Organotherapy, or, Treatment by means of preparations of various organs / by H. Batty Shaw.

MODERN METHODS OF TREATMENT

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BY

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PREFACE.

PROBABLY no part of Treatment is more interesting than that based upon the application of preparations derived from various organs of animals. At the same time, very considerable *odium sanctum* has in the past attached itself to Organotherapy, and probably this was entirely due to the sensational claims of over-zealous followers of the early teaching of Brown-Séquard. The great successes following upon the use of thyroid substance in suitable cases and the remarkable activity of suprarenal extract have had a salutary effect; observers are once more turning their attention to the elucidation of internal secretion, and, as a result, new ideas have sprung up around the comparatively modern discoveries of the internal secretion of the pancreas. The recent investigations in this country and abroad concerning the enzymes resident in the cells of the intestinal mucosa are further evidences of the fruitfulness of Brown-Séquard's theories.

The present publication is an attempt to place before the reader a short account of the physiology, etc., of the glands of the body with special reference to internal secretion, and to supply a review of the practical applications in disease of the derivatives of various organs.

The sections dealing with the anatomy and physiology of the organs are largely derived from Quain's

Anatomy and from Professor E. A. Schäfer's Text Book of Physiology.

Some apology may be needed for the large number of references introduced into the volume in the form of footnotes. The writer's object in doing this is not only to make full acknowledgment of the sources of information from which the compilation has been made, but also to some extent to afford a guide to the bibliography of a subject which is unusually extensive.

A final duty and pleasure is to acknowledge the unvarying courtesy and patience of the publishers.

H. B. S.

September, 1905.

CONTENTS.

Section II.

SUPRARENAL GLANDS.

Section III.

ALIMENTARY TRACT, INCLUDING THE PANCREAS AND LIVER.

CHAPTER XIII.

CHAPTER XIV.

CHAPTER XV.

Section IV.

GENITO-URINARY ORGANS.

CHAPTER XVI.

CHAPTER XVII.

Section V.

OTHER ORGANS AND TISSUES.

CHAPTER XVIII.

LIST OF ILLUSTRATIONS.

ORGANOTHERAPY.

INTRODUCTION.

In remote ages, when religion and medicine were more closely associated than they are now, the use of the organs of animals as special forms of sacrifice was a common practice, as it was thought that some divine intervention might be invoked; as a sequel, in which may be traced a very human desire for some certain practical benefit that might be derived from such sacrifice, the officiating priest was allowed to make use of part of the sacrifice for his own purposes as food. With the advent of the scientific methods of Hippocrates, the study of the efficacy of various organs as remedial agents apart from any use as sacrifices was developed, and Celsus and Dioscorides recommended the use of various animal organs for the relief of those symptoms in man which were considered to be due to defective action of the same organ; hence the use of the pigeon's or wolf's liver for hepatic disorder, the brain of the hare for tremors, the lung of the fox for dyspnœa, and the use of rennet for disorders of the stomach and abdomen generally. Pliny recommended the use of the testicles of the donkey and of the stag as aphrodisiacs, and to this day there still remains the practice of employing castoreum for menstrual disorder. Nor was the use of organs always of a beneficent order, for darker agencies were thought to be invoked; and so we read the following prescription:

"Fillet of a fenny snake,
In the cauldron boil and bake;
Eye of newt, and toe of frog,
Wool of bat, and tongue of dog,

Adder's fork, and blind-worm's sting,
Lizard's leg, and owlet's wing,
For a charm of powerful trouble,
Like a hell-broth boil and bubble."

Macbeth, Act IV., Sc. I.

Despite the use of the organs of animals in the darker ages, little of real value was discovered, and it was not till the dawn of modern scientific inquiry that, from the chaos of ancient and mediæval practices, facts were ascertained which prepared the way for the development of modern organotherapy.

