on this limitation of the disease to women in regions of low endemicity. In England the preponderance of females over males affected was very marked at one time, and varied between the wide limits of one man to seven women in one goitrous locality, and one man to fifty women in another. In France, in the year 1873, the approximate proportion of men to women affected was two to five, a figure which represents fairly accurately the proportion for the Western Himalayas at the present day. In villages where the endemicity of the disease is very high the

proportion between the sexes approaches one to one. In one village of Chitral, I found seventy-nine cases of goitre amongst 139 females of all ages, and seventy-seven cases amongst 136 males of all ages. In the chart which I now show the percentage number of male and female sufferers from goitre in the village of Awi, in Chitral, where the endemicity

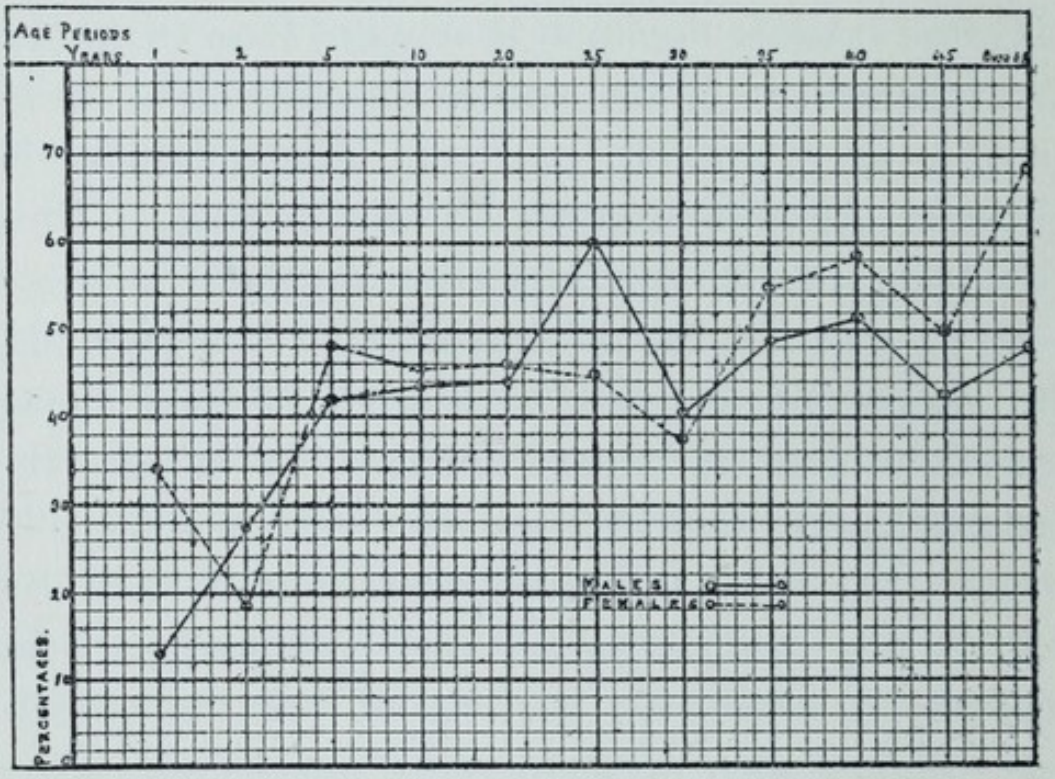

FIG. 1.—Chart showing percentages suffering from goitre at different age periods in the village of Awi in Chitral. Total population examined, 426; children under 15, 269; adults, 157.

of the disease is very high, is shown at different age periods; the chart shows that both sexes are more or less equally affected (fig. 1).

Baillarger's conclusions on the sex incidence of goitre, based as they are on an analysis of 52,489 goitrous individuals in sixty-three departments of

France, accord so closely with my own findings that I can do no better than quote them :—

(1) The proportion of men to women affected is very variable in different districts.

(2) The proportion is less as the severity of the endemic is less, and greater as the severity of the endemic is greater, approximately one to one in regions of high endemicity.

Baillarger found that this rule was more marked in regions of high mountains, and less so in the plains.

Age Incidence of Goitre.

Endemic goitre is considerably commoner amongst children than is generally supposed. The enlargement of the gland in children is usually small, and it is for this reason frequently overlooked. In considering the question of the susceptibility of children to goitre, a distinction has to be made between children introduced into a goitrous locality, or subjected to goitrous influences for the first time, and those who have been born in an endemic centre of the disease. In the former case children are more susceptible to the disease than adults. The spread of goitre in the village of Nagar, to which I have already referred, is a striking illustration of this fact. Amongst children born in goitrous localities the numbers affected with goitre appear to vary greatly in different villages. I have found in two or three

villages of Chitral that the number of young children affected was very high, and that even breast-fed children were goitrous in some cases. In contra-distinction to these villages, I have found goitre to be rare amongst the infants of the villages of Gilgit, and to be practically never met with before the second year of life (fig. 2). It

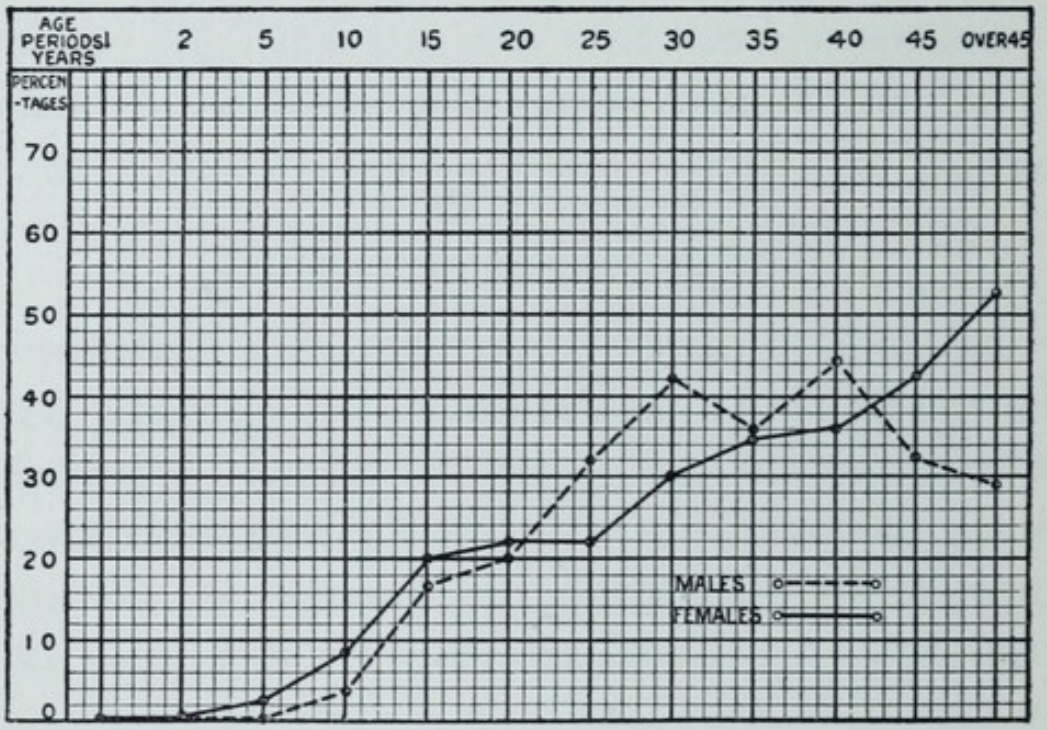

FIG. 2.—Endemic goitre in Gilgit. Chart showing percentages suffering at different age periods. Total population examined, 1,533; children under 15, males 375, females 330; adults, males 447, females 381.

is possible that this marked difference may to some extent be accounted for by the gradual acquirement of a natural resistance to the disease in the children of villages where the endemic has prevailed for centuries—a resistance which may be sufficient to protect them until the critical period of puberty is reached.

The occurrence of goitre in breast-fed children is perhaps the most interesting point connected with the age incidence of the disease. I have met with goitre in infants only in villages where the endemicity of the disease was high and the individual goitres amongst the mothers of the infants particularly large and degenerated. The disease is, as a rule in these cases, congenital. There is experimental evidence to show that the offspring of partially thyroidectomized bitches are born with thyroids as much as twenty times larger than normal. The large degenerated goitres of some women, which are functionally less perfect than the normal gland, put them in a position which is comparable to the partially thyroidectomized bitches of the experiments. Animals operated upon in this way have been noted to suffer from tetany prior to whelping, a circumstance which points to the inadequacy of the thyroid mechanism. The mothers of cretins and of children born with congenital goitre also very commonly suffer from tetany in Gilgit and Chitral during pregnancy. In these women then there is also a considerable degree of thyroid insufficiency, and their children may as a consequence be born with thyroid glands larger than normal. Now while it is probable that the great majority of all cases of goitre in infants can be accounted for in this way, we must, till the causal agent of endemic goitre has been discovered, recognize the possibility that the disease may be

capable of spread by means to which breast-fed infants are as much exposed as the adult.

Congenital goitres are usually uniform enlargements of small size which disappear spontaneously a few months after birth. The beneficial result of change of residence apparently applies also to residence *in utero*.

Comparatively prevalent as goitre is among children, my own observations lead me to believe that it is not so common as Professor Kocher's school would have us think. Professor Kocher and Dr. Vannod, of the Swiss Goitre Commission, have kindly furnished me with some recent statistics which show that in Lauterbrünnen, Sumiswald, and Wassen, 59 to 87 per cent. of children between the ages of 8 and 15 years are goitrous. In other parts of Switzerland also they have obtained similar results.

On the other hand, Bircher, a contemporary Swiss observer, regards Kocher's figures as misleading, since he has not been able to find that the disease is so excessively common amongst the young men who present themselves for military service. Commenting on Kocher's figures, Bircher has said: "It appears absolutely impossible that such an endemic should appear amongst school children, whilst amongst the guards on duty, who were but a little older, the endemic must already have become so slight." It is clear that statistics of this nature will depend entirely on what the observer regards as a goitre.

If all cases are included as "goitre" in which the gland is only palpable, but where it may not be visibly enlarged, then the percentages will be excessively high. I am of opinion that in the compilation of statistics only such thyroid glands as are visibly enlarged should be classed as "goitre." My own figures have been arrived at on this basis. The size of the thyroid varies very greatly within normal limits, so that what may be normal for one individual may be abnormal for another. It also varies for different localities and countries. Bayon found that the thyroid gland of Londoners who had died from causes wholly unconnected with the organ were about half the weight of the normal thyroid of residents in certain cities on the Continent.

It seems clear, however, that children frequently develop some thyroid enlargement which disappears with increasing age, a fact which may in part account for the apparent disparity between the numbers of goitrous children and of conscripts.

Goitre very commonly arises in both sexes about the age of puberty; it is at this time more than at any other that young people are most likely to develop it. I find in the fact that the thyroid gland is largely concerned with the functional development of the generative system an explanation of the greater susceptibility of young people to goitre at this period. The thyroid gland at puberty is called upon to exercise to the fullest degree its

functional activity, as it is also during the state of pregnancy. The added strain of goitrous influences may tax the gland's resources to a degree which will necessitate hypertrophy during these states. Indeed, without the added factor of endemic

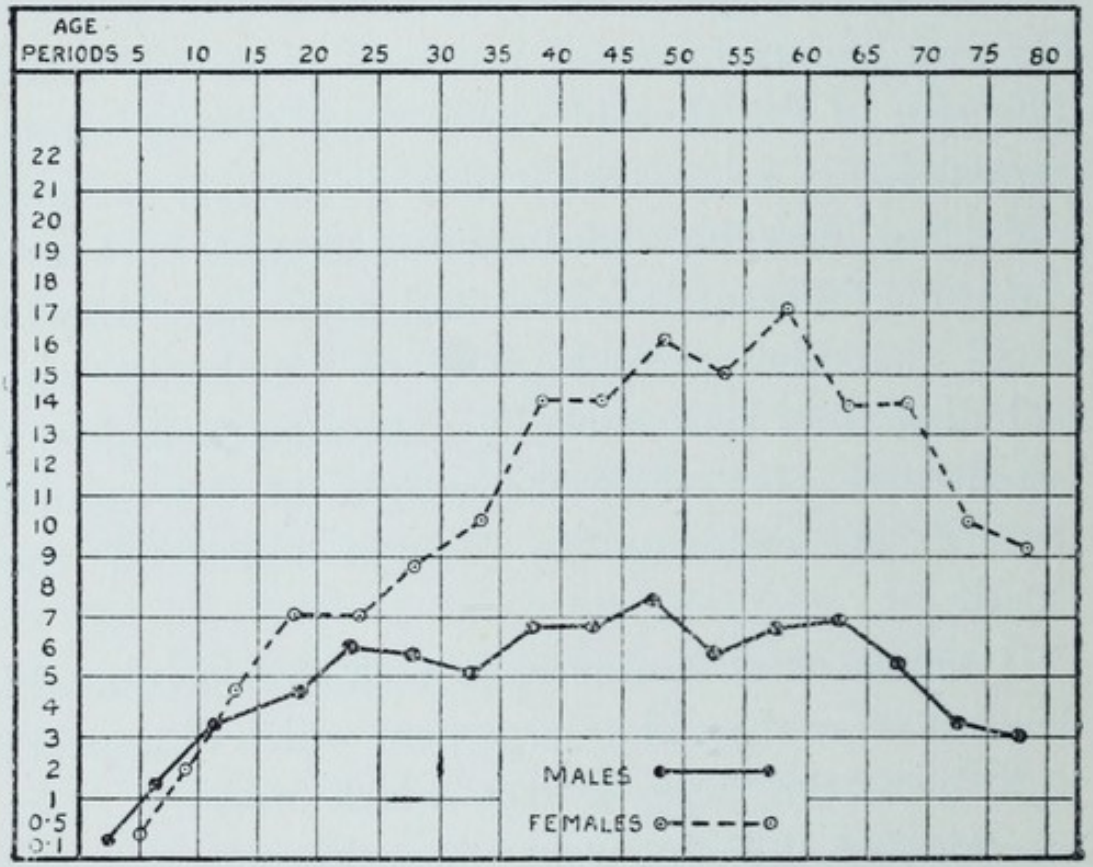

FIG. 3.—Age incidence of endemic goitre in France per 1000 of population; total population, 992,732; goitrous, 13,090; goitrous males, 4,606; goitrous females, 8,484; proportion of males to females goitrous, 1·84 per cent. (Prepared from Baillarger's figures.)

goitrous influences, swelling of the thyroid is apt to occur at puberty and during pregnancy.

"The relationship which has been known from time immemorial to exist between the sexual organs and the thyroid in man and other animals, and has hitherto been a mystery without any explanation, may possibly be the last reminiscence of

ERRATUM.

Fig. 3 should read: Proportion of males to females goitrous, 1 to 1·84. (Prepared from Baillarger's figures.)

a time when the thyroid glands were the uterine glands of the palæostracan ancestor" (Gaskell).

With increasing age the susceptibility to goitre diminishes in the case of men, but increases in the case of women during the child-bearing period of life. These facts are well brought out in the chart which I now show (fig. 3). It has been constructed from the figures given by Baillarger, and takes count of over 13,000 cases of goitre. Baillarger considered that in the case of children only the more evident goitres were noted in the documents from which he obtained his figures, and that a very large number of incipient goitres were not recorded. Certainly many more children suffer from goitre than would appear from Baillarger's figures:—

From the chart it is seen: (1) That goitre is rare in the early years of life; (2) that there is no great disproportion between the number of cases in the two sexes up to the age of 20 years; males are less affected than females in the proportion of 1 to 1·75; (3) that the proportion of cases of goitre in the population below the age of 20 years is about half that in the population above this age; (4) after the age of 20 there is a great increase in the number of women sufferers, and the proportion of men to women affected becomes 1 to 2·4. This fact makes clear the influence of the child-bearing period of life on the development of the malady.

Secondary Factors in the Development of Goitre.

The influence of secondary factors in favouring the development of goitre is very great. They may be classified as follows:—

(1) Factors directly influencing the thyroid gland by which it is rendered less able to counteract the action of the toxic agent of goitre without undergoing hypertrophy.

(*a*) Hereditary influences: The children of goitrous women appear to be more likely to develop enlargements of the thyroid gland about the age of puberty, than the children of normal women.

(*b*) The marked influence of age, sex, puberty, sexual activity, menstruation, pregnancy, on the activity of the thyroid gland; the added strain of these influences on the gland markedly favours the development of goitre in endemic areas.

(*c*) The influence of unhygienic conditions of life: defective air space, improper food or defective food supply, residence on damp soil, the "causes multiples" of the older French writers. Each of these factors places an additional burden on the thyroid gland's functional activity, and to this extent favours the action of the toxic agent of goitre.

(*d*) The influence of certain infective diseases on the thyroid gland: notably rheumatism, rheumatoid arthritis, malaria, measles, &c. These, by inducing

inflammatory states of the organ, and thereby limiting its functional capacity, or by making undue demands upon the organ's functional powers, favour the development of goitre, and the further enlargement of already existing goitres.

(*e*) The influence of emotional states: The development of goitre may be greatly favoured by fright or continued mental strain.

Under all these circumstances it is the accumulation of demand in the presence of the excitant of goitre which determines the enlargement of the thyroid gland.

(2) Factors which favour the entry of the excitant into the body of man: A social status which involves life under insanitary conditions and a means of livelihood closely connected with the soil open a ready avenue to infection.

(3) Factors favouring the action of the excitant of the disease after its entrance into the body.

(*a*) Susceptibilty: Newcomers to an infected district are especially liable to goitre, and also persons of a lymphatic or nervous constitution (Bauer).

(*b*) The nature of the water: We shall see that an organically impure water favours the development of the living excitant, and, it may be, increases its virulence, and that water containing lime may possibly act as a favouring influence by inducing a state of increased activity of the thyroid gland.

It is possible, also, that very hard waters or

water holding mineral matter in suspension may aid in the development of goitre by producing abnormal states of the intestinal mucosa.

These factors are those which I have found to be of chief importance in the regions where my researches have been carried out, but I believe that any factor which throws a strain on the thyroid gland's power of compensation will favour the development of goitre.

Some or other of these factors observers of the last century considered to be the essential cause of the disease. Their importance is undoubtedly great, but, I believe, secondary only to the true causal factor which still remains to be discovered.

The Influence of Water.

From the earliest times popular belief has attributed to water the causation of goitre. At the present day there are few who doubt the truth of this belief which is regarded as an established fact. It is true that there is an enormous mass of evidence in favour of it, but the evidence is not always infallible and is indeed often of little scientific value. "All the world says such and such a water causes goitre, therefore it must be so" is the gist of much of the evidence on which the belief in the goitre-producing properties of water is based. We will now examine the evidence and determine for ourselves whether or not the belief is well founded.

Many authors, especially Billiet, Grange, Chabrand, St. Lager, Collin, and more recently Graf, have referred to the fact that men wishing to escape military service have made a practice of drinking the water of certain "Kropfbrünnen," with a view to the production of a goitre sufficiently large to secure their exemption. Grange has asserted that he has known such individuals, and St. Lager also affirms that young men who have succeeded in evading their duty in this way have confessed their unpatriotic action to him. St. Lager tells us also that he has confirmation of the fact from doctors, clergy, and magistrates. Collin, in 1897, recorded that the water of Villard Clément, in Bourneville, has been used for this purpose. Dr. Graf, speaking on the subject of the etiology of goitre, at Vienna, in January, 1912, said that "in some places the recruits were in the habit of drinking the water from certain springs, with the result that after about four weeks of the practice they showed a marked hypertrophy of the thyroid gland which caused their rejection by the recruiting authorities of the Army. When the manœuvre was successful they drank the same water for a second period of four weeks, taking the precaution to boil it previously, and the goitre disappeared as readily as it came." In estimating the value of this evidence and without in any way impeaching its veracity we must not fail to remember, firstly, that the men were not under control at the time

when they drank the supposed goitre-producing water, and secondly, that we have no evidence whatever to show what proportion of malingerers succeeded in producing goitre in themselves as compared with the total number of those who made the attempt.

More valuable are the instances of communities who have access to two distinct sources of water-supply, the one supposed to be goitre-producing, the other not. A case of this kind is referred to by Baillarger, where in the Commune of Vanaillers in the Haute-Savoie, the inhabitants have the choice between two waters, one of which springs from calcareous soil and the other from marly soil. All those who drink from the first are exempt from goitre, while those who drink from the second "pay a large tribute to the endemic."

My own experience has provided one striking example of the freedom from the disease which is enjoyed by communities as a result, to all appearances, of drinking a peculiar water. Eight villages of the Gilgit Fan derive their water-supply from the Kirgah stream, and in all of them goitre is to be found. A ninth village is supplied by a spring issuing from amongst granite rocks and of exceptional purity, chemically and bacteriologically. All those who drink exclusively from the water of this spring before it has become contaminated by passage over the soil are exempt from goitre. Not

only does the water not cause goitre but it is popularly believed to have a curative action, and sufferers from goitre are known to resort to it for this reason. Some support is lent to this belief by the fact that women who have suffered from goitre frequently lose the swelling after marrying men of this village and coming to reside permanently in it. Such cases of goitre as I saw there amongst women were imported cases, and were of such a nature, cystic, adenomatous, and the like, that change of residence was not likely to result in their disappearance. The curative action of some waters is referred to by St. Lager and also by Macnamara.

In the spring of 1912, I examined, with Dr. St. George, an endemic centre of goitre in South Antrim. The people of this district are of the weaver-farmer class, and derive their water-supply from shallow wells, which are very imperfectly protected from sources of pollution. There are three schools in the district, two of which are National schools for the children of the villagers. The third is a boarding school for middle-class boys and girls. We found that in the National schools 10 per cent. of the children showed well-marked goitres, while in the boarding school the children were free from any trace of thyroid swelling. All the cases of goitre amongst the children of the National schools came from three groups of houses where the wells were grossly polluted.

The boarding school children, on the other hand, were provided with a spring water issuing from chalk, which was thoroughly protected and pumped into the school buildings by a windmill pump. The children of the boarding-school are newcomers to the district. They are of an age—12 to 15 years—at which goitre is especially liable to develop. Considerable numbers of the children sleep in the same dormitory. All these are the ideal conditions for the development of goitre in "epidemic" form, yet the children are wholly free from goitre, and, I am assured, have always been so. I can conceive of nothing which so readily accounts for the freedom from goitre enjoyed by these children as the perfection of their water-supply.

There are many authentic instances where individuals or communities have remained free from goitre while resident in a goitrous locality, as a result, apparently, of drinking rain or cistern water, or of boiling the water before use. Kocher has recorded that he found the children of inn-keepers who drink wine only, exempt from the disease, while other children suffered severely.

Perhaps the most important evidence of the influence of water in producing goitre is that afforded by the effect on the endemic of changes which have been made in the sources of water-supplies to affected communities.

Goitre has been known to make its appearance

in a town or village as a result of the introduction of a new water-supply. The increase of goitre in Vienna, which was observed about the year 1885, has been attributed by Billroth, Graf, and others, to the introduction in 1870 of a new water-supply from Kaiserbrunn, in Styria, where goitre is endemic. In other cases goitre has disappeared after the sinking of new wells on the spot where the disease has been endemic, and Ewald gives many examples of such cases. In contra-distinction to these, we must place the records of observers, who found that goitre became much more common in the colliery district of Nottingham after the deepening of the wells. Chatin tells us that the people of the villages of Saillon were formerly healthy, and mentally and physically sound, in striking contrast to the people of a neighbouring village who lived amid precisely similar conditions of life with the exception of their water-supply; Saillon changed its water-supply and coincident with this change goitre, and later cretinism, appeared amongst its inhabitants.

The notable improvement in the condition of the people of Bozel in Tarentaise, following on the introduction of a new water-supply is much quoted, and with reason, since the observations with regard to this place have been so carefully made and so accurately recorded. In the year 1848, the Sardinian Commission estimated that there were in this village amongst a population of 1,472 no less than 900

goitrous individuals and 109 cretins. At that time a pipe water-supply was introduced from the neighbouring village of St. Bon, a distance of only 800 metres. The condition of life of the people of the two villages was in all respects identical, with the single exception of the water-supply, yet in Bozel the endemic prevailed with the greatest intensity, while St. Bon was free from it. After the introduction of the St. Bon water into Bozel, "no more cretins were born amongst the families who used the new water-supply exclusively." St. Lager narrates that in the main village he has seen goitres only among some old men, and adds the remarkable fact, "that these tumours continue to develop amongst those who live in the hamlets where they are forced to use the old water; it is there only that new cases of cretinism arise." In the year 1864, or sixteen years after the introduction of the new water-supply, Bozel was visited by the Lombardy Commission, when only 39 goitrous individuals and 58 cretins were found in the village.

Rupperswyl, near Aarau, changed its water-supply in the year 1884, taking the new supply from a goitre-free district. In 1885, 59 per cent. of the children were goitrous; in 1886, 44 per cent.; in 1889, 25 per cent.; in 1895, 10 per cent.; in 1907, 2·3 per cent., while cretinism has wholly disappeared. The disease continues to prevail where the old water is used.

A similar improvement has been noticeable all

over England and Wales within recent years, and Ewald mentions that the beneficial result of improvement in water-supplies has been observed in Geneva, Villidmé, Rheims, and many other places. The Swiss National Commission for the study of goitre has instituted extensive inquiries with regard to this point. The opinion of the vast majority of Swiss medical men practising in goitrous districts is almost unanimous in attributing the notable decrease in the prevalence of the disease to the introduction of new and well-protected water-supplies, and to the improved hygienic conditions of life of the people. Many of these medical men record the fact that formerly the water-supply was derived from surface streams which were very inadequately protected, and that the introduction of the up-to-date method of conveying the water to the consumers in concrete pipes is responsible for the great improvement in the condition of the people. It is true that some hold the opinion that the disease is not diminishing in Switzerland, and certainly the high percentage of goitre amongst school children recorded by Drs. Vannod and de Mestral would seem to suggest that it is not. But we have already seen, both that their figures must not be accepted without reserve, and that a true index of the endemicity of goitre must include other particulars than the mere enumeration of thyroid enlargements. And it is a fact on which all Swiss observers are agreed that the large goitres which were formerly

so common are rapidly disappearing, or have altogether disappeared, from many districts—a sure sign, to my mind, of the diminished virulence of goitre-producing agencies.

Such a mass of evidence as this appears to afford conclusive proof that certain waters contain some substance which is capable of giving rise to thyroid enlargements. In the main it is of very great weight, though being indirect in character it cannot be said to be conclusive. Many of the facts considered apart are not wholly free from objection. The statement that the water of "goitre-wells" has caused goitre in those wishing to escape military service is a statement only, and is not supported by controlled observations. The freedom from the disease enjoyed by those who have made a practice of drinking certain waters may be a circumstance capable of explanation in other ways than that which attributes the disease to water. Cases are on record where goitre has been shown not to have any connexion with the water-supply. While it is true that persons who have used boiled water, rain or distilled water, have escaped the disease, there are equally authentic cases where like precautions have failed to protect others. Considerable improvement in the condition of sufferers from goitre has been asserted to take place, and even cretinism to diminish or completely disappear where the water supply has not been changed. The Commune of Saint-Avre, in Savoie, is an example of such a

case. Fortunately within the last few years evidence of a more direct character has been forthcoming, which demonstrates that water is undoubtedly associated with the development of goitre.

The observations of Marine and Lenhart with regard to goitre in fish, under natural conditions, is of great importance in this connection.

These observers have also studied the disease as it occurs in artificially bred trout. I shall have occasion to refer to their work in some detail in my next lecture, but here I may say that it leaves no room for doubt but that water is not without influence in the production of goitre.

The Influence of Water as shown by Experiment.

Many observers have endeavoured to provide experimental proof of the goitre-producing properties of certain waters. The first attempt in this direction was that of Hacquet, who in 1782, according to St. Lager, drank the water of a goitre-producing well, and "lived convinced of its action on the thyroid gland."

Bircher, about 1880, experimented on young dogs with the water of Kropfbrunnen, and also with the sediment therefrom, but with negative results.

Lustig and Carle carried out experiments on a

horse and several dogs in Turin. The animals were brought from a non-goitrous locality, and the experiments were conducted in a place free from the disease. They were given the water of certain infected parts of the Valley of the Aosta, in North Italy. The horse, which was kept in fine condition, thoroughly well stabled, fed, and groomed, developed after a few weeks a slowly progressive and evident swelling of one thyroid. This was extirpated and the experiment continued. The other lobe then increased in size, but after the discontinuance of the water the swelling of the lobe diminished to such an extent that it could not be felt.

Thirteen dogs, mostly young, were given the water of the Buthier stream, which was believed to be goitre-producing ; one of these animals showed unmistakable enlargement, first of the left lobe, and one month later, after the left lobe had been removed by operation, the right lobe was visibly enlarged. The administration of the natural Buthier water was then discontinued, and the same water was given after it had been filtered. The swelling of the right lobe, as a consequence, gradually diminished, and ultimately disappeared. These observers state that in perhaps one other dog some swelling of the thyroid took place, but they lay little stress on this doubtful case.

Ten young and healthy dogs were given the same Buthier water, which was boiled and filtered.

These animals remained goitre-free. A young goitrous puppy was brought to a goitre-free district. Water supposed to be capable of causing goitre was given to it, and the goitre continued to grow. When the animal was given the same water filtered, the goitre disappeared completely after several months.

In 1903, I carried out similar experiments on dogs in certain villages of Chitral. Five of these animals drank the natural water of the particular village in which the experiment was conducted, while five others had the same water boiled. One dog drinking the untreated water of Awi showed a swelling of the thyroid gland. No change was observed in the animals drinking the boiled water.

In 1905, I carried out a more extensive series of experiments on dogs in Gilgit. Five puppies were given the natural water of Kashrote, a village in which there is a high percentage of goitre. Five puppies of the same age had the same water boiled, and five others the same water filtered. The experiment lasted 130 days. No alteration in size of the thyroid could be detected in any of the animals by manual examination. Five other puppies were given larger quantities of the residue removed by filtration from Kashrote water, but in these also no result was observed after 130 days. These animals were not killed, however, so that early changes in the gland which might have been

detected by microscopical examination may have escaped observation.

In 1906, I gave five healthy young men and three young monkeys the untreated water, which was taken from a water channel supplying the goitrous village of Kashrote, at a point about 200 yards below the village. Five other young men were given the same water boiled, and four others the same water filtered. The men were encamped on ground which had never been cultivated and were under military guard. The results were wholly negative, and the experiment was discontinued after ninety days. Of six young recruits who were selected as controls, and who lived the ordinary life of the sepoy in barracks, one developed a noticeable enlargement of the thyroid gland during the period the experiment lasted.

In the spring of 1907, I gave six selected young men the residue separated by filtration from the very muddy water of Kashrote. Two of them had suffered from goitre during a former visit to Gilgit, but had got rid of the swelling on leaving the district. They were subjected to the experiment on their return to Gilgit. Both developed considerable swellings of the gland. The other four remained perfectly normal. The swelling in these two cases made its appearance on the thirteenth and fifteenth day of the experiment respectively.

In the autumn of 1907, I produced an obvious goitre in myself by drinking the Kashrote water residue.

In the spring of 1908, and again in 1909, I repeated the experiments in a larger number of men. The results showed that of thirty-six individuals who drank large quantities of the suspended matter, separated by filtration from a water supposed to be capable of causing goitre, ten developed a noticeable swelling of the thyroid, while six showed a swelling which was of a transitory character only.

E. Bircher, in 1908, experimented on apes, dogs, and rats, in Basle, giving them the water from so-called goitrous springs in Rupperswyl. In apes, no perceptible results were obtained. In dogs, the results were positive, but as these animals suffer very frequently from goitre in the neighbourhood of Basle (*vide* Wilms), these results were scarcely decisive. Rats, after some months, showed manifest hyperplasia of the thyroid gland, in the sense of a true formation of goitre. Bircher, in 1909-10, repeated his experiments at Aarau, and showed that "it was possible to produce the formation of goitre in animals from water derived from goitrous springs, even when it has been conveyed to a distance."

Experimenting on rats, he succeeded in producing goitre both by the natural water and also by the filtered water of the goitrigenous springs. He also experimented by giving rats the residue of supposed goitre-producing water remaining on the candle of a Berkefeld filter after filtration. For the

first six months no result was observed, but on continuing the experiment for twelve, fifteen and eighteen months, a considerable development of goitre resulted.

Wilms has also produced goitre in rats in the same way as Bircher, and has satisfied himself "that water filtered through a Berkefeld filter produced goitre in rats just the same as that which was not filtered." He has also concluded, as a result of his experiment on white rats, that "at upwards of a temperature of 70° C. the noxious substance is destroyed."

Répin (1910-11) has produced goitre in rats by giving them the water from a notoriously goitrous locality in the neighbourhood of St.-Jean-de Maurienne. Not only was the disease produced in the locality itself, but also in Paris, to which place the water had been sent every other day from the goitrous district. In contra-distinction to Wilms he was not able to render the water innoxious by a temperature of 99° to 100° C. for several minutes. In Répin's paper, in which he details the results of these experiments, he states that the water was "boiled for several minutes." He tells me, however, that this statement is not quite exact, as the water was not boiled but was placed in a flask and immersed in boiling water and thereby "raised to a temperature of 99° to 100° C. for several minutes." The photograph (fig. 4) represents the changes which Répin brought about in the size of the

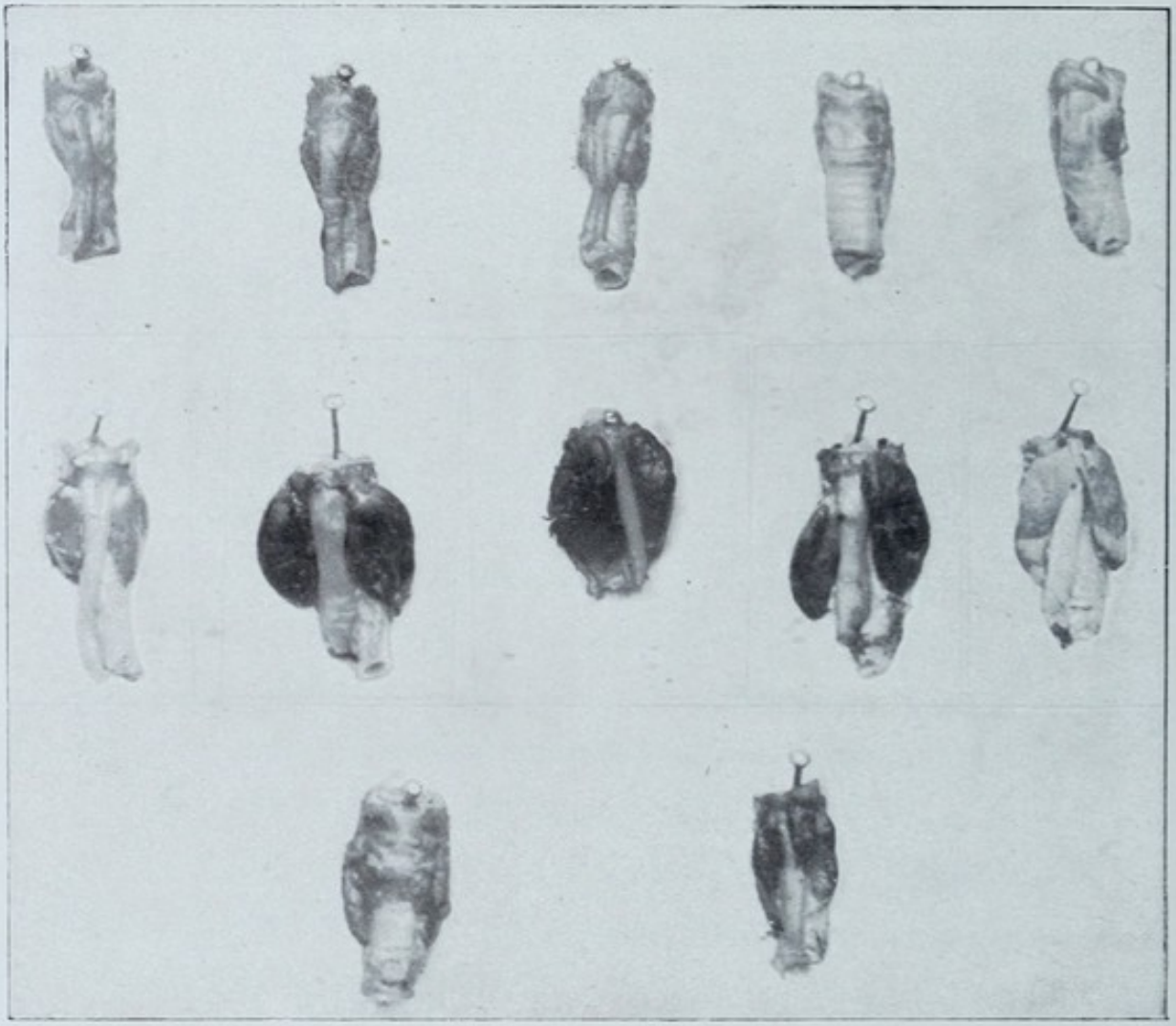

FIG. 4.

thyroid gland of rats as a result of giving them goitrigenous water for a period of nine months. The first line shows the thyroid apparatus of normal rats as seen from behind; the second, the experimentally produced goitres; whilst the third line shows the enlargement which resulted from the consumption of water "raised to a temperature of 99° to 100° C. for several minutes." He reports that "all animals which consumed the untreated water developed a thyroid hypertrophy of such dimensions that the total volume of the enlarged organ was at least ten times that of the normal gland; the lobes were embossed, hard, and of a very bright colour. The parathyroids were equally enlarged in volume." In the case of the animals which consumed the water that had been raised to a temperature of 99° to 100° C., he records that "the goitre is still very manifest but much less voluminous than that of the animals which had untreated waters."

The Swiss Goitre Commission, appointed, I believe, in 1909, has carried out very extensive experiments with a view to the artificial production of goitre in animals. Large numbers of rats, dogs, rabbits, guinea-pigs and monkeys have been employed. The Commission made use of the water of Rupperswyl, as did Bircher. Drs. Vannod and de Mestral, referring to the results observed in rats, report as follows: "Not only have we never demonstrated any hypertrophy of the thyroid, but

the animals which drank the water of Rupperswyl for the longest time—seven and a half months—were found to have thyroids smaller than the control animals. Microscopical examination showed no trace of proliferation of epithelium." They also report that of the twenty-eight dogs experimented on by the Commission, "the only one which showed an enlargement of the thyroid amounting to a pronounced goitre was a very young dog, drinking the water of Sumiswald Well." And with regard to the six monkeys employed, they state: "The weight of the thyroid of the control monkeys varied between ·15 and ·25 grm., while the weight of the thyroid of the monkeys of the experiments varied between ·35 grm. (St. Imer water) and ·22 grm. (Lauterbrunnen water). They conclude that these waters had no action on the thyroid gland of monkeys.