Brown-Séquard in 1869 first pointed out anew the possible uses of organic extracts, etc., and foreshadowed that principle of "internal secretion" which has been productive of so much research, and of that triumph of modern medicine, the treatment of myxœdema. "All glands, whether they have excretory ducts or not, give to the blood useful principles, the absence of which is felt when they are extirpated or destroyed by disease." Twenty years later these theories were applied to practical purposes, and though there was lack of success in the case of the particular organ chosen for the demonstration of the new idea, other organs have yielded material whose beneficial effects are acknowledged on all hands.[1]

Treatment by means of other organic extracts failed too, and probably from the same reason, that too little was known of the nature of their secretion, or of the way of preparing extracts or administering them. Not until the application of thyroid treatment had been shown to have such certain results, did organotherapy recover from the over-confidence of its earlier supporters. It is largely due to close clinical study that the marvellous powers of the thyroid secretion were first suspected. Reverdin in 1883 was the first to call attention to the curious train of symptoms

[1] The term "organotherapy" has been used to describe this form of treatment. Landouzy, in 1895 introduced the term opotherapy (ὀπός=juice) and other terms have been suggested, as séquardotherapy, histotherapy, zoopotherapy.

that followed the loss of the thyroid gland by operation. He called it "operative myxœdema," whereas Kocher, who had at the same period noted the same changes, preferred to speak of it as "cachexia strumipriva," seeing that the weakness and other symptoms followed upon the loss of the thyroid gland. It soon became recognised that Gull's "cretinoid state," Ord's "myxœdema," Charcot's "pachydermic cachexia," Bourneville's "myxœdematous idiotcy," and Kocher's "cachexia strumipriva" were practically one and the same thing, and for the first time Brown-Séquard's theory of internal secretion received that scientific support which hitherto it had lacked. From this period onward, organotherapy has been amplified by the study of other organs, carried out on the same scientific plans as were adopted in the case of the thyroid gland, and the scope of the subject has been greatly enlarged. At present the greatest success has followed the study of the thyroid, of the suprarenal body, and of the ovary. Most other organs have been studied on the same lines, but the brilliant results of the earlier studies have hardly been secured to the later ones: there is even now a tendency towards some revulsion against the plaudits in favour of the brilliant thyroid results, as facts are gradually accumulating which tend to show that there are limitations beyond which even thyroid treatment is inefficacious; these will be referred to in a succeeding chapter.

Treatment by means of organs may temporarily be carried out by the use of grafts, by subcutaneous injection of various preparations, or the expressed juice or gland as a whole, or extracts prepared by various processes may be given by the mouth. In some cases, as *e.g.* in the use of pancreatin, pepsin, etc., either the actual desiccated tissue is used, or a glycerine preparation; and in the case of the suprarenal gland only a part is of use.

One of the great disappointments of organotherapy has been the failure to re-establish, by means of grafts, various glandular activities. Vassale and Gley, as a result of

observations on animals, were able to establish efficient treatment by means of subcutaneous injections of extracts of the thyroid. To this succeeded the period of medication by the mouth, the success of which is so well known.

The later investigations, in which the thyroid gland has been looked upon as a natural product from which active principles may be extracted, have not yielded those uniformly good results which an assumed parallelism with opium and morphine would warrant, and treatment by the native thyroid substance has been the more successful. More thorough analysis of the symptoms caused by glandular disorder promises better things for the future, for though the thyroid gland is responsible for much that can be remedied by medications derived from it, the discovery by Sandstroem of parathyroidal tissue has led to the view that the effects of athyrea are really two-fold in character, part being due to the absence of thyroid proper and part to the absence of parathyroidal tissue. The anatomical similarity of the pituitary body to the thyroid has led investigators to attribute to this structure functions allied to those of the thyroid.

Poucet has developed the idea that it is possible to excite thyroid function by manipulation (thyroidal-erythism) of the gland—a method of doubtful efficacy, but the existence of which shows to what extent possible medication in this direction has captivated Continental writers.

Turning to another gland, the suprarenal, so great was the successful application of thyroidal treatment, that disappointment was equally intense when it was found that the suprarenals were unable to give as good results : the use, however, of adrenalin has become very extensive, so that though we may not be armed with a remedy for suprarenal inadequacy, yet recent observations have shown that the suprarenal is capable of providing us with a substance the local use of which is of extreme value.

Little has been discovered which leads to a satisfactory generalisation of the methods by which preparations of

organs exert influence on the various tissues of the body. Poehl has elaborated a theory largely based on chemical action on the part of the various agents used. Spermin, cerebrin, thyroiodin, adrenalin, etc., are looked upon as katalysators, a term introduced by Oswald to describe agents which can influence temporarily the metabolic changes going on in the body. The digestive ferments also belong to this group of agents. Without the presence of these katalysators the low temperature of the body would be inadequate for the consummation of the various chemical changes taking place in the body. Oxydase is the name given to such a katalysator present in leucocytes which is capable of effecting chemical changes, and others have been described.[1] Spermin is a katalysator which exerts a hastening effect on the changes in the body activities, as proved by its effect on the bacilli producing phosphorescence (Fürst & Tarchanoff). Adrenalin is also an energetic katalysator, more especially in the direction of reduction, and Poehl considers that glycosuria following the use of adrenalin is due to this reducing process.