Since the date of the report from which I have quoted, the Commission have been successful in producing the disease in rats, by feeding these animals with the natural water of Sumiswald and Lauterbrunnen. While in Bern, in the spring of 1912, and again in the autumn of the same year, Professor Kolle was good enough to show me some of these enlarged glands, and also some which had been produced by E. Bircher. The enlargements produced by Bircher were more marked and were considerably darker in colour than those produced by the Commission.

Experiments on animals have also been carried out by Grassi and Manaron (1903-04) and by V. Wagner and Schlagenhaufer (1910) with results which varied considerably. The former observers concluded that the excitant of goitre can be conveyed to man in various media, of which water is in all probability one.

While many points with regard to these experiments remain to be discussed, we may at this stage of our inquiry accept as certain at least that (1) with the possible exception of rats, animals do not readily acquire the disease under experimental conditions; and that (2) *water is capable of conveying in some manner*, as yet incompletely determined, *the toxic agent of endemic goitre.*

In my next lecture, I shall deal with the nature of the toxic agent, and endeavour to indicate the source from whence it is derived.

LECTURE II.

My previous lecture determined with the conclusion that water is capable of conveying in some manner the toxic agent of goitre. It is my intention to-day to examine more minutely the nature of the goitrigenous agency in water and to consider from whence it is derived.

Since the toxic agent of the disease exists in water it must be present in a state either of solution or of suspension. In either case it is derived from the rocks or soil with which the water comes in contact.

The Influence of Soil.

An immense amount of most painstaking research has been conducted in the hopes of finding in some property or constituent of the soil an explanation of the origin of goitre. Many observers have attached much importance to *humidity of the soil;* especially Fodéré, who at one time regarded a damp soil as the most essential factor in the production of the disease. Macnamara also, in India, laid such stress on the frequency with which goitre was associated with damp and marshy soils, that

he attributed to the disease a malarial origin, an opinion which was also held by Tourdes, Morel, and others. It is true that goitre does commonly occur on damp, marshy soils, but it also occurs on the driest soil and in some of the most arid parts of the world. A damp, unhealthy situation may, however, favour the development of goitre in the same general way that it may favour the development of many other endemic diseases. There are many instances in the literature of the beneficial effects of good drainage, as for example, in the outskirts of Strasburg, where "as a result of drainage and the disappearance of the marshes, the disease was markedly reduced" (St. Lager).

Geological Structure of the Soil, and its Relationship to Goitre.

It is to the geological structure of the soil, however, and its possible relationship to goitre, that the greatest amount of research has been devoted. Very great importance has been, and is, attached to this aspect of the soil's connection with the disease, an importance due largely to the work of Billiet, McClelland, Grange, St. Lager, Berry, Bircher, and more recently Répin. But the results arrived at by these observers, though they may be true of the district in which the observations were made, are not always applicable to goitre as it is found to prevail in other countries.

Billiet was amongst the first to investigate and lay stress upon the distribution of the endemic on definite geological formations. He found that goitre was indigenous to the argillaceous calcareous schists, especially those containing talc-schists, mica, and deposits of gypsum. In villages which were situated on Jurassic and Neocomian earths he did not find goitre. His researches were carried out at Chambéry, in Savoy.

McClelland found in Kumaun in the Himalayas, in contra-distinction to Billiet, that villages situated on the argillaceous schists were free from goitre, as were those situated on siliceous sandstones, amphibolites, granite, gneiss and mica slates. He demonstrated the close connection between lime-stone rocks and goitre. McClelland is so often stated to have attributed goitre to the habitual use of hard water—a statement which is not in accordance with his teachings—that I may be permitted to quote his conclusions in his own words: "The exciting cause has been traced to certain strata of the earth, under circumstances calculated pointedly to suggest that water is the medium by which it is conveyed to the bodies of men; although the analysis of such water has proved insufficient to detect any ingredient to which we can directly ascribe their effects, except lime. Finally, that having thus far traced the source of the endemic, we have reached, in regard to the exciting cause of goitre, the utmost limits of our

knowledge; but whether there be any other strata capable of yielding the particular contagion than those we have described, and whether the water is the only medium by which it can be conveyed, are points which still remain to be determined."

The extensive researches of Grange, in the Alps, led him to the conclusion that while the endemic prevailed in the marine molasse, it was most prevalent on the Liassic, and general on the Triassic formations—the marls, limestones, and magnesium limestones. He found the disease less marked on the coal measures and very generally absent on granite formations. Alluvium was only affected when the alluvial deposit was derived from goitrous neighbourhoods. These findings led Grange to believe that magnesium in the water was the cause of goitre.

The general truth of Grange's observations for the region in which they were made was confirmed by the report of Élie de Beaumont in the year 1851, especially as regarded the association of the endemic with the dolomite rocks of Triassic origin.

Grange's observations received additional support from the findings of Zambroni and Garrigou in the Pyrenees; of Heidenrich in mid-France; of Virchow in Lower Franconia. Baussingault, in New Grenada, found the same association with limestone rocks, though the disease was not confined to them.

Next in importance to the researches of McClel-

land and Grange, come those of James Berry, in England, who showed that the endemic of goitre coincided everywhere with calcareous rocks, and that the disease prevailed not only on limestone but also on calcareous sandstones. His present view is that while much more common on these rocks than any other, it is not exclusively limited to either of them.

St. Lager sought to attribute to the metal-bearing rocks, notably those containing iron and copper pyrites, the causation of goitre. He attributed the disease to the presence of iron in the water.

Bircher, as a result of extensive researches in Switzerland, has concluded:—

(1) That goitre occurs only upon marine deposits and especially upon the marine sediments of the Palæozoic, Triassic and Tertiary periods.

(2) That the eruptive rocks, the crystalline rocks of the Archæan groups, the sediments of the Jurassic, Cretaceous and post-Tertiary seas, as well as all fresh-water deposits, are free from the disease.

He affirms that where goitre appears on the rocks of the second group the affected outcropping stratum has only a moderate density, and has as a basis one of the formations mentioned in the first class, so that the sources of the springs extend down to them. Or, on the other hand, endemic centres of goitre are to be found in isolated islands composed of rocks of the first class, on which in other parts of the world where these formations

appear in large ranges, goitre is endemic. He considers also that the influence of the rocks of the first class is often weakened, or made to disappear, through superimposed fresh water strata. Bircher, by extending his studies to other European countries, convinced himself that goitre occurs especially on rocks of the Silurian, Devonian, Carboniferous and Permian systems.

Johannesen, in Norway, comes to the same conclusions as Bircher. Höfler also, in Tôlz, found that while goitre was very commonly met with in the marine strata, the fresh-water formations were exempt. Researches in France, Germany, America, Spain, Asia, &c., have, according to Ewald, furnished further proof of the general truth of Bircher's conclusions.

Now while there can be no doubt that goitre is very much more commonly associated with limestone and dolomite formations and with marine deposits generally, this association is not a constant one. It must be admitted that not only are these formations often free from the disease, but also that *goitre can and does prevail on almost every other geological formation from the most ancient to the most modern.* Bircher's teaching, that the eruptive and other rocks mentioned in the second class, are free from the disease, is erroneous. Goitre is undoubtedly rare on these rocks, but it cannot be affirmed that they are goitre-free. As long ago as 1848, the Sardinian Commission found that no

formation excluded the occurrence of goitre and cretinism, but that endemics were to be met with more frequently on the older than on the more recent formations.

Berry has pointed out that Jurassic and Cretaceous rocks are, in England, not wholly free from goitre.

Kocher, also, has shown that the Jurassic formations and fresh-water deposits are not exempt in the neighbourhood of Bern.

Chatin has brought forward many illustrations to show that goitre is found on volcanic earths, on granite, on oolite limestone, on marl, on alluvial deposits, &c., in short on soils of all kinds, while St. Lager also has cited a great number of places where goitre occurred without any connection with dolomite rocks.

Lorenz has arrived at the conclusion, as a result of his independent researches in the Canton Grisons, that there is no valley, perhaps even no district, in which goitre or cretinism, slight or isolated though the cases may be, does not occur. He agrees that the majority of cases are to be found on marine deposits, but that villages on such deposits, and on Trias, may be free from the disease. He finds that the smallest number of cases occur on primitive rocks, or non-marine deposits, and has met with the disease in certain districts on crystalline rocks.

Hirsch also has been led to the conclusion that goitre occurs on all geological formations, but that it is met with on all the older formations, including

the Trias, more frequently than upon the more recent.

Wellams, in West Africa, has described an endemic on metamorphic rocks, while in Bega, in New South Wales, goitre occurs on granite.

My own experience in Chitral and Gilgit has led me to conclude that no geological formation excludes the occurrence of goitre. In parts of Chitral the disease is very much more common in certain villages situated on limestone rocks, and the fact is so striking that it is difficult to avoid the conclusion, arrived at by McClelland in the Himalayas so many years before my time, that it was almost possible by studying the characters of the neighbouring rocks to predict whether or not the inhabitants would be afflicted with goitre. But more extended acquaintance with the disease soon taught me that not only were limestone rocks often exempt from the disease but also that it prevailed in abundance in villages situated on granite rocks. In the eighty miles of country between Gilgit and Astore there is hardly a village in which goitre is not common, and often cretinism also, yet the whole of this country is made up of an "igneous complex composed of several varieties of granite." (MacMahon.)

The iron-pyrites theory of St. Lager is open to the same objections. The disease is not limited to iron-bearing rocks, nor is it always found on such rocks. Some of the most highly goitrous localities

in the world are those in which the soil is practically iron-free, while in many localities in which iron is abundant, as, for example, in the mining districts of France, the disease is frequently absent.

With the assistance of Mr. Hayden, of the Geological Survey of India, I have made a minute microscopical and chemical examination of the soils of certain villages in Gilgit. It was found that the amount of lime, magnesium, or iron, in these soils bore no relationship whatsoever to the extent of goitre amongst the villagers living on the soil. In the soil of the most goitrous village, lime was found in considerably less amount than in that of another which was free from the disease; while iron was present in the soils of all villages in such small amounts as to render it most unlikely to be the cause of disease of any kind. Even in soils in which iron was found in rather more marked quantities, the excess did not correspond with any excessive prevalence of goitre amongst the inhabitants.

Baillarger, in his masterly review of the whole subject in 1873, concluded that "it had not been shown that goitre prevailed exclusively on any particular soil, but that it seemed to be proved that the endemic is extremely common on the dolomite formations and rare on others." This conclusion needs no modification even at the present day.

Chemical Substances in Water and their Relationship to Goitre.

Analyses of goitre-producing waters—of which there are probably thousands on record—have failed to show that dissolved salts of lime, magnesium, or iron, can be regarded as the essential cause of goitre. I, myself, have been unable to trace any definite relationship between the amount of goitre present in any village and the amount of any single dissolved ingredient in its water which can be detected by chemical tests. Goitre is found in villages where the water is hard, and contains lime and magnesium in abundance, and in villages where it is soft and contains these mineral ingredients in very small amounts. It is absent also in many villages where the water is very hard, and the literature provides many examples of this truth. Indeed, it is affirmed by some observers that there are springs containing chalk and magnesium in large amounts which not only do not cause goitre but under whose use goitre actually disappears. Zschokke has recorded that this is true of the Betherstein water; and Christener that the Weissenberger hot lime waters possess a curative property. I have, however, observed in Gilgit and Chitral that amongst the inhabitants of goitrous villages where the water was very hard the individual goitres were, as a general rule, larger and more degenerated than in neighbouring villages

where the water was softer, a fact which may not be a coincidence only. It may be that a hard water will favour the action of the goitrigenous agency, but such waters are not capable by virtue of their hardness alone of causing goitre. It is interesting to record the fact that Grange himself, who was the author of the "magnesium theory" of the disease, abandoned the view as a result of his more extended geological researches.

Baillarger, surveying the whole subject in the year 1873, arrived at the conclusion that "chemical analyses do not support the view that goitre is due to the presence of chemical salts in the water."

Nor is this view supported by experiment. Goitre is not observed to result from the administration of salts of iron over long periods of time to anæmic girls, nor can the salts of lime, magnesium, iron, potash or soda, give rise to the disease when administered to animals under experimental conditions. The brothers Berry failed to notice any changes in the thyroid glands of guinea-pigs, either by macroscopical or microscopical examination, as a result of feeding these animals on the chemical salts mentioned, for a period of nine months.

Of late years, however, the view that goitre is due to some substance dissolved in the water has been revived, and the supporters of this view are seeking to find in radio-active substances, especially radio-thorium, fresh support for their theory. According to Répin, goitrigenous waters have a

high carbonic acid content, by virtue of which carbonates and sulphates of lime and magnesium are held in solution. He considers also that the radio-activity of a mineral water may have an influence in the production of goitre. He believes that all goitrigenous waters are true mineral waters of a peculiar kind, and holds that their points of exit from the earth's interior—for such waters must come from great depths—are to be found in the lines of dislocation of the lithosphere, and by preference in the most recent or those which have not yet had time to become obliterated. He considers that these waters exercise on the general metabolism a powerful action of which the thyroid hypertrophy is only the reverberation. He bases his hypothesis on the work of Senator, Leopold-Lévi, de Rothschild, and others, who have shown that the thyroid mechanism controls the metabolism of lime. He explains the enlargement of the thyroid as an effort on the part of the gland to maintain, by augmenting its secretion, the chemical balance of the organism in the presence of a state of hypercalcification, induced by the use of water containing lime. His experiments on rats have confirmed him in this opinion (fig. 4). He has recorded that even heating the water to 100° C. for several minutes does not deprive it wholly of its goitre-producing properties. He believes prolonged boiling, or expulsion of its carbonic acid content, to be necessary to cause a precipitation

of the dissolved salts on which, in his opinion, the goitre-producing properties of the water depend.

The views of Répin may be summed up thus: That goitrigenous water is invariably mineral water; that in this water exists some chemical ingredient —possibly salts of lime and magnesium, possibly radio-active substances—which is the active principle in the production of goitre and resists a temperature of 99° to 100° C. for several minutes. Now Wilms has shown that water raised to a temperature of 70° C. loses its toxic properties, and this result is in conformity with my own findings, and those of Bircher, Breitner, Lobenhoffer, and others. But even if a temperature of 100° C. did not destroy the toxic agent of the disease, the fact would not exclude the possibility of an infective agent as the cause of goitre. I have, for example, isolated from the fæces of sufferers a spore-bearing bacillus which not only resists boiling for several minutes, but also exercises a curative influence on the disease when employed as a vaccine. The fact that Bircher has produced goitre in rats by means of water filtered through a Berkefeld filter might be quoted in support of Répin's views, but here again such treatment of the water is not sufficient to exclude the possibility of an infective agent, since this method of filtration does not render the water sterile. I am not prepared, therefore, to accept as final Répin's view as to the effect of heat on goitrigenous water.

Nor am I able to agree with his view that the goitre-producing properties of a water may be due to its radio-activity. Répin holds that goitrigenous waters are amongst the purest known, but he has advanced no bacteriological observations in support of a statement of such moment. The bacteriological researches of the Swiss Goitre Commission have proved that such waters almost invariably show an infinitely higher bacterial content than innocuous water, and we know that in radio-active waters the bacterial content is low. My own experience is in direct opposition to that of Répin, and exactly parallel to the results of the Swiss Commission. I am also informed by Professor Kolle that this Commission has failed to confirm in Switzerland Répin's supposition as to the radio-active properties of goitre-producing waters.

The lime and magnesium theory has already been dismissed as untenable; and in answer to the claim that goitre is due to the mineral character of the water, I have the authority of Dr. Cresswell Howell, of Bega, in New South Wales, for stating that goitre, to his personal knowledge, occurs in this locality, where the only source of water-supply is rain—while Veichardt mentions the case of the people of Eichstätt who are goitrous, though they drink rain water only. Similarly, in other goitre-infected regions, the only drinking water is derived from snow, a fact responsible for the popular belief whereby goitre is attributed to the consumption of

snow water. There are also recorded instances where the disease has arisen in persons drinking distilled water only. In this connection, I would refer again to the outbreak of goitre in the Bishop Cotton School, at Simla, where whatever may have been the cause of the disease it certainly was not the water-supply, and this is only one of many similar instances with which the literature supplies us.

While, therefore, I would not go so far as to deny that the peculiar waters with which Répin is dealing may possess some quality which tends to excite the functional activity of the thyroid gland, it is immediately obvious that the explanation offered by him cannot be accepted as a complete and satisfactory theory of the origin of the disease.

Two main facts emerge from a study of the geological relations of the soil to goitre, viz.: (1) That the disease appears to show a preference for certain soils; and (2) that it can, nevertheless, prevail on soils of any geological formation. Knowing, then, as we now do, that the essential cause of goitre is not a dissolved mineral ingredient derived from limestone soils, we must seek elsewhere an explanation for the connection of the disease with the soil.

The Nature of the Toxic Agent of Goitre.

Such an explanation must involve some prior determination of the nature of the toxic agent of the disease.

Now the arguments upon which are based the explanation I have to offer, rest upon a consideration of the behaviour of the endemic itself, upon deductions drawn from authenticated outbreaks, on my own observations in endemic centres, upon the conclusions to be drawn from the valuable work of Marine and Lenhart, who have studied the disease as it occurs in artificially bred trout, and finally upon my own experiments on man, and still more recently Bircher's on rats.

In a previous section dealing with the behaviour of the endemic we arrived at the conclusion that the evidence pointed to the existence of a living excitant. Nor can any other conclusion satisfy the difficulties presented by the outbreaks at Nagar, and in the Boys' School at Simla, to which reference has already been made. To these instances I am able to add the experiences of Dr. Cresswell Howell, of Bega, in New South Wales. He has been kind enough to send me an account of an endemic of goitre in his district. The affected area is a stretch of undulating country about 30 miles long by 20 miles broad, and lies in a depression among high hills. The prevailing rocks are granite. The people are all of the farming class. The water-supply is rain water, which is collected from the roofs of the houses and stored in tanks. These tanks are only cleaned out on the rarest possible occasions. Dr. Howell informs me that he has examined the deposit in about one hundred of these tanks and found it

swarming with bacteria and animalculæ of all kinds. A large number of young adults suffer from "a not very serious form of goitre." The swelling is invariably bilateral, gives rise to no pain, and rarely gives rise to symptoms. The goitre usually develops about the period of adolescence. Cretinism is also met with, but it is not of a severe type. Here we have an endemic which, if it can be attributed to water at all, can only be due to the drinking of rain water, which has become fouled by the washings from the dusty roofs, and by its storage in dirty tanks. Clearly in this case also the disease is due to no dissolved ingredients, but to some living excitant, which finds in these tanks the necessary nutrient material for its life and growth.

Of my own observations, I will now direct your attention to those that deal with the village situated on the Gilgit Fan.

Prevalence of Goitre in the Villages of the Gilgit Fan.

The photograph which I am about to show will give some idea of the nature of the country (fig. 5). The alluvial Fan which is seen on the right bank of the Gilgit river is approximately ten square miles in extent, and has a gentle slope from its apex, in the nullah, from which it derives its water-supply, to the river. Nine villages or hamlets are scattered over this Fan;

Lent by Mr. John Murray.] [*From Col. Durand's "Making of a Frontier,"* 1900.

FIG. 5.—Gilgit Valley : Western end, showing in the foreground the unprotected water-channels or kūls.

collectively they are known as "Gilgit," but each has its own particular name. Eight of these villages are supplied by water from the Kirgah stream, which is mainly derived from the melting of the snows on the hills above. The ninth village, Barmis, to which reference has

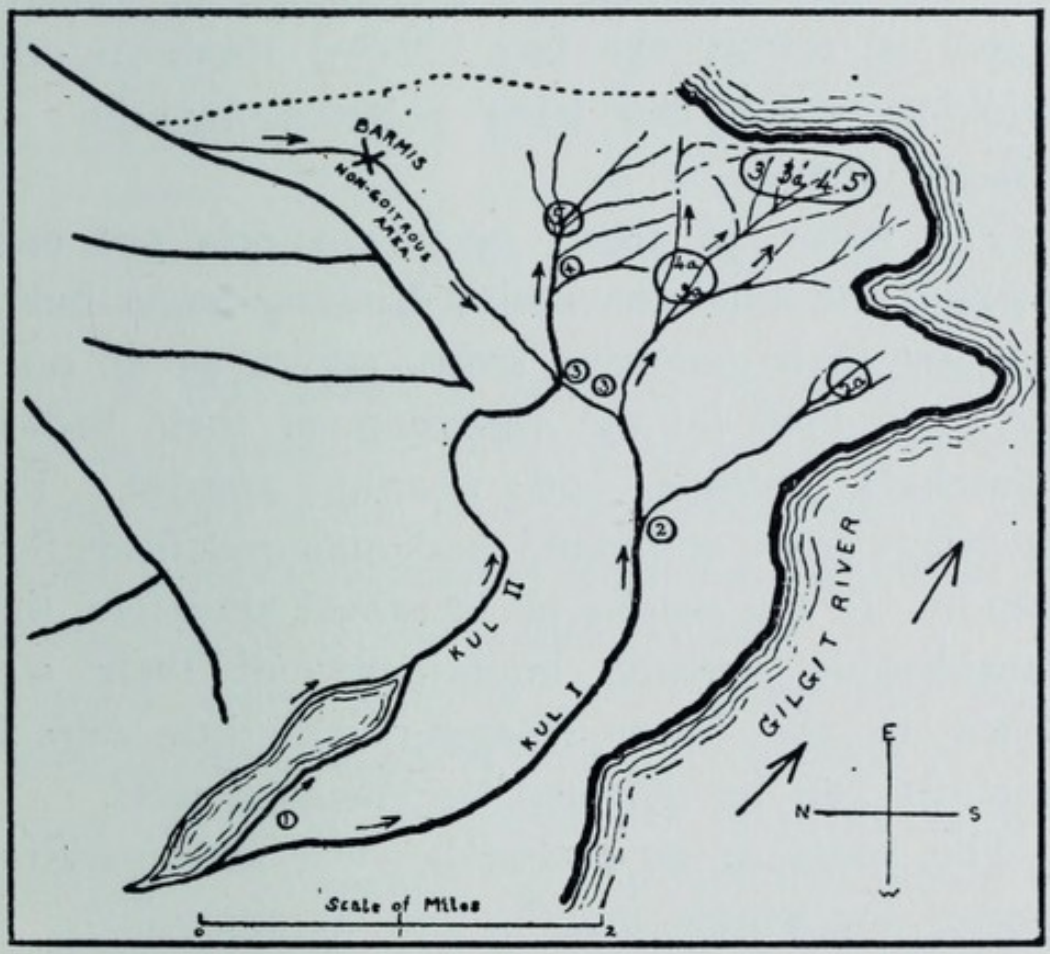

FIG. 6.—Diagrammatic sketch of Gilgit water-supply. 1, Basin; 2, Umphris; 2A, Damyal; 3, Majinpharri; 4 and 5, Ky K; 3A, 4A, Sonyar; 3′, 3A′, 4′, 5′, Kashrote.

already been made, is supplied by a spring which is not goitre-producing. We are at present only concerned with the eight villages supplied by the Kirgah stream. I now show a rough diagrammatic map of the water-supply of these eight

villages (fig. 6). The water comes from a single source and is conveyed to the different villages in open kūls or channels. From the diagram it will be observed that there are two main channels on the banks of which the villages are situated one below the other. Each village in this way receives the drainings of the village or villages above it, till at the last village, Kashrote, the drinking water has been polluted by the six villages above.

The water in these open channels not only supplies the inhabitants with drinking water but it irrigates their extensive crops, serves as an open sewer, is used for the cleansing of their bodies, household utensils and wearing apparel. The drainings from cultivated and manured fields flow into it. It can readily be imagined, therefore, that considerable organic impurities find their way down to the lower villages; yet little organic impurity can be detected by chemical tests.

The water at its source is clear and sparkling during the winter months, but at the village of Kashrote it is grey from the presence of fine sediment, especially when irrigation is in progress. During the summer, when the snows are melting, much fine silt is carried down from the nullah.

In the following table I have indicated the prevalence of goitre in these villages, as determined by me in the winter of 1904. The figures are accurate, especially as concerns children and

males; but as concerns women I had often to rely on the statements of their male relatives as to whether they were goitrous or not.

	Village	Population	Houses	Infected houses	Per cent. of infected houses	Per cent. of persons infected in infected houses	Per cent. of total population goitrous
1.	Basin ...	93	15	9	60·	21·2	11·8
2.	Umphris ...	385	66	42	63·6	28·3	20·
2A.	Damyal ...	181	30	20	66·6	30·3	18·8
3.	Majinpharri	718	108	68	63·2	24·2	20·
4 and 5.	Ky-K ...	229	33	23	71·5	30·	26·9
3A. / 4A.	Sonyar ...	458	63	52	82·5	30·	24·5
3, 3A. / 4, 4A.	Kashrote ...	128	24	21	87·	36·	45·6

From this table it is seen that the percentage of infected houses, of infected individuals in these houses, and of the total population suffering from goitre, goes on increasing from the highest to the lowest village on the water-channels.

In a paper which I read before the Royal Medical and Chirurgical Society of London in 1906, when describing the prevalence of goitre in these villages, I commented on the fact that where the polluted water of the main channel was joined by the purer supply from the Barmis spring the progressive increase of the disease was arrested.

The chemical composition of the water as it flows through the villages is the same as at its source. Only this difference could be detected in the water taken from the channel at Kashrote: it contained a larger amount of mineral matter in

suspension, more vegetable debris, more amorphous matter, more animalculæ, and on plate cultures it showed a much richer bacterial flora than the water at its source or higher up the kūl. It is, therefore, obvious that the increase in the disease bears a relation to the increasing organic impurity of the water, and we are again driven to the hypothesis that the toxic agent is a living excitant.

Endemic Goitre in Artificially-Bred Trout.

Consistent with these conclusions are the deductions to be drawn from the paper written by Drs. Marine and Lenhart, and entitled: "Observations and Experiments on the so-called Thyroid Carcinoma of Brook Trout, and its relationship to ordinary Goitre." These observers found that the so-called thyroid carcinoma was "severe endemic goitre" (fig. 7). Any peculiarity which the tumour in fish shows is due to the fact that the thyroid gland in fishes is not encapsuled, consequently as it enlarges it tends to grow into neighbouring structures.

I shall now quote those parts of Drs. Marine and Lenhart's paper which have a special bearing on the present subject:—

"Our observations and experiments were made during October and November, 1909, at a large private fish hatchery in the mountains of Pennsylvania. The arrangements of the houses and

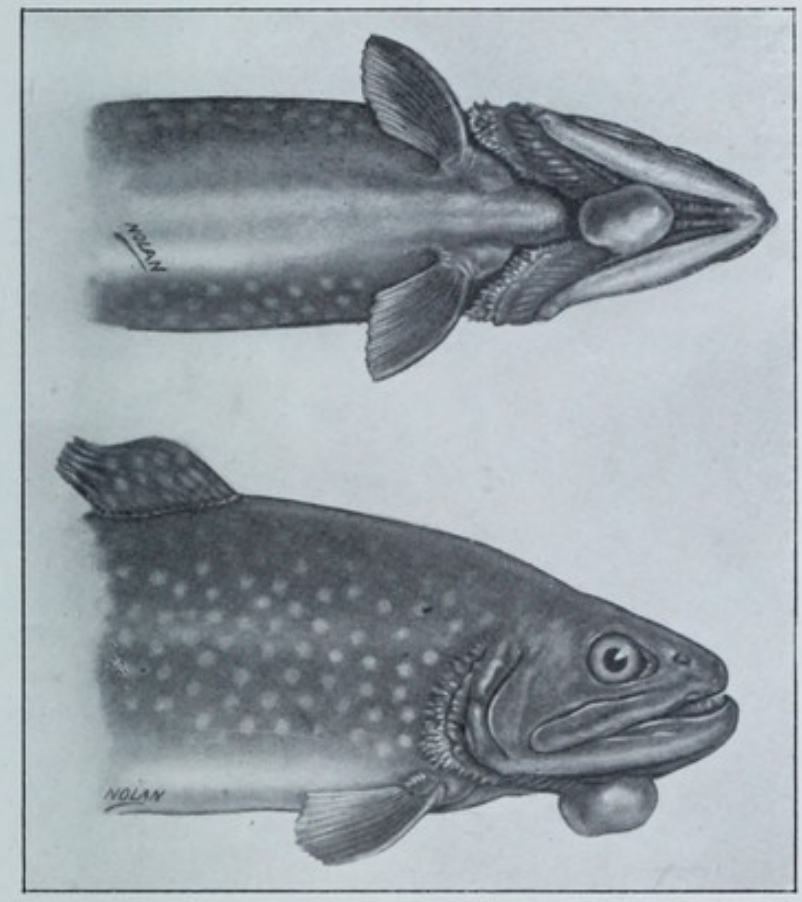

FIG. 7.—Large external goitre in trout (Marine and Lenhart).

retaining tanks is quite simple. This is shown in the figure (fig. 8). The tanks are arranged in a single series down the course of the brook. The water-supply is likewise simple. There is but a single spring supplying the upper six houses, while the lower five receive the water that has passed through the upper six, together with that from a second small spring and a 6-in. pipe line from a large stream about a quarter of a mile to the left. On account of the increased water-supply, and for the clearer understanding of certain observations to be mentioned later, it is best to divide the series of tanks into an upper and a lower division. Between the upper and lower division of houses (that is between houses VI and VII) the water follows the original brook for a distance of about a quarter of a mile. Then it is again collected by means of a dam and enters the lower division of houses with the additions to its volume above mentioned. The water coming from the spring above all houses to the first house—a distance of about fifty yards—is also allowed to follow its natural bed. Apart from these two exceptions, the water is carried in covered race-ways made of lumber.

"Houses I, II, III and IV contain eight months'-old fish. Houses V, VI, VII, VIII contain $1\frac{2}{3}$-year-old fish, and houses IX, X, and the first pair of tanks in House XI contain $2\frac{2}{3}$-year old fish. The last pair of tanks in house XI contains $1\frac{2}{3}$-year-old

fish. . . . the three most important localities as regards the effect of water-supply and water pollution are houses VI, VII, and the last pair of tanks of house XI, which contain fish of the same age, that is, 1⅔ years."

As a result of their examination of specimens of fish taken without choice from all the tanks, also specimens of different ages from the raceways above and below all houses, and lastly specimens of the larger 3⅔-year-old fish from the trout stream near by, the authors concluded that: "Fish which lived in the raceway above all houses and which have never been confined in the tanks maintain normal thyroids throughout their lives. Then, beginning with the series of tanks, it was shown that the 8-month-old fish are markedly affected even in the uppermost of all the tanks, and that there is a gradual increase in the degree of thyroid proliferation, which reaches its greatest extent and severity in the last house (VI) of the upper division. Beginning with house VII there is a marked improvement and lessening of the active thyroid proliferation coincident with the greatly increased water-supply and the probable purification of the water from the upper division in its passage for a quarter of a mile along the original bed of the brook. The improvement cannot be followed definitely throughout the remaining houses of the lower division, for the reason that the 2⅔-year-old fish are housed here, but the general impression is that

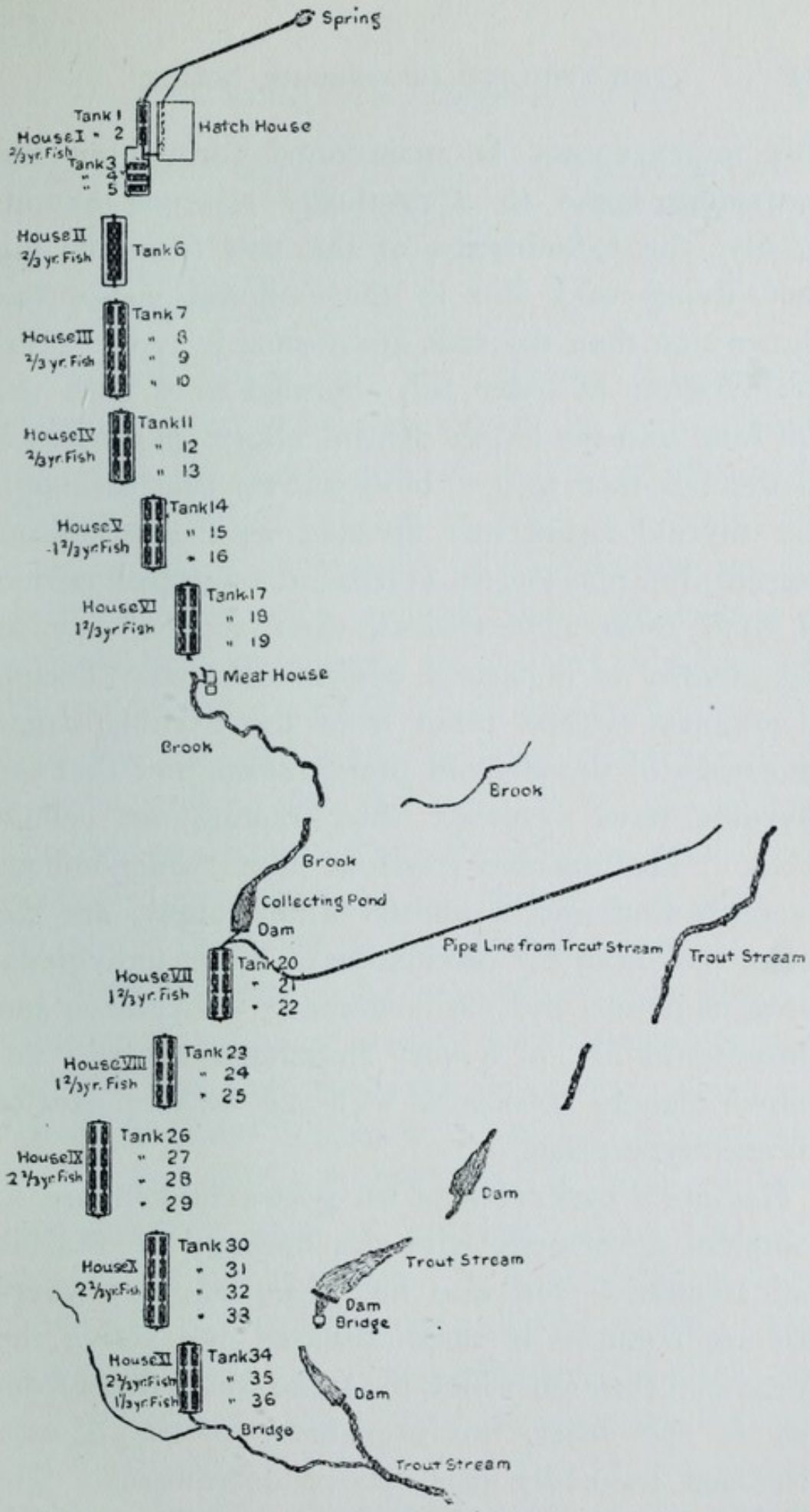

FIG. 8.—Semi-diagrammatic drawing of the plan, arrangements and location of the hatchery, water-supplies, houses and retaining tanks. (Marine and Lenhart.)

this improvement is maintained throughout the remaining tanks to a gradually lessened extent. Lastly, the examination of the fish from the tail race, living wild, but in the polluted water, has shown that their thyroids are normal in type. Also examination of older fish obtained from both the tail race and the larger stream above the entrance of the tail race into it, have shown that, although the thyroid tissue has invaded all the structures beneath the pharyngeal mucosa at some past period of their lives, nevertheless, their stay of five to six months in a natural environment has effected a complete natural relief from the exciting cause or causes of the thyroid proliferation, and that the thyroids have resumed their resting or colloid state." The authors conclude that "overfeeding, overcrowding, and a limited water-supply, are the major factors in the production of filthy, unhygienic tanks or ponds, and the unsanitary, unhygienic, and filthy tanks are in a very important but still unknown manner associated with the development of thyroid hyperplasia."

Gaylord's observations on goitre in fish are in complete agreement with the findings of Marine and Lenhart. He also has observed that where fish are confined in tanks situated one above the other, and through which the same water flows from one to the other, the prevalence of the disease increases markedly from above downwards. He gives the following table, which shows this increase:—

Water above the tanks...	...	...	Fish goitre free.		
,, in first tank	...	...	...	3 per cent.	goitrous.
,, in second tank	...	...	...	8	,, ,,
,, in third tank	...	...	...	45	,, ,,
,, in fourth tank	...	...	...	84	,, ,,

You will notice that the account of goitre in artificially bred trout corresponds in a remarkable way with my description of goitre in the eight villages of Gilgit, written in 1905. There is the same increased prevalence of the disease as the water becomes more polluted, and a diminution in the amount of the disease as a result of dilution of the impure water with the fresh spring water. The trout also conform to that striking characteristic of endemic goitre, viz., the capacity of spontaneous recovery on removal from the infected area. The markedly place-character of the disease, even in the case of these fish, is thus well illustrated.

Now it is clear in the case of the trout that the influence of water in causing the disease cannot be doubted, and that whatever substance caused the disease remained behind in the tank. Anyone who has watched artificially bred trout in tanks will have observed their habit of "nosing" about the walls and bottom of the tanks. It is precisely in these places that suspended matter deposits itself. This deposit is made up of the remnants of food, and forms a nidus for the growth of numerous bacteria and animalculæ. I hold that it is in this deposit we must look for the causal agent of the disease, since it existed neither in the water flowing into

the first tank, nor in that escaping from the last, in sufficient quantity to cause goitre.

Let us see what further evidence we have in this direction. I have stated that young soldiers who come to Gilgit frequently develop goitre within a few months. I have examined these soldiers for goitre on three different occasions, about six months after the biennial reliefs. On the first two occasions it was noted that the recruits suffered to the extent of 20 to 22 per cent. On the third occasion, only 5 per cent. were found to be goitrous. Now it is the custom of the men to cook their own food, and for this purpose each man is provided with a large assortment of brass vessels. These he "cleans" by picking up a handful of silt from the bottom or sides of the open water channel, which runs past the barracks. The vessel is polished vigorously with the silt, and then rinsed in the foul water of the channel. After the third biennial relief, it was decided to introduce a system of "messing" amongst the men. This system involved one man cooking the food of a number, instead of each man cooking for himself. Consequent upon this change, the number of cooking-pots cleansed in the way I have indicated was very considerably reduced. It may have been a coincidence that I found only 5 per cent. of the recruits amongst the men goitrous, but I do not think so, and am inclined to attribute the fall of the incidence of the disease from 20 to 5 per cent. to a lessened infection from the

soil by way of cooking-pots and infected hands which followed as a consequence of the "messing" system. This system was, however, not popular amongst the men, so they reverted to their former habits of cooking, when I found that the percentage of goitre amongst the recruits again rose.

Marine and Lenhart believe, as a result of their observations, that goitre is the symptomatic manifestation of a metabolic and nutritional disturbance, and that food is the major factor acting to bring about a fault of nutrition favourable for goitre development. Comparing their results with the conclusions to which we have already been forced, we may admit that whereas a "metabolic theory" of goitre is not inconsistent with some of the facts, it fails to provide an explanation for all. On the other hand the "micro-organism theory" not only provides a satisfactory explanation of the development of the disease in artificially bred trout, but also of the experiments and observations which we have hitherto discussed. While recognizing that a limited water-supply in the case of fish, or a limited air space in the case of man, over-crowding and over-feeding with a highly artificial and incomplete food, are factors which markedly favour the development of goitre, I am of opinion that these factors are of secondary importance only, and that the essential cause of the malady is a living organism.

To the "micro-organism theory" further weight

is added by a consideration of the results of experiments directed to the production of goitre in man and in animals.

Experimental Production of Goitre in Man.

The general conditions under which my own experiments were conducted may be summarized as follows: The men who volunteered for the experiments were young, usually between the ages of 18 and 25; they were newcomers to the district; they were under observation for some time prior to the commencement of the experiment; they lived in a non-goitrous part of Gilgit, not far from the village of Barmis, under the strictest guard; they were encamped on ground which had never been cultivated; they did no work and were not permitted to handle the soil; they were provided with water for all domestic purposes which was brought from the Barmis spring at its point of exit from the hillside; the water, as an added precaution, was boiled. In no case was the restraint imposed upon the men broken through. Water, purposely made muddy by agitation while flowing through its channel, was brought daily from the village of Kashrote where goitre is very common. It was filtered in large quantities through a Berkefeld house filter. The deposit on the candle was washed off in distilled water, and a quantity of the dark grey mixture, equal to about 4 oz., was given to each

FIG. 9. — Davia. Shows appearance of neck at the time the experiment was commenced. There was a small nodular mass in the isthmus of the thyroid gland.

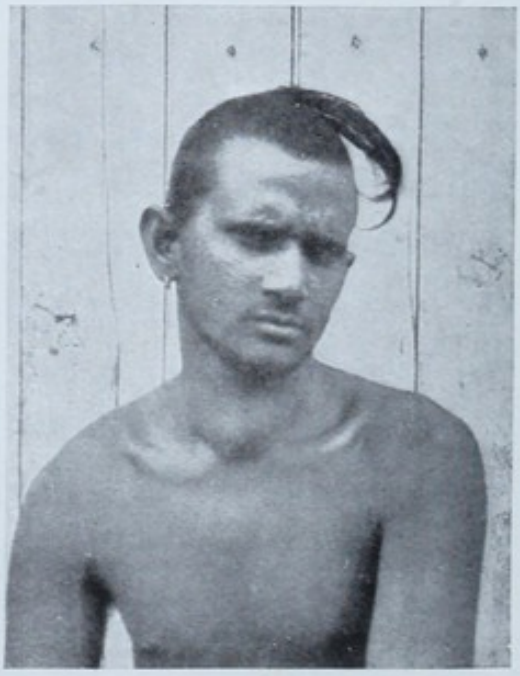

FIG. 10.—The same subject. Photograph taken on the twenty-fifth day of the experiment.

subject in milk every morning before the first meal of the day.

The first experiment was carried out in the spring of 1906. Six healthy young men, aged between 18 and 20, were the subjects. Two of these had formerly resided in Gilgit and had suffered from small enlargements of the thyroid. These swellings had disappeared on their leaving Gilgit, with the exception of a small nodule in the isthmus of one of them. It was thought that these men were likely to prove more susceptible to goitrous influences than men who had not previously suffered from the disease. The other four men were in all respects normal. A swelling of the thyroid gland made its appearance in both of the men who had formerly suffered from goitre. In one case it appeared on the thirteenth, in the other on the fifteenth day of the experiment. The swellings fluctuated considerably from time to time, reached their point of maximum size about the thirtieth day, and then retreated to a point of enlargement at which they remained stationary. In two other cases an increased pulsation in the vessels of the neck may have been the evidence of an increased functional activity of the gland, but no appreciable swelling of the organ took place during the fifty-three days the experiment lasted.

The photographs which I now show represent one of these cases before and after experiment. (figs. 9 and 10).

In October of 1907, I submitted myself to the same experiment. My house was situated in the Barmis village and my drinking water was the innocuous water of the Barmis spring. The photographs indicate the change which was observed in my thyroid gland as a result of the experiment, which lasted one month. The circumference of my neck increased by $2\frac{1}{2}$ cm. I first noticed the swelling on the fifteenth day of the experiment. The enlargement fluctuated from time to time, as is observed to be the case in all commencing goitres (figs. 11 and 12).

In the spring of 1908, the experiment was repeated in the case of six other young men in whom the thyroid was perfectly normal. In two cases an appreciable swelling of the thyroid gland occurred which gave rise to an increase in the circumference of the neck in both cases, of $1\frac{1}{2}$ cm. In a third case the man was conscious of a sense of "fullness of the throat" at times; there was an increase of 1 cm. in the circumference of the neck and throbbing of the vessels was from time to time observed. The other three cases showed no appreciable change during the thirty days the experiment lasted.

Coincident with this experiment six other young men living under precisely similar conditions were given, for a period of thirty days, the *boiled* suspended matter which had been separated by filtration from the muddied Kashrote water. It

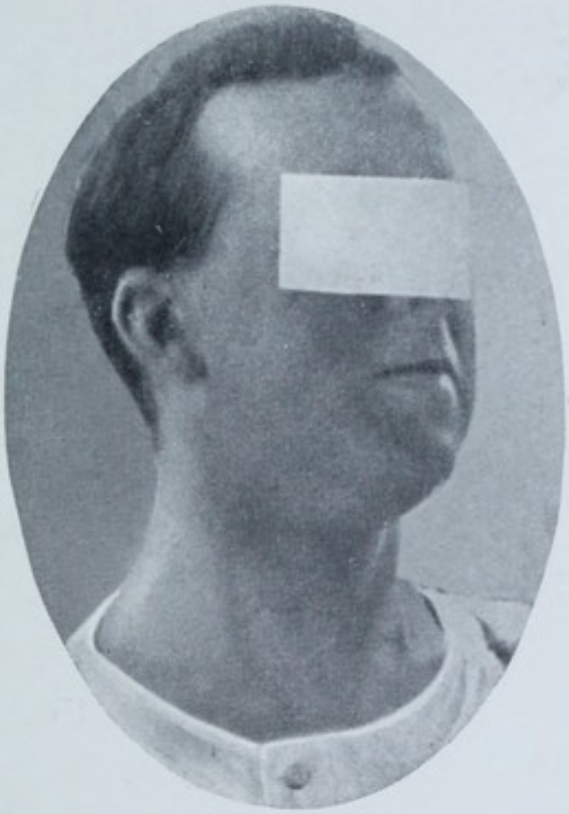

FIG. 11.—Normal appearance of author's neck. Measurement, 40 cm

FIG. 12.—Photograph of author's neck taken on the twenty-fifth day of experiment. There is an evident enlargement of the thyroid gland especially noticeable on the right side. Measurement, 42½ cm.

was subjected to boiling for ten minutes. Neither by manual examination, measurement, nor photography, could an increase in size of the thyroid be detected in any of the six individuals.

Similar experiments were carried out in the autumn of 1907, with the exception that the residue in this case was not separated from the water by filtration, but the water was allowed to sediment and the deposit administered as indicated. Thirteen healthy young men were given this sediment, not only before the first meal of the day, but also in the afternoon, before the second meal. Of these nine showed no change in the thyroid gland which could be detected by clinical examination. In two others a uniform swelling of the organ was observed on the tenth day of the experiment. In both cases the swelling gave rise to feelings of discomfort, and complaint was made of throbbing in the neck and of the tightness of collar bands which had previously fitted well. The measurement of the neck showed an increase of 1 cm. in one case, and of 1½ cm. in the other. The enlargement persisted up to the 20th day of the experiment, and then gradually disappeared; the gland was observed to have regained its normal size on the thirtieth day, when the experiment concluded. In the remaining two cases a more marked reaction on the part of the thyroid was observed. In these the right lobe was the more swollen. The measurement of the neck increased in one case by 1½ cm. and in the other by slightly over 1 cm.

Simultaneously with this experiment thirteen other young men were given the Kashrote water sediment which had previously been *boiled* for ten minutes. It was administered at the same time and in the same doses. In none of these men could any reaction on the part of the thyroid gland be detected. The experiments lasted for thirty days.

In the Spring of 1910, large quantities of the residue, separated from the muddied water of Kashrote by means of a Berkefeld house filter, were administered night and morning to ten young men of the average age of 22. Of these, four showed no reaction whatever on the part of the thyroid gland during the fifty-five days the experiment lasted. One developed a slight enteritis on the fifteenth day, when the experiment in his case was discontinued. Well-marked changes were observed in the remaining five cases. In one of these, in addition to the complaints of tightness of the shirt collar and throbbing in the neck, the measurement of the neck increased by $1\frac{1}{2}$ cm. The swelling was first noticed on the sixteenth day of the experiment, and the right lobe was more prominent than the left. The degree of enlargement can be well seen from the photographs (figs. 13 and 14).

In a second case the reaction was more marked and resulted in an increased measurement of the neck of $2\frac{1}{2}$ cm. The photographs of the case are

FIG. 13.—G. M. Shows appearance of neck at the time the experiment was commenced. Measurement, 33½ cm.

FIG. 14.—The same subject. Photograph taken on the thirtieth day of the experiment. Measurement, 35 cm.

FIG. 15.—S. A. Shows appearance of neck at the time the experiment was commenced. Measurement, 33 cm.

FIG. 16. — The same subject. Photograph taken on the thirtieth day of the experiment. Measurement, 35 cm.

FIG. 17.—The same subject. Photograph taken on the thirtieth day of the experiment. Shows subject's method of fastening his shirt-band, which buttoned comfortably prior to the commencement of the experiment.

especially good and show the subject's method of fastening his shirt-band, which had previously fitted well (figs. 15, 16, 17).

In a third case the swelling was more marked in the isthmus, which was felt as a rounded boss under the finger; it partially disappeared behind the sternum when the trachea was at rest.

In a fourth case the circumference of the neck increased by 1½ cm., and in a fifth by 1 cm. In the first four cases the swelling persisted, in the fifth case it disappeared spontaneously, and while the patient was still drinking the residue.

Concurrently with this experiment ten other individuals were given the same quantities of Kashrote water residue which had previously been *boiled*. Five of these men were selected as having small enlargements of the thyroid. The duration of the experiment in this case also was fifty-five days. In no case could the slightest increase in size of the thyroid gland be detected by any method of examination. In the five men who were the subjects of small goitres the original and final measurements of the neck were as follows :—

	cm.	cm.
D.B.	34	33½
T.R.	34	33
D.R.	32	30½
K.	35	34½
R.	33½	33

These results show that the tendency to alteration in size of the thyroid was in the direction of diminution and not of increase.

All the cases of artificially-produced goitre were rapidly cured by the administration of thymol.

The combined results of these experiments may be summarized as follows :—

(1) Of thirty-six individuals who consumed the untreated suspended matter of a notoriously goitre-producing water, twenty-one exhibited no change in the thyroid gland which could be detected clinically, ten developed a notable enlargement, while five showed a swelling of the organ of a transitory character.

(2) Of thirty-one individuals who consumed the same suspended matter, which had been previously boiled, none showed any reaction in the direction of increase in size of the thyroid.

In order to determine the effect of the administration of *filtered* water to selected individuals under the conditions of the experiments above quoted, I gave seven men the filtered Kashrote water at the same time that ten others were consuming the suspended matter separated from it by the Berkefeld filter. In four of these individuals the thyroid gland was perfectly normal on the date the experiment commenced ; the other three were subjects of incipient goitres. All seven drank only the filtered Kashrote water for fifty-five days. At the end of this time and during the course of the experiment, not only had no increase in size of the thyroid taken place in any of the individuals, but the existing goitres of the

three men showed a considerable reduction in size. It is to be remembered that the suspended matter removed from the water by filtration had produced a thyroid swelling in five out of ten individuals who consumed it, while the subjects of the present experiments were consuming the filtered water.

With the exception of the experiment with filtered water—which, owing to the small number of men employed, I do not regard as wholly conclusive—these observations have been repeated sufficiently often and the results have been so constant in character, that I feel myself justified in drawing the following conclusions:—

(1) Thyroid enlargement can be experimentally produced in man within a few weeks by the administration of the suspended matter separated by filtration from goitre-producing waters.

(2) Thyroid enlargement cannot be so produced when the suspended matter is boiled.

(3) The goitre produced in this way must almost certainly be due, not to the mineral, but to the living component of the suspended matter.

(4) While it cannot be said to be definitely proved by these experiments that filtration through a Berkefeld filter wholly deprives the water of its goitre-producing properties, water so treated does not appear to be capable of causing goitre in man within a period of fifty-five days.

The results of these experiments and the observations I have already quoted to you indicate that *the*

living excitant of goitre exists in greatest abundance in the deposit at the bottom and sides of water-channels, tanks, wells, and other receptacles of goitre-producing water.

E. Bircher's Experiments.

I propose next to consider E. Bircher's experiments on rats. His results, published in various papers since the year 1909 up to the present time, may be summarized as follows :—

(1) Goitre can readily be produced in rats by the natural water of goitre-producing springs.

(2) The thyroid enlargement does not arise till after several months' subjection to the toxic substances contained in the water.

(3) These toxic substances are destroyed by heat (boiling).

(4) They are not removed from the water by filtration through a Berkefeld filter.

(5) By centrifugalization it is possible to render goitre-producing water innocuous.

(6) The addition of certain chemical substances, such as hydrogen peroxide, to the water renders it harmless. (Marine and Lenhart have shown that the addition of small amounts of iodine, in the form of Lugol's solution, to the water causes a rapid disappearance of the thyroid hyperplasias of trout.)

(7) Dialysis removes the goitre-producing substances from the water.

(8) Substances separated from the water by the membrane of the dialyser are capable of producing the disease.

In his earlier papers, Bircher has stated that the residue left on the candle of the Berkefeld filter after filtration does not cause goitre, but in his later papers (1911) he corrects this statement and points out that while consumption of this residue for a period of nine months fails to produce any intense goitrous degeneration of the thyroid, goitres are produced after twelve, fifteen, eighteen, and twenty months' consumption of this residue.

The photograph which I now show, and with which Dr. Bircher has been kind enough to provide me, illustrates these various methods of producing goitre in rats (fig. 18).

Bircher's latest conclusions, as a result of his experimental work, appear to be that the water of goitrous localities derives from certain soils an organism which imparts to it a toxic substance of a colloid nature, and it is this substance that excites the thyroid enlargement. He further believes that this organism is itself responsible for the production of cretinism, while the colloidal poison alone causes goitre. He bases this somewhat complicated conclusion on the fact that he and Wilms have produced goitre by means of filtered water. But, since the disease can also be produced by the residue on the candle and by the residue on the membrane of the dialyser, it appears

FIG. 18.—The first line represents the appearance of the normal thyroid gland of a white rat. The second shows the result of feeding rats on non-goitre-producing water. The third the result of feeding rats on goitre-producing water. The fourth the result of feeding rats on a goitre-producing water passed through Jura earth and through a Berkefeld filter. The fifth shows goitres produced in rats by the residue left on the membrane of the dialyser and by the residue left on the candle of a Berkefeld filter after the passage of goitre-producing water. (By permission of Dr. E. Bircher.)

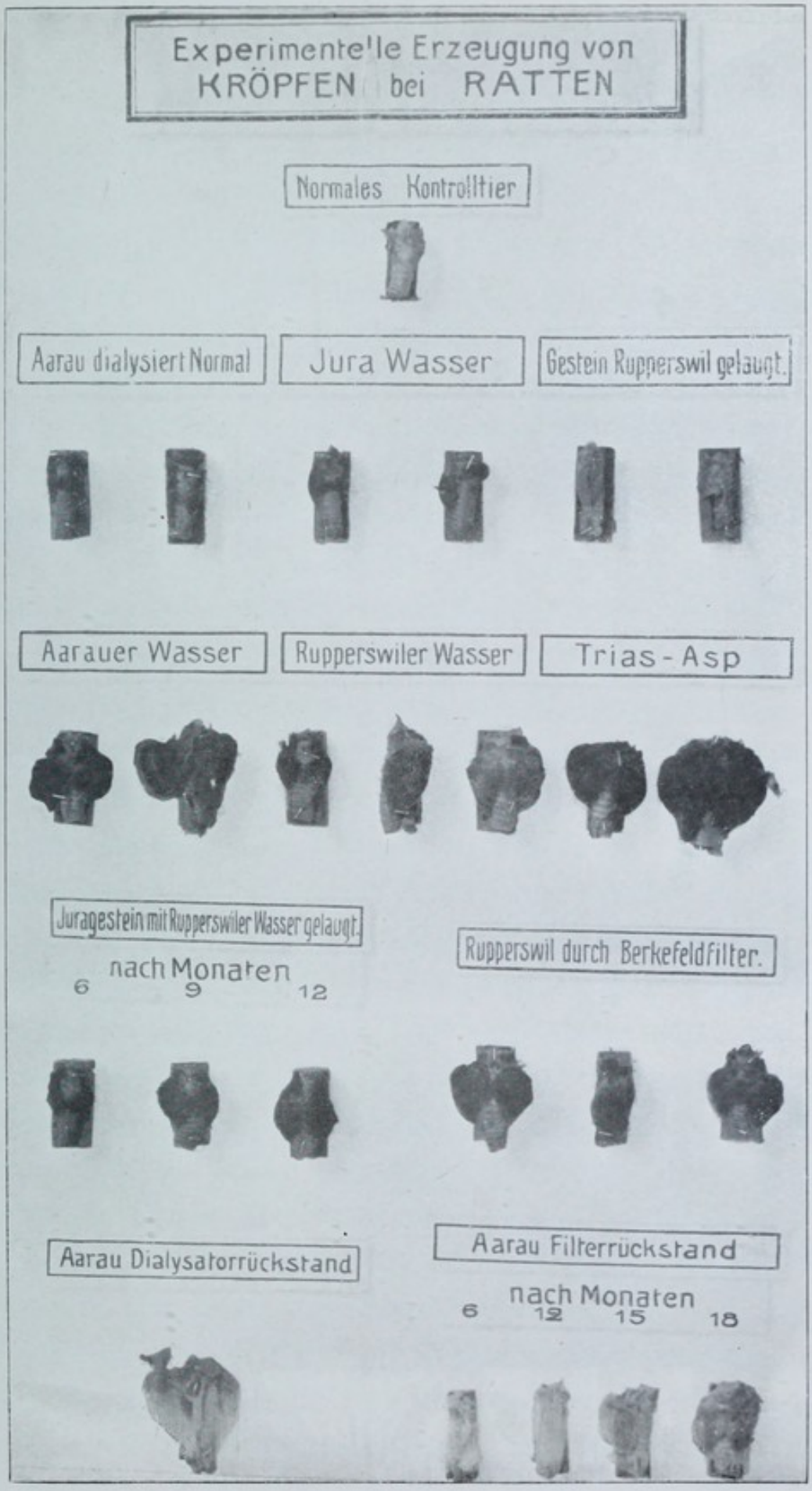
Experimentelle Erzeugung von
KRÖPFEN bei RATTEN
Normales Kontrolltier
Aarau dialysiert Normal
Jura Wasser
Gestein Rupperswil gelaugt.
Aarauer Wasser
Rupperswiler Wasser
Trias - Asp
Juragestein mit Rupperswiler Wasser gelaugt.
nach Monaten
6
9
12
Rupperswil durch Berkefeldfilter.
Aarau Dialysatorrückstand
Aarau Filterrückstand
nach Monaten
6
12
15
18

FIG. 18.

to me to be simpler to conclude that the organism itself passed through the pores of the Berkefeld filter in their experiments.

It is well known that the passage of a water through a Berkefeld candle does not render the water sterile, and that the smaller bacteria (Schmidt) and ultra-microscopic organisms can find their way through it. This is particularly likely to occur when a filter is in constant use unless the candle is cleansed with care, and frequently boiled and renewed. Indeed, unless this is done it may become a source rather than a preventative of infection. Dr. Bircher has told me that a much longer period is required in which to produce goitre in rats by means of filtered water, a fact which appears to me to indicate that this method of filtration removes only a part of the goitre-producing substance. My experiments have shown that while the candle of a Berkefeld filter removed from the water a substance which caused goitre in 50 per cent. of men within a period of fifty-five days, the same water cleansed by this method of filtration failed to produce the disease in a limited number of men during the same period. It is possible, of course, that an organism living in water may impart to it toxic products, which, being in solution, will readily permeate the filter, but whether or not this is the case the organism which gives rise to such products must be regarded as the essential cause of the malady. Bircher's water is, in my opinion, in-

adequately filtered, and I must confess that for my own part until it has been demonstrated in man that adequate filtration fails to render a goitrigenous water innocuous, I shall be unable to accept in their entirety the deductions of Bircher.

Bircher had produced goitre in rats only after the animals had been subjected for several months to the action of the excitant of the disease, while in men a reaction has been observed by me as early as the thirteenth to the fifteenth day. Now it is known that under natural conditions the disease can make its appearance in a much shorter time than several months, in a period in fact which corresponds closely with my findings in the case of the experimentally produced goitre of man. But this apparent difference is to be accounted for by the fact that the minute size of the lobes of a rat's thyroid would make the recognition of the earliest stages of the enlargement a matter of extreme difficulty. Indeed, unless animals were killed every day from the thirteenth day of the experiment onwards, it would be impossible to detect the beginning of the swelling. In man, on the other hand, the larger size of the gland, and the ease with which its changes in size can be appreciated by measurement and photography, make easy the recognition of the earliest signs of enlargement. Bircher was able, in the case of rats, to carry his experiments to a point which is not legitimately possible in the case of man.

His goitres in rats are, therefore, relatively as large as those which are found in man after exposure to goitrous influences for a period of twelve months or longer. His results differ from mine only in this respect that I have noted the earliest stages of the disease in man, while he was able to prolong the experiments sufficiently to give rise to voluminous goitres.

Bircher found, when experimenting with the residue removed from the water by filtration through a Berkefeld filter, that he was able only to use a very few animals owing to the difficulty of procuring from the candle sufficient residue. In the case of my experiments in man I overcame this difficulty by making the water muddy at the time it was drawn, thereby obtaining a residue which contained the excitant of the disease in large amount. Considering the small amount of residue used by Bircher, the results produced thereby (fig. 18) are very marked.

I consider, therefore, that Bircher's results in rats substantiate my previous findings in man, and that *the presence in suspension in goitre-producing waters of a living agent, which is the direct or indirect cause of the disease, has been demonstrated;* and with this conclusion Dr. Bircher has expressed to me his agreement.

The following are the characteristics exhibited by experimentally produced goitre in men.

(1) It usually appears about the fifteenth day of the experiment.

(2) It shows a marked tendency to fluctuate in size.

(3) It reaches its point of maximum size between the twenty-fifth and thirtieth day of the experiment.

(4) The enlargement of the gland is not great, nor is it progressive under the conditions of the experiment.

(5) It is accompanied, as a rule, with certain subjective symptoms of throbbing in the neck, feelings of fulness and discomfort.

(6) It may completely disappear under the conditions of the experiment.

Soil a Vehicle of Infection.

Having, then, thus determined the toxic agent of goitre to be a living excitant—there remains the problem of the relationship of the disease to the soil.

The following are the facts which it is necessary to co-ordinate and explain :—

Firstly : The greater prevalence of the disease among the poorer, and especially the labouring classes, whose habits of life render them more susceptible to infections that lurk in the soil. McKenzie, as long ago as 1898, suggested the presence of the toxic cause of goitre in the soil in order to account for the prevalence of the disease amongst the people of certain parts of Lanarkshire.

Secondly : It is a well known fact that the inhabitants of country districts whose habits of life

bring them into contact with the soil show a much larger percentage of victims than inhabitants of towns.

Thirdly: We have the authority of St. Lager and others for the statement that the toxic agent of the disease can be conveyed to long distances by alluvial earths. I have myself had no opportunity of corroborating or disproving its truth.

Fourthly: The extraordinary history of the disappearance and recrudescence of the disease in Martigny (Valais) requires some explanation other than the water-borne theory. The facts of this case as quoted by St. Lager are: "In the year 1818, owing to a great flood, the soil of the valley, which was moist and marshy, was suddenly covered by plant earth, to a depth of one metre, which had been carried from the mountains." As a result of this renewal of the soil, goitre and cretinism progressively diminished. Later these diseases again increased, due, it is stated, to the introduction of a new water supply. It is not unlikely, however, that re-infection of the soil was largely responsible for its recrudescence.

Fifthly: We have the proposition of Baillarger that vegetables grown in goitrous localities may be a source of the disease. Though this is not a point of evidence on which I wish to lay much stress, I may remark that I have myself observed three cases in which I was able to exclude all other possible sources of infection known to me.

Sixthly: There are the instances, quoted by St. Lager and others, to the effect that the drinking of water rendered innocuous by boiling or distillation is not in itself sufficient invariably to secure immunity in the case of persons resident in goitrous localities.

We have also the authority of New Zealand physicians for stating that goitre prevails in parts of the North Island, where the only water used by the people of the district is that of the boiling springs.

Seventhly: I have the evidence of certain experiments which I am about to detail, to show that mere boiling or filtering the water is not sufficient to prevent or cure the disease so long as the possible avenues of infection from the soil are not excluded. These experiments were conducted in 1904 and 1905. I assumed that if water were the only source of the disease, boiling and filtering ought to place sufferers in as favourable a position for cure as removal from the district, inasmuch as boiling is definitely known to render the water innocuous. Consequently, I selected a number of goitrous and non-goitrous individuals, to whom boiled and filtered water was administered for a period of two months. A second batch of goitrous and non-goitrous individuals was selected as controls, and these were allowed to drink the untreated water of the district. No restrictions were placed upon the men whose habits of life exposed them to continued infection from the soil. This experiment

was carried out in one of the most goitrous villages in Chitral, and I am satisfied that the men drank only the boiled and filtered water provided for their use. It was repeated in Gilgit. I found as a result that neither boiling nor filtering the water sufficed to protect from the disease, nor did pre-existing goitres cease to increase in size.

The cumulative evidence of these experiments, together with the other facts and observations which have been dealt with in this section, affords, to my mind, conclusive proof of the proposition which I now lay down, that *soil is also a vehicle of the contagium vivum of goitre.*

Briefly, to recapitulate, we have now decided that the toxic agent of goitre is a *contagium vivum* conveyed by certain waters and contained in certain soils. I propose next to examine the peculiarities of the soil which favour its prevalence.

We have already remarked that limestone and lime-bearing rocks are those most commonly associated with the disease. Now these rocks are among the most porous as well as the most widely distributed of all geological formations. If, therefore, my deductions as to the nature of the disease are correct these widespread and porous rocks would naturally provide its most normal habitat. The suitability of the soil does not depend upon its chemical composition, but rather upon its organic constituents. Kocher has drawn attention to the fact that in the neighbourhood of Bern,

where goitre occurs, there is usually an abundance of organic matter in the rocks. The opinion of E. Bircher, expressed in 1908, that the nutrient materials necessary for the life of the excitant of goitre, are derived from the remains of the extinct flora and fauna of marine deposits, though it points in the same direction, is one that is based on the slenderest of grounds. I believe that the presence in the soil of animal or vegetable matter, whether its deposition be remote or recent, may convert any soil, no matter what its geological origin, into a suitable habitat for the *contagium vivum* of the disease. A manure heap or a cesspit, for example, is much more likely to afford the necessary nutriment than the remains of the extinct flora and fauna, and is indeed a common source of such nutriment.

I am confirmed in this view by studies I have made of the topography of a large number of goitrous villages in Gilgit and Chitral, where I have observed that the presence or absence of goitre in a given village is largely a matter of the ease or difficulty with which the drinking water can become polluted. Further illustrations of the fact are provided by the two following cases :—

The troops in Drosh (Chitral) are quartered in a fort on the hillside some 400 ft. above the village. The water-supply of the fort is the same as that of the village and is diverted from the main stream of glacier water by means of a channel far removed from all sources of pollution. It reaches the fort

comparatively pure and is stored in a large cistern through which the water is constantly flowing. Goitre is very rarely met with amongst the troops, though their habits of life render them peculiarly susceptible to goitrous influences. The main stream flows onwards to the village and is used to irrigate the fields, the open water channels being subject to the forms of pollution I have mentioned. Goitre is common in the village.

The village of Niyat, in Chilas, is situated at a height of 10,000 ft. above sea level. For a great part of the year it is under snow. The drinking water is conveyed from the main stream by means of a channel which passes through cultivated fields and the village street on its course to the consumers. During its passage it is subject to the foulest forms of pollution, for the people of Niyat are in their habits not far removed from the lower animals. There is scarcely an individual in this village who is not goitrous, and water-borne diseases, especially enteric fever and dysentery, are very common. Not more than a mile further down the valley is a hamlet which derives its water supply also from the main stream. But in this case, more by good luck than good guidance, the water reaches the villagers comparatively pure. Goitre is very rare in this village.

I do not suggest for a moment that pollution *per se* is the essential cause of goitre, but I do suggest that pollution provides the nutrient material which

admits of the life of the *contagium vivum* of the malady not only in the soil, but in the water associated with it. I would venture to mention in this connection that when in Switzerland last spring, Mr. James Berry and I were shown by Professor Kocher and Dr. Vannod the notorious "goitre-well" of Sumiswald. The water pumped from this well was quite clear and sparkling, but apparently issued from the bowels of the earth charged with goitre-producing properties. I found, however, on making a careful search, that within 40 ft. of the well a cesspit was concealed, under the lee of an old house, which, from the sandy nature of the soil, and its position with respect to the well, must have for years supplied the nutrient material for the bacterial flora with which the water abounded. I believe that a source of pollution of goitre-producing waters can always be found if carefully sought for: this at least has been my experience in those parts of the world where I have studied the disease. With Bircher's view, as to the influence of the extinct flora and fauna of the marine deposits, I am in entire disagreement.

On the other hand, a pure water is in itself antagonistic to the life of the living excitant, for we know that the addition of such a water to a goitre-producing one diminishes proportionately its harmful properties, while waters of known purity are frequently used as curative agents by sufferers from goitre.

Richardson quotes the observation of Zschokke that the inhabitants on the right bank of the Aar were more subject to goitre and cretinism than those on the left; the only difference that could be observed being that the water on the right bank was more contaminated with animal and vegetable excretions than that on the left. Similar observations are recorded by St. Lager, Baillarger, Macnamara, and others.

It may be argued that if my contentions are correct all polluted waters should be a source of goitre. But this is no more a necessary sequence than that all polluted waters should cause typhoid fever. Indeed, the analogy between the spread of goitre and of typhoid fever is not inapt, so far as water, as a vehicle for both these maladies, is concerned. For the conditions which favour the life of the typhoid bacillus in water will favour also the life of the *contagium vivum* of goitre, and those precautions which have resulted in a great decrease of water-borne diseases, such as typhoid fever, have resulted also in a decrease of goitre. One not infrequently meets with reports in which enteric fever and goitre are bracketed together as having diminished in prevalence as a consequence of adequate protection of water-supplies. But just as a polluted water will not cause typhoid fever unless it contains the *Bacillus typhosus*, so a polluted water will not cause goitre unless it contains the living excitant to which this disease is due. And as typhoid fever can be

spread by agencies other than water—agencies which even two or three years ago were wholly unsuspected—so *we must recognize the probability of other sources of infection in goitre and not seek to explain every case by a slavish adherence to the "water-theory" only.*

How any Water becomes Goitrigenous.

It is now easy to provide an explanation of the fact that a water which does not cause goitre in one place may become goitre-producing, or that a goitre-producing water may lose wholly or partially its noxious property. Since water picks up the causal agent of the disease from the soil it will pick it up only from those soils which contain it. A water which is organically pure may pass over such a soil and become goitrigenous as a result. The beneficial influence of adequate protection of water from the soil is exemplified by those many instances in which the simple canalization of the supposed goitre-producing water has been followed by the disappearance of the endemic. St. Lager records that he "has often seen cretinism disappear and goitre diminish without the waters having been changed, but only as a result of their canalization." He has observed "in Savoy, in Switzerland, in Piedmont and in Dauphiné, numerous examples of the amelioration in the sanitary state of the population after pipes had been established to conduct into the village waters

of springs or rivulets which formerly flowed over the soil." St. Lager was at some pains to attribute this result to the loss of the goitre-producing power of the water consequent on a deposition of its dissolved salts in the pipes, while other writers have endeavoured to explain the disappearance of the disease in such cases on the ground that the villagers had ceased to drink water and now drink only wine. But such explanations as these are quite inadequate. Waters which are apparently rendered harmless by canalization have, in my opinion, never been goitre-producing at their source; their canalization has but prevented the entry of the *contagium vivum* of the disease from the soil.

On the other hand, a water which has become goitrigenous may lose this property as a result of dilution with a purer water, examples of which I have brought to your notice, or by Nature's usual methods of purifying water: the action of air and sunlight, and by subsidence. The importance of the purifying action of subsidence and the rapidity with which it renders a water comparatively harmless is well illustrated by the case of the artificially bred trout. The water in the tanks was goitre-producing, but not the water which flowed into the first or escaped from the last tank.

A water may be conveyed in pipes for long distances and produce the disease among the consumers at a distance, provided it is goitre-producing at its source. Flowing rapidly through

pipes it is not subjected to these purifying influences to the same extent. Thus the water-supplies of towns which are derived from goitrous districts may give rise to the disease in the towns so supplied.

What then are the ideal conditions for the development of goitre? They are to be found in a country district with an agricultural population living on a porous soil, which soil contains much organic matter and by virtue of its porosity or slope admits of the ready passage of organic matter into the unprotected streams and wells that are the water-supply of the people. It is in mountainous countries where limestone rocks abound that these conditions are most frequently found in combination. Consequently, goitre is pre-eminently a disease of the hills, and its relationship to the soil is clear.

Is Infection by Contact Possible?

Before closing this section of my discourse, I desire to refer to certain cases which are of especial interest and importance to the etiologist. One such case, in my own experience, is that of a party of soldiers who were encamped for some months in a desert place, far removed from all human habitation. One tent was occupied by eight men, one of whom suffered from a small parenchymatous goitre. When the men had been in camp for about two months, another man in this tent developed a well-marked and rapidly enlarging goitre. The man

had been in the habit of eating his food out of the same dish as the first goitrous soldier, and the two men were in other ways also intimately associated the one with the other. The water-supply in this case was not at fault.

I find amongst my records another and almost identical instance of this sort, and the writings of von Kutschera provide others. Cases of this kind are, in my experience, exceptional, but they indicate the possibility that infected water and infected soil are not the only means by which the *contagium vivum* of this disease can be conveyed to man, though to my mind they are not sufficient to justify von Kutschera's dictum that personal contact alone can suffice to spread the disease.

The prophylaxis of goitre consists in the adequate protection of the water-supply and a proper precaution against infection on the part of persons whose means of livelihood necessarily brings them into personal contact with infected soil.

Microscopical and Bacteriological Examination of Water.

Many attempts have been made to find in the suspended matter of goitre-producing waters an organism responsible for the production of the disease.

Klebs suspected certain infusoria, to which he gave the name "*naviculicula*," and which he found

in goitrous springs of Strasburg and Bohemia, as being the essential cause of goitre.

E. Bircher found that certain diatoms were peculiar to waters from definite geological formations, and noted that eucyonema abounded in water from those formations on which goitre prevailed. He did not, however, incriminate any diatom as the cause of the disease. I, myself, have noted that eucyonema is very common in the goitre-producing waters of Gilgit, as did also Johannesen in goitre springs of Norway.

Bircher also found a rod-shaped bacillus in the waters of goitrous districts, but not in the waters taken from regions where the disease was not prevalent. He was unable to find the bacillus in the contents of two goitrous cysts in young people. Lustig and Carle examined bacteriologically the water of twenty-five wells in the valley of Aosta, but failed to find the bacillus of Bircher. They noted the presence of a bacillus which liquefied gelatine, but which was innocuous when injected into animals. Tavel isolated thirty-three different bacteria from the water of goitre-producing springs, while he found only nine in non-goitre-producing wells in the same locality.

In Gilgit, I found a much larger bacterial flora in the goitre-producing waters of Kashrote than in the non-goitre-producing water of Barmis spring. Two bacteria were especially abundant in the goitrigenous water, while they were absent from the pure spring water. One of these was a moderately thick

rod, which did not retain the stain by Gram's method. It generally appeared in pairs. The second was a minute coccus-like organism, growing in small transparent and rounded colonies. This organism also failed to retain the stain by Gram's method.

Very much more important are the recent findings of the Swiss Goitre Commission. Through the kindness of its members I am in a position to lay before you a brief *résumé* of its work. The following table, which has been prepared for me by Dr. Vannod, gives the result of quantitative bacteriological examination of waters from goitrous and non-goitrous districts. It shows the number of colonies in given volumes of water as determined by plate cultures on agar :—

Goitrous Localities			Goitre-free Localities		
	Vol. of water in centimetres	Colonies		Vol. of water in centimetres	Colonies
Canton of Bern.					
Sumiswald well	0·10	1,450	Fleusier...	0·10	1
	0·50	6,250		0·50	6
Lauterbrunnen stream ...	0·10	6,400	St. Imier	0·10	13
	0·50	49,330		0·50	19
Canton Grisons.					
Tartar fountain	0·10	28,900			
	0·50	50,600			
Zizers fountain	0·10	212			
	0·50	3,410			
Canton Valais.					
Naters old source ...	0·10	640			
	0·50	1,242			
Granges wells	0·10	648			
	0·50	2,665			
Gassijmaw wells ...	0·10	5,100			
	0·50	12,200			

The next table shows the results of quantitative bacteriological examination of waters from very goitrous localities in Switzerland, and from localities where the disease is comparatively rare.

Highly Goitrous Localities			Localities where Goitre is Rare		
Village	Vol. of water	Number of colonies	Village	Vol. of water	Number of colonies
Naters	0·10	640	Brigue	0·10	17
	0·50	1,242		0·50	150
Munt	0·10	2,665	Louèche-Ville ...	0·10	2
	0·50	7,100		0·50	5
Gampissin ...	0·10	5,100	Savieze ...	0·10	11
	0·50	12,220		0·50	44
Sierre	0·10	1,134	Montigny-Ville	0·10	9
	0·50	5,760		0·50	17
Granges ...	0·10	640	Monthey ...	0·10	9
	0·50	3,500		0·50	43
Abbaye de St. Maurice	0·10	1,320			
	0·50	12,420			
Troistorrents ...	0·10	31,860			
	0·50	72,900			
Les Evouettes ...	0·10	810			
	0·50	5,740			

Drs. Vannod and De Mestral have concluded as a result of their extensive bacteriological investigations :—

"(1) That in the majority of cases there seems to be a connection of cause and effect between the richness of the water in bacterial germs and the frequency of goitre. This is peculiarly striking :—

"(*a*) In the case of waters poor in bacteria and proceeding from localities where goitre is prevalent to a small extent: as in Brigue, Louèche-Ville, Savieze, Montigny-Ville and Monthey.