This chemical view of the specific activity of various animal tissues affords some assistance, but it is probable that principles of a much more purely biological character underlie the reaction of the body tissues in general to the special action of gland cells : chemical and physical laws as they are understood at present do not suffice. More knowledge is required of the relationship existing between zymogen and enzyme and of those occult antienzymes without which beneficent enzymes would become agents of the most destructive character ; when these principles are clearly understood, then, and then alone, it may be possible to explain those disorders which at present at any rate do not appear to be directly related to the one firmly established principle of pathology—parasiticism.

[1] Portier, *Soc. de biol.*, 1898, p. 452

Section I.

THE THYROID AND PARATHYROID GLANDS.[1]

CHAPTER I.

ANATOMY.

The Thyroid Gland.—The thyroid is one of the ductless glands of the body, and consists of an isthmus and two lateral lobes, which are usually connected with one another. Each lateral lobe is conical, the apex being directed upwards, and extends from the fifth or sixth rings of the trachea to the inferior cornua and alæ of the thyroid cartilage : the isthmus usually covers the second, third, and fourth rings of the trachea. The action of swallowing is accompanied by elevation of the gland with the thyroid cartilage, to which it is closely bound by fibrous tissue. Examination of the thyroid gland through the skin yields indefinite results, for very frequently the isthmus cannot be defined, although present. In the normal condition, this is to be explained by the fact that the sternohyoid, sternothyroid, omohyoid, and sternomastoid muscles overlap the organ. Further, the isthmus may be absent altogether (1 in 20), and even the lateral lobes may be absent (Handfield Jones, v. Eiselsberg). Sometimes the isthmus and two lateral lobes are present, but disconnected.

Connected at its lower end with the isthmus of the

[1] The writer acknowledges his indebtedness for much information on this subject to the writings of G. R. Murray and Walter Edmunds; to the monograph of Jeandelize, "Insuffisance thyroidienne et parathyroidienne"; to that of Gabriel Gautier, "Les médications thyroidiennes," and to the volume on "Serum-, Bakterientoxin- und Organ-Präparate" of Max v. Waldheim.

thyroid gland or with either of the lateral lobes (mostly the left) is the so-called pyramid or middle lobe of the thyroid, found in a third of all cases (v. Eiselsberg). Its

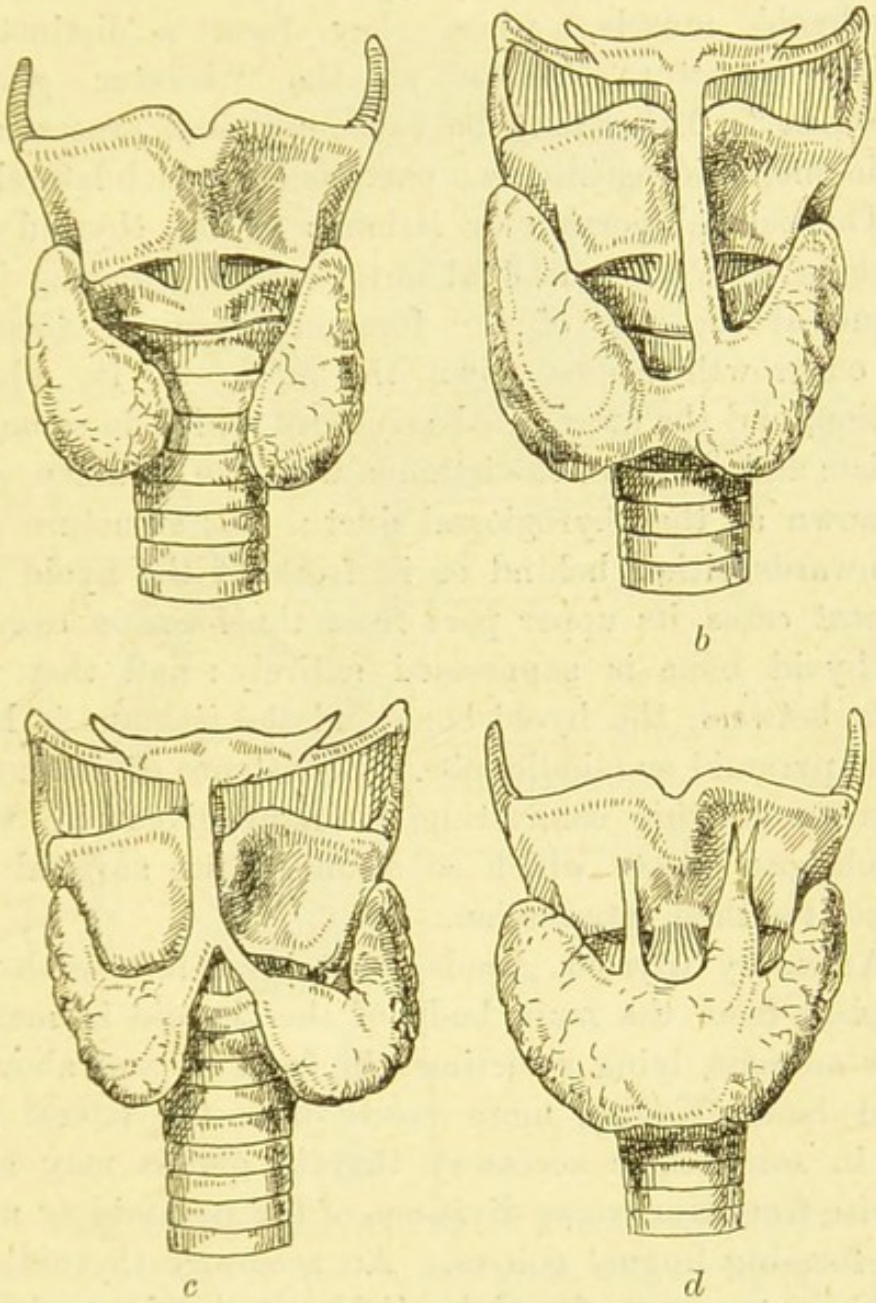


Fig. 1.—The Thyroid Gland.

a, Example of absence of the isthmus of the thyroid gland; *b*, pyramidal process attached to the left lobe of the thyroid gland; *c*, bifurcation of lower end of the pyramidal process, one branch going to each lobe of the gland; *d*, double pyramidal process arising on isthmus and ending on the thyroid cartilage.

(Dr. C. F. Marshall, *Journ. of Anat. and Physiol.*, 1895, p. 234.)

upper end is attached to the hyoid bone by fibrous or muscular tissue; in a large proportion of cases this

structure presents glandular characteristics up to the hyoid bone; much less frequently the attachment to the latter is fibrous; rarely it is muscular, and the muscular elements are either independent or apparently derived from the thyrohyoid muscle, when they form a distinct anatomical structure known as the "levator glandulæ thyroideæ." There may be two pyramidal processes or a single one dividing into two parts, one for each lateral lobe.

The central portion or isthmus of the thyroid gland develops from an epithelial outgrowth originating in the tongue at the site of the foramen cæcum. Gradually the outgrowth passes down the neck to its ultimate position, and the attenuated structure which in some cases persists and connects the isthmus with the foramen cæcum is known as the thyroglossal duct; this structure passes downwards either behind or in front of the hyoid bone; in most cases, its upper part from the foramen cæcum to the hyoid bone is suppressed entirely: and that which exists between the hyoid bone and the isthmus is known as the pyramid or middle lobe. Persistence of the duct-like character of this connecting remnant gives rise to the thyrolingual cysts which so often require surgical interference for their suppression.

Accessory thyroid glands have been met with quite detached from the main body of the thyroid in man and other animals, lying sometimes in front of and above the hyoid bone (Kadyi), more rarely near the lateral lobes, and in some cases accessory thyroid glands may appear to arise from transverse divisions of the pyramid or middle lobe forming lingual goitres. An accessory thyroid gland of this nature was found by Seldowitsch,[1] in a girl aged 14 years; its removal was followed by the development of myxœdema. Accessory thyroid glands have also been found in the mediastinum and pleura,[2] and Paton[3] has

[1] Oppenheim, *Lehrb. der Nervenkrankh.*, 1902, s. 1175.

[2] Osler's "System of Medicine," 1901, p. 836.