"(*b*) In the case of waters rich in bacteria, and proceeding from localities where goitre is

very abundant, as in Naters, Munt, Gampissin, Salguenen, Sierre, Granges, Fully, Abbaye de St. Maurice, Troistorrents, and Les Evouettes.

"From the point of view of qualitative bacteriological examination the cultures of water in Agar have shown everywhere the same colonies.

"(1) White lanceolated, varying in size.

"(2) Grey, transparent, rounded and very small.

"We have always found they consist of (*a*) little bacilli in rods, and (*b*) of cocci, the two species decolorizing by Gram's method. The cultures rich in bacteria presented almost always a marked fluorescence."

It is thus seen that bacteriological examination of the water, while it has so far failed to incriminate as a cause of goitre any particular organism, demonstrates that goitre-producing waters are eminently those in which micro-organisms find the nutrient materials for their life and growth.

Some authors assert that many goitre-producing waters are practically sterile, but it has not been demonstrated by experiment that such sterile waters are capable of producing disease in any form, nor do I believe it possible.

In my next lecture I shall deal with the habitat of the *contagium vivum* of goitre in the body of sufferers from the disease.

LECTURE III.

It is my intention to-day to direct your attention to the progress which has been made towards the identification in the human body of the particular *contagium vivum* which we have now ascertained to be the immediate cause of endemic goitre. We have seen that all attempts have so far failed to identify it outside the body of man; we will now proceed to consider what evidence there is of its existence in the body of sufferers from the disease.

On the entry of the *contagium vivum* with the food into the human intestine three courses are open to it:—

(1) It may invade the blood and tissues, giving rise to a chronic infection.

(2) It may reach the thyroid gland and exert its harmful influence in the gland itself.

(3) It may remain in the intestinal tract, there producing poisonous substances which, on absorption, initiate the changes in the thyroid gland.

We shall now consider the evidence for and against these three possible modes of action of the organism, examining, in the first place, the possibility of a chronic blood infection.

The Blood in Goitre.

In the year 1898, Dr. Grasset published an account of a hæmatozoön, which he found in the fresh peripheral blood of sufferers from goitre of ten to fifteen days' standing. This organism was found in various forms: (1) As a spherical body larger than a blood corpuscle, having no nucleus and containing no pigment; each had a free flagellum, four times as long as the diameter of a red blood corpuscle, which moved in a rapid and disordered manner; (2) as segmented bodies, agglutinated or separate; (3) and as irregular-shaped bodies containing pigment but no nucleus. Grasset was careful to point out that none of the goitrous patients whose blood was examined were the subjects of malaria.

Though I have often sought, in recent cases of the disease, for the parasitic elements described by Grasset, I have consistently failed to find them. McKenzie records a like experience. None of the numerous observers who have studied the blood in goitre have recorded the presence of blood parasites. Grasset himself does not appear to have followed up his discovery with more detailed observations as to the life-history of the organism. The Swiss Goitre Commission has devoted much attention to the question of the presence of blood parasites in goitre, but always with negative results. Malarial parasites are often seen in the blood of

sufferers from goitre in malarious districts, and it is possible that other blood parasites also may be met with in goitrous individuals, but up to the present time no organism has been found in the blood-stream to which the disease could be attributed.

Nor have blood inoculation experiments yielded any positive results. In 1907, I inoculated 2 c.c. of blood, taken from a young man, the subject of a recent goitre, into the flank of a young monkey. Two inoculations were made at intervals of seven days, but no results were observed. The monkey remained in perfect health.

Parasitic Thyroiditis of Chagas.

It is in these particulars as well as in its symptomatology that the endemic goitre which we are discussing differs from the "parasitic thyroiditis" recently described by Dr. Carlos Chagas. This disease, which is endemic in Brazil, approximates in one of its forms so very closely to endemic goitre that I would ask your permission to make a slight divergence from my main theme in order to lay before you the results of Dr. Chagas' most important work, and to point out its bearing on the subject immediately before us. "Parasitic thyroiditis" is due to a trypanosome, the *Schizotrypanum cruzi*, possessing peculiar features, and is conveyed from man to man by a biting insect, the *Conorrhinus megistus*. According to Brumpt, other insects also can act as hosts, especi

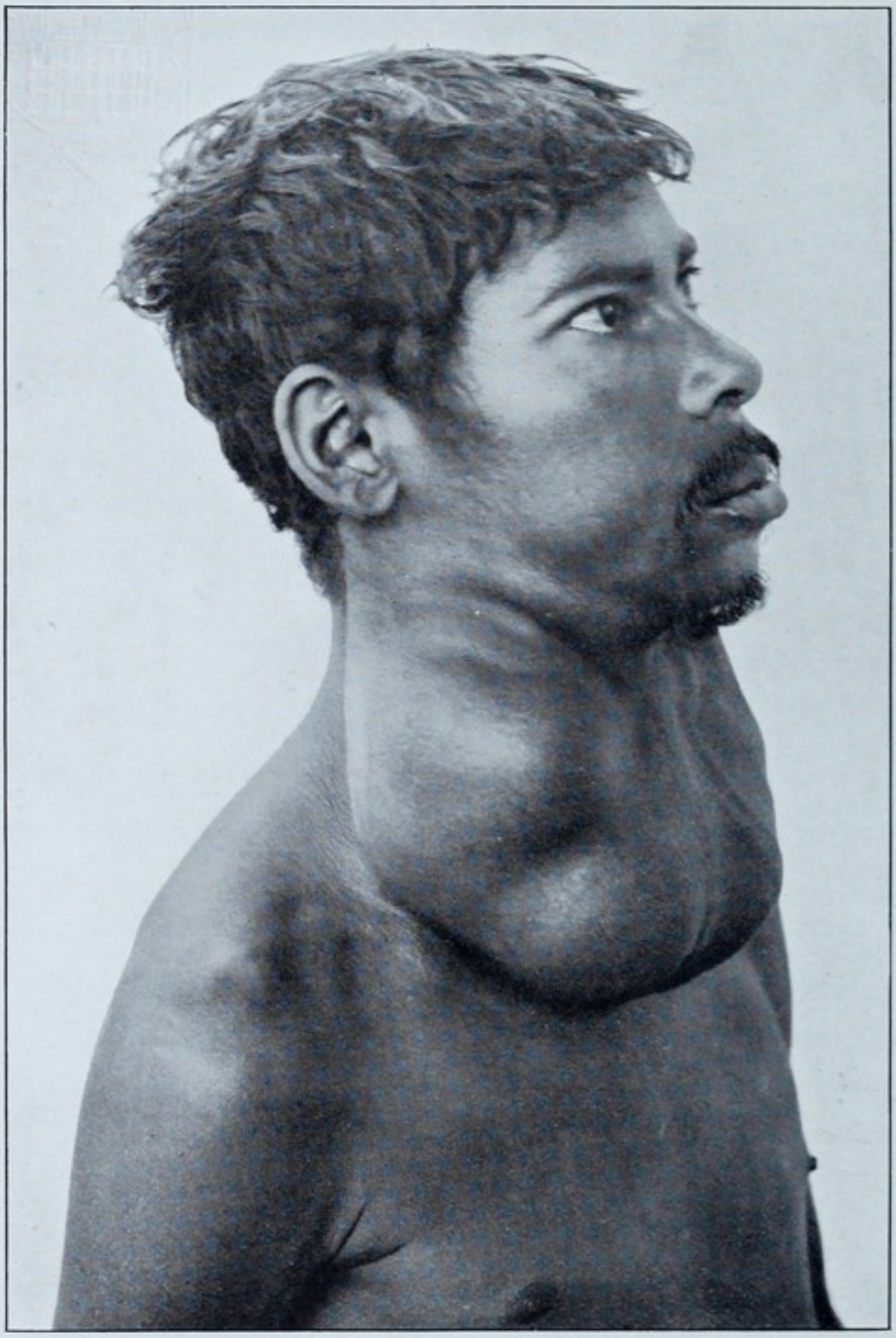

FIG. 19.—Goitre considered by Chagas to be a case of "chronic parasitic thyroiditis." Photo by Dr. Carlos Chagas.

ally the bed bug (*Cimex lectularius*), the excreta of which are highly infective. The malady, as the name implies, is essentially an acute condition. It is attended with pain in the thyroid gland, continued fever often high, enlargement of the lymph glands, spleen and liver, and nervous symptoms of peculiar malignancy. Trypanosomes are readily found in the blood-stream during the acute stage of the disease. The temperature remains elevated while the parasites are present in the blood. It affects young infants chiefly and gives rise to an enormous mortality amongst them. If the disease does not terminate fatally within fifteen to thirty days of its onset it lapses into a chronic form of illness, which is said to be characterized by the presence of goitre, often of very large size, and symptoms due to partial or complete loss of function of the thyroid mechanism, nervous symptoms, and affections of the heart. These symptoms are classified by Chagas, who groups them into "four forms." Patients show a peculiar colouring of the skin "different from the paleness of anæmia, and likened by Professor Austrigesilo to the appearance of pale bronze." Dependent on the degree of thyroid derangement the symptoms may be slight, of moderate intensity or very pronounced. It is possible, therefore, to meet with cases which are practically indistinguishable from the usual type of goitrous individual met with in endemic localities in Europe (fig. 19).

According to Chagas, these large degenerated goitres are the result of a schizotrypanum infection acquired during the early years of life. It is not possible to distinguish such cases from cases of true "endemic goitre" by blood examination, since the trypanosome, which is said to cause the goitre, disappears from the blood-stream after the acute symptoms have subsided.

Chagas has given two illustrative cases of the development and progress of the malady in adults, which may serve to show in what respects it contrasts with endemic goitre.

"A Syrian who came to an infected zone lived in a house infected by the *Conorrhinus megistus* for several months. He had pain and swelling of the thyroid gland with slight febrile reaction. Six months later the thyroid was larger and the schizotrypanum was found in the blood. Heart rhythm changes were also present."

"A woman, aged 30, a newcomer to the infected zone, came to the hospital complaining of pain in the thyroid and slight rise of temperature. The liver was somewhat enlarged. Chagas demonstrated the trypanosome infection by inoculation experiments in guinea-pigs. Some time afterwards the patient developed intensive general convulsions, which were favourably influenced by thyroidin. Two months later she died, with a very large thyroid, and the microscopical changes brought about by the schizotrypanum were established."

I find, in the writings of Chagas and his helpers, no reason to doubt the accuracy of many of his conclusions with regard to the acute form of the disease he has described. It is not equally clear, however, that the chronic goitres are due to the same cause which gives rise to the acute illness. Professor Kolle of Bern has informed me that, though he has produced some thyroid swelling in a rabbit by the injection of a culture of *Schizotrypanum cruzi* into the artery leading to the gland, it has not been possible to induce the formation of a true goitre in this way.

Thyroid enlargements amounting to the formation of true goitre can, according to Bayon, be brought about by the injection of certain bacteria or their toxins into the gland; so that did the injection of a culture of trypanosomes give rise to a like result it could not be regarded as peculiar.

The work of Chagas is of the greatest interest, since, if it is confirmed, we shall have to recognize the existence of a form of endemic thyroiditis, due to a protozoal organism, together with the very important fact that a form of endemic goitre can be conveyed from man to man by certain biting insects.

We must not lose sight of the possibility that two forms of endemic thyroidomegaly—if I may use the term—may prevail side by side in the same district, in the same way that two different forms of splenomegaly may be found to be

endemic in the same locality. Nor must we lose sight of the possibility that a trypanosome infection may co-exist in the same individual with goitre initiated by the endemic influences I have indicated to you. The only criticism of Dr. Chagas' admirable work which I am at present disposed to make is that he does not appear to have excluded, in a manner which leaves no room for doubt, the possibility that the form of trypanosomiasis which he has described may be an infection superimposed upon "endemic goitre," and not, as he considers the infection to be, the veritable cause of this malady in Brazil. However this may be, there can be no doubt of the differences which exist between the "parasitic thyroiditis" endemic in Brazil and the goitre endemic in Europe and in the Himalayas. Nevertheless, Dr. Chagas' work reminds us forcibly that all cases of goitre in endemic localities need not necessarily originate from the same cause.

Returning to our consideration of the hæmatology of endemic goitre, we find that blood changes of a fairly definite character are almost always to be met with. I have made blood counts in seventy-three cases of goitre at all stages of the disease. The earliest case examined was that of a young man who had first noticed the thyroid enlargement four days previously. The total leucocyte count showed no marked deviation from normal; no blood parasites were found. The blood count was as follows: Polymorphonuclear cells, 58 per cent.;

small mononuclear cells, 23·5 per cent.; eosinophile cells, 10·5 per cent.; large mononuclear cells, 8 per cent. A case in which the thyroid enlargement was of twenty days' duration showed, in addition to the absence of blood parasites from the peripheral blood, a blood count as follows: Polymorphonuclear cells, 47·6 per cent.; eosinophiles, 4·6 per cent.; small mononuclear cells, 36 per cent.; large mononuclear cells, 12·6 per cent. The blood counts in two cases of experimentally produced goitre in men, in whom the thyroid enlargement was definitely known to have been present for only fifteen days, gave the following results: Polymorphonuclears (1) 44·8 per cent., (2) 50·4 per cent.; eosinophiles (1) 8 per cent., (2) 7 per cent.; small mononuclears (1) 36·7 per cent., (2) 33·6 per cent.; large mononuclears (1) 10·5 per cent. (2) 9 per cent.

From a study of the seventy-three cases examined I found the polymorphonuclear leucocytes to be constantly below normal limits with one exception only. These cells may form as little as 30 per cent. of the total leucocytes present in peripheral blood; the average count for the seventy-three cases was 46·5 per cent. The small mononuclear cells were above normal limits in all but six cases. The percentage of these cells in peripheral blood has reached as high a figure as 45 per cent. The average count for the seventy-three cases was 32·2 per cent. The eosinophile cells

were above normal limits in all but eight cases. These cells have been found in some cases to form as high a proportion of the total leucocytes in peripheral blood as 20 per cent. The average count for the seventy-three cases was 10 per cent. The large mononuclear cells were within normal limits in all but seventeen cases. If we convert these figures into percentages, we find that the polymorphonuclear leucocytes are below normal in 98·9 per cent. of cases; the small mononuclear leucocytes are above normal limits in 92·5 per cent. of cases; the eosinophile cells are above normal limits in 88 per cent. of cases, while the large mononuclear cells are increased in only 23 per cent. of cases. It was observed that these changes are most marked in recent cases.

Examination of the fæces for intestinal worms showed that while often to be found, there was no evidence of their presence in the majority of the cases. The eosinophilia, therefore, cannot be accounted for in this way.

In blood taken from the thyroid gland itself by means of a hypodermic needle it was found that eosinophile cells were present in very large numbers. Twelve cases were examined in this way.

In the year 1906, I drew attention to these blood changes. Marine published similar findings in 1910, and pointed out that there was in addition a diminution of the hæmoglobin index and of the

number of red blood corpuscles. The total number of leucocytes he found to be reduced in simple goitre. Miss Charlotte Millar has also found in cases of simple goitre an absolute reduction in the numbers of polymorphonuclear leucocytes down to 50 per cent. of the normal, and a hyperlymphomatosis of from 30 to 50 per cent. More recently Bauer, working in Tyrol, has also observed the increase of lymphocytes in this disease, while Lidsky and Kottman have found that the coagulability of the blood is increased.

The blood changes of exophthalmic goitre so far resemble those of endemic goitre that the polymorphonuclear cells are diminished and the mononuclear cells are increased in numbers. But by a somewhat strange antithesis, observed by Marine, the reduction of the red blood corpuscles and the increase of the eosinophile cells present in endemic goitre contrast with an increase in the former and a decrease in the latter in the exophthalmic form of goitre. These blood changes are not sufficiently characteristic as to make it possible by blood examination to distinguish, in doubtful cases, between endemic and exophthalmic goitre. In opposition to Professor Kocher, who emphasizes the importance of blood examination as a differential test in early cases of Graves's disease, I am strongly of opinion that it is valueless for this purpose, and that its employment is calculated to lead to many errors of diagnosis and to the adoption of

surgical methods of treatment which are not justified by the gravity of the patient's condition.

The blood changes in cases of endemic goitre give one an indication that perhaps in the intestinal tract is to be found the seat of infection, since similar changes are met with in certain intestinal infections.

Having failed then to find in the blood any indication of a chronic infection, we now turn to an examination of the thyroid gland itself and the changes which it undergoes in this disease.

Pathogenesis of Endemic Goitre.

By reason of the lack of material it is not possible to study in the human subject the very earliest changes which result in the development of goitre. Goitres which are removed by operation are usually the seat of extensive degenerative changes which obscure the picture of the fundamental process. Our knowledge, therefore, has been acquired by a study of uncomplicated thyroid enlargements in animals, and is largely the result of the work of such observers as Horsley, Marine, Lenhart, Bayon, and others.

Now, though the following account of the pathogenesis of goitre, which I have compiled from the writings of our best known workers on the subject, and largely verified by my own histological studies, is, I believe, *in the main, an accurate record of the changes* which take place, yet I am myself not fully satisfied that it affords a full and

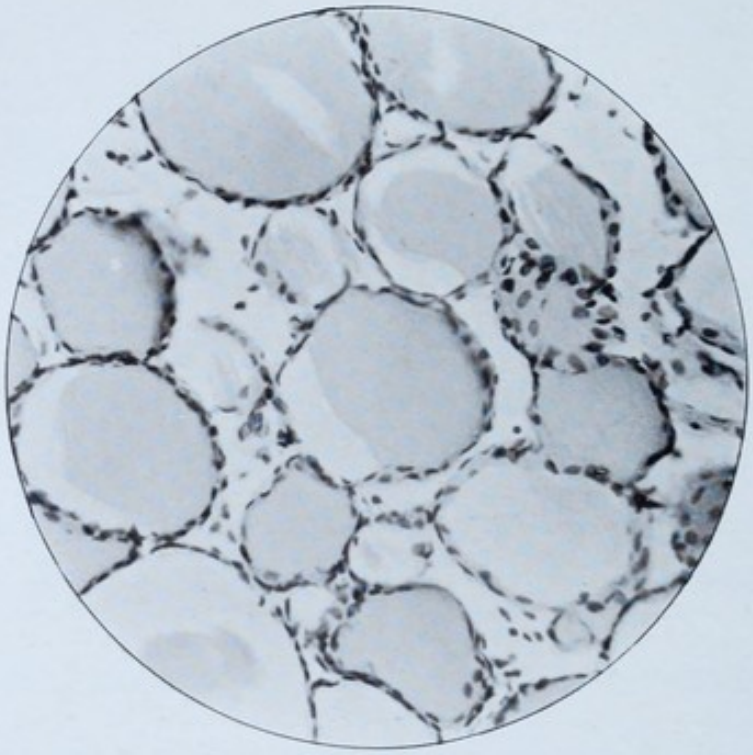

FIG. 20.—Normal thyroid gland of guinea-pig (Farrant).

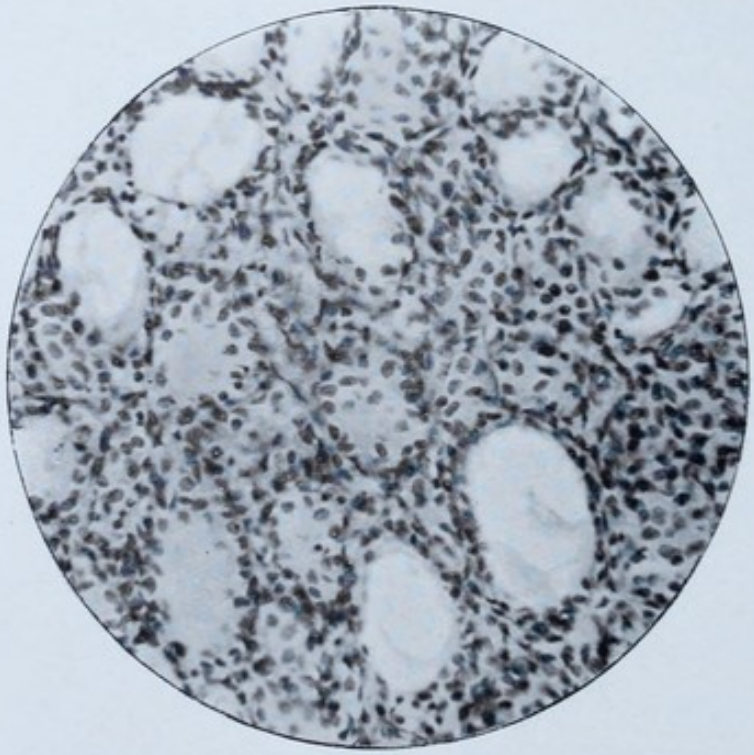

FIG. 21.—Moderate degree of hyperplasia of guinea-pig's thyroid, produced by injection of diphtheria toxin (Farrant).

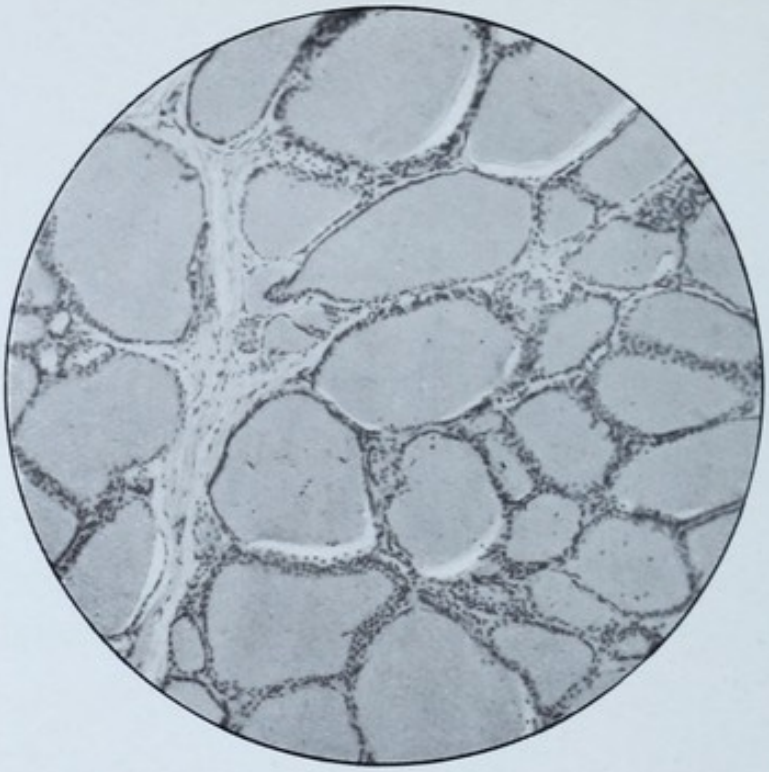

FIG. 22.—Normal thyroid gland of man (Marine and Lenhart).

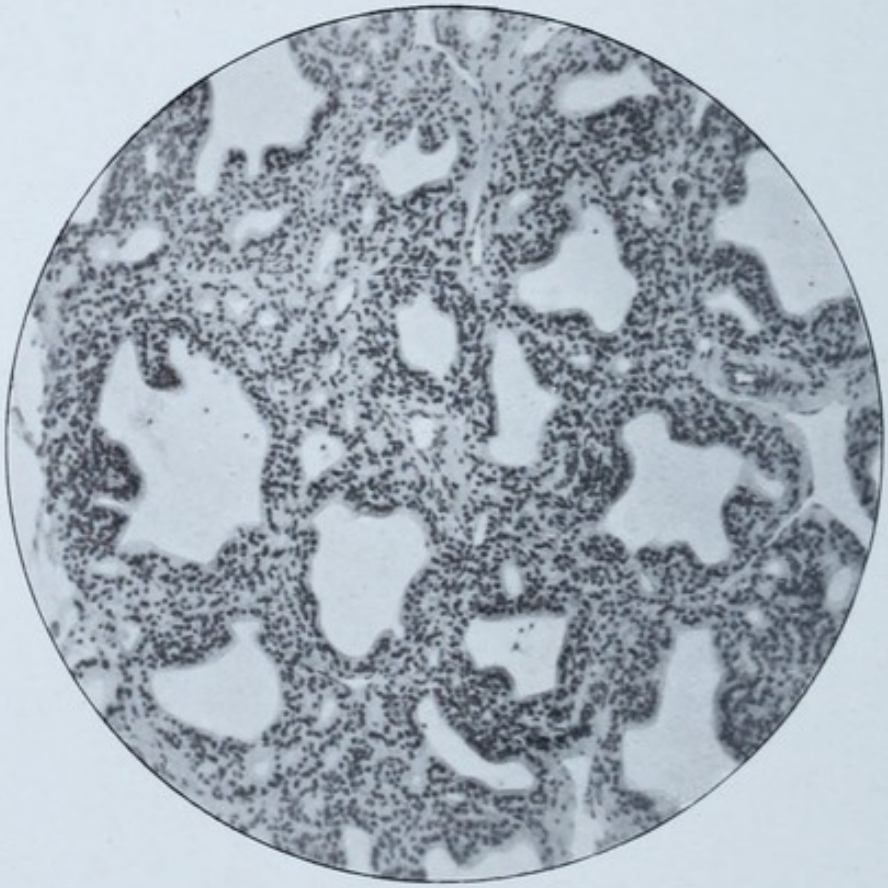

FIG. 23.—Thyroid hyperplasia in dog, showing folding of cellular lining of vesicles (Marine and Lenhart).

satisfactory explanation of the different stages in the development of parenchymatous and colloid goitre.

According to Marine and Lenhart, the earliest changes are to be observed in the blood-vessels, the epithelium and the stroma of the organ, and these changes vary with the degree and stage of the process. There is, in the first place, a markedly increased blood-supply to the gland. The capillaries and larger vessels of the stroma are dilated and there is an increased secretion of colloid substance which is more liquid, thinner, and takes the stains much more lightly than usual (Bayon). The next step in the process is an increase in size of the cells lining the vesicles, which may vary greatly in degree. The cells may be cubical in mild degrees to high columnar in the severer degrees of hyperplasia. They are more closely packed, more highly granular, and the nucleus is more deeply staining than is the case in the normal gland (figs. 20 and 21). Should these changes occur rapidly the cellular lining of the vesicle may undergo folding or plication, an appearance which is constantly observed in the severer degrees of hyperplasia, but never to the same extent in simple goitre as in exophthalmic goitre (figs. 22 and 23). The cells may become so high as to fill the whole lumen of the vesicle, as I myself have observed to be the case in goats in which severe degrees of hyperplasia were induced by experiment

(figs. 24 and 25). At this stage of the process the gland may not have increased in size; and there may be little or no colloid in the vesicles, its increased fluidity possibly favouring its discharge into the lymphatics and blood-stream. According to Marine, however, there is a degree of enlargement proportional to the degree of hyperplasia. Marine and Lenhart have called this "the pre-clinical stage of goitre."

Coincident with the process of parenchyma hyperplasia, hyperplastic changes take place in the connective tissue stroma. These fibrotic changes may be slight or marked, diffuse or localized.

Bayon has demonstrated that following the glandular hyperplasia a desquamation of the epithelial lining of the vesicles occurs. The desquamated cells coagulate and form with the colloid "casts," which, in his opinion, further irritate the epithelium to increased secretion and proliferation. The increased secretion is retained in the vesicles and as a result of the pressure of the colloid the lining epithelium of the vesicles loses its polyhedral shape and becomes cubical, or even pavement-like (fig. 26). The dilated vesicles lose their rounded outline and become irregular in shape. Their walls become thin and may rupture, the coalescence of adjacent dilated vesicles giving rise to cyst formations. Vestiges of previous active hyperplasia are to be found in the form of occasional projections of the wall (fig. 27) of the dilated vesicles, which are

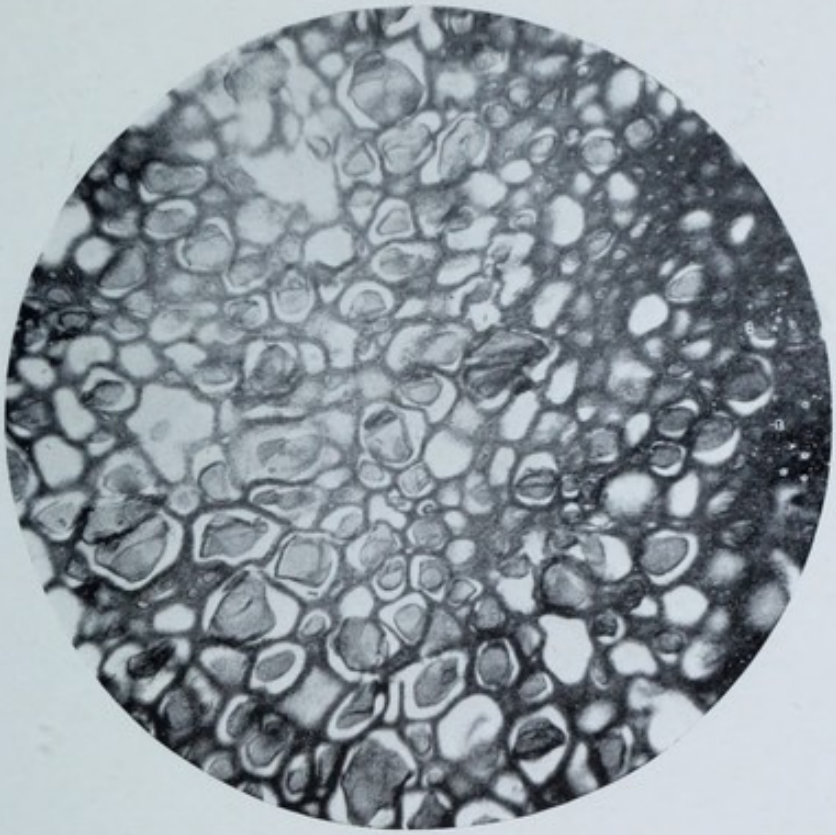

FIG. 24.—Normal thyroid gland of goat × 100.

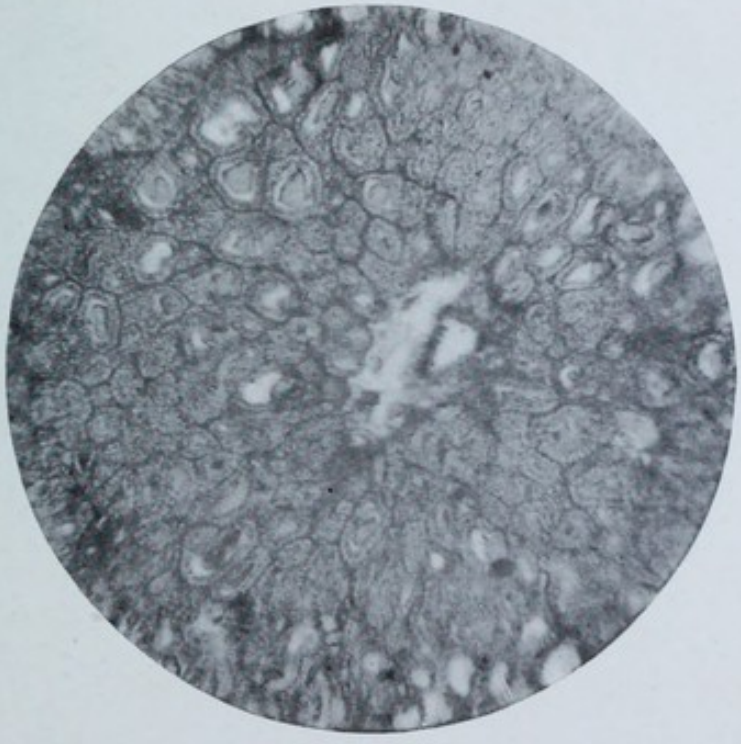

FIG. 25.—Thyroid hyperplasia in goat × 100.

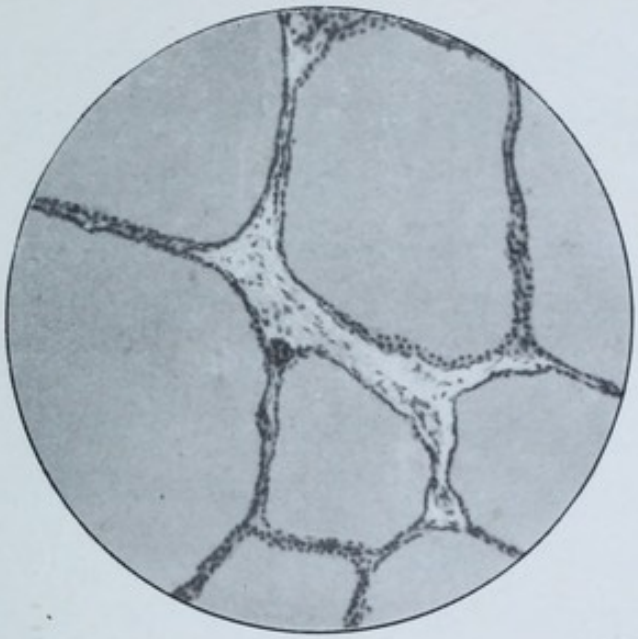

FIG. 26.—Colloid goitre in sheep. (Marine and Lenhart.)

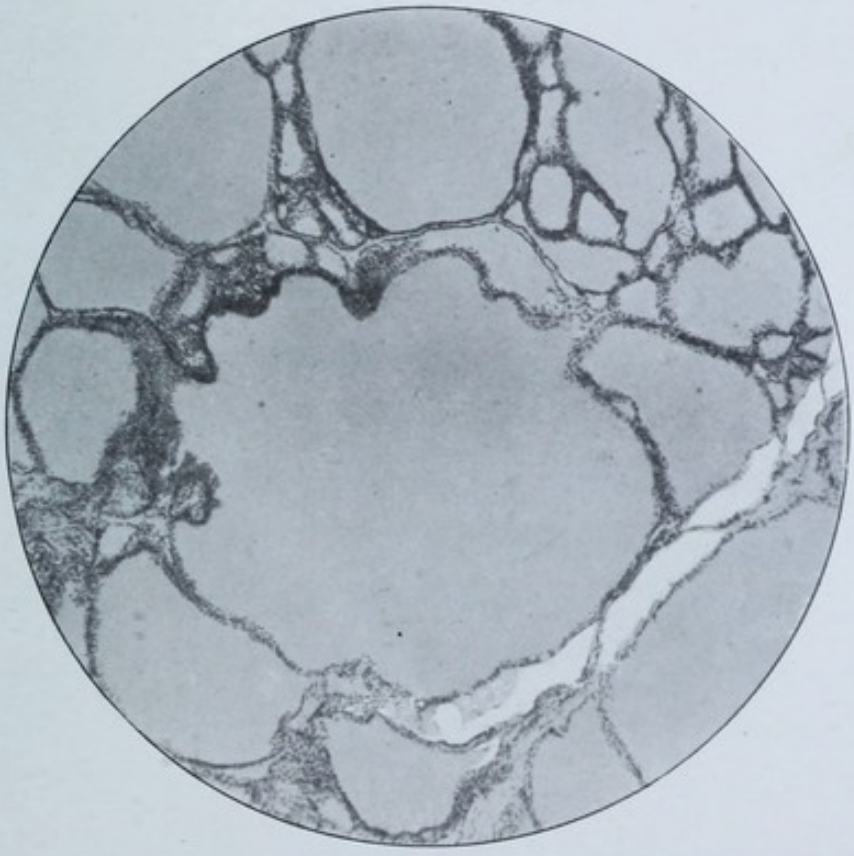

FIG. 27.—Colloid goitre in man (specimen from Pathological Laboratories of Munich).

covered with cubical or columnar epithelium according to the stage of the process, in an increase in the connective tissue stroma and in obliterating endarteritis of the vesicles. Marine and Lenhart describe the process as a reversion of the gland to the "colloid state," and speak of the goitres so formed as "colloid goitres," a term which is, I think, more applicable at this stage of the process than "parenchymatous goitre," and one which should not be limited to those "parenchymatous goitres in which the colloid material is unusually abundant and obvious" (Berry).

The whole process is catarrhal, and in a sense compensatory in character, and results in the formation of an increased amount of colloid substance, which is to a large extent retained in the gland. The changes appear to differ in no essential from those described by Hürthle, Horsley, Murray, and Edmunds, as taking place in the portion of thyroid left behind after partial thyroidectomy in animals—a fact to which McKenzie drew attention in 1898.

"Colloid" goitres formed in this way may be subject to recurring attacks of hyperplasia, and consequently the gland increases in size by a step-like process, which accounts for the increases observed in the size of goitres at certain seasons in goitrous localities.

Since King and Horsley demonstrated that by pressure the colloid secretion could be made to

pass from the alveolus by way of the interalveolar lymphatic spaces to the lymph vessels, it has been generally accepted that this is the route which the secretion follows in its course to the blood-stream. Biondi has shown that it may also find its way into the lymphatics as a result of rupture of the alveolar walls; while Hürthle has demonstrated, by the injection of Berlin blue into the lymphatic spaces, the existence of minute intercellular channels which form lines of communication between the alveolus and the interalveolar lymph spaces. If it is true that under normal circumstances the thyroid secretion is discharged into the blood-stream in this way, then in the development of goitre it appears evident that some impediment must exist to the escape of the secretion by way of the lymphatics. The work of Gutknecht, Todbelsky, and Horne indicates that this is probably the case, since colloid is absent from the lymphatics in a large proportion of cases of goitre, but present in the veins of the enlarged gland. Forsyth has made the interesting suggestion that in goitre there is a retention of colloid in the gland owing to the obstruction of the main lymphatic channels by a parasitic organism, and that the secretion, finding its way blocked by the usual channel, reaches the blood-stream *via* the veins—a circumstance which would account for the absence of myxœdema in most cases of goitre.

Now since the changes which take place in the

process of the formation of a "colloid goitre" are largely the result of the mechanical pressure exerted by the increased and increasing colloid secretion (Forsyth), it follows that the radially exerted pressure of the colloid, together with the mutual lateral pressure of adjoining cells, will result in the obliteration of the intercellular channels of Hürthle. In this way the first line of communication of the vesicle with the lymph channels may be interfered with. On the other hand, the colloid itself may be so altered as to make its escape by the usual channels more difficult. We know that under the abnormal conditions which give rise to goitre, the colloid is largely made up of desquamated cells which coagulate in the secretion, thus increasing its consistency and rendering it very viscid. Further, with the increase of the intensity of the toxic substance, there is a greater injury to the secretory cells of the gland and an increased degree of desquamation results in consequence. So that with increasing goitrous influences—that is to say, with the increase of goitrigenous poisons in the blood—we may expect that not only will individual goitres be larger, but also that more people will be goitrous—the increase of the toxic agency having brought about a correspondingly increased alteration in the colloid secretion, which impedes its flow from the gland. Although the available evidence points to an impediment to the escape of colloid from the gland, the increase of the secretion in goitre may

be readily explained by that other hypothesis which attributes to the secretion the power to neutralize in the gland itself toxic substances which are carried to it by the blood-stream. If this hypothesis is correct, the increase of the colloid in goitre would represent simply an increased production and storage of secretion in the gland consequent on an increase of toxic substances in the blood. The question of the cause of the retention of colloid in the thyroid gland in simple goitre is one which calls for investigation.

The changes which I have described as characteristic of endemic goitre occur, as a rule, uniformly over the whole gland, but may be more apparent in some parts than in others. Amongst vesicles which have undergone the process of active hyperplasia and subsequent distention with colloid may be found others which have not been affected, and which retain their normal characters.

There may also develop in the gland rounded or circumscribed masses apart from the main body of the goitre. These are usually called "simple adenoma," or "fœtal adenoma," according to their histological appearances. They may occur either in the form of a single nodule or of several nodules scattered through the gland which, in developing, encroach on the normal tissues, causing atrophy. This adenomatous form of goitre is one which is very common in goitrous localities. It is, according to Bircher and Wilms, almost constantly met with

in the artificially induced goitre of rats, in which animals a preponderating tendency to nodose hypertrophy is said to occur.

Thyroid glands which have undergone the parenchymatous changes described are rarely of large size. They tend to suffer, and, indeed, are peculiarly liable to secondary degenerative changes, that is to say, to complications engrafted on the fundamental process. Thus fatty degeneration, with a corresponding atrophy of the secretory cells of the gland, is common in all parenchymatous goitres; while cysts are found in all but the smallest goitres, and are often of large size. They may form by the distension and coalescence of vesicles due to atrophy of the vesicle walls as a result of pressure from the imprisoned colloid. Cysts may also form in consequence either of degenerative changes in the sclerotic connective tissue, or of hæmorrhages. Fibrotic changes may progress to such an extent as to produce a cirrhosis of the gland, causing atrophy and obliteration of vesicles. This process, however, rarely results in sufficient destruction of glandular tissue to cause myxœdema. The blood vessels of the enlarged organ may become varicose and dilated to an enormous extent, or deposits of lime and other salts may take place in the gland. All these changes may be combined in the same organ, giving rise to the most varied pictures on histological examination, and to the large degenerated tumours characteristic of goitrous localities.

It is important to remember that degenerative processes early attack the thyroid gland which is, in the first instance, the subject of continued and increased glandular activity. The point is of the greatest importance to the physician, for it is obvious that to be successful, medicinal treatment must be commenced early, and that once degenerative processes have progressed to any extent, and have resulted in the formation of adenoma and cysts, medicinal treatment in any form must prove unavailing. In the great majority of all cases of parenchymatous goitre which come before the physician, the functional activity of the gland is impaired to some extent, and the patient exhibits symptoms corresponding in degree to the degree of impairment of glandular function.

We may sum up the changes which take place in the thyroid gland as a result of goitrous influences by saying that these influences *at first stimulate the organ to increased activity, but that the increased activity so induced is early followed by damage to the secretory epithelium, and by degenerative changes which impair its functional activity.*

There is reason to believe that a large proportion of all individuals who are subjected to goitrous influences show some degree of thyroid hyperplasia, though this may not lead to the actual formation of visible goitre. Marine and Lenhart found that of 450 specimens of trout taken from the tanks to which we have already referred, a

thyroid hyperplasia was present in every case. E. Bircher examined the thyroid glands of thirty individuals dying from causes unconnected with goitre in the hospital at Aarau. He found the majority of these showed some degree of degeneration. It was only in the glands of wholly youthful subjects that the thyroid was found to be normal.

Thyroid Hyperplasia Variously Induced.

Bayon has shown that all stages of simple goitre can be produced in various ways by experiment: (1) By ligaturing the thyroid artery; (2) by the injection of an emulsion of soot in sterile water into the thyroid gland; (3) by the injection of typhoid toxins into the gland; (4) by poisoning with phosphorus. As a result of his experimental work, he has concluded that "any cause which is capable of altering the function of the thyroid so as to damage its secretory epithelium can lead up to the production of colloid, diffuse, or nodular goitre." When I come to consider the experiments dealing with the transmission of goitre from man to animals, it will be shown that thyroid enlargement can be produced by feeding goats on a highly fæcal polluted water, and that very marked hyperplasias can be brought about as a result of feeding these animals with cultures of micro-organisms grown from the fæces of goitrous individuals. The many forms of "thyroiditis" are

examples of goitre due to micro-organisms of the class "bacteria," while certain protozoal organisms can also cause thyroiditis. Lastly, goitre can be produced by the poisonous substances generated in the body of man and animals, either as a result of metabolic processes or by the normal bacterial inhabitants of their intestinal tract. Examples of goitre due to poisons of this nature are the goitre of pregnancy and the congenital goitre of puppies born of a partially thyroidectomized bitch.

We thus see that "goitre" can be produced in a number of ways, but chiefly by the action of micro-organisms and toxic irritants. It is highly probable, therefore, that in the case of "endemic goitre" there must exist an irritant either in the form of a micro-organism present in the gland itself or of toxic substances circulating through it.

The Sterility of Goitre.

Many attempts have been made to find in the thyroid gland more definite evidence of the nature of the goitre-producing substance than that which is afforded by the pathological findings I have described. Since the year 1902, I have made repeated, but unsuccessful, examinations of blood obtained by thyroid puncture in recent cases of goitre.

Very careful histological examinations have been made by Hofer, Bonnet, and Pick in the

case of trout goitres, but with negative results so far as the detection of a micro-organism was concerned.

Dr. Helen Chambers has examined 259 cases of innocent goitre, thirty of which were pure parenchymatous enlargements. She has recorded that "several hundred sections have been made in some of the cases, and these have been treated by various methods of staining organisms in tissues. Bacteriological examination, including animal inoculation, has been made in a few cases. The result has been entirely negative. Nevertheless, the histological characters suggest a toxic substance present in the thyroid gland—in some cases diffuse, in others localized."

Professor Kolle, of the Swiss National Commission on Goitre, speaking on the work of this Commission, has stated: "Neither the use of the newest staining methods—for instance, Giemsa's staining of smear preparations, as well as the silver method, with sectional preparations—nor examination based on the newest principles of microscopy (dark ground illumination), has supplied us with any grounds of proof of the presence of a specific excitant in the thyroid gland that has undergone strumous degeneration, or in the blood of patients affected with goitre. If acute inflammatory processes in the goitre or general infective diseases fail to be present, the goitres, as Tavel has already stated, are completely sterile." He goes on to

remark: "One naturally thinks of protozoa as excitants. But if they are present they must be demonstrable, and demonstrated before they can be reckoned with. . . . Our endeavours to prove the presence of specific substances or specific elements by means of immunization and immunity-reactions, have been completely negative. It is the same thing whether one employs as an antigen the goitrous tissue, or its extracts, or the blood of goitrous patients, or extracts of fæces. It has been impossible to demonstrate the presence of anti-bodies, either in the blood of goitrous patients, or in the thyroid gland. The immunization of animals with the substances mentioned supplies—upon use of the various reactions, for example, of the precipitin or of the complement agglutination—no reasons for supposing the presence of specific elements or poisons." The Swiss Commission also carried out extensive inoculation experiments with a view to determining whether micro-organisms or other substances existed in the thyroid, which could produce the disease when introduced into animals. Pieces of goitre were transplanted into the abdominal cavity of four apes. After one month the transplanted tissue was absorbed. The animals remained healthy. An emulsion of fresh goitre juice was injected intravenously into three rabbits, one dog, and one monkey. The result was *nil*, the animals remaining perfectly healthy. A similar emulsion was injected intravenously into five rabbits

every week for three months. The result was negative.

Veichardt and Schittenhelm have recently demonstrated the presence of antibodies in the blood serum of rabbits inoculated with goitre-producing water. Their experiments, which promise fruitful results, are not yet completed.

Gelbride has examined bacteriologically the contents of eight cystic goitres. In seven the results were negative; in the eighth he obtained a culture of the *Streptococcus vermiformis* of Sternberg. Horand also has reported the presence of a parasite in a goitrous cyst. In neither of these cases, however, is there sufficient evidence to justify the suspicion that the organisms found are causal agents in the production of goitre. The greatest care must be exercised in investigations of this kind. I, myself, have amongst my records, a microphotograph of a diotom (navicula) found in the blood obtained by thyroid puncture from a case of goitre. Having regard to the fact that Klebs found naviculæ to be present in goitrigenous, and absent in non-goitrigenous waters, the discovery of this organism exercised my mind greatly for some time. My repeated failure to meet with it again in the blood convinced me that the source of the diatom was the water in which my hypodermic needle had been sterilized. Nor is this the only organism I have met with, but in the other cases also I have convinced myself that their presence was accidental.

We see, then, that up to the present time there is no evidence of the existence in the thyroid gland of goitrous individuals of any specific *contagium vivum*—whether microscopic or ultra-microscopic—to which the malady could be attributed. We are led to consider, therefore, whether the increased glandular activity, and the changes which follow it, may not be due rather to some toxic substance circulating in the blood-stream, and emanating from an organism resident in the intestinal tract.

It is impossible to prosecute the inquiry without some appreciation of the proper functions of the thyroid gland.

The Function of the Thyroid Gland.

The fact that the antitoxic and bactericidal resources of the body are largely dependent on the functional perfection of the thyroparathyroid mechanism is, I believe, as clearly established as is the influence of this mechanism on metabolism. I desire now to draw your attention to a few proofs of the thyroid gland's antitoxic action. Sajous showed in 1902 that the injection of various bacterial toxins into man and the lower animals excited, more or less actively, according to their virulence, the thyroid gland's functional activity, while Bayon's researches show that the injection of bacterial toxins into the gland may lead to the

actual formation of goitre. Farrant also has lately induced marked thyroid hyperplasia by the injection of diphtheria toxin into guinea-pigs (figs. 21 and 22); he demonstrated that the hyperplasia so induced could be controlled and greatly mitigated by the administration of thyroid extract at the same time as the toxin. Fassin found that the germicidal power of the blood was diminished by thyroidectomy. Charrin, Vincent, and Jolly drew attention to the fact that animals deprived of their thyroid glands are rendered very susceptible to infectious diseases, to which they readily succumb. Hürthle observed that by ligaturing the bile ducts in dogs, the thyroid secretion was increased; he attributed this change to the passage of certain constituents of the bile into the blood. Although this is doubtless possible, it may with equal reason be assumed that the operation, by depriving the intestinal contents of the biliary secretion, hastens putrefactive processes and thereby fosters the absorption of an excess of toxic substances into the blood-stream from the intestine. Turrô has found that the juices of swine's and sheep's thyroids dissolved almost entirely the comma, typhoid and anthrax bacilli, as well as the *Bacillus coli communis* and streptococcus. Gley showed that the blood serum of thyroidectomized dogs is more toxic than normal serum and gives rise to convulsions when injected into animals, while de Luca and d'Angerio have found that the urine of these animals contains

a higher percentage of toxic substances than is normal, and that thyroid extract administered to them counteracted this toxicity.

While making every allowance for errors of observation, these and other findings of a like nature justify the belief that the thyroid gland contributes largely to the body's antitoxic and bactericidal resources.

In some animals, low in the phylogenetic scale—amphioxus, ascidians and lower vertebrata—the thyroid gland communicates with the pharynx by means of a duct. In fishes also this is the case, so that in these animals the thyroid secretion enters the body by way of the alimentary tract. It may be, as has been suggested by Andriezen, that the thyroid secretion is absorbed in fishes through the vascular arches, and enables the respiratory organs to take up oxygen and carry on the gaseous metabolism more readily. But, in view of the secretion's antitoxic and bactericidal action, its discharge into the pharyngeal cavity is, to my mind, an indication that it is intended to exercise this action in the alimentary tract. We have seen that trout develop goitre when confined in filthy, unhygienic tanks which are swarming with micro-organisms. It is highly probable that under these circumstances the thyroid gland is stimulated to increased activity, and that in consequence there is, at first, an increased discharge of colloid into the alimentary triact. But the reaction of the gland is earl

followed by an imprisonment of colloid in the organ, and other degenerative changes occur, which result in the formation of visible goitres.

These facts suggested to my mind the possibility that the *contagium vivum* of goitre might exist in the intestinal tract, a possibility to which the results of blood counts also pointed. Blum, in 1900, expressed the belief that goitre was due to the presence of a living excitant in this situation, but he advanced little proof in support of his contention. Let us now examine the evidence which, I believe, demonstrates the truth of this view.

Intestinal Antiseptics in the Treatment of Goitre.

Acting on the assumption that the intestinal tract might be the seat of infection, I began in the year 1905 to try the effect of intestinal antiseptics in selected cases of the disease. My first case was that of a man suffering from a fairly large parenchymatous goitre. The man was admitted into hospital, and salol prescribed. No result was observed during the first ten days. I then left Gilgit, and on my return, six weeks later, I found a very notable change had taken place in this case during my absence. Not only had the goitre almost completely disappeared, but there was a striking change in the man's general appearance. He was considerably thinner and the skin had lost

its muddy look and become much clearer. Thinking that residence in hospital, and the comparative freedom from goitrous influences which is thereby entailed, had been in part responsible for the change, I commenced treating selected cases as external patients. All these patients continued to live under the same conditions of life as those under which the disease had been acquired; I further selected thymol as likely to prove a more efficient intestinal antiseptic than salol.

The photographs which I now show will illustrate the results of the treatment :—

Fig. 28, Case 58. — Uniform parenchymatous goitre, of five years' standing, in man aged 30. Circumference of neck 42 cm. Thymol administered, 10 gr., night and morning. Treatment lasted three and a half months. Final measurement of the neck 36½ cm. (Fig. 29.)

Fig. 30, Case 62.—Uniform enlargement of the thyroid in man aged 35, said to be of twenty days' standing. Much pulsation and engorgement of vessels in vicinity of gland. Circumference over widest part 41½ cm. Thymol administered, 10 gr., night and morning. The second photograph was taken on the eighteenth day, when treatment was discontinued. Measurement of neck 38 cm. (Fig. 31.) The swelling disappeared completely six weeks later, although the administration of thymol was not continued after the eighteenth day.

Fig. 32, Case 64. — Uniform parenchymatous

FIG. 28.—Case 58. Shows the appearance of patient's neck previous to the commencement of treatment by thymol. Measurement, 42 cm.

FIG. 29.—The same case three and a half months later. Measurement, 36½ cm.

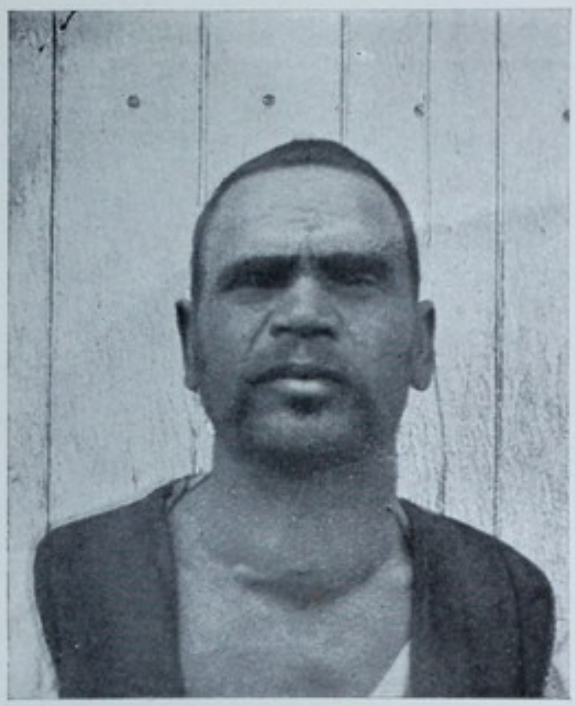

FIG. 30.—Case 62. Appearance of patient's neck prior to the commencement of treatment by thymol. Measurement, 41½ cm.

FIG. 31. — The same case eighteen days after the commencement of treatment. Measurement, 38 cm.

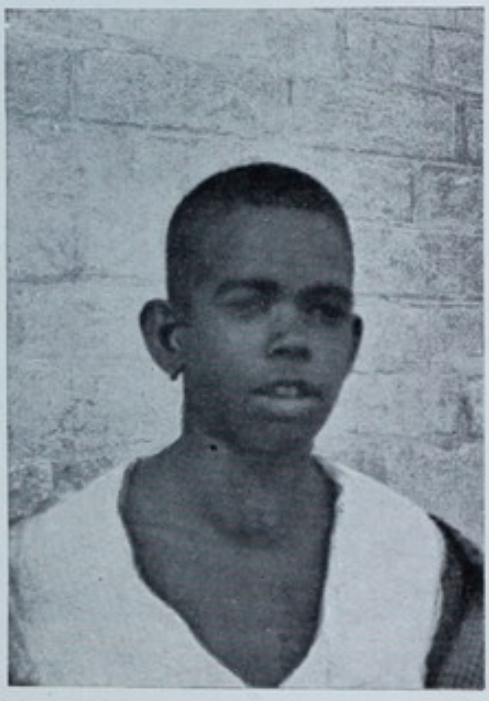

FIG. 32.—Case 64. Appearance of neck prior to the commencement of treatment.

FIG. 33.—The same case at the end of one month's treatment.

goitre in boy, aged 14, of two months' standing. Thymol, 10 gr., night and morning was prescribed. Photograph shows appearance of the neck on the thirtieth day of treatment, when the patient discontinued the use of the drug. (Fig. 33.)

I have treated well over 100 cases of goitre in this way, but in eighty-two only was I able to observe the final result of the treatment. Of these eighty-two, sixty-eight were cured, or so markedly benefited as to be practically so; while fourteen were unaltered, or only benefited to a very slight degree. All were selected cases. Thirty-three were of three months' standing or less, twenty-five were of twelve months' standing or less, while twenty-four were of a year's standing or more. The great majority of these cases which could be regarded as cured or very greatly benefited were of less than one year's standing. A few were of longer duration, as in Case 58, a photograph of which I have shown. These were uniform parenchymatous enlargements, some of them showing marked pulsation and engorgement of the vessels of the neck. The majority of such cases react at once to treatment by thymol, and in some the swelling disappears with great rapidity. One meets with a few cases, however, which, though they appear to differ in no essential from others, are quite uninfluenced by the treatment, or indeed by any other medicinal treatment employed. Older cases respond less readily to treatment, but in

some of these also the results are quite surprising (figs. 28 and 29). Cases in which there are changes in the gland of a permanent character are either not influenced by the treatment, or a certain shrinking of the gland around the cyst or tumour mass takes place, rendering them more clearly defined. This treatment, like all others of a medicinal nature, is applicable only to cases of recent origin where degenerative, cystic and adenomatous changes have not yet taken place. Where such changes have occurred no form of medicinal treatment is of the slightest use.

When thymol is prescribed in such large doses as 10 gr. twice daily, the patient's dietary should, of course, contain no solvents of the drug; otherwise most unpleasant symptoms of thymol poisoning may result. When this rule is observed, no ill effects follow its use, even when administered for such long periods as three months. Apart from a few complaints of burning pain around the anus, none of my patients have been in the least inconvenienced by the treatment. The drug is best administered in the form of a coarse powder washed down by a draught of water. The bowels should be active, and if there is any tendency to constipation an occasional purge should be given.

A striking result of this treatment, and one which is noticeable in most of the photographs I have shown is the loss of subcutaneous fat which occurs. The patient becomes more clean limbed, and

the skin assumes a healthier tint. Colonel Macnab, I.M.S., employed this treatment in the case of the boys of the Bishop Cotton School at Simla, to which reference has been made, with excellent results. Other medical men in India have also used it with success.

β naphthol, also, acts beneficially, though I have not given it the same extended trial as thymol.

The chief interest which attaches to the treatment of goitre by thymol is etiological rather than therapeutical. The germicidal power of thymol is very great. Ratimoff placed it fourth in the list of germicides, arranged according to potency (mercuric chloride, silver nitrate, iodine, and thymol). It is interesting to note that it is only slightly less powerful than that "specific" for goitre —iodine—in its germicidal action.

Cooper, in his recent researches on the bactericidal action of the cresols and allied bodies, states that in the absence of particulate organic matter, thymol is twenty-five times as powerful a disinfectant as phenol, and ten times as powerful as the cresols to *Bacillus typhosus*. He also showed that emulsified thymol is twenty-three times as powerful as phenol in the absence of particulate organic matter, and seven and a half times as powerful in the presence of 3 per cent. of dried fæces. So that it is a very powerful germicide indeed.

Now thymol is not readily soluble in water

(1 in 1500), so that in the absence of any of its solvents, such as fats, oils, alcohol, and vinegar, it is very sparingly absorbed into the system, when administered in the form of a coarse powder. Its action is, therefore, in all probability, a local one in the gut. I regard the action of the drug as very strong, though not conclusive evidence that the habitat in man of the organism responsible for the production of goitre is the intestinal tract. It is clear that even a powerful antiseptic like thymol will not reduce the bacterial flow of the gut by a great deal. It is, I believe, estimated that it affects a reduction of these organisms of about one-thirteenth. Yet even this reduction is sufficient to relieve the strain on the thyroid. The drug appears to act either by destroying the living excitant of goitre, or by reducing its numbers or activity in such a way that the production of toxic substances is lessened, and the thyroid gland is relieved of the excessive demand for its secretion which necessitated the hypertrophy.

It is well known that iodine is regarded as a specific for goitre. I believe that its beneficial action is largely due to its powerful germicidal properties, which are even more marked than those of thymol. It acts possibly also by supplying to the thyroid that ingredient on which the antitoxic activity of its secretion depends. The internal administration of iodine also leads to leucocytosis, a very desirable object to attain where there is usually

a marked reduction of the polynuclear cells of the blood. Its use is attended with a loss of weight and subcutaneous fat, and if the treatment is carried to excess, dangerous wasting and palpitation of the heart and other symptoms may arise.

Lactic Acid Bacillus in the Treatment of Goitre.

The action exercised by the lactic acid ferments when applied to the treatment of recent cases of goitre affords additional evidence that the agent responsible for the production of goitre has its habitat in the intestinal tract of man. In carrying out this line of treatment I have used the fresh cultures in milk of the *Bacillus bulgaricus*. I have treated up to the present time only eight cases in this way, but the results have been very striking. My patients were under treatment for a period of from one month to six weeks. To some, 12 to 20 oz. of "soured milk" was given every morning before the first meal of the day, to others 10 oz. was given in the morning and 10 oz. in the evening. The cases were all of several months' standing, and during treatment there was no change whatever in the manner of life of the patients. They were treated as external cases, and carried out their work in the fields as usual. The results cannot be attributed, therefore, to change of locality, habits of life, or water-supply. Of these

eight cases, four were cured, two improved, and two showed no appreciable difference after six weeks. In those cases which were benefited by the treatment, it was observed that the thyroid gland began to show evidence of diminution in size about the tenth day of treatment, and that the patients lost flesh. The latter fact is of great interest, insomuch as it is observed to occur also as a result of the treatment of goitre by means of iodine and thymol. Fig. 34 shows one of these cases before treatment commenced, and fig. 35 the same case thirty days later. The change not only in the size of the thyroid, but in the boy's whole appearance, is very remarkable.

A case was lately reported by Mr. Harold Chapple, which has an interesting bearing on the relationship of intestinal toxæmia to goitre. The woman—who had been suffering from intestinal stasis—was operated upon by Mr. Arbuthnot Lane. As a consequence of the operation, she not only improved very greatly in health, but the goitre became less than half its former size. The goitre was reported to have been cystic, but it is highly probable that the condition was in part one of "colloid goitre."

Vaccines in the Treatment of Goitre.

In the course of my researches I noticed that a plentiful amœbic infection was present in the intestinal tract of sufferers from goitre in Gilgit.

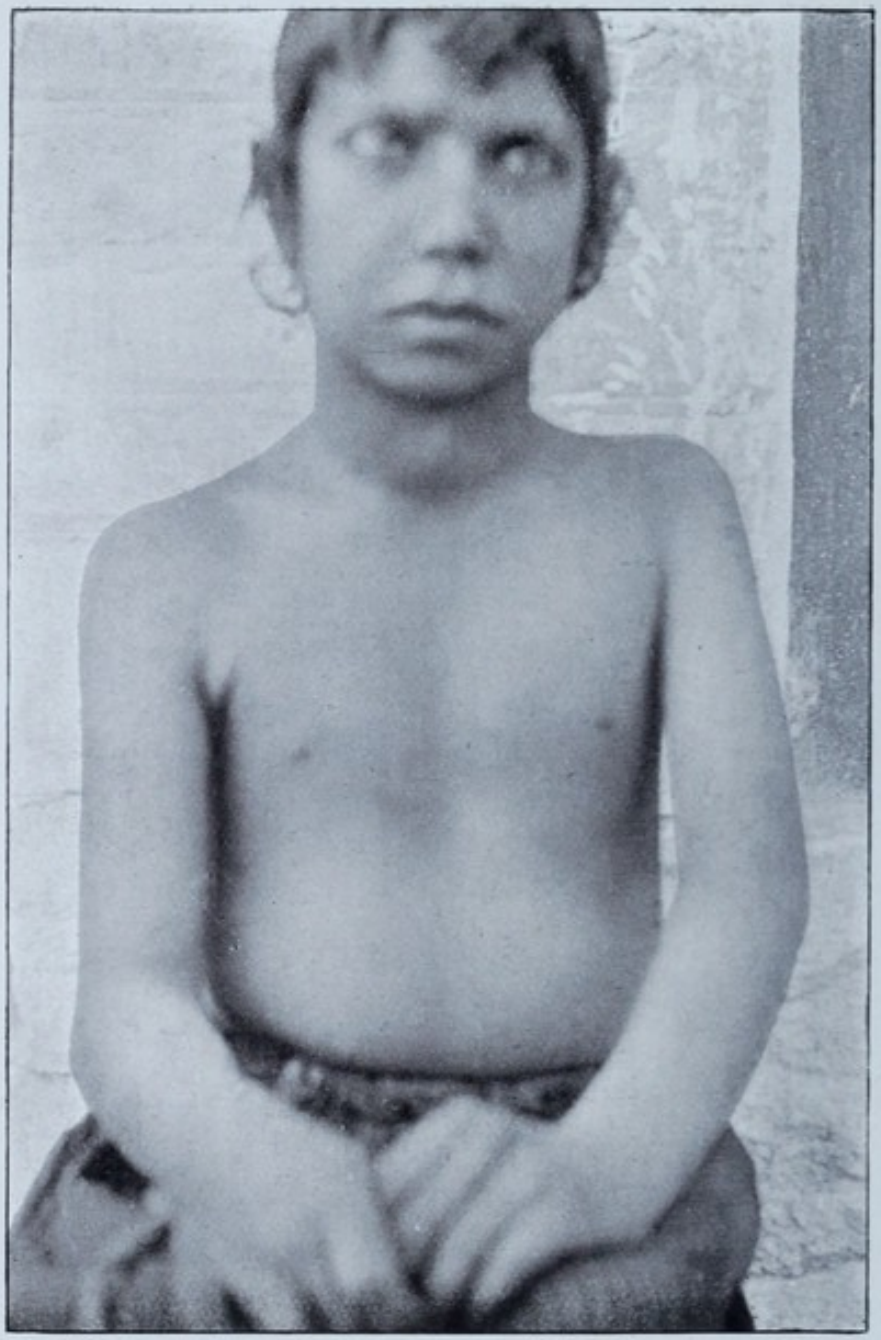

FIG. 34.— Goitre in boy, aged 12, treated by "soured milk."

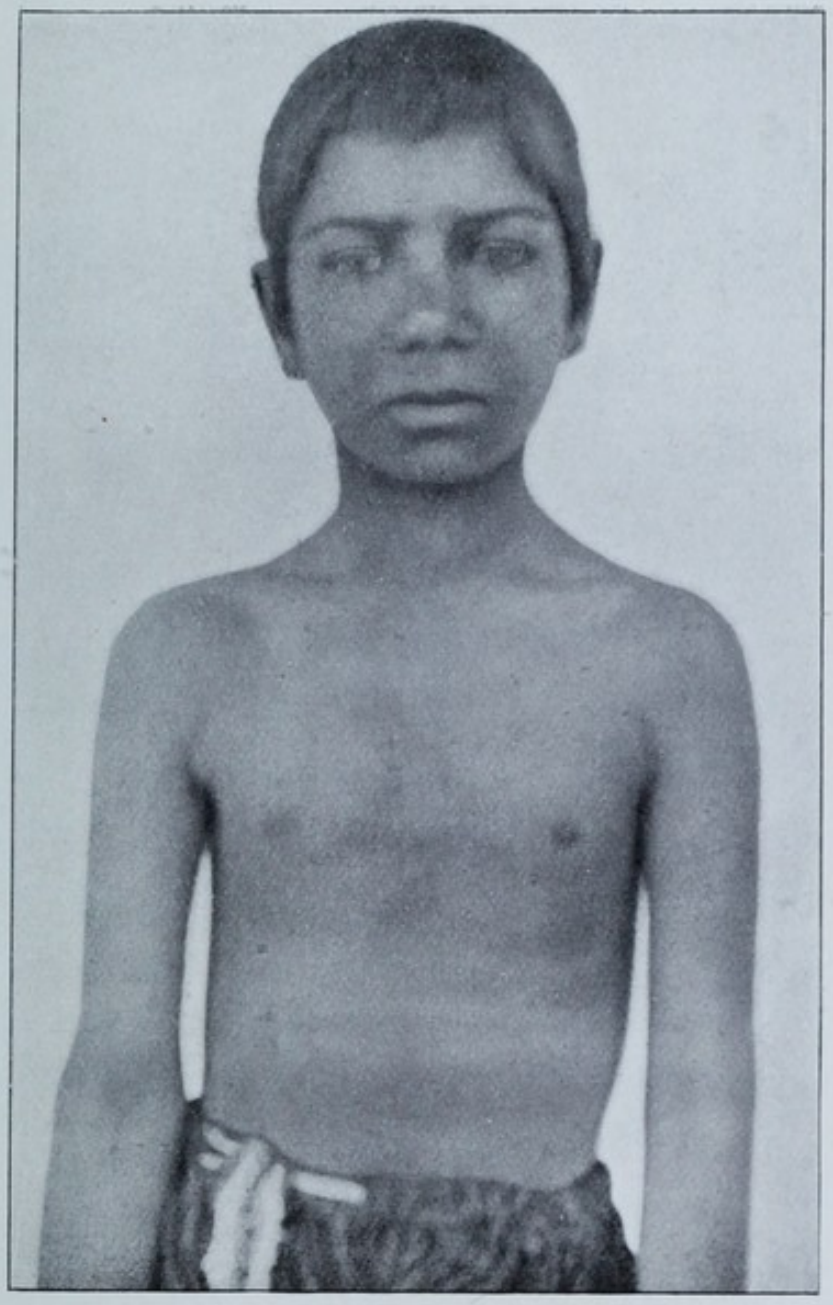

FIG. 35.—The same case after thirty days' "soured milk" treatment. Note complete disappearance of goitre and great loss of subcutaneous fat.

In endeavouring to cultivate these organisms, I was struck with the constant character of the bacillary growth which appeared in the medium I employed. This medium was that recommended by Musgrave for the cultivation of amœbæ. It occurred to me to prepare a vaccine from such bacteria as grew in this medium, and to employ it, as an experimental procedure, in the treatment of recent cases of goitre. At this stage of my investigation no attempt was made to isolate any particular organism. The vaccine employed was, therefore, a composite one, and contained organisms capable of growth on an alkaline and feebly nitrogenous medium. This vaccine was administered in selected cases in doses of from 150 million to 350 million; the inoculations were made at intervals of from seven to ten days. The results obtained were most striking; the photographs which I now show will serve to illustrate them.

(1) The man was a water-carrier, aged 19. The thyroid was uniformly enlarged and measured 38·5 cm. The swelling was of six weeks' standing. The patient had two inoculations only, one on the first day of treatment of 150 million, and a second one on the seventh day of 250 million. The goitre completely disappeared as a result; the final measurement of the neck was 36 cm. The patient carried on his work as water-carrier, lived in the same place where he had acquired the disease, and drank the same goitrigenous water during the

whole course of treatment. (Figs. 36 and 37.) The chart (fig. 38) represents graphically the diminution in the size of the thyroid gland which took place.

(2) In this case the goitre was considerably larger. The patient had six inoculations at intervals of from seven to ten days. The duration of the treatment was sixty days. The neck measured 38 cm. before treatment, and 33·5 cm. after treatment. The man carried on his work as a coolie during the whole course of treatment; his habits of life were not in any way altered. The chart represents graphically the diminution in the size of the goitre which took place. (Figs. 39, 40, and 41.)

It was then noted that the bacterial growth in the medium referred to was composed, as a rule, almost wholly of a bacillus which presented the main characteristics of the *coli* group. A vaccine prepared from this bacillus was administered in doses ranging from 150 million to 350 million. The photographs (figs. 42 and 43) are those of a man treated in this way. The patient was aged 23. The goitre was of the uniform parenchymatous type; there was a small nodular mass in the isthmus. The circumference of the neck measured 42 cm. before treatment and 37·5 cm. after treatment. The patient had seven inoculations in fifty-six days. The chart shows the measurements of the neck at various stages of the treatment, also

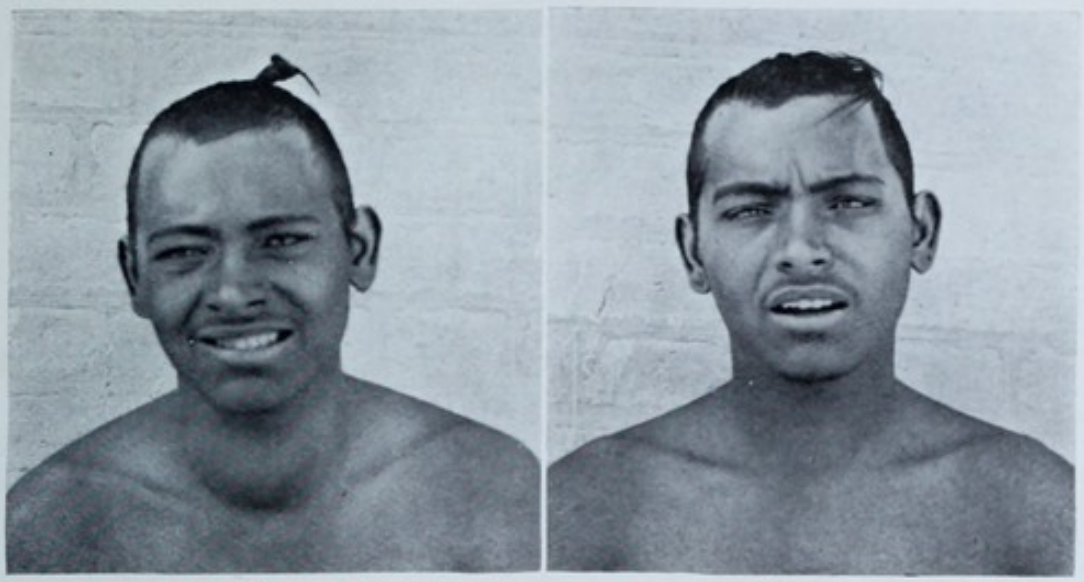

FIG. 36.—Before, 38·5 cm. FIG. 37.—After, 36 cm.

Parenchymatous goitre treated with "mixed" vaccine.

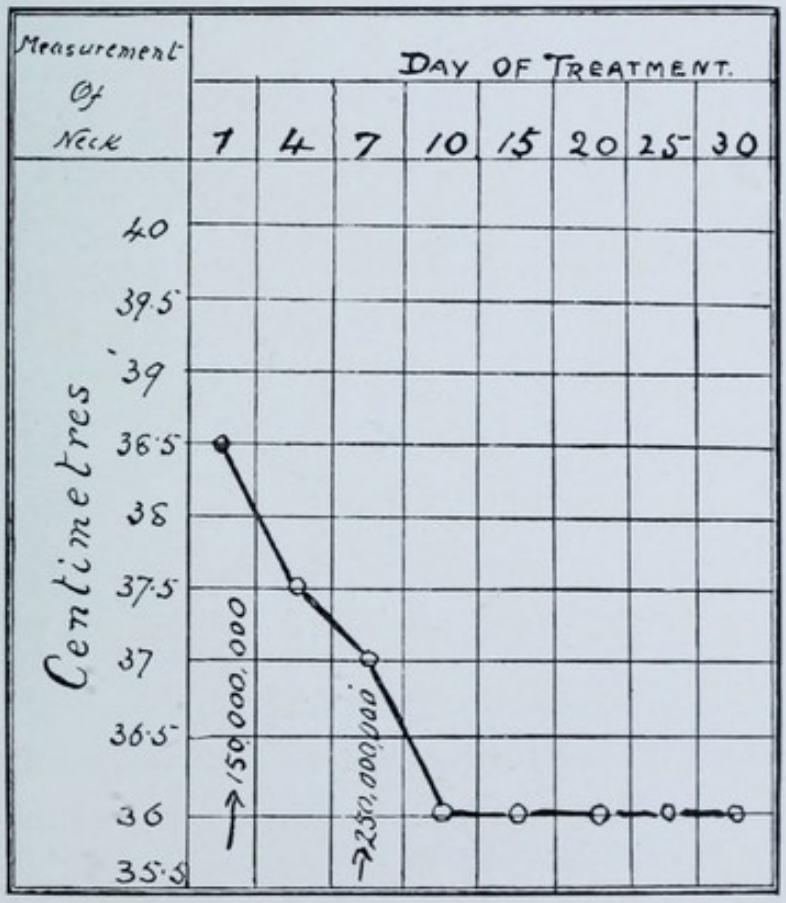

FIG. 38.—Chart showing measurements of neck at various stages of treatment, with doses and times of administration of vaccine.

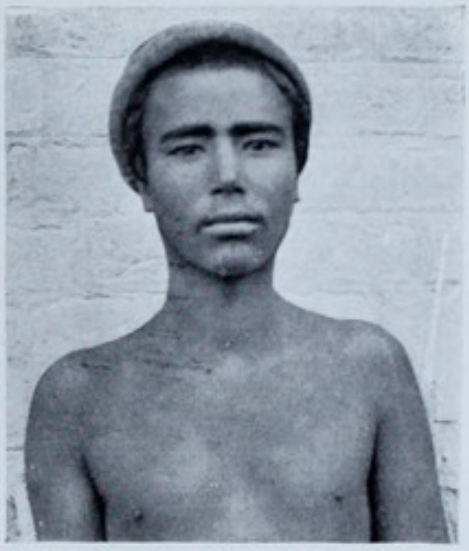

FIG. 39.—Before, 38 cm. FIG. 40.—After, 33·5 cm.
Parenchymatous goitre treated with "mixed" vaccine.