[3] *Transact. Cl. Soc., London, B.M.J.*, 1904, vol. i., p. 357.

described an accessory thyroid body occurring in the right sub-maxillary region in a girl aged 16 years. Intra-tracheal and intrapharyngeal accessory thyroids have also been met with.[1]

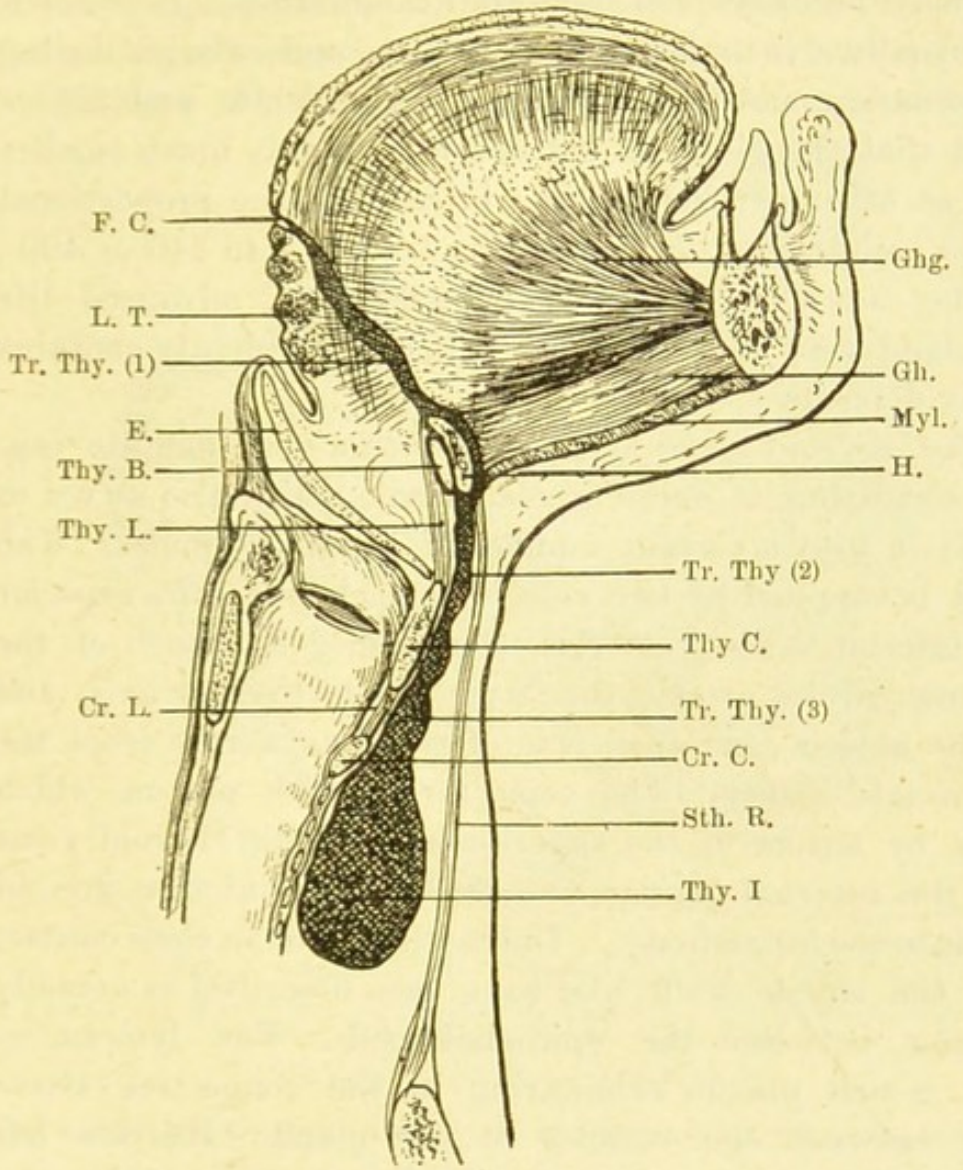


Fig. 2.—Thyroglossal Tract and its Relations.

F.C., Foramen cæcum; Tr. Thy. (1), Thyroglossal tract above hyoid bone; Tr. Thy. (2), Thyroglossal tract in front of thyrohyoid ligament; Tr. Thy. (3), Pyramidal lobe; Thy. I., Isthmus of thyroid gland; Ghg., Geniohyoglossus muscle; Myl., Mylohyoid muscle; L. T., Lingual tonsil; H., Hyoid bone; Thy. B., Thyrohyoid bursa; Thy L., Thyrohyoid ligament; Sth. R., Sternohyoid raphé; E., Epiglottis; Thy. C., Thyroid cartilage; Cr. C., Cricoid cartilage; Cr. L., Cricoid ligament.