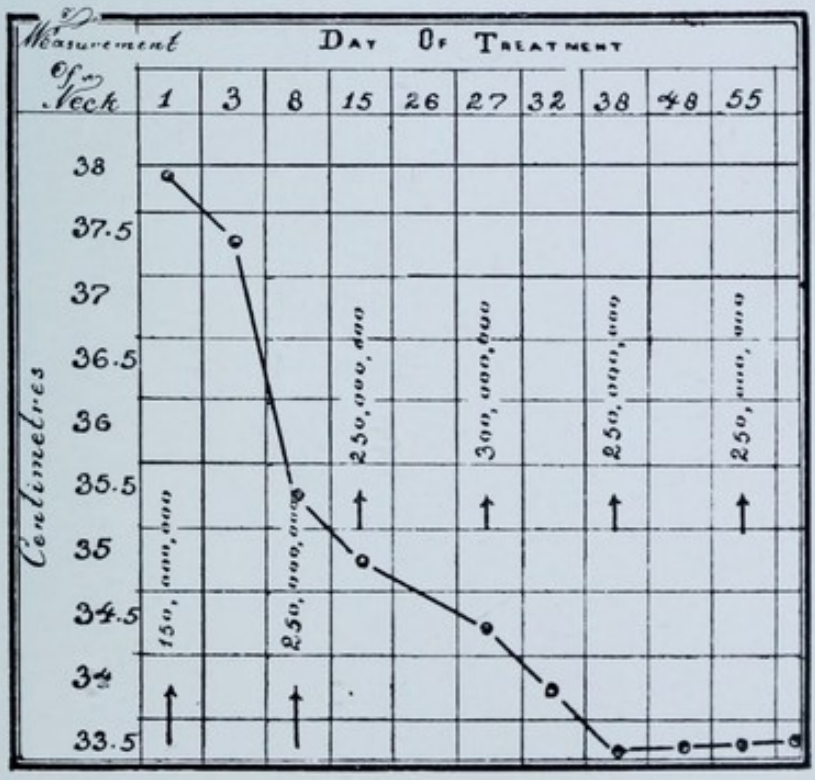

FIG. 41.—Chart showing measurements of neck at various stages of treatment, with doses and times of administration of vaccine.

FIG. 42.—Before, 42 cm.

FIG. 43.—After, 37·5 cm.

Parenchymatous goitre treated with "coli" vaccine.

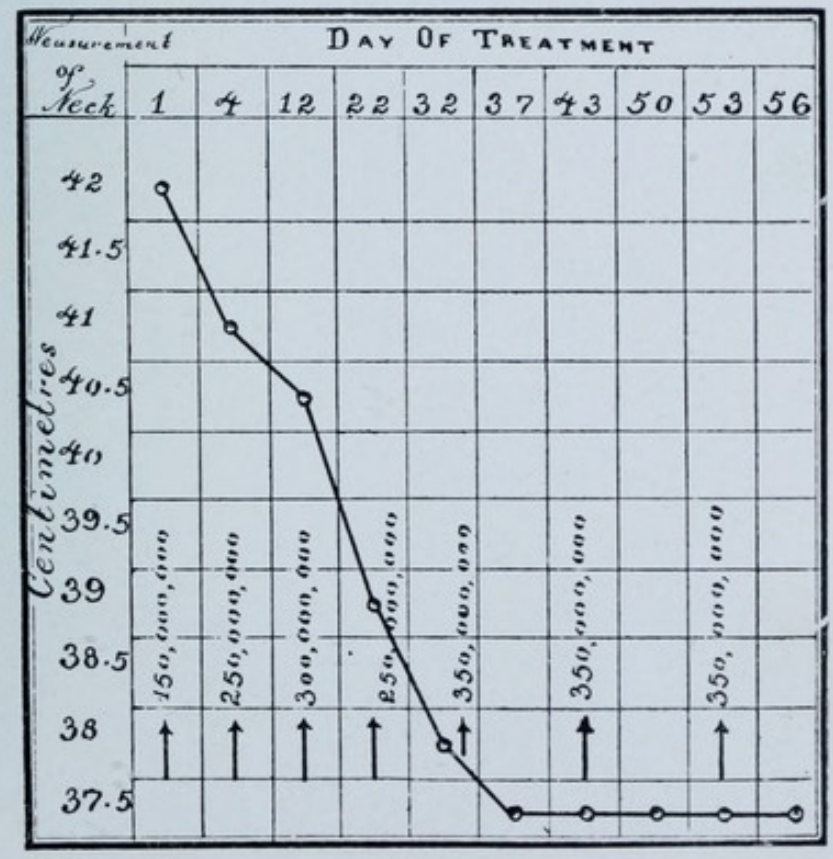

FIG. 44.—Chart showing measurements of neck at various stages of treatment with doses and times of administration of vaccine.

FIG. 45.—Before, 39 cm.

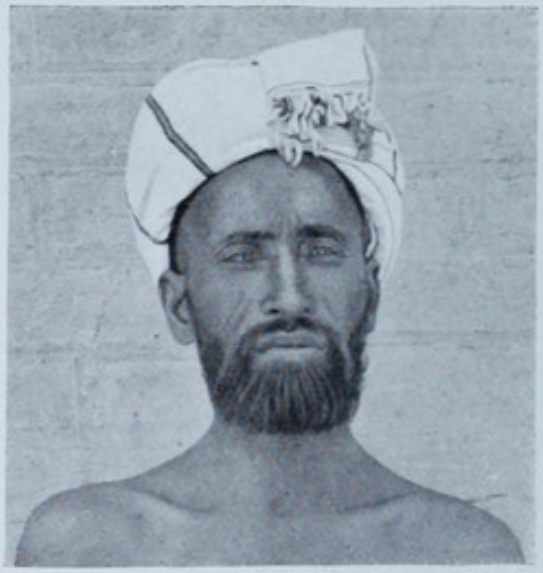

FIG. 46.—After, 36 cm.

Parenchymatous goitre treated with "staphylococcus" vaccine.

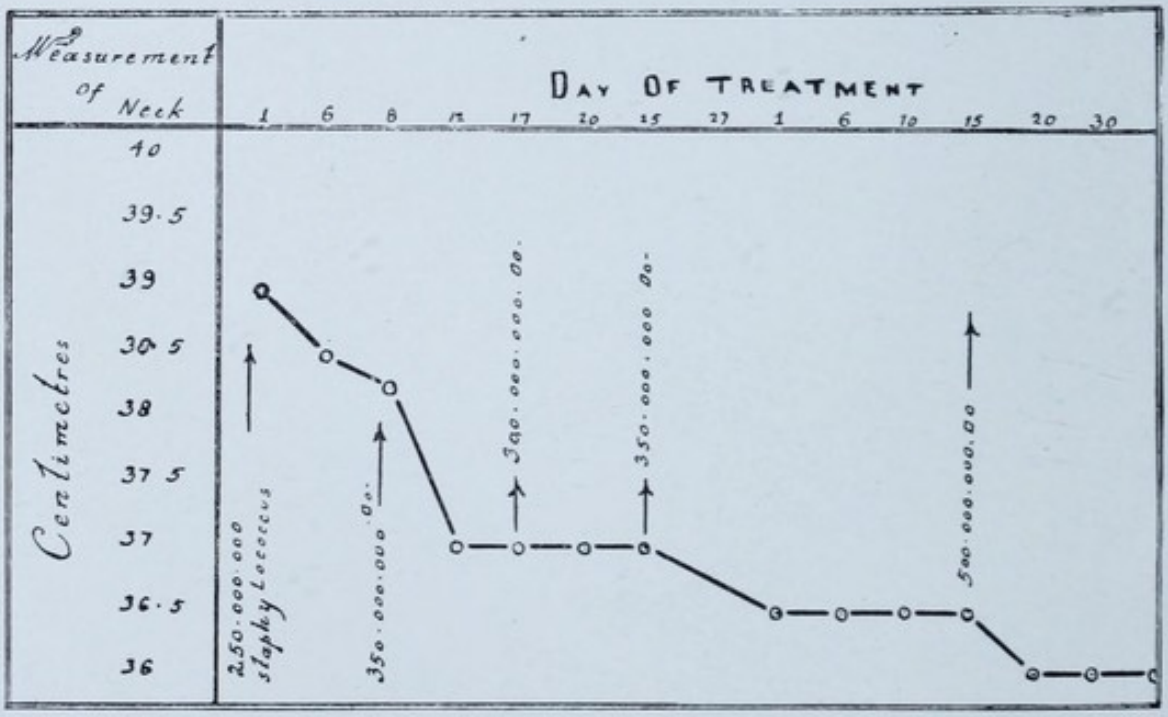

FIG. 47.—Chart showing measurements of neck at various stages of treatment, also doses and times of administration of vaccine.

FIG. 48.—Before, 41 cm.

FIG. 49.—After, 37·5 cm.

Parenchymatous goitre treated with vaccine made from spore-bearing organisms.

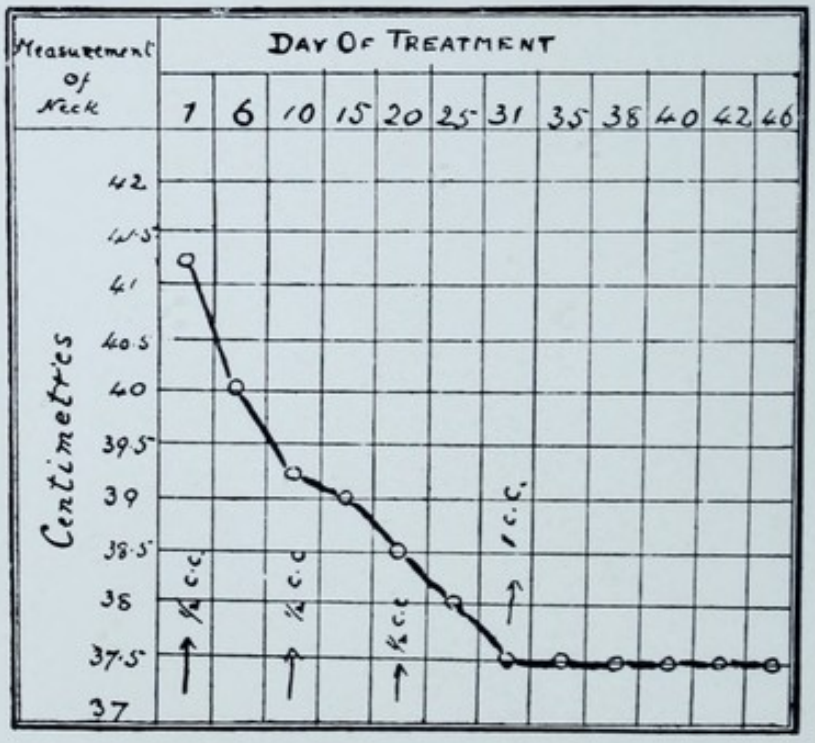

FIG. 50.—Chart showing measurements of neck at various stages of treatment, with doses and times of administration of vaccines.

the doses and times of administration of the vaccine. (Fig. 44.)

The next step was to test the effect of vaccines made from bacteria which were not derived from the patient's own intestine. I consequently employed a staphylococcus vaccine which I had been using in the treatment of cases of caries of bone then in hospital. I employed it in four cases, but two of these were not suitable for any form of medicinal treatment, one being cystic and the other adenomatous. In the two remaining cases, which were uniform enlargements, the results were quite as striking as in the case of the "composite" or "coli" vaccine. The man whose photograph I now show was one of these cases. He had five inoculations of from 250 million to 500 million. The measurement of his neck diminished from 39 to 36 cm. He was under treatment for sixty days and carried on his duties as a policeman during the whole of the time. (Figs. 45, 46 and 47.)

In the next case the patient was treated with a vaccine prepared from a spore-bearing organism isolated from the fæces of an Australian pony which was suffering from goitre of a few weeks' standing. In this case also it will be noticed that the result is eminently satisfactory. The circumference of the neck diminished from 41 to 37·5 cm. (Figs. 48, 49 and 50.)

Forster's dysentery vaccine was tried in two cases,

but without any beneficial result; one of these subsequently responded to treatment with the composite vaccine referred to. In all, thirty-three cases of goitre have been treated by means of the vaccines mentioned. Of the four vaccines which were successfully employed, the "composite" vaccine appeared to give the best results.

In a paper which I communicated to the Royal Society of Medicine in January of last year, I have discussed the various points raised by this treatment of simple goitre. I then drew attention to Metchnikoff's discovery that certain microbes of our normal intestinal flora are harmful by reason of the poisonous substances—indols and phenols—to which they give rise in the intestines. Metchnikoff showed that the organisms of the *coli* group, the staphylococcus and certain spore-bearing organisms, were amongst the normal inhabitants of the intestine which are responsible for the production of these poisons. He showed by experiment that fibrotic changes in the liver, kidneys and arteries, were due to their action; he did not, unfortunately, note their effect on the thyroid gland.

Now the vaccines that I have employed were prepared from organisms similar to these normal and harmful inhabitants of the intestines. There is at present no evidence that any one of these possesses a specific influence in the production of goitre. The conclusion, therefore, is suggested that the thyroid gland is called upon to combat

several poisons normally present in the human intestine. When to these is superadded the specific virus of goitre, an abnormal element is introduced, and an extra strain is thrown upon the gland; unassisted, it undergoes hypertrophy in many cases, but if assisted in any one direction it is capable of performing the additional task which has been imposed upon it, and of combating the abnormal virus. On the assumption that no one of the different vaccines which I have employed contains the specific organism of goitre, my explanation of their action in this disease would be that they cause the disappearance of the goitre by relieving the thyroid of part of its normal work, thus enabling it, without continuing in a state of hypertrophy, to destroy or successfully combat the specific toxin of goitre.

The vaccine treatment of goitre is further confirmation of the view which I have enunciated, that goitre is due to the presence of a living organism of disease in the intestinal tract. It demonstrates also that the thyroid gland is markedly influenced by the nature of the bacterial flora of the gut, and that one of its chief functions is to protect the body from the many toxic substances which find their way into the blood-stream from the alimentary canal. It is interesting in this connection to recall one of the less prominent of the results which v. Eiselberg observed to follow removal of the thyroid gland in lambs, namely, a pronounced degree of calcification of the aorta;

a pathological change which was doubtless due to the unrestrained action of those poisons which Metchnikoff assures us are produced daily and hourly in our own intestines.

The remarks which I have made with regard to the treatment of goitre by thymol apply also to its treatment by means of vaccines. The method is of use only in fairly recent cases of the disease in which degenerative processes have not yet involved the gland to any extent.

A conspicuous feature of this treatment, and one which brings it into line with the treatment by iodine, intestinal antiseptics and the *Bacillus bulgaricus*, is the fact that the patients lose flesh and the skin becomes of a healthier tint. The common factor in all these methods of cure is to my mind the fact that they destroy or inhibit the action of the toxic agent of the disease. Iodine, thymol, and *B. bulgaricus* do so by their antisepticizing action in the gut, while the vaccines employed attain the same end by a more complicated process of immunization. Cases in which these various therapeutical measures may be employed with success are those which also respond to treatment by thyroid extract, showing that the goitre is a response to a demand for thyroid secretion which, when supplied artificially, enables the hypertrophied organ to subside. Iodine, thymol and vaccines destroy or inhibit the action of the agent which institutes the demand, but since they do so com-

paratively rapidly, and while the organ is still enlarged, the secretion which is stored up in the dilated vesicles is for a time in excess, the demand for it having been removed. The excess of secretion, therefore, which continues to reach the blood-stream, until such time as the gland regains its normal equilibrium, exerts its influence in increasing the metabolic processes of the body, and a loss of subcutaneous fat is the result.

Let me now briefly recapitulate the evidence in favour of the intestinal tract as the seat of infection in goitre. The toxic agent of the disease reaches this situation through the medium of water or food, a situation into which the secretion of the thyroid gland is known to be thrown in certain of the lower animals. This secretion possesses, to a high degree, bactericidal and antitoxic powers. A powerful antiseptic which exerts its action in the gut cures the disease, as does the lactic acid bacillus, which acts by inhibiting the production by the intestinal flora of poisonous indols and phenols. Lastly, vaccines, prepared from organisms which are known to be normal inhabitants of the bowel, cause the disappearance of goitre. It is my belief that short of the actual identification of the toxic agent of the disease, stronger evidence of the truth of my contentions could hardly be conceived.

It has been objected that intestinal toxæmia is nowadays made to account for many disorders for which no better explanation can be found. This

may be so, but I hope that those who have listened to my argument will agree with me that the evidence before us removes this view of the causation of goitre from the region of doubtful hypothesis to that of practical certainty. It is true that Nature has provided a sentinel in the liver, standing at the exit of the portal system, to deal with the poisons which are produced in the intestinal tract, but Nature has provided also an additional safeguard in the shape of an antitoxic secretion in the blood, which encounters the poisons absorbed from the bowel at the very point of their absorption. To emphasize the importance of the thyroid's antitoxic function is not to minimize the importance of the liver; both are units in the great army of defence, and to put one such unit out of action is to throw a greater strain on another.

In my next and last lecture I shall deal with the experiments which I have carried out with the object of transmitting the disease from man to animals.

LECTURE IV.

THE process of reasoning which we have followed has led us to the conclusion that the contagium vivum of endemic goitre inhabits the intestinal tract of man ; but the culminating test of the truth of this conclusion can only be afforded by a recognition of this organism as present in the intestinal content, and its transmission from man to animals. This point has not yet been attained.

THE FÆCES IN GOITRE.

I have examined microscopically the fæces of a large number both of goitrous and of normal individuals in Gilgit.

In a paper published in the *Quarterly Journal of Microscopical Science*, in 1909, I have figured and given a brief description of the varieties of *Amœbæ* met with. In 103 cases of goitre in which the fæces were examined, I found amœbæ present in eighty-seven. In forty-eight cases they were found in large numbers, in twenty-seven in moderate numbers, and in twelve only after considerable time had been spent in searching for them. The fæces

of 101 non-goitrous individuals, living in the same locality, were also examined. In twenty-nine of these amœbæ were present; the infection was plentiful in eight, moderate in nine, and scanty in twelve. The eight-nucleated cysts, which are typical of one of the varieties of amœbæ met with, were found also in samples of fæces sent to me by Colonel Macnab, I.M.S., from cases of the disease which occurred in the boys' school at Simla. *While no definite statement can be made as to the pathogenicity of these amœbæ*, their *possible* importance is obvious when it is remembered that goitre is due to an organism carried by water.

I must take this opportunity to point out clearly that I do not assert, and have never asserted, as is sometimes stated by Continental writers, that goitre is due to the presence in the intestines of the amœbæ I have described. My study of these organisms was but the beginning of an investigation of the protozoa parasitic in the intestines of residents in localities where goitre is endemic—an investigation which I regard as of primal importance.

Various experimental procedures have been adopted by the Swiss Goitre Commission with a view to demonstrating the presence of a specific virus in the fæces :—

(1) Intravenous injections of a filtered solution of *normal fæces* have been made into rabbits. The operation was repeated seven times in one case, but with negative results.

(2) Intravenous injections of a filtered solution of *goitrous fæces* have been made into rabbits. The operation was repeated eight times. The thyroid did not enlarge.

(3) Intravenous injections of a solution of normal fæces in chloroform and of goitrous fæces in chloroform have also given negative results.

There still remains, therefore, much work to be done; and it is my hope, should the circumstances of my service permit, to continue the prosecution of research in this direction.

Experiments dealing with the Transmission of Goitre from Man to Animals.

Since the year 1906 I have repeatedly endeavoured to transmit goitre from man to animals by infecting the water-supply of the latter with the fæces of sufferers. No effects being observable in dogs, I undertook a series of experiments on goats in the hopes of arriving at results of a positive character.

Female goats were selected for these experiments. They were taken from the same flock, were between the ages of 1 and 2 years, and were not pregnant. This point is of importance, since the increased activity of the thyroid gland during pregnancy would vitiate the results observed on microscopical examination of the organ. The goats were brought from a non-goitrous locality,

high up in the mountains about 40 miles distant from Gilgit. Their thyroids were carefully examined and were found to show no signs of hypertrophy. In the majority either the gland could not be distinguished from the surrounding tissues or could be felt only with the greatest difficulty. Where the organ was palpable it was found to be oval in shape and about the size of a small almond. The goats were divided into batches, which will be referred to as I, "controls" (three goats); II, "Batch X" (six goats); III, "Batch Y" (seven goats). Each batch was confined in a separate pen. The animals were all fed on the leaves and young branches of trees, in order to exclude as far as possible sources of contamination from the soil. The experiment was designed so as to foul the drinking-water of "Batches X and Y," while that of the "controls" remained pure. The apparatus which I devised for this purpose is represented by the figure (fig. 51):—

It consisted of a drum, A, which was fitted with a tap. A covered wooden box, B, having a perforated false bottom of wire gauze under which was a wooden trough sloping towards an outlet pipe, B. This outlet pipe led into a flask C, which was fitted with a perforated cork, so as to ensure freedom from contamination by soil, dust, &c. The drum, A, was filled with a non-goitre-producing water which had been previously boiled. A trickle of water from the drum, A, was allowed to pass

continuously into the box, B. This box was partially filled with soil taken from the most goitrous village

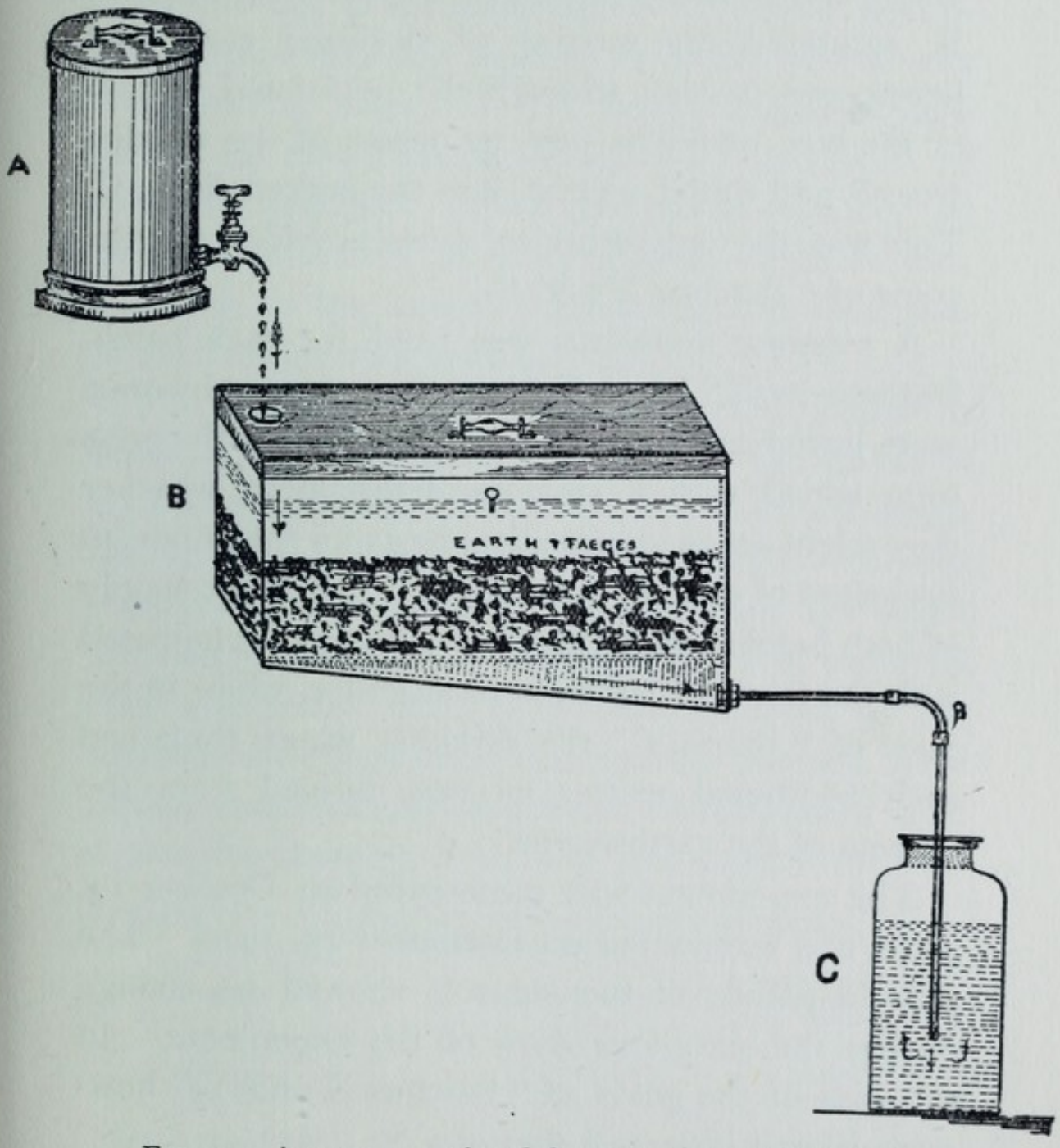

FIG. 51.—Apparatus employed for contaminating the water.

in Gilgit. The soil was sterilized by steam at 230° F. for thirty minutes, and was then mixed with the fæces of sufferers from incipient goitre.

Fresh fæces were added to the mixture several times a week during the course of the experiment. The water from the drum, A, trickled into the box, B, saturated the mixture of sterilized earth and fæces, and passing through the perforated bottom of the box, found its way, by means of the wooden trough and outlet pipe, B, into the corked flask, C. This was the only drinking water provided for the goats of "Batches X and Y."

A separate apparatus was used for each batch. In the case of "Batch Y," however, 500 earthworms were introduced into the box, B. The earthworms were added with a view to determining whether they might act as intermediate hosts for the organism suspected of causing the disease. The water supply of both batches was, therefore, grossly contaminated with the fæces of sufferers from goitre, while in the case of "Batch Y" the drinking water contained such additional matter as was derived from the excreta of the earthworms.

The experiment was commenced on October 13, 1910, and terminated on December 15, 1910. The thyroid glands of the controls showed no change during the sixty-four days of the experiment. In the case of the goats of "Batches X and Y," however, it was observed that—

(1) All the animals lost in weight.

(2) Many of them suffered from diarrhœa.

(3) Fifty per cent. of the goats in each batch showed enlargement of the thyroid gland.

It was observed that the thyroid glands of two

of the goats in "Batch X" showed signs of enlargements, as determined by palpation, as early as the thirteenth day of the experiment. A second noticeable feature was the manner in which the glands fluctuated in size. It will be remembered that goitre in man, whether artificially produced or naturally acquired, shows the same tendency to fluctuate in size in its early stages. This is due, I believe, to the alternate emptying and distension of the vesicles with colloid.

The animals were killed by a goorkha, skilled in severing the head from the body at one stroke of his kookrie (knife). The neck was dissected immediately and the gland rapidly exposed. It was observed in several cases that the size of the organ diminished considerably before it could be removed from the body. The right and left lobes of the thyroid, with their long and narrow isthmus, were rapidly removed and weighed. The following table shows the complete results of the experiment:—

TABLE I.—"CONTROLS"—THREE IN NUMBER—WHICH CONSUMED ONLY PURE WATER.

Weight of goat	Weight of thyroid	Proportionate weight of thyroid to body weight
(1) 60 lb.	3·2 grm.	$\frac{1}{10000}$
(2) 43 ,, ...	2·05 ,, ...	$\frac{1}{10439}$
(3) 65 ,, ...	3·2 ,, ...	$\frac{1}{10100}$

TABLE II.—"BATCH X"—SIX IN NUMBER—WHICH CONSUMED ONLY FÆCALLY CONTAMINATED WATER.

Weight of goat	Weight of thyroid	Proportionate weight of thyroid to body weight
(1) 48½ lb.	3·6 grm.	$\frac{1}{6854}$
(2) 26½ ,, ...	2·93 ,, ...	$\frac{1}{4500}$
(3) 38 ,, ...	2·3 ,, ...	$\frac{1}{8000}$
(4) 30 ,, ...	1·5 ,, ...	$\frac{1}{10000}$
(5) 22½ ,, ...	2·32 ,, ...	$\frac{1}{4800}$
(6) 29 ,, ...	1·35 ,, ...	$\frac{1}{10700}$

TABLE III.—"BATCH Y"—SEVEN IN NUMBER—WHICH CONSUMED FÆCALLY CONTAMINATED WATER, AS IN THE CASE OF "BATCH X," TOGETHER WITH THE EXCREMENTITIOUS PRODUCTS OF EARTHWORMS.

Weight of goat	Weight of thyroid	Proportionate weight of thyroid to body weight
(1) 50½ lb.	4 grm.	$\frac{1}{7000}$
(2) 41½ ,, ...	4·3 ,, ...	$\frac{1}{4650}$
(3) 56 ,, ...	3·7 ,, ...	$\frac{1}{7530}$
(4) 55½ ,, ...	3·6 ,, ...	$\frac{1}{7700}$
(5) 49½ ,, ...	5·4 ,, ...	$\frac{1}{4572}$
(6) 45 ,, ...	1·9 ,, ...	$\frac{1}{11700}$
(7) 39 ,, ...	1·9 ,, ...	$\frac{1}{10000}$

It will be seen from the tables that the weight of the "control" animals' thyroid was in all cases about $\frac{1}{10.000}$ part of the body weight. In "Batch X" the thyroids of two goats showed no deviation from the normal weight; in two the weight of the thyroid was considerably more than normal; while in the remaining two it was twice as much as that of the "controls." In "Batch Y" two goats had thyroid glands of the same weight as the "controls"; three had thyroids considerably weightier, while two had thyroids twice the weight of those of the "controls."

Allowing for variations in size of the normal thyroid of these goats of from $\frac{1}{8.000}$ to $\frac{1}{11.000}$ part of the body weight, it will be admitted that about 50 per cent. of the animals in "Batches X and Y" showed enlargements of the thyroid gland. It is possible that conclusions based on the weight of such a variable organ as the thyroid gland may prove fallacious, but as the goats were taken from the same flock and were of the same season and sex, the margin of error was reduced to the minimum.

Since the same results were observed in the goats of "Batches X and Y," earthworms would not appear to be concerned in the spread of the disease.

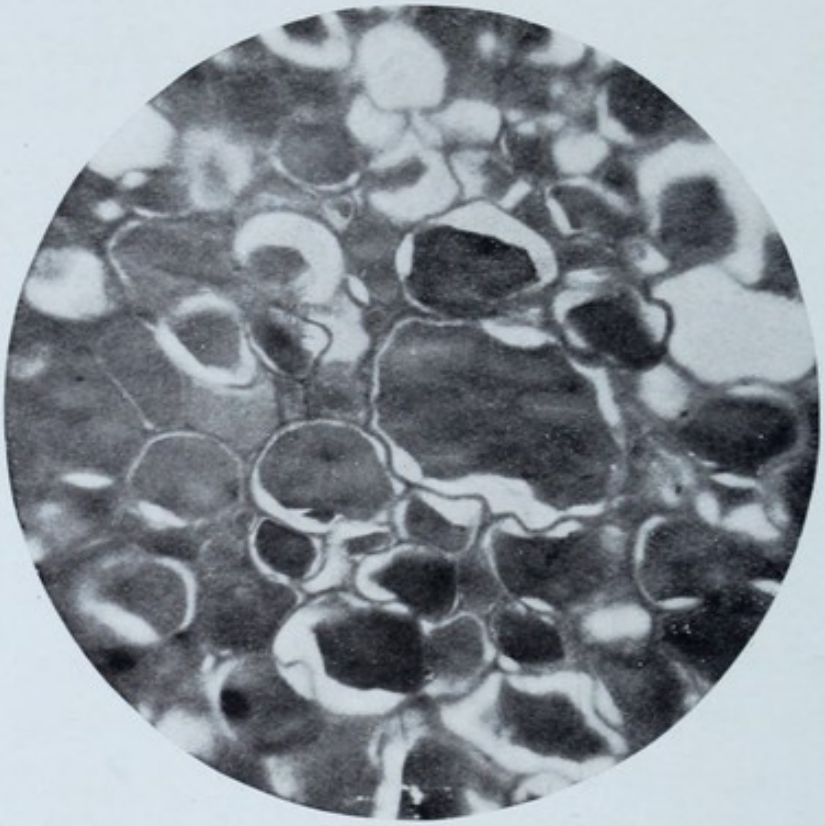

FIG. 52.—Enlargement of thyroid gland of goat experimentally produced. × 100.

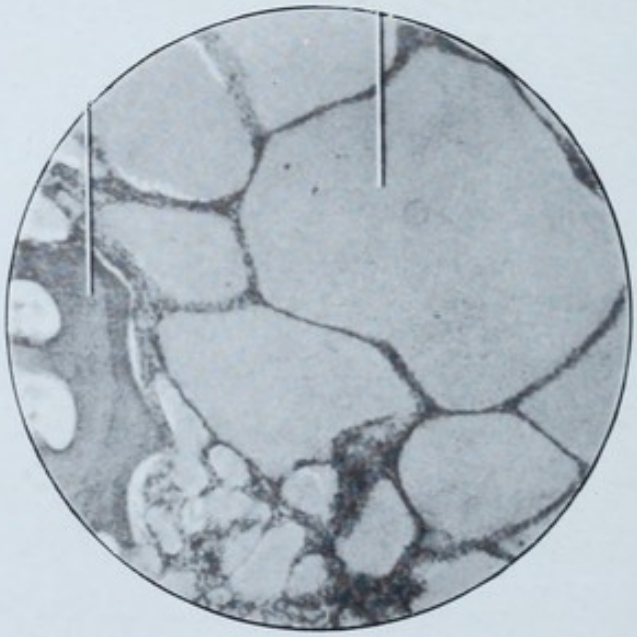

FIG. 53.—Colloid goitre in trout (Marine and Lenhart).

Marked differences were observed in the microscopical appearances of the thyroid in these animals. In the control animals the vesicles were found to be small, round, compact, and lined with cubical epithelium. The space between the vesicles was filled with masses of rounded cells, and many vesicles were seen in the field of the microscope (fig. 24). In the thyroids of these animals which showed the greatest increase in size as determined by weight, the vesicles were much larger, their walls markedly thinner, and their outline more irregular, while fewer appeared in the field of the microscope than in the case of the normal gland. The epithelium lining the vesicles was much flattened, and the intravesicular cellular tissue was markedly less in amount than in the case of the normal gland (fig. 52). Glands which showed an intermediate degree of enlargement presented in some parts of the section the appearances of normal tissue, while in others the dilated vesicles, flattened epithelial lining and the scarcity of intravesicular cellular tissue were characteristic of the more enlarged organs. In short, every degree of variation was met with, from the small, round, compact vesicle of the normal organ to the cyst-like dilatation of the vesicle of the enlarged gland. The increase in size of the enlarged thyroid appeared to be due wholly to the distension of the vesicles with colloid material. The photomicrographs [figs. 24 and 52] show these points of distinction clearly.

For the purpose of comparison I now show you a photomicrograph of a large external trout goitre, which is taken from a paper by Marine and Lenhart. The large dilated vesicles filled with colloid and the thinning of the vesicle walls are well seen. (Fig. 53.)

This experiment proves that an enlargement of the thyroid gland of goats can be induced by infecting the water-supply with the fæces of sufferers from goitre. It does not amount to proof that the enlargement so induced is due to the action of a specific living excitant of goitre; it might be due only to the organic impurity of the water.

In 1911 I repeated this experiment. Twelve female goats, aged two years, were employed. In this case the animals were much better fed, their ration consisting of one pound of grain and as much Lucerne grass as they could eat. The experiment was continued for 107 days. At the end of this time seven of the animals were taken at random and killed in the manner I have described. The following table shows the weights of the thyroid glands as compared with the body weight of the animals:—

No.	Weight of animal	Weight of thyroid	Proportionate weight of thyroid to weight of animal
I	42 lb.	2·8 grm.	1 : 7,466
II	42 ,,	3·0 ,,	1 : 6,999
III	38 ,,	1·3 ,,	1 : 14,600
IV	55 ,,	3·1 ,,	1 : 8,800
V	45 ,,	2·5 ,,	1 : 9,000
VI	46 ,,	1·4 ,,	1 : 16,400
VII	28 ,,	1·7 ,,	1 : 8,000

In three of these animals the thyroid gland was considerably larger than normal. The increase in size, however, was not so marked as in the first experiment, a difference which may be attributed to the fact that the animals in the experiment were better fed and gained in weight—whereas those in the first experiment had *lost* in weight. Two animals had thyroid glands below the normal weight, while two showed no marked deviation from the normal size. The histological appearances of the glands of these animals varied very considerably. I shall indicate only the appearances observed in the case of those glands which were above the normal weight (Nos. 1, 2 and 7). Nos. 1 and 2 were identical in appearance. The vesicles were on the whole larger, more irregular in shape, and the total amount of colloid was greater than in the case of the normal gland. The epithelium lining the vesicles was somewhat higher than normal. The thyroid in these cases did not present the same degree of dilatation and irregularity of the vesicles, nor the marked flattening of the epithelium, which was observed as a result of the first experiment. Indeed, apart from the increase in size of the organs, it cannot be said that the histological appearances differed to any marked extent from the normal gland.

The histological appearances of the thyroid gland of goat No. 7 revealed a considerable degree of hyperplasia. The vesicles were small, the amount of colloid comparatively scanty, the lining epithe-

lium was columnar and the vessels of the gland were dilated. The gland was markedly more cellular than any other in the present experiment. (Fig. 54.)

Experiments on goats were also carried out to test the effect of feeding these animals on cultures of micro-organisms grown from the fæces of goitrous individuals.

Four female goats, aged 2 years, were given forty-eight-hour cultures on Musgrave's agar of such organisms as grew on this medium after inoculation with the fæces of a goitrous individual. An emulsion of the bacteria present was introduced into the stomach of the animals by means of a funnel every other day for sixty-one days. At the end of this time a similar emulsion of a spore-bearing bacillus, which had been isolated from the fæces of a goitrous horse, was administered on alternate days for a further period of forty-seven days. The animals were then killed and their thyroid glands examined microscopically. The following table shows the weight of the thyroid gland in each case relative to the body-weight of the animal:—

No.	Weight of animal on January 20, in lbs.	Weight on May 7, in lbs.	Increase in weight, in lbs.	Weight of thyroid	Proportionate weight of thyroid to body-weight of the animal
I	42	54	12	1·0 grm.	1 : 27,000
II	48	65	17	2·3 ,,	1 : 13,000
III	37	40	3	2·0 ,,	1 : 10,000
IV	32	41	9	1·6 ,,	1 : 12,000

FIG. 54.—Thyroid hyperplasia in goat. × 500

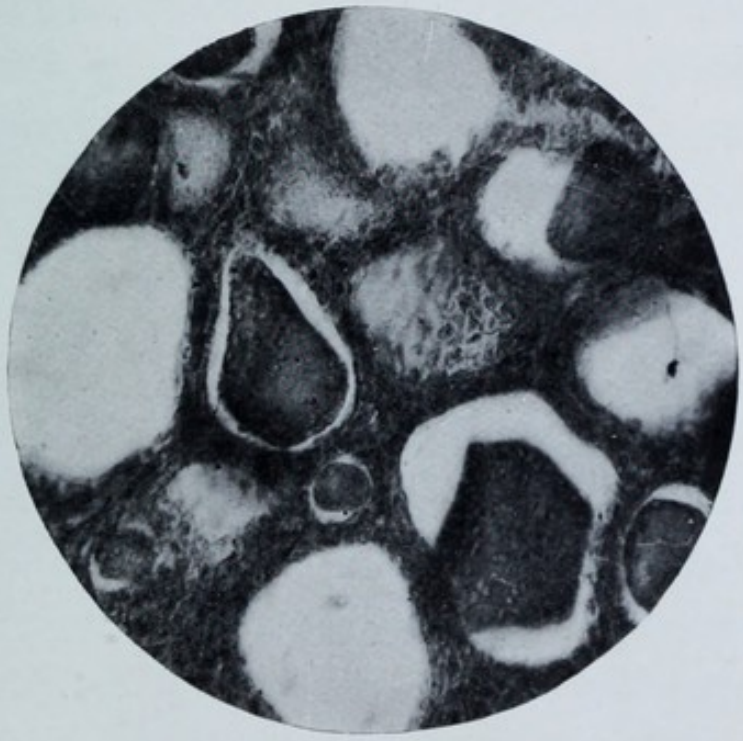

FIG. 55.—Normal thyroid gland of goat. × 500.