(From "Diseases of the Tongue," by Henry T. Butlin and Walter G. Spencer.)

Each lateral lobe measures about two inches in length,

[1] Theisen, *Amer. Journ. of the Med. Sc.*, 1902, N.S., No. 123, p. 1050.

an inch and a quarter broad and three-quarters of an inch thick ; the isthmus is a quarter to a third of an inch deep. The weight of the gland in the adult is about one ounce : the right lateral lobe is usually larger than the left, and this may be obvious in clinical examination. In women it is usually a little larger than in men, and enlarges during menstruation and in pregnancy. Hale White and others found that the gland in old age is relatively much smaller than at other periods of life ; in infancy the proportional weight compared with that of the body is 1 to 240 or 400 ; in the adult 1 to 1,800 (Krause) ; in advanced life the gland may become indurated, and frequently contains earthy deposits.

The thyroid gland is supplied with a very definite capsule consisting of dense areolar tissue, which also serves to divide it into a certain number of irregular lobules. The gland is supplied by two vessels on each side—the superior and inferior thyroid arteries, the former a branch of the external carotid artery, the latter of the thyroid axis, and by the arteria thyroidea ima, derived as a rule from the innominate artery. The veins form a rich plexus, which opens by means of the superior and middle thyroid veins into the internal jugular, and through the inferior thyroid vein into the innominate. The capillaries lie in close contact with the vesicle walls, and have been described as actually existing between the epithelial cells. The lymphatics form a rich plexus originating in the connective tissue lying between the vesicles of the gland. Hürthle has been able by means of intermittent pressure to drive the contents of the lymphatics into the vesicles, Baber found colloid matter within the lymphatics similar to that within the vesicles, and Sir Victor Horsley has been able to demonstrate that by pressure the contents of the vesicles may be driven into the lymphatics. The capsule is so definite that it is possible to shell out the gland with comparative ease and without much hæmorrhage ; when left *in situ* the capsule appears capable of preventing the

entrance into the circulation of the secretion of any surface of the gland that may be left bare as the result of amputation of part of the gland. The nerves of the gland are derived from the middle and inferior cervical ganglion of the sympathetic nerve, and their branches extend to the epithelial cells, but not actually into them (Edmunds).

Minute Anatomy.—In view of the complexity of

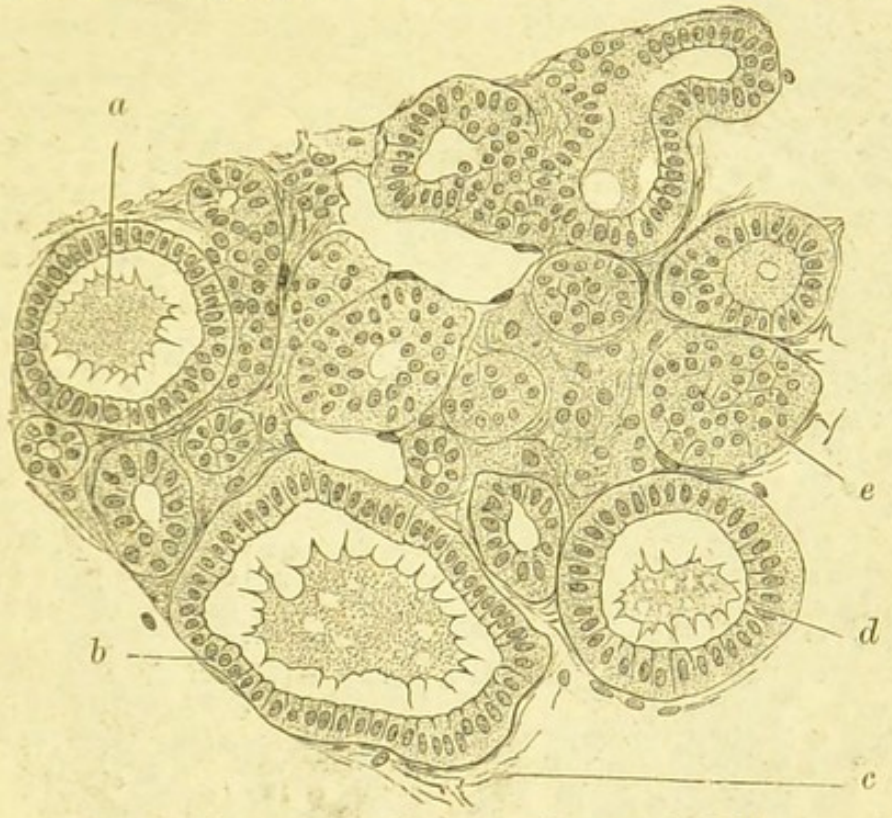


Fig. 3.—Section of Thyroid Gland (× 220).

a, Colloid; *b*, Epithelium; *c*, Connective tissue; *d*, Transverse section of an acinus; *e*, Tangential section of an acinus.

(Stöhr's "Lehrbuch der Histologie.")

the study of thyroid action, it is necessary to point out the essential characters of thyroidal tissue. As is well known, the gland consists of a number of vesicles visible even to the naked eye, and measuring ·045 mm. to 1 mm. across: their shape is variable—spherical, square, polyhedral, branched, etc. In old age the vesicles may be much larger, forming cysts. The vesicles contain colloidal substance, which is either a direct result of the secretory activity of the single low columnar or cubical epithelium (colloid cells) lining the vesicles, or else is a result of the complete

dissolution of certain other cells which have been described as "reserve" cells: this colloidal substance may occur also in the areolar tissues separating the vesicles from one another, and, as already stated, it may even be found in the lymphatic vessels. The vesicles may contain, besides the ordinary yellow glairy fluid, detached epithelial cells, and