It will be observed from the table that :—

(1) All the animals increased in weight. In Case No. 2, the increase was very marked. In Case No. 3, in which the thyroid was of normal weight, the animal increased only three pounds in weight.

(2) In three cases out of four the thyroid gland was smaller than normal; in Case No. 1 very markedly so.

There was, therefore, in these animals no evidence of any enlargement of the thyroid gland (goitre). But well marked histological changes were observed in all animals in which the thyroid showed considerable deviation from the normal weight. I shall refer only to two of these :—

In No. 1, the vesicles were round or oval, lined with cubical or low columnar epithelium; the colloid was small in amount; a large area of parathyroid-like tissue formed about one-half of the total sectional area of the gland. This area was wholly cellular and showed an absence of colloid. The capillaries and vessels of the stroma were dilated; there was some increase of the connective tissue stroma of the organ, especially around the blood-vessels, the walls of which appeared somewhat thickened.

In No. 2, formed vesicles were almost wholly absent, or were filled with round imperfectly-staining cells and cellular *débris;* where vesicles were seen they were lined with irregular, high columnar epithelium, the lining being often incomplete in

parts. Stainable colloid, with the exception of a few densely stained particles, was almost wholly absent. The stroma was increased markedly in amount, and formed a network, the meshes of which were filled with round cells and cellular *débris*. The capillaries of the organ were not noticeably altered. The appearance of the gland, together with the greatly increased weight of the animal (seventeen pounds), were suggestive of a commencing myxœdema. (Figs. 55 and 56.)

The peculiar histological features of these cases find a parallel in some cases of rat goitre, due to the consumption of the Aarau water residue, recently recorded by E. Bircher, which are sufficiently interesting to merit detailed description. One of these cases is that of a young rat which was given the residue mixed with its food for a period of twelve months. The growth of the animal was considered to have been backward. The thyroid gland showed a moderate enlargement about the size of a pea. On section the gland presented the appearance of an irregular frayed network. Microscopically normal follicular tissue was nowhere to be seen. The nodose hypertrophy, which is said to be so characteristic of rat goitre, was conspicuously absent. There was a pronounced cellular disintegration and desquamation of the epithelium into the lumen of the vesicles. The epithelial lining was incomplete and frayed; the cell nuclei were altered in appearance and in their staining characters. The vesicles

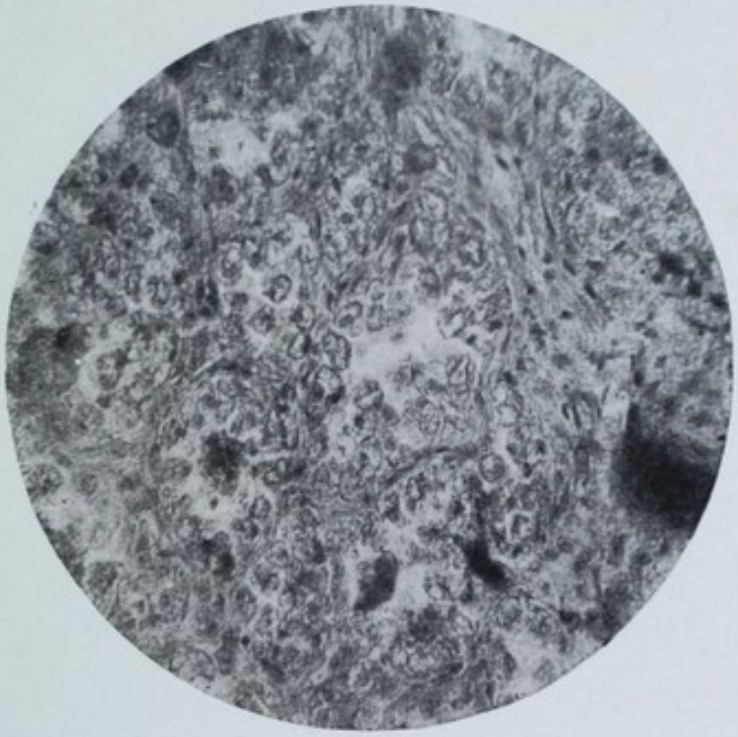

FIG. 56.—Degenerative changes seen in thyroid gland of goat fed on bacterial cultures. × 500.

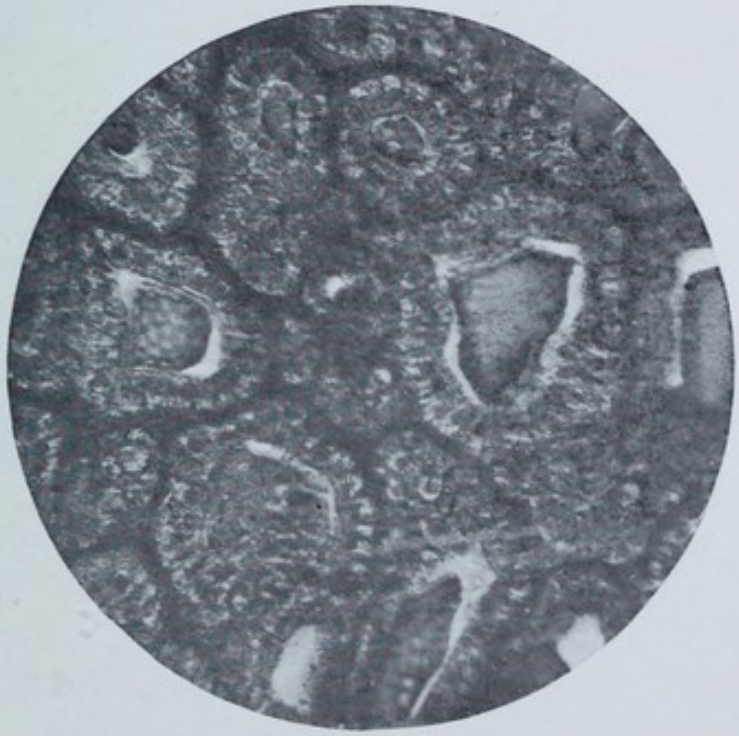

FIG. 59.—Thyroid hyperplasia in goat fed on bacterial cultures × 500.

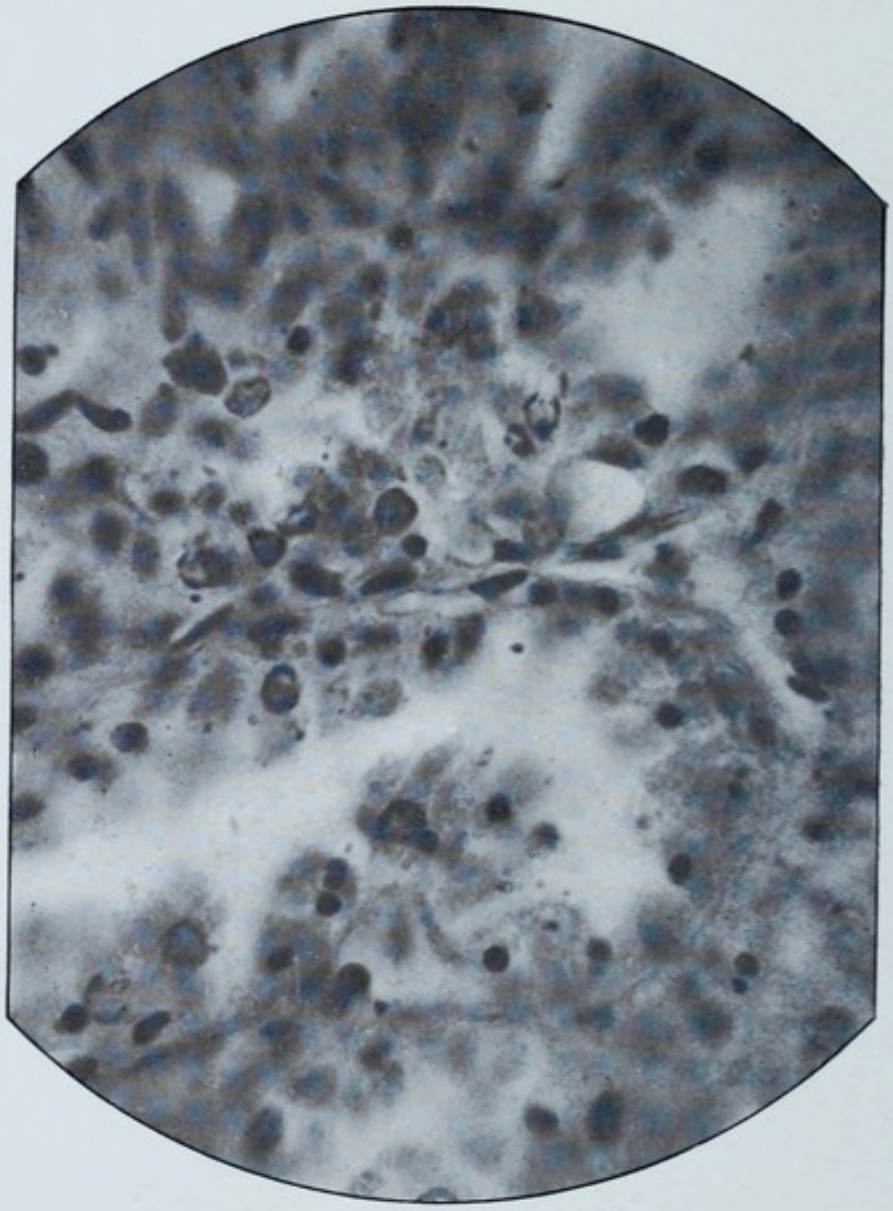

FIG. 57—" Struma degenerativa " (E. Bircher).

were irregular and communicated one with another, forming irregular spaces. The blood-vessels were dilated, and perivesicular hæmorrhages had taken place. Small particles of intensely staining hæmatogenous colloid were present in the vesicles; the colloid was not vacuolated. Many small darkly-staining nuclei were present. The whole presented a picture of a confused cell chaos. Bircher diagnosed the case as one of "struma degenerativa" (fig. 57). Similar changes were observed in goitres produced in rats by means of the material separated from the water by the septum of the dialyser. In these also the nodose hypertrophy, characteristic of rat goitre, was absent.

With regard to the defects of growth especially observed in those rats fed on the residue of goitrigenous waters, and on which Bircher lays such stress—having myself seen the conditions under which these animals are kept, conditions which, though by no means bad, are certainly favourable to the development of many diseases other than goitre or cretinism—I feel bound to record my opinion that in attributing these defects to the specific agent of goitre, Bircher is overlooking other common causes of defective growth.

Coincident with my last experiment, four other female goats were given the same cultures in the same way and for the same length of time, but, one hour prior to the administration of the culture, a few grains each of the carbonates of lime, mag-

nesium, and sodium were given to the animals. My object in giving them these salts was to ascertain whether the development of goitre was favoured thereby. Three of the four goats were killed at the end of 108 days. The following table shows in each case the weight of the thyroid relative to the body-weight of the animal.

No.	Weight of animal on Jan. 20, in lbs.	Weight of animal on May 7, in lbs.	Increase in weight in lbs.	Weight of thyroid	Proportionate weight of thyroid to body-weight of the animal
I	44½	55	10½	1·5 gm.	1 : 18,200
II	41	55	14	1·45 ,,	1 : 16,000
III	37½	45	7½	2·1 ,,	1 : 10,630

No. 1 showed on microscopical examination a slight increase in the connective tissue stroma; scanty, darkly staining colloid; vesicles, round or oval, and either filled with cells or lined with a high columnar epithelium. The vessels were dilated. The changes indicated a well-marked hyperplasia. (Fig. 59.) No. 3 was normal in appearance.

In No. 2 the histological appearances were the same, but in this case the vesicles were larger and the cells lining them of a lower columnar type, while the colloid was rather more plentiful. The addition of alkalies in this experiment did not appear to influence the result to any extent.

In short, of seven animals fed on bacterial cultures, five not only failed to exhibit any enlarge-

ment of the thyroid gland, but were found to show an actual diminution in the size of the organ. On the other hand, four of these five glands showed a marked hyperplasia.

Four other goats were given the salts of lime, magnesium, and soda, for the same period of time as in the previous experiment. Two of these animals were killed. The thyroid glands were of about normal size. One of these on microscopical examination showed also some signs of hyperplasia.

These experiments may be summed up as follows: In animals which drank only water highly polluted by fæces for periods up to 108 days, there was a tendency on the part of the thyroid to be larger than normal, and to exhibit on microscopical examination an increase in size of the vesicles, irregularity and thinning of their walls, and distension of the vesicles with colloid: in animals which were fed on cultures of bacteria for the same length of time there was a tendency on the part of the thyroid gland to be smaller than normal, while the histological appearances of the organ were those of an active hyperplasia, often very pronounced. I think it possible that future investitions will show that this apparent difference of result is nothing more than a different stage in the process of development of goitre.

Of the experiments with bacterial cultures the two most striking results are the marked hyperplasia and the accompanying diminution in size of the

gland. This hyperplasia is in conformity with that produced by Sajous, Bayon, and more recently Farrant, as a result of the injection into animals of bacterial toxins (Fig. 21); the diminution in size has been noted by other experimenters. Edmonds found in one of his dogs in which partial thyroidectomy had been performed that the remaining lobe, though it showed marked hyperplasia on microscopical examination, was macroscopically smaller than normal. Farrant also has concluded that the earliest stages of hyperplasia are associated with a diminution in size rather than an increase.

It remains only briefly to contrast these results with the histological changes apparent in the goitres artificially produced by Bircher, and the Swiss Goitre Commission. Bircher was good enough to give me an opportunity of examining his specimens in his laboratory at Aarau. Undoubtedly pronounced changes had taken place in the glands, but these changes, in my opinion, generally bore a closer resemblance to those usual in exophthalmic goitre rather than those which we are accustomed to expect in simple goitre. Papillary outgrowths of the alveolar walls, for example, were very marked, while the distension of vesicles with imprisoned colloid was rarely noticeable. Branchings and ramifications of the alveoli were frequent. Moreover, in two sections I observed considerable blood effusion into the substance of the gland, a fact for which I can offer no explanation.

ADDENDUM.

In a comprehensive paper on the etiology of endemic goitre, published within the last few days, (*Ergebnisse der Chirurgie und Orthopädie*, Band v, Berlin, 1913) E. Bircher refers to an extensive series of experiments which have lately been carried out by Sazuki, under the direction of Professor Wilms, of Heidelberg, with a view to studying the action of organic poisons in the production of goitre. These experiments, as quoted by Bircher, are as follows :—

(1) By feeding animals (rats ?) on cooked rice mixed with rat fæces and by the subcutaneous injection of rat fæces moderate-sized enlargements of the thyroid gland of a diffuse form were produced.

(2) Feeding with decayed fish. Negative result. The animals showed disturbances of growth and died rapidly.

(3) Feeding with decayed meat. Negative result.

(4) Feeding with calf's thymus. Negative result.

(5) Subcutaneous injection of the dead body in small and large doses gave negative results. The animals (so treated) soon died.

(6) Subcutaneous injections of tyrosin gave negative results.

(7) Subcutaneous injections of acetonitrile yielded negative results.

(8) Feeding with rat fæces mixed with iodide of potassium yielded negative results.

(9) Feeding with rat fæces mixed with thyroidin yielded negative results.

Commenting on these results Bircher says: "These different experiments show that though the organic poisons are not capable of producing goitre, yet the feeding and subcutaneous injection of fæcal matter can lead to goitrous changes, as has already been shown by McCarrison; and, further, that iodine preparations, such as potassium iodide and thyroidin, are capable of exercising a restraining influence on the formation of goitre."

This confirmation of my experiments by Wilms and Sazuki lends further striking support to my contention that the excitant of the disease is resident in the intestinal tract.

Professor Langhans very kindly gave me in Bern a manuscript report of the histological changes which he had observed in the rat goitres, produced by the Swiss Goitre Commission as a result of seven months' feeding on Lauterbrunnen water; at the same time I was permitted to see the specimens themselves. Briefly summarized Langhan's observations show that there occurred no new formation of follicles, no branching of the alveoli, no characteristic nuclear changes. He has noted degenerative processes proportionate to the period of exposure to goitrous influences, desquamation of the epithelium lining the vesicles, and increase in volume of the protoplasm. The nucleus he found to lie near the base of the cell "very eccentrically placed," but he observed none of the alterations in structure described as not infrequent by Bircher. The alveoli were mostly filled with desquamated cells.

Histological research, therefore, has established the fact that marked changes occur, and has provided a description of several, but further experiments are necessary to establish the sequence of these changes, their interdependence on one another, and their bearing on the etiology of the disease.

Gentlemen, I have concluded my argument. I have endeavoured to put as succinctly as possible the ascertained facts and the logical conclusions whereon are based my belief that the essential

cause of endemic goitre is a micro-organism that finds its home in the intestines of man, and there creates a toxin which so influences the thyroid gland that it undergoes the enlargement which is the dominant symptom of the infection. In searching the existing literature on the subject, I have endeavoured to omit no observation and to pass by no fact that appeared to merit attention; and I have been careful to set down as a fact within my personal knowledge nothing which I have not satisfied myself to be accurately true. Nor have I attempted to propound deductions without setting forth the premises from which I believe them to result.

I am, however, well aware of, and I have been at some pains to explain, the incompleteness of our present knowledge of the facts essential to a final determination of the etiology of goitre. As we have passed from stage to stage in our argument, suggestions have arisen and side-issues been aroused, each of which still offers a field of fruitful promise to the investigator, and any of which may bring to light fresh facts that may cause us eventually to modify the belief which, to my mind, the evidence at present before us justifies.

It is impossible to consider the parasitic thyroiditis described by Dr. Carlos Chagas, or the ingenious methods by which Dr. Bayon has produced enlargements of the thyroid gland, without being impressed with the possibility that in the near

future we shall have to recognize several distinct causes of endemic thyroidomegaly—and therefore several distinct diseases of the thyroid gland—of which the endemic goitre we have been discussing is, in fact, but one. But of this at least there can be no doubt: to the disease which we have been investigating, with its widespread prevalence and appalling consequences, can be attributed no small fraction of the sum-total of human suffering, and incomplete as our knowledge of its causation is, we know enough to make it certain that good sanitation, cleanly houses, cleanly food, and the provision of water-supplies which are not fouled by the excreta of man and beast, are measures which promise an extermination of the disease.

Mr. President and Gentlemen, I would venture once more to offer my thanks for that you have given me this privileged opportunity of setting forth the extent of our knowledge of this disease.

LITERATURE.

For complete Bibliography up to the year 1867 *see* "*Etude sur les Causes du Crétinisme et du Goitre endémique*," *by Dr. J. Saint-Lager. Paris*, 1867 (*Baillière et fils*).

ADAM, TH. "Über das endemische Vorkommen des Kropfes bei Pferden in Augsburg," *Wochenschr. f. Tierheilkunde u. Viehzucht*, 1876, xx, p. 13.

ADAMI, J. E. "Etiology and Symptomatology of Goitre," *Montreal Med. Journ.*, 1900, xxix, pp. 1-17.

—— *Practitioner*, London, 1900, lxiv, pp. 56-74; and *New York Med. Journ.*, 1895, lxxvii.

ANDRIEZEN. "Origin and Evolution of the Thyroid Function," *Brit. Med. Journ.*, 1893, ii, p. 678.

—— ["An Account of Amphioxus and its hypobranchial Organ pouring Secretion into Pharynx"], *ibid.*, 1893, ii, p. 678.

ARMAINGAUD. "De la non-décroissance de l'endémie goitreuse en France," *Rev. d'Hyg.*, Paris, 1894, xvi, pp. 607-17.

—— "Sur l'opportunité de rappeler l'attention sur la question du goitre endémique aux points de vue étiologique et prophylactique," Toulouse, 1891, 20 pp.

ASHMEAD, A. S. "Note on the Etiology and Natural Cure of Goitre," *New York Med. Journ.*, 1895, lxii, p. 241.

—— "Der Kropf in Pennsylvanien," *Zentralbl. f. Laryng.*, 1904.

BAILLARGER. "Le goître et le crétinisme," *Recueil des travaux du comité consult. d'hygiène publique de France*, Paris, 1873.

BALLET, G., et ENRIQUEZ. "Goitre expérimental par injection souscutanée d'extrait thyroïdien," *Bull. et Mém. Soc. méd. des Hôp. de Paris*, 1894, ser. iii, xi, 805 and 941-943.

BALLNER, BAUER, and STREIT. "Komplement-bindungs versuche bei endemischen Kropf," *Zeitschrift. f. Chir.*, 1912.

BAUER, J. "Klinische Untersuchungen über den endemischen Kropf in Tyrol," *Verhandl. d. Congr. f. inn. Med.*, Wiesbaden, 1912, xxix, p. 545.

BAUMANN. "Über die Jodverbindungen d. Schilddrüse," *Münch. med. Wochenschr.*, 1896, xliii, pp. 309, 398.

—— "Über die Wirksamkeit des Thyrojodins," *ibid.*, 1896, p. 476.

BAUMANN, E. and GOLDMANN, E. "Ist das Jodothyrin (Thyrojodin) der lebenswichtige Bestandteil der Schilddrüse?" *Münch. med. Wochenschr.*, 1896, p. 1153.

BAUMANN, E. "Über das normale Vorkommen von Jod in Thierkörper," *Zeitschr. f. physiol. Chemie.*, Strassb., 1895-96, xxi, pp. 319, 481.

—— "Über den Jodgehalt der Schilddrüsen von Menschen und Thieren," *ibid.*, 1896-97, xxii, p. 1.

BAYON. *M.S. Communication*, 1907.

BERARD et DANYAU. "Goitre congénital," *Bull. de la Soc. de Chir.* (1861), 1862, ii, ser. ii, p. 108-114.

BÉRARD ET THÉVENOT. "Note sur l'étiologie des goitres," *Comptes rend. Soc. de. Biologie*, Par., 1907, lxii, p. 44.

BERESOWSKY. "Über die kompensatorische Hypertrophie der Schilddrüse," Zieglers *Beiträge zur pathologischen Anatomie*, Jena, 1892, xii, pp. 122-130.

BERRY, J. "Lectures on Goitre, its Pathology, Diagnosis and Surgical Treatment," *Brit. Med. Journ.*, London, 1891, i, pp. 1269-1273, 1326-1330.

—— "Diseases of the Thyroid Gland," London, 1901.

BIEDL. "The Internal Secretory Organs: Their Physiology and Pathology," Translated, London, 1912, pp. vi, 586, with Bibliography, pp. 140.

BIELYAYEFF, V. A. ["Changes of the Blood in Basedow's Disease and in Goitre"], *Russk. Vrach.*, St. Petersburg, 1911, x, p. 255.

BILLIG, A. "Struma congenita, ein Geburtshinderniss," Heidelberg, 1892.

BILLIET ET MOREL. "Sur le goître et le crétinisme," *Ann. med. Psych.*, Paris, 1854, 2 ser., vi, pp. 221, 229, 530; 1855, 3 ser., i, p. 41.

BIONDI. "Beitrag zur Struktur und Funktion der Schilddrüse," *Berliner klin. Wochenschr.*, 1888, xxv, p. 954.

Bircher, E. "Zur Pathogenese der kretinischen Degeneration," *Beihefte z. med. Klinik* v. Berlin, 1908, iv, pp. 149-180.

—— "Zur experimentellen Erzeugung der Struma, zugleich ein Beitrag zu deren Histogenese," *Deutsch. Zeitschr. f. Chir.*, Leipzig, 1910, ciii, pp. 267-363.

—— "Die kretinische Degeneration (Kropf, endemischer Kretinismus und Taubstummheit) in ihren Beziehungen zu andern Wissensgebeiten," "Abderhalden, Fortschritte der naturwissenschaftl. Forschung," ii, 1910.

—— "Zur Frage der Kropfätiologie," *Deutsch. med. Wochenschr.*, Leipz., 1910, xxxvi, p. 1705.

—— "Zur experimentellen Erzeugung der Struma, zugleich ein Beitrag zu deren Histogenese," *Deutsch. Zeitschr. für Chir.*, 1910, ciii, pp. 267-363.

—— "Weitere Beiträge zur experimentellen Erzeugung des Kropfes. Die Kropfätiologie ein colloidchemischer Problem," *Zeitschr. f. exp. Pathologie u. Therapie*, 1911, ix, pp. 1-21.

—— "Weitere histologische Befunde bei durch Wasser erzeugten Rattenstrumen und Kropfherzen," *Deutsch. Zeitschr. für Chir.*, 1911, cxii, p. 368.

—— "Fortfall und Änderung der Schilddrüsenfunktion als Krankheitsursache," Wiesbaden, 1911.

Bircher, H. "Der endemische Kropf, und seine Beziehungen zur Taubstummheit und zum Kretinismus," Basel, 1883.

—— "Das Myxödem und die cretinische Degeneration," *Volkmann's klin. Vorträge*, 1890, Chir., No. 110, p. 357.

Blauel. "Zür Aetiologie des Kropfes," *Münch. med. Wochenschr.*, 1910, lvii, pp. 9-11.

Blum. "Über der Halogenstoffwechsel und seine Bedeutung für den Organismus," *Münch. med. Wochenschr.*, 1898, xlv, pp. 231, 267, 271, 335.

—— "Neue experimentellgefundene Wege zur Erkenntnis und Behandlung von Krankheiten, die durch Autointoxikationen bedingt sind," *Virchow's Arch.*, Berl., 1900, clvii, pp. 375-405.

Bock, F. W. "Simple Goitre treated with Boric Acid," *Amer. Med.*, Phila., 1905, ix, p. 473.

Boéchat, S. A. "Des sinus lymphatiques du corps thyroïde."

BRAULT, J. "Note sur le goitre à Alger," *Janus*, Haarlem, 1911, xvi, p. 205.

BREITNER. "Über die Ursache und Wesen des Kropfes," *Wiener. klin. Wochenschr.*, 1912, xxv, p. 82.

BRESSON. "Epidémie de Thyroïdite aiguë observée à St. Etienne parmi les enfants de troupe du 9. régiment de ligne," *Réc. de mem. de med. milit.*, Paris, 1864, xii, p. 273.

BRISSARD. "Sur la fréquence du goitre chez aliénés," *Rev. med. de la Suisse-Rom.*, Genève, 1906, xxvi, pp. 632-634.

BRUMPT, E. "Etude expérimentale de la trypanosomose américaine de C. Chagas," *Bulletin de l'Académie de Médecine*, 1912, 3 ser., lxvii, p. 428.

*BRUNNER, C. "Ein Fall von acut eiteriger Strumitis, ursacht durch das *Bakterium coli*," *Cor.-Blatt. Schweiz. Aerzte*, Basel, 1892, xxii, pp. 298-307.

CARPI. "Über morphologische Blutveränderungen bei Struma und Morbus Basedowii," *Berlin. klin. Wochenschr.*, 1910, xlvii, p. 2059.

CHABRAND. "Du goitre et du crétinisme endémiques et de leurs véritables causes," Paris, 1864.

CHAGAS, CARLOS. "Novo Tripanozomioze humana," *Memorias do Instituto Oswaldo Cruz*, 1909, i, fasiculo 2.

—— "Nova entedu de morbida do homem," *ibid.*, 1911, iii, p. 2.

—— "Neue Trypanosomen, Vorläufige Mitteilung," *Archiv. f. Schiffs. u. Tropenhygiene*, Leipzig, 1909, xiii, p. 120.

CHAMBERS, G. "Observations on Simple Goitre occurring at Puberty, with Special Reference to the Use of Thyroid Extract in its Treatment," *Canad. Journ. Med. and Surg.*, Toronto, 1911, xxix, p. 249.

CHAMBERS, Miss H. "Observations on the Pathology of Innocent Goitre," *Brit. Med. Journ.*, 1909, ii, pp. 855-859 *et seq.*

CHAPPLE. "A Study of the Life-histories of Fifty Cases of Chronic Intestinal Stasis treated by Short-circuiting or Colectomy," *Clin. Journ.*, 1911, xxxviii, p. 102.

CHARRIN, A. "Les défenses naturelles de l'organisme," Paris, 1898.

CHATIN. *Vide* St. Lager.

CHEVRANT, P. "Note sur l'étiologie du goitre," *Arch. de méd. et de pharm. mil.*, Paris, 1911, lvii, p. 14.

CLEMENS. "A New Sign in the Rheumatism of Childhood," *Arch. of Pediat.*, 1910, xxvii, p. 353.

COGHILL. "The Hypodermic Treatment of Bronchocele by Ergotine," *Lancet*, 1877, ii, p. 158.

COLLIN. "Note sur le goître aigu dans la garnison de Briançon, pendant l'année 1860," *Rec. de mém. de med. mil.*, Paris, 1861, iii, 3 ser., vi, pp. 1-21.

COLQUHOUN, D. "On Goitre," *New Zealand Med. Journ.*, Wellington, 1910, viii, pp. 17-71.

CONTAMESSA, G. "Di una piccola epidemia di gozza," *Gazz. d. osp.*, Milano, 1906, xxvii, p. 1239.

COOPER. "The Bactericidal Action of the Cresols and Allied Bodies and the best means of employing them," *Brit. Med. Journ.*, 1912, i, pp. 1234-1240, 1293-1297, 1359-1363.

COTTES, G. W. "Goitre and Thyroidism," *New York State Journ. Med.*, New York, 1910, x, pp. 467-72.

CRILE, G. W. "Goitre: some Biological Considerations," *Detroit Med. Journ.*, 1911, xi, p. 201.

CULLEN, G. M. "The Earlier Literature of the Thyroid Gland," *Edinburgh Med. Journ.*, 1891-92, xxxvii, pp. 531-545.

CZERNICKI. "De la non-transmissibilité du goître aigu épidémique," *Gaz. hebd. med. et chir.*, Paris, 1881, 2 ser., xviii, p. 611.

DAVIDSOHN, C. "Über den schlesischen Kropf," Virchows *Archiv. f. path. Anat.*, &c., Berlin, 1911, ccv, pp. 170-208.

DAVIS, S. R. "Congenital Goitre in Lambs," *Vet. Journ. and Ann. Comp. Path.*, London, 1898, xlvii, pp. 25-27.

DEPAGE. "À propos du goitre en Belgique," *Ann. Soc. belge de Chir.*, Brux., 1896-7, iv, pp. 267-279.

DIEDOFF, V. P. "Goitre in Kokanda," *Vrach. Gaz.*, St. Peters., 1904, xi, pp. 1489-91.

DOCK, G. "Goitre," *N. Orl. Med. and Surg. Journ.*, 1909-10, lxii, pp. 251-58.

—— "System of Medicine," Osler and Macrae, 1909, vol. vi, p. 403.

Dock, G. "Goitre in Michigan," *Med. News*, Phila., 1895, lxxvii, pp. 60-63.

Dor, Louis. "Pathogénie et anatomie pathologique des goitres et des cancers thyroïdiens," *Gaz. des Hôp.*, 1903, pp. 501-505, 519-521.

Duncan, L. C. "An Area of Endemic Goitre in the Philippine Islands," *Amer. Med.*, Phila., 1905, x, p. 861.

Durham, H. E. "On persistence of the Thyreoglossal Duct," *Med. Chir. Trans.*, 1894, lxxvii, pp. 199-226.

East, H. "Goitre in India," *Med. News*, N.Y., 1905, lxxxvii, p. 1193.

Ebbell, B. "Det endemiske strumas Ætiologi," *Norsk. Mag. f. Lægevidensk*, Kristiania, 1910, 5 R, viii, pp. 1131-41.

Edmunds, W. "Pathological Effects Produced in the Central Nervous System by Thyroid Excision and by Thyroid Feeding," *Trans. Path. Soc.*, London, 1902, liii, p. 343.

—— "The Pathology and Disease of the Thyroid Gland," Edinburgh and London, 1901.

—— "The Changes in the Central Nervous System Resulting from Thyro-parathyroidectomy," *Proc. Roy. Soc. Med.*, 1912 (Neur. Sect.), p. 179.

—— "Further Observations and Experiments on the Pathology of Graves's disease," *Journ. Path. and Bact.*, Edinburgh and London, 1898, v, p. 33.

—— "Further Observations and Experiments on the Thyroid and Parathyroid," *ibid*, 1900, vi, pp. 64-72.

—— "Further Observations on the Thyroid Gland," *ibid.*, 1903, viii, pp. 288-93; 1907-8, xii, pp. 101-6.

Eiselberg, O. v. "Die Krankheiten der Schilddrüse," *Deutsche. Chirurgie*, Lief, 38, Stuttgart, 1901.

—— "Über vegetative Störungen bei jungen Schafen und Lämmern nach Schilddrüsenextirpation," *Verhand. d. Deutsch. Gesellsch. f. Chir.*, Berlin, 1893, xxii, p. 82.

—— *Virchow's Archiv. f. path. Anat.*, 1898, cliii, p. 1.

Enderlen. "Diagnose und Therapie des Kropfes," *Deutsch. med. Wochenschr.*, Leipzig and Berl., 1910, xxxvi, p. 2033.

Epidemics of Goitre—"Zur Geschichte des akuten Kropfes in den Armeen," *Preussische militärarztl. Zeitung*, 1862, pp. 138, 145.

EPIDEMICS OF GOITRE, 1862, in Clermont (Courcelle in *Rec. de mem. de méd. milit.*, 1864, 3 ser., xi, p. 133).
—— In Kolmar, 1862 and 1863 (Gouget, *ibid*, 1862, 3 ser. vii, p. 289-328; 1863, 3 ser. x, pp. 180, 271).
—— In Embrun, 1863 (Département Hautes-Alpes), (Hédoin, *ibid.*, 1864, 3 ser., xi, pp. 465-88).
—— Hoffmann, *Ärztl. Intelligenzblatt*, 1862, ix, p. 62.
—— Macnamara, "Diseases of Himalayan India," London, 1880.
—— Worbe, "Epidémie de goître aigu," *Rec. de méd. de Paris*, (1867), 3 ser., xviii, p. 104, xix, pp. 273, 369.
—— In St. Etienne, 1873 (Michaud, *Gaz. méd. de Paris*, 1874, 4 ser., iii, pp. 17, 67).
—— New Breisach, 1869-70 (Müller, *Rec. de mém. de méd. milit.*, 1871, 3 ser., xxvi, pp. 244-55).
—— Belfort, 1877 (Viry et Richard, *Gaz. hebdom. de Paris*, 1881, 2 ser., xviii, pp. 457, 480).
—— Chouet, "Étude critique sur l'étiologie du goître en général, à propos des épidémies du goître aigu dans la garnison" (Clermont-Ferrand, *Rec. de mém. de méd. milit.*, 1881, 3 sér., xxxvii, pp. 353-76).
EWALD, C. A. "Die Erkrankungen der Schilddrüse, Myxödem und Kretinismus," Liepzig, 1909.
—— "Zur Frage der Kropfätiologie," *Deutsch. med. Wochenschr.*, 1910, xxxvi, p. 766.

FABRE, J. P. A. "Traité du goître et du crétinisme et des rapports qui existent entre ces deux affections," Paris, 1857.
FABRE and TRÉLLAT. "Goître congénital chez l'enfant; goître chez la mère," *Bull. Soc. d'obst. de Par.*, 1908, xi, pp. 34-37.
FARRANT, R. "Thyroid Action and Reaction, with Special Reference to the Formation of Thyroid Tumours," *Proc. Roy. Soc. Med.*, 1912-13, vi (Path. Sect.), pp. 21-48.
FASSIN, L. "Influence de l'inoculation d'extraits thyroïdiens sur les propriétés actives du sérum," *Comptes rend. Soc. de Biol.*, Paris, 1907, lxii, p. 388.
—— "Influence de l'ingestion de corps thyroïdes sur les propriétés alexiques du sérum," *ibid.*, 1907, lxii, p. 467.

FASSIN, L. "Modifications de la teneur du sérum en alexine chez les animaux thyroïdectomisés," *Comptes rend. Soc. de Biol.*, Paris, 1907, lxii, p. 647.

FAVRE et THÉVENOT. "Le Goitre chez le nouveau-né," *Soc. de Chir. de Lyon*, 21 mars, 1907, et *Rev. de Chirur.*, 1907.

FAYRER, J. "On Bronchocele," *Lancet*, 1874, ii, pp. 580, 617.

FINKBEINER. "Neandertalmerkmale bei Kretinen," Julius Springer, Berlin, 1912.

FJELLANDER, G. "Endemisk struma i Husley distrikt," *Hygiea*, Stockholm, 1911, lxxiii, pp. 856-857.

FODÉRÉ. "Traité du goitre et du crétinisme," Paris (1800), an viii.

FORSYTH, D. "The Parathyroid Glands, their function and relation to the Thyroid Gland," *Quarterly Journal of Med.*, Oxford, 1907-1908, i, pp. 150-173.

—— *Clinical Journal*, 1909, xxxiv, pp. 251-256 *et seq.*

FOVILLE. "Goître et crétinisme," *Annales d'hyg.*, Paris, 11 ser., 1876, xlvi, pp. 64, 193.

FRAENKEL, S. "Über die Wirksamkeit des Thyreo-antitoxins," *Wiener med. Blätter*, 1896, No. 51.

FREY. "Verbreitung des Kropfes im Kanton Aargau," Dissertation, Bern, 1873.

GARRIGOU, F. "L'endémie du goitre et du crétinisme, envisagée dans les Pyrénées au point de vue de les rapports avec la nature géologique du sol," *Gaz. hebd. de Méd. et de Chir.*, Paris, 1874, 2 ser., xi, pp. 270, 284.

GAUTHIER, G. "Fonctions du corps thyroïde; pathogénie du goitre endémique, du goitre sporadique, du goitre exophthalmique, hypothyroïdation et hyperthyroïdation," *Rev. de Méd.*, Paris, 1900, xx, pp. 225-243.

GAYLORD und M. PLEHN. "Über Geschwülste bei niederen Wirbeltieren, Travaux de la deuxième Conférence internationale pour l'Étude du Cancer," Paris, 1910, p. 787.

GILBRIDE, J. J. "Cultures from the Thyroid Gland in Goitre: a Bacteriologic Study of Fourteen Cases," *Journ. Amer. Med. Assoc.*, Chicago, 1911, lvii, p. 1988.

GIORDANO, G. "Ricerche ematologiche su alcuni case di gozzo semplice e di gozzo Basedowiano," *Gazz. internaz. di Med.*, Napoli, 1911, xlv, p. 1.

GLEY. "Détermination de la toxicité du sérum sanguin chez les chiens thyroïdectomisés," *Archives de Physiol.*, Paris, 5 ser., 1895, viii, p. 770.

—— "Les rélations actuelles entre la physiologie et la pathologie de la glande thyréoïde," *Rev. génér. des Sciences*, janv., 1898.

GONNET (C.). "Le goitre congénital," *Rev. mens. de Gynéc., d'Obstet., et de Pédiatr.*, Paris, 1909, iv, pp. 113-121.

GOSSE. "Ueber die Ätiologie des Kropfes und des Kretinismus," *Schweizer Zeitschr. für Medizin, Chirurgie und Geburtshilfe*, Zurich, 1853, pp. 73-102.

GRAF. "Etiology of Goitre," *Gesellschaft der Aerzte*, Vienna. *See Lancet*, 1912, i, p. 128.

GRANGE. "Nouvelles recherches sur les rapports qui existent entre la présence du goître dans un pays et la nature géologique du sol [Abstr.], *Comptes rend. Acad. de Science*, Paris, 1850, xxxi, p. 58.

—— "Rapports sur les causes du goitre," *Arch. gén. de Méd.*, Paris, 1850, 4 ser., xxiv, pp. 243-247.

GRASSET. "L'hématozoaire du goitre," *Comptes rend. Acad. de Science*, 1898, xxvii, p. 75, *Brit. Med. Journ.*, 1898, iii, p. 915.

GRASSI AND MANARON. "Rendiconti della reale accademia de Lincei," 1903-1904, xii a xiii.

GUERRERO (P.). "Investigaciones sobre etiologia del bocio endemico," *Juventud med.*, Guatemala, 1911, xi, No. 1, pp. 1-5.

GUTTINGER. "Die Veränderung der Struma und des Halsumfanges bei Rekruten während des Militärdienstes," Dissertation, Zurich, 1891.

GUTKNECHT. "Die Histologie der Struma," *Virchow's Archiv f. Path. Anat.*, Berl., 1885, xcix, pp. 314, 419.

HALLIN. "Om Struma," *Hygiea*, Stockholm, 1867.

HALSTED, W. S. "An Experimental Study of the Thyroid Glands of Dogs, with especial Consideration of Hypertrophy of this Gland," *Johns Hopkins Hospital Reports*, Balt., 1896, i, pp. 373-408.

HANDMANN. *Münch. med. Wochenschr.*, mai, 1910, No. 22.

HARL, KASPAR. "Zur Pathologie und Therapie der Struma," Dissertation, Würzburg, 1880.

HATT. "Slight General Enlargement of Thyroid Gland as found in School Children," *Lancet*, 1911, i, p. 575.

HAUSHALTER, P., et JEANDELIZE, P. "Notes sur un centre ancien d'endémie crétino-goitreuse dans une commune de Meurthe-et-Moselle," Paris, 1903, 11 pp.

HAYMAKER, S. R. "A Case of Cutaneous Pigmentation with Lesions in the Adrenal Glands," *Proc. New York Path. Soc.*, 1902, n.s., l, p. 136.

HEIDENREICH. "Der Kropf," Ansbach, 1845.

HELLIN. "Struma und Schilddrüse," München, 1893.

HESSE, E. "Die Verbreitung des Kropfes im Königreich Sachsen mit besonderer Berücksichtigung der geologischen Verhältnisse," *Archiv f. klin. Med.*, 1911, pp. 102, 217.

—— Die Verwertung der militärischen Untersuchungsbefunde zur Erforschung des Kropfes," Sonderabdruck aus der *Deutsch. Militärarztl. Zeitschr.*, 1911.

HILDEBRAND, O. "Die Behandlung des Kropfs," *Therap. d. Gegenw.*, Berlin, 1906, xlvii, pp. 22-24.

HIRSCH, A. "Kropf und Kretinismus," Handbuch der historisch-geographischen Pathologie, Stuttgart, 1883.

HITZIG, THEODOR. "Beiträge zur Histologie und Histogenese der Struma," *Archiv für klin. Chirurgie*, Berlin, 1894, xlvii, pp. 464-502.

HÖFLER. "Über die kretinistischen Veränderungen an der Leben den Bevölkerung des Bezirkes Tölz," 1881.

HOLDER, A. B. "Goitre; a New Habitat," *New Orleans M. and S. Journ.*, 1889-90, n.s., xvii, pp. 552-554.

HOLLAND. *Microscop. Journ.*, i, p. 176.

HORAND, R. "Examen à l'ultramicroscope du liquide du goître kystique; présence d'un parasite," *Rev. gen. de Clin. et de Thérap.*, Paris, 1911, xxv, p. 71.

HORNE. "On Colloid in the Lymphatics and Blood-vessels of the Thyroid in Goitre," *Journ. Anat. and Physiol.*, London, 1892, xxvii, pp. 161-168.

—— "The Blood-vessels of the Thyroid Gland in Goitre," *Lancet*, 1892, ii, pp. 1213-1216.

HORSLEY, SIR V. "Physiology and Pathology of the Thyroid Gland," *Brit. Med. Journ.*, 1896, ii, pp. 1623.

HORSLEY, Sir V., *Festschrift für R. Virchow*, Berlin, 1891, Band i.
—— "Remarks on the Function of the Thyroid Gland," *Brit. Med. Journ.*, 1892, i, pp. 215-219, 265-268, 1113.
HOWLE, CRESWELL. *MS. Communications*, 1909-10.
HUNT. *Journ. Amer. Med. Assoc.*, 1907, xlix, p. 240.
HÜRTHLE. "Über den Sekretionsvorgang in der Schilddrüse," *Deutsche med. Wochenschr.*, Leipzig and Berlin, 1894, xx, pp. 267-70.
—— "Beiträge zur Kenntnis des Sekretionsvorganges in der Schilddrüse," *Pflüger's Arch. f. gesammte Physiol.*, Bonn, 1894, lvi, pp. 1-44.

ISENSCHMID, R. "Zur Kenntnis der menschlichen Schilddrüse im Kindesalter, mit besonderer Berücksichtigung der Herkunft aus verschiedenen Gegenden im Hinblick auf die endemische Struma," *Frankfurter Zeitschr. f. Pathol.*, Wiesb., 1910, v, pp. 205-54.
IZABOLINSKI, M. "New Investigation of the Etiology of Endemic Goitre," *Vrach. Gaz.*, S. Petersburg, 1910, xvii, pp. 149, 199, 236.

JABOULAY. "Poissons atteints de goîtres malins héréditaires et contagieux," *Lyon Méd.*, 1908, cx, 335.
—— "Poissons goitreux expérimentaux," *ibid.*, 1908, cxi, pp. 595-597.
JEANSELME, E. "Distribution du goitre et du crétinisme dans l'Indo-Chine française et dans le Gunnan," *Rev. de Méd. et d'Hyg. trop.*, Paris, 1910, vii, p. 317.
JOHANNESEN. "Strumaets aetiologiske forhold og udbredelse i Norge," Kristiania, 1889.
—— "Verbreitung und Ätiologie des Kropfes in Norwegen," *Zeitschr. für klin. Med.*, Berlin, 1891, xxiv, pp. 194-208.

KANTHACK, A. A. "The Thryeoglossal Duct," *Journ. Anat. and Physiol.*, 1891, xxv, pp. 155-165.
KISHI. "Zur Aetiologie der Struma" [Japanese text, German abstract, Hft. 8], *Mitt. d. med. Gesellsch. zu Tokyo*, 1905, xix, pp. 389-393.
KLEBS. "Studien über die Verbreitung des Kretinismus in Österreich sowie über die Ursach der Kropfbildung," Prag., 1877.

KLOEPPEL, F. C. "Vergleichende Untersuchungen über Gebirgsland und Tieflandsschilddrüsen," *Ziegler's Beitrage, z. Path. Anat.*, Jena, 1910, xlix, pp. 579-94.

KOCHER, T. "Zur Pathologie und Therapie des Kropfes, 3 Abschnitt. über Entzündung des Kropfes," *Deutsche Zeitschr. für Chirurgie*, Leipzig, 1873-4, x, pp. 417-53.

—— "Vorkommen und Vertheilung des Kropfes in Kanton Bern. Ein Beitrag zur Kenntnis der Ursachen der Kropfbildung," Bern, 1889.

—— "Zur Verhütung des Kretinismus und kretinoider Zustände nach neuen Forschungen," *Deutsche Zeitschr. für Chirurgie*, Leipzig, 1892, xxxiv, pp. 556-626

—— "Die Schilddrüsenfunktion im Lichte neuerer Behandlungsmethoden verschiedener Kropfformen," *Korrespondenzbl. f. Schweizer Aerzte*, Basel, 1895, xxv, pp. 3-20.

KOLLE, W. "Über Ziele, Wege und Probleme der Erforschung des endemischen Kropfes," *Korrespondenzbl. f. Schweizer Aerzte*, Basel, 1909, xxxix, pp. 577-588.

KUTSCHERA, A. "Zur Epidemiologie des Kretinismus," *Med. Blätter*, Wien, 1909, xxxii, pp. 563, 577, 587.

—— "Die Übertragung des Kretinismus vom Menschen auf das Tier," *Wiener klin. Wochenschr.*, 1910, xxiii, p. 1593.

—— "Der endemische Kretinismus, seine Ursachen und seine Behandlung," *Das österreichische Sanitätswesen*, Beitrage zu No. 7, February 16, 1911.

—— "Die Ätiologie des Kropfes und des Kretinismus," *Der Amtsarzt*, No. 12, 1911.

—— (Etiology of Goitre), Vienna Gesellschaft der Aerzte, *Lancet*, 1912, i, p. 128.

LAULANIÉ, M. "Nouveaux faits pouvant servir à la détermination du rôle des corps thyroïdes," *Gaz. méd. de Paris*, 1891, viii, 7 s., pp. 253-6.

—— *Comptes rendus Soc. de Biol.*, Paris, 1891, iii, 19 s., pp. 307-312.

LEBERT. "Die Krankheiten der Schilddrüse und ihre Behandlung," Breslau, 1862, viii (2 l.).

LEBOUR, G. A. "On the Geological Distribution of Endemic Goitre in England," Newcastle-upon-Tyne.

LEMOS, A. "Il boico y il cretinismo en la provincia de Mendoza," *Revista medico-quirurgica de Buenos-Ayres*, 1877.

LEOPOLD-LEVI et DE ROTHSCHILD (H.). "Endocrinologie. Nouvelles études sur la physiopathologie du corps thyroïde et des autres glands endocrinés," 2me Série, Paris, 1911.

LEVY, A. G. "Changes occurring in the Blood of Dogs after removal of the Thyroid," *Journ. of Pathol. and Bacteriol.*, Edinburgh, 1898, v, pp. 316-330.

LEVY, A. "Ueber eine Kropf-Epidemie in der Knaben Besserungs-Anstalt zu Hagenau," *Arch. f. off. Gsndhtspflg.*, Strassb., 1889, xiii, pp. 194-198.

LIEBER, ANNA. "Zur Kasuistik der Struma congenita," *Wiener med. Wochenschr.*, 1908, lviii, pp. 340-343; and *Mitt. d. Gesellsch. f. inn. Med. u. Kinderh. in Wien*, 1908, vii, Beit., pp. 28-32.

LOBENHOFFER, W. "Verbreitung des Kropfes in Meterfrankin," *Mitteil. a. d. Grenzgeb. d. Med. u. Chir.*, Jena, 1912, xxiv, pp. 475-511.

LOMBARD, H. C. "Étude sur le goitre et la crétinisme et sur leur cause atmosphérique," Lausanne, 1874.

—— "Sur les fonctions du corps thyroïdien, &c.," *ibid.*, 1883.

LOMBROSO, C. "Ricerche sul cretinismo in Lombardia," *Gaz. med. ital.-lomb.*, Milano, 1859, p. 253.

LORENZ. *Vide* Beihefte z. med. Klinik v. Berl., 1908, p. 149.

DE LUCA and D'ANGIARO. "The Antitoxic Power of the Thyroid Gland," *New York Med. Journ.*, 1897, lxv, p. 462.

LÜCKE, A. "Die Krankheiten der Schilddrüse" (Pitha und Billroth's "Handbuch für Chirurgie"), Stuttgart, 1875.

LUSTIG, A. "Über die Ätiologie des endemischen Kropfes," *Verhandl. des X. internat. Med. Kongresses* zu Berlin, 1890, ii, iii, Ab. p. 99.

—— "Sul' etiologia del gozzo endemico," *Settimana med. di Sperimentale*, Firenze, 1896, l, p. 229.

—— e CORLE. "Sull étiologia del gozzo endemico," *Giorn. d. R. Accad. d. Med. di Torino*, 1890, 3 ser., xxxviii, pp. 689-716.

MCCARRISON, R. "Observations on Endemic Goitre in the Chitral and Gilgit Valleys," *Med.-Chir. Trans.*, 1906, lxxxix, pp. 437-470.

McCarrison, R. "Further Observations on Endemic Goitre in the Chitral and Gilgit Valleys," *Lancet*, London, 1906, i, p. 1110.

—— "Further Researches on the Etiology of Endemic Goitre," *Quarterly Journal of Medicine*, London, 1908-1909, ii, pp. 279-289.

—— "Observations on Endemic Cretinism in the Chitral and Gilgit Valleys," *Proc. Roy. Soc. Med.*, 1908, ii (Med. Sect.), pp. 1-31.

—— "Observations on the Amœbæ in the Intestines of Persons suffering from Goitre in Gilgit," *Quarterly Journal of Microscopical Science*, 1909, liii, pp. 723-736.

—— "A Summary of further Researches on the Etiology of Endemic Goitre," *Proc. Roy. Soc.*, London, B. 1909, lxxxi, p. 31, and 1910, B. lxxxiii, pp. 335-337.

—— "Further Experimental Researches on the Etiology of Endemic Goitre," *Annals of Tropical Medicine and Parasitology*, 1911, v, pp. 1-14.

—— "The Experimental Transmission of Goitre from Man to Animals," *ibid.*, pp. 187-199, 3 plates.

—— "A Summary of Further Experimental Researches on the Etiology of Endemic Goitre" (Second Series), *Proc. Roy. Soc.*, 1910-11, lxxxiii, pp. 335-337.

—— "A Second Series of Experiments dealing with the Transmission of Goitre from Man to Animals," *Annals of Trop. Med. and Parasitology*, 1911, v, pp. 453-471.

—— "The Vaccine Treatment of Simple Goitre," *Proc. Roy. Soc. Med.*, 1912, v (Med. Sect.), pp. 37-48.

—— "A *Résumé* of Researches on Endemic Goitre," *Indian Med. Gaz.*, 1911, xlvi, pp. 253-260, 1 pl.

McClelland. "Some Inquiries in the Province of Kemaon relative to Geology, including an Inquiry into the Causes of Goitre," Calcutta, 1835.

—— "Observations on Goitre," *Trans. Med. and Phys. Soc.*, Calcutta, 1834, vii, pp. 145-155; *Dublin Journ. of Med. Sc.*, 1837, ii, pp. 295-340.

—— "Sketch of the Medical Topography or Climate and Soils of Bengal, and the North-West Provinces," London, 1859.

McKenzie. "Endemic Goitre and its Occurrence in Lanarkshire, with some Observations on the Pathology of the Disease," *Glasgow Med. Journ.*, 1899, li, pp. 15-29.

McKenzie, D. "The Etiology of Endemic Goitre and Cretinism," *Lancet*, 1911, ii, p. 1432.

Mackenzie, M. "On the Etiology of Endemic Goitre," *Med. Exam.*, London, 1877, ii, pp. 854-856.

MacMahon. "The Geology of Gilgit," *Quart. Journ. Geol. Soc.*, 1900, lvi, pp. 337-368.

Macnamara, F. N. "Climate and Medical Topography in their Relation to the Disease Distribution of Himalayan India, &c.," London, 1880.

—— "Distribution of Goitre in India" (Davidson, "Hygiene and Diseases of Warm Climates," 1893).

Marine, D. "The Histology of the Thyroid in Simple and Toxic (Exophthalmic) Goitre, with Remarks on Similar Changes in the Dog," *Cleveland Med. Journ.*, 1907, vi, pp. 45-52, 1 pl.

—— and Lenhart. "Colloid Glands: their Etiology and Physiological Significance," *Bull. Johns Hopkins Hosp.*, 1909, xx, pp. 131-139.

—— "On the Occurrence of Goitre (Active Thyroid Hyperplasia) in fish," *Ibid.*, 1910, xxi, pp. 95-98.

—— "Relation of Iodin to the Structure of Human Thyroids," *Archives of Internat. Medicine*, 1909, iv, pp. 440-493.

—— "Effects of the Administration or the Withholding of Iodin-containing Compounds in Normal Colloid or actively Hyperplastic (Parenchymatous) Thyroids of Dogs," *Ibid.*, 1909, iv, pp. 253-270.

—— "The Pathological Anatomy of the Human Thyroid Gland," *Ibid.*, 1911, vii, pp. 506-535.

—— "Further Observations and Experiments on the So-called Thyroid Carcinoma of the Brook Trout (*Salvelinus fontinalis*) and its Relation to Endemic Goitre," *Journ. of Exper. Med.*, 1911, xiii, pp. 455-475, 2 pl.

—— "Colloid Glands (Goitres): Their Etiology and Physiological Significance," *Bull. Johns Hopkins Hospital*, 1909, xx, pp. 131-139.

—— "Observations and Experiments on the so-called Thyroid Carcinoma of Brook Trout (*Salvelinus fontinalis*) and its Relation to ordinary Goitre," *Journ. of Exper. Med.*, 1910, xii, pp. 311-337, 2 pl.

MARTHE, F. "Quelques recherches sur le développement du goitre," Dissertation, Bern, 1873.

MARTIN, P. "On the Function of the Thyroid Body," *Proc. Roy. Soc.*, 1857, viii, pp. 315-318.

MASOIN. "Toxicity of the Urine after Thyroidectomy" (Abstr.), *New York Med. Record*, 1894, xlv, p. 246.

MAUMENÉ. "Recherches expérimentales sur les causes du goitre," *Compt. rend. de l'Acad. des Sciences*, Paris, 1866, lxii, p. 381.

MAYET, L. "Anthropologie médicale, le crétinisme et le goitre endémiques en France, plus particulièrement dans les Alpes françaises," *Prov. Méd.*, Paris, 1908, xix, pp. 437-442.

—— "Études sur la répartition géographique du goitre en France," *Arch. génér. de méd.*, 1900, iv, pp. 179-207.

—— "Goitre et crétinisme endémiques," *Biologica*, Paris, 1912, ii, pp. 6-13, and *Provence Méd.*, Paris, 1911, xxii, pp. 473-476.

—— "L'Étude sur la répartition géographique du goitre en France," *Arch. gén. de. Méd.*, Paris, 1900, n.s., pp. 179-207.

MAYET, LUCIEN. "Goitre et crétinisme endémique," *Biologica*, 1912, ii, 6.

MAYO, C. H. "Goitres of the Young," *South Med. Journ.*, Nashville, 1908, i, pp. 18-21.

METCHNIKOFF. "Etudes sur la flore intestinale," *Annales de l'Institut Pasteur*, Paris, 1908, xxii, pp. 929-955, and *ibid.*, 1910, xxiv, pp. 755-770.

MICHALSKY (H). "Eine neue Behandlung der Struma," *Zeitschr. f. phys.-diätet. Therap.*, Leipzig, 1908, xi, 745-750.

MIKULICZ. "Über Thymusfütterung bei Kropf und Basedowscher Krankheit," *Berl. klin. Wochenschr.*, 1895, xxxii, 342-346.

MOONEY, E. W. "Congenital Goitre: with Report of Cases," *Arch. Pediatr.*, New York, 1910, xxvii, pp. 930-37.

MORLIER. "De l'étiologie du goître endémique," *Thèse de Paris*, 1854.

MORONE. "Ricerche ematologiche nelle affezioni della tiroide," *Rif. Med.*, Napoli, 1910, xxv, p. 813.

MORRIS, H. C. L. "Notes on the Etiology of Goitre," *Brit. Med. Journ.*, 1895, ii, p. 13.

MOSCATELLI. "Beiträge zur Kenntnis der Milchsäure in der Thymus und Thyreoida," *Zeitschr. für physiol. Chemie*, 1888, xii, p. 417.

MOSLER, F. Ziemssen's "Cyclopædia of Practice of Medicine," 1878, viii.

MÜHLBERG. "Kropf und Kalk," *Korrespondenzbl. für Schweizer Ärzte*, 1878, No. 21.

MÜLLER, C. "Über morphologische Blutveränderungen bei Struma," *Mediz. Klinik*, Wien, 1910, vi, pp. 1340-1342.

MÜLLER, N. "Der Kropf," *Medizinskoje oborrenje*, 1884.

MUNARON, L. "Da Studi sull'endemia gozzigena in Italia (Questioni principali; concetto fondamentale delle nuove indagini), *Arch. di farmacol. sper.*, Roma, 1909, viii, pp. 367-376.

MUNSON, E. L. "The Occurrence of Goitre among the Indians of the United States," *New York Med. Journ.*, 1895, lxii, pp. 513-518.

MURRAY, G. R. "The Signs of Early Disease of the Thyroid Gland," *Brit. Med. Journ.*, 1909, i, pp. 381-384.

—— "Diseases of the Thyroid Gland: 1. Myxœdema and Cretinism," London, 1901.

—— "The Pathology of the Thyroid Gland," *Lancet*, 1899, i, pp. 667-678, 747-752.

MUSGRAVE. "Amœbas," Dept. of Interior, Bureau of Gov. Laborat., Biol. Laborat., No. 18, Manila, 1904.

MUSGROVE, T. W. "Goitre in Washington [State]," *Med. Sentinel*, Portland, Oregon, 1904, xii, 81.

NAUMANN. "Om Struma och dess Behandlung," Lund, 1891.

NAWALICHIN. "Das Lymphgefässsystem der Glandula Thyroidea," *Pflüger's Archiv f. gesammte Physiol.*, Bonn, 1874, viii, p. 613.

NEALE. "State of the Blood in Goitre," *Med. Times and Gaz.*, 1854, o. s. xxix, n. s. viii, p. 430.

NICHOLSON. "The Treatment of the Auto-intoxications of Pregnancy by Thyroid Extract," *Scottish Medical and Surgical Journal*, 1903, xii, p. 204-14.

NIEPCE, B. "Traité du Goître et du crétinisme, suivi de la statistique des goitreux et des crétins dans le bassin de l'Isère en Savoie, dans les départements de l'Isère, des Hautes-Alpes et des Basses-Alpes," Paris, Baillière, 1851, 2 v. 8vo; x, p. 501; xxxviii, p. 200.

NIVET. "Goitre endémique et épidémique," *Gaz. hebd. de Med.*, Paris, 1874, vi, p. 55.

—— "Traité du goitre, appuyé sur des documents statistiques inédits et accompagné d'une carte de la distribution du Puy-de-Dôme," Paris, 1880, Baillière, 297 pp., 1 map.

OCHSNER, A. J. "Goitre," *Internat. Clin.*, Philad., 1910, 20th, ser., iv, p. 123.

ORD and WHITE. "Certain Changes observed in the Urine in Myxœdema after Administration of Glycerine Extract of Thyroid Gland," *Brit. Med. Journ.*, 1893, ii, pp. 217-222.

OSWALD. "Die Chemie und Physiologie des Kropfes," *Virchow's Archiv für Path. Anat. u. Phys.*, Berlin, 1902, clxix, pp. 447-479.

—— "Was wissen wir über die Chemie und die Physiologie der Schilddrüse," *Pflüger's Archiv f. gesammte Physiol.*, Bonn, 1900, lxxix, pp. 450-461.

OSWALD, A. "Die Rolle der Schilddrüse im Körperbauhalt und der Kropf. Nebst Hinweisen auf die wirtschaftliche Bedeutung der Kropfkrankheit," *Vrtljschr. d. naturf. Gesellsch. in Zürich*, 1912, lvi, pp. 393-414.

PANTOUCHOFF, J. J. "Goitre in Svanet (Russ. Caucasus),' *Russk. Med.*, St. Petersburg, 1890, xv, pp. 20-24.

—— "Der Kropf in Soanetien," *Zentralbl. f. Laryngol.*, 1893.

PARCHAPPE. "Étude sur le goitre et le crétinisme."

PICK. "Der Schilddrüsenkrebs der Salmoniden (Edelfische)," *Berliner klin. Wochenschr.*, 1905, xlii, pp. 1435-1445.

PODHILSKY, A. "Über das Vorkommen des Colloids in den Lymphgefässen der strumöserkrankten menschlichen Schilddrüse," *Prager med. Wochenschr.*, 1892, xvii, p. 197.

PODHILSKY, A. "Uber das Vorkommen des Colloids in den Lymphgefässen der strumöserkrankten menschlichen Schilddrüse," *Prager med. Wochenschr.*, p. 211.

PROCA. "Bacille flourescent des eaux goitregènes," *Journal de Med. de Bordeaux*, 1906, No. 42.

—— "Insuffisance thyroïdienne et bacilles mucinogènes de l'eau," *Compt. rend. Soc. de Biol.*, Paris, 1906, lx, 989.

RAGAZZI. "Recherches anatomiques sur le goitre," *Thèse de Berne*, Berlin, 1885.

RATIMOFF. "*Biedermann's Centralblatt*," xii, p. 360.

REICH. "Über Struma retrovisceralis mit Holskyphose und über laterale Nebenkröpfe," *Beiträge zur Klin. Chir.*, Tübingen, 1911, lxxii, pp. 463-490, 1 pl.

REINBACH. "Über die Bildung des Colloids in Strumen," *Ziegler's Beiträge*, Jena, 1894, xvi, pp. 596-640.

"Relazione della commissione nominata d'ordine di S. M. il Re di Sardegna per studiare il cretinismo," Turino, 1848.

"Relazione della commissione de reale Istituto Lombardo di Scienz. e Litt. del Cretinismo in Lombardia," Milano, 1864.

RÉPIN. "Nouvelles recherches sur la radio-activité des sources goitrigènes," *Comp. rend. Acad. des Sci.*, Paris, 1908, cxlvii, pp. 703-705.

—— "Les eaux goitrigènes," *Revue d'Hyg.*, Paris, 1911, xxxiii, pp. 317-420.

—— "Radioactivité de certaines sources goitrigènes," *Semaine Médicale*, Paris, 1908, xxviii, pp. 455, 526.

—— "Goitre expérimental," *Comptes rend. Soc. de Biol.*, Paris, 1911, lxxi, pp. 225-227.

—— "Distribution géographique du goître en Algérie," *Bull. Soc. Pathologie exotique*, 8 Mai, 1912, v, No. 5.

—— "La pathogénie du goitre endémique," *Revue générale des Sc. pures et appliquées*, Paris, 1910, xxi, pp. 736-753.

RIBBERT. "Über die Regeneration des Schilddrüsengewebes," *Virchow's Archiv.*, cxvii, *Zentralbl. für Chir.*, Leipzig, 1890, xvii, p. 675.

RICHARD, —. "Le goitre chez le nouveau-né," *Thèse de Lyon*, Décembre, 1906.

RICHARDSON. "The Thyroid and Parathyroid Glands," London and Philadelphia, 1905.

Riesmann. "Goitre and Cretinisme," "Reference Handbook of the Medical Sciences," 1903, p. 389.

Robinson. "Endemic Goitre or Thyrocele," London, 1885.

Roos. "Zur Kenntniss der Jodothyrins," *Zeitschr. für Physiol. Chemie.*, Strassb., 1889, xxv, pp. 1, 242.

Royan. "Étude sur l'étiologie du goitre," *Rec. de mém. de méd. mil.*, iii sér., x.

Rozycki. "Der Kropf, und seine Behandlung. Eine monographische Skizze mit besonderer Berücksichtigung der Exstirpation desselben und mit einer statistischen Tabelle dieser Operation," 56 pp. München, 1868.

Saint-Lager. "Étude sur les causes du crétinisme et du goitre endémique," Paris, 1867.

—— "Deuxième série d'études sur les causes du Crétinisme," &c., Lyon, 1868.

Sajous. "The Internal Secretions and the Principles of of Medicine," i, 4th ed., Philadelphia, 1911.

Sanarelli. "Le condizioni attuale delle endemie gozzigene in Italia," *Giorn. d. r. Soc. ital. d'ig.*, Milano, 1895, xvii, pp. 173-192.

Sanderson-Damberg, *Frankf. Zeitschr. f. Pathol.*, 1911, vi, Heft ii, S. 312.

Schäffle, K. "Notes on Family Goitre," *Journ. Amer. Med. Assoc.*, Chicago, 1909, lii, p. 212.

Schein. "Das Schilddrüsen-Sekret in der Milch," *Wiener med. Wochenschr.*, 1895, xlv, pp. 513, 558, 600.

Schittenhelm und Weichardt. "Der endemische Kropf." Berlin, 1912.

Schlagenhaufer und Wagner v. Jauregg. "Beiträge zur Ätiologie und Pathologie des endemischen Kretinismus," Wien, 1910.

Schmidt. "Über den Mechanismus der Bakterienfiltration mit Berkefeldfiltern," *Zeitschr. fur Hyg. und Infektions-Krankheiten*, Leipzig, 1910, lxv, pp. 423-434.

Schnitzler, J. "Ueber die Aetiologie der Strumitis: ein Beitrag zur Lehre von den haematogenen Infektionen von Dr. E. Tavel. Basel, C. Sullmann, 1892." [*Rev.*] *Internat. klin. Rundschau*, Wien, 1892, vi, p. 1023.

Schranz. "Beiträge zur Theorie des Kropfes," *Archiv. für klin. Chir.*, Berl., 1886-7, xxxiv, pp. 91-159.

SCHWALBE, C. "Die Ursachen und die geographische Verbreitung des Kropfes," 1879.

SCOTT, J. N. "The Roentgen-Ray Treatment of Goitre,' *Journ. Missouri Med. Assoc.*, St. Louis, 1911-12, viii, p. 151.

SENATOR. Fall von Myxödem., *Berl. klin. Woch.*, 1887, xxiv, p. 154.

SERGENT, E. "Distribution géographique du Goitre endémique en Algérie," *Bull. Soc. path. exot.*, Paris, 1912, v, pp. 122-124, 1 pl.

SHEPHERD, F. J., and DUVAL, E. W. "The Histopathology of Goitre," *Trans. Amer. Surg. Ass.*, Phila., 1909, xxvii, pp. 56-70.

—— "The Histopathology of Goitre, based upon the microscopical study of over fifty cases of thyroidectomy, with histories of the most important," *Annals of Surg.*, Phila., 1909, l, pp. 84-91, 4 pl. [Discussion, 344.]

SIEVERS. "Till Kännedomen om Struma i Finland," *Finska. Lük.-Sällsk. handl.*, Helsingfors, 1894, xxxvi, pp. 157-208.

—— "Beitrag zur Kenntnis der Struma in Finnland," *Finska Lükerre allskapits Handligar*, 1894, M. 3.

SIMON, J. "Comparative Anatomy of the Thyroid," *Proc. Roy. Soc.*, 1844, v, p. 515.

SLIPEWICZ. "Über die Entstehung des endemischen Kropfes," *Gaz. hebd.*, 1874, No. 2; *Zentralbl. für Chirurgie*, 1874, p. 137.

SLOAN, A. T. "Goitre in Animals," *Lancet*, 1887, i, 1082.

—— "The Geographical Distribution of Goitre," *Edinburgh Med. Journ.*, 1893-94, xxxix, pp. 1004-1009.

SPURWAY, J. "Goitre in England," *Brit. Med. Journ.*, 1906, i, p. 1037.

STEVANI, R. "Il tiroidismo endemico," *Boll. a. mal. a orecchio. d. gola e d. naso*, Firenze, 1906, xxv, pp. 153-164.

STEVENSON, L. E. "The Treatment of Goitre by Distilled or Rain Water," *Lancet*, Lond., 1903, ii, p. 493.

SWISS GOITRE COMMISSION. M.S. communications, 1912.

SYMONDS. "On some Varieties of Bronchocele," *Lancet*, 1893, ii, p. 1118.

TAIT, LAWSON. "Enlargement of the Thyroid Body in Pregnancy," *Edinburgh Med. Journ.*, 1875, xx, pp. 993-1002.

TAUBER. "Zur Frage nach der physiologischen Beziehung der Schilddrüse zur Milz," *Virchow's Archiv*, Berlin, 1884, xcvi, 29.

TAUSSIG. "Die Infektionstheorie des Kropfes und des Kretinismus," *Repert. d. prakt. Med.*, Berl., 1912, ix, 10.

—— "Etiology of Goitre," *Vienna Gesellschaft der Aerzte. vide Lancet*, 1912, i, p. 128.

TAVEL. "Über die Ätiologie der Strumitis," Basil, 1892.

TAYLOR, A. E. "The Treatment of Goitre by the Use of Distilled or Rain Water," *Lancet*, 1903, ii, p. 1324.

THÉVÉNOT, L. "Goitre et congestions de la thyroïde chez le nouveau-né," *Obstétrique*, Paris, 1909, n.s., ii, pp. 208-217.

THURSFIELD. "The Etiology of Goitre in England," *Lancet*, 1885, i, pp. 1074-1077, and *Trans. Soc. of Medical Officer of Health*, London, 1884-5, pp. 198-308.

TONKIN, T. J. "A Goitrous Centre in Northern Nigeria," *Brit. Med. Journ.*, Lond., 1905, i, p. 396.

TONNEL. "La formule étiologique du goitre," *Echo méd. du Nord*, Lille, 1911, xv, pp. 234-41.

TOURDES. "Du Goître à Strassbourg," 1854.

TURRÓ. "Sur l'action du sac thyroïdien sur le vibrion du choléra et le B. d'Eberth," *Comptes rend. Soc. de Biologie*, Paris, 1906, lx, p. 464.

VANNOD. "Les eaux goitreuses," *Ann. de schweiz. balneol. Gesellsch.*, Aarau, 1911, vii, pp. 32-36.

—— Various Reports to the Swiss Goitre Commission, 1908-12.

VETLESEN. "Aetiologisk studier over Struma," Kristiania, 1887.

VIANNA. "Contribuição para o estudo de anatomia pathologica da 'Molesta de Carlos Chagas,'" *Memorias do Instituto Oswaldo Cruz*, ano 1911, tomo iii, faciculo ii.

VINCENT, S. "Internal Secretion and the Ductless Glands," *Lancet*, 1906, ii, pp. 348-353, 430-434.

VINCENT, S. "Internal Secretion and the Ductless Glands," London, 1912.

VINCENT and JOLLY. "Some Observations upon the Functions of the Thyroid and Parathyroid Glands," *Journ. of Physiol.*, 1904, xxxii, pp. 65-86, and "Further observations," *Journ. Physiol.*, 1906, xxxiv, pp. 295-305.

VIRCHOW. "Uber Kretinismus namentlich in Franken," *Verhandl. phys. med. Gesellsch. in Würzb.*, 1851, ii, pp. 230-70.

WAGNER v. JAUREGG. ["Etiology of Goitre"] *Vienna Gesellschaft der Aerzte, vide Lancet*, 1912, i, p. 128.

—— "Über endemischen und sporadischen Kretinismus und dessen Behandlung," *Wiener klin. Wochenschr.*, 1900, xiii, 419-427.

WEGELIN, CARL. "Zur Histogenese des endemischen Kropfes," *Correspondenz-Blatt für Schweizer Aerzte*, Basel, 1912, xlii, pp. 321, 376.

WEICHARDT and SCHITTENHELM. "Endemische Kropfes," &c., Berlin, 1912.

WEINLAND, G. "Ueber Häufigkeit und Wachstum der Kropfe bei den weiblichen Pfleglingen der k. Heilanstalt Wessenau," *Med. Cor.-Bl. d. württemb. artzl. Landesver.*, Stuttgart, 1910, lxxx, pp. 1053-61.

WEISS. "Über Tetanie," *Volkmann's Sammlung klin. Vorträge*, No. 189.

WELLMAN. "A Contribution to the Study of the Etiology of Goitre," *Journ. Trop. Med. and Hyg.*, 1908, xi, p. 53.

WERELIUS, A., and RYDIN, C. G. "Goitre among the Insane: A Study based on the Examination of 4,184 Patients," *Journ. Amer. Med. Assoc.*, Chicago, 1911, lvii, p. 449.

WILLIAMS, J. "The Etiology of Goitre," *Med. Press and Circular*, Lond., 1887, xliii, p. 97, and *Prov. Med. Journ.*, Leicester, 1887, vi, pp. 98-100.

WILMS, M. "Experimentelle Erzeugung und Ursache des Kropfes," *Deutsch. med. Wochenschr.*, Leipzig, 1910, xxxvi, p. 604.

WOAKES. "The Pathogeny and Treatment of Brochocele or Goitre," *Lancet*, 1881, i, p. 448.

WÖLFLER. "Über die Entwickelung und den Bau der Schilddrüse mit Rücksicht auf die Entwicklung der Kröpfe," Berlin, 1880, pt. 15.

WÖLFLER. "Über die Entwickelung und den Bau des Kropfes," *Arch. für klin. Chir.*, Berlin, 1883, xxix, pp. 1-98, 754-866, 23 plates.

YUSHTSHENKO, O. I. "Investigation of the Phenomena of Auto-intoxication in the Insane and in Animals with Impaired Functions of the Thyroid Gland," *Russk. Vrach.*, S. Peterburg, 1910, ix, pp. 160-164.

ZABALUYEFF, V. E. "Goitre and Caries of the Teeth of Children attending School in the Nicholas Pavdinski Factory, County of Verkhotursk, Government of Perm.," *Vrach. Gaz.*, St. Peterburg., 1905, xii, 203-206.

ZIELINSKA. "Beiträge zur Kenntniss der normalen und Strumösen Schilddrüse des Menschen und des Hundes," *Virchow's Archiv*, Berlin, 1894, cxxxvi, pp. 170-194.

v. ZOEGE-MANTEUFFEL. "Die Ausbreitung des Kropfes in den Ostseeprovinzen," *Deutsche Zeitschr. f. Chir.*, Leipzig, 1894, xxxix, p. 576.

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SKETCH MAP SHOWING THE APPROXIMATE DISTRIBUTION OF ENDEMIC GOITRE. By ROBERT McCARRISON.