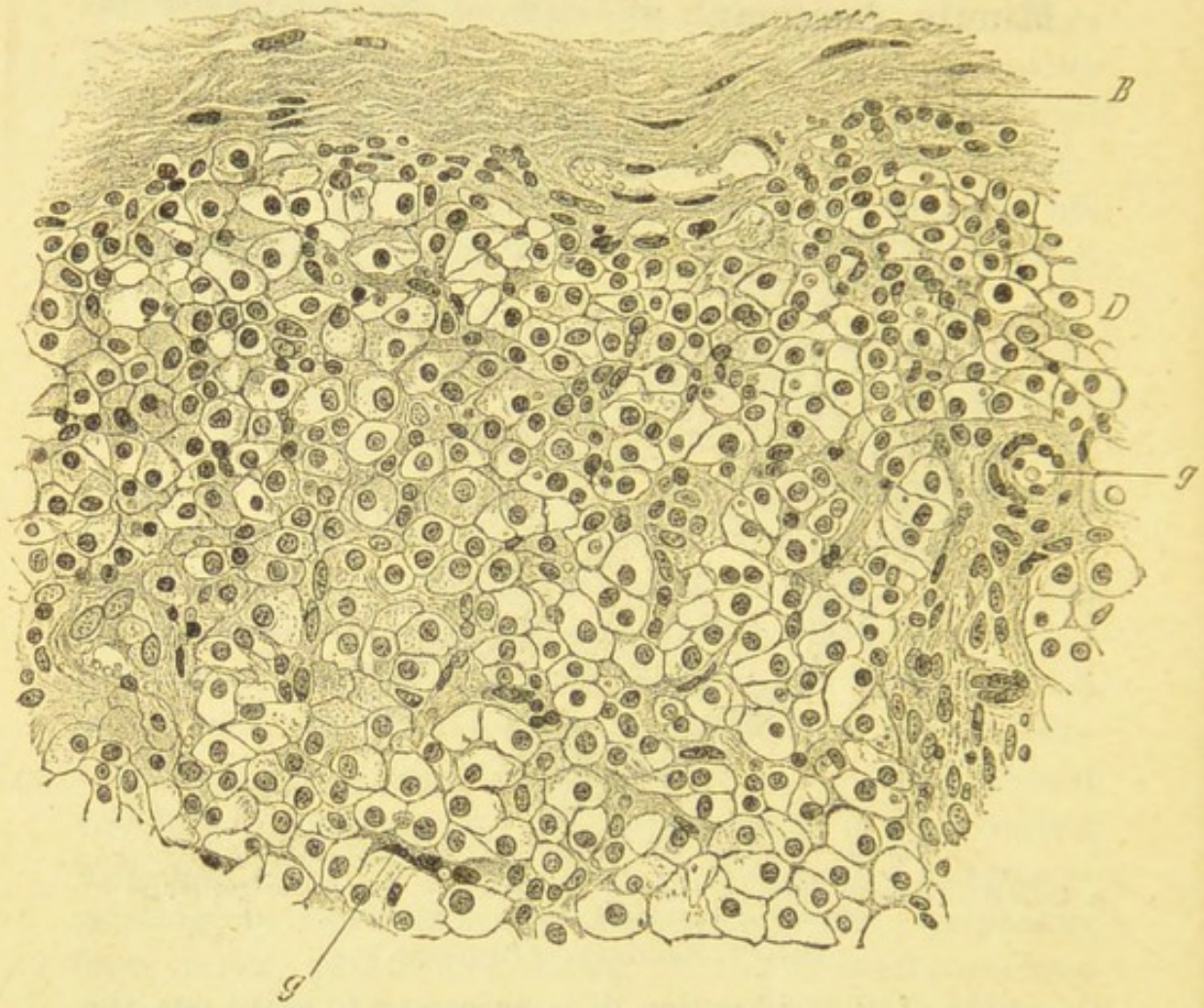


Fig. 4.—Parathyroid Gland of an Eight-year old Child (× 325).
B, Capsule; *D*, Parenchyma; *g*, Blood vessels.
(Kölliker's "Handbuch der Gewebelehre.")

white and red corpuscles. The colloid material readily stains with ordinary microscopical dyes, but in certain cases it fails to take up the stain. It is an important fact that the fore part of the anterior lobe of the pituitary body derived from the epiblast of the stomadæum contains follicles like those of the thyroid, and lined by epithelium which secretes colloid.

The "plasma cells" of Waldeyer have been noticed in the interstitial connective tissue of the gland. These cells form one of the varieties of fixed connective tissue cells; they are characterised by marked vacuolation, and occasionally by the presence of fine granules; in one variety the granules are coarse and readily stain with eosin. These cells are frequently elongated when coarse granules are not present, but when these form a feature they are usually spheroidal.

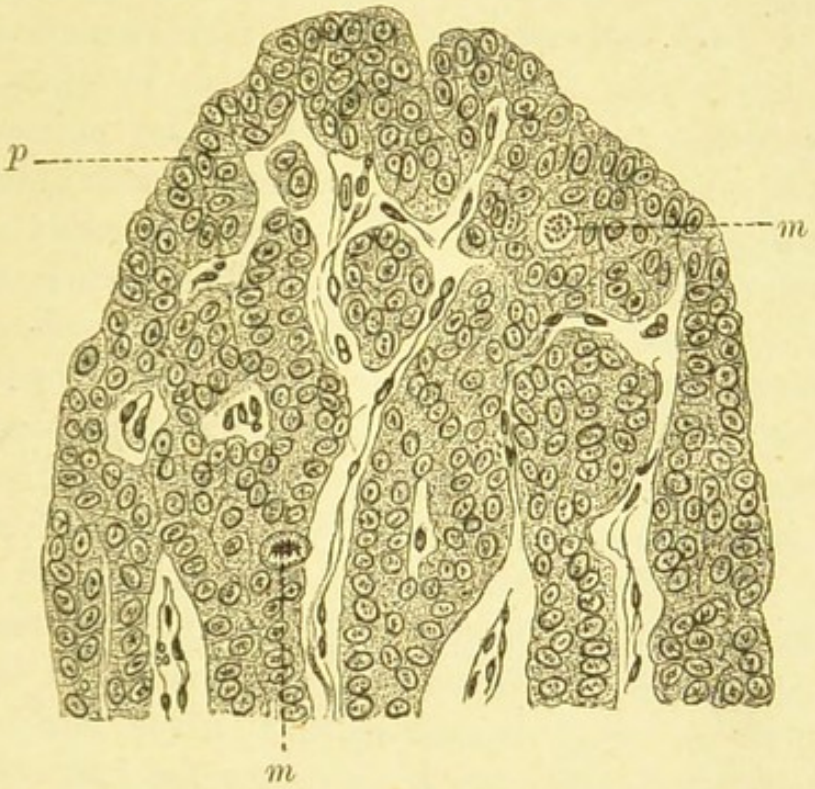


Fig. 5.—Parathyroid Gland of a Cat; Showing the Parathyroid Cells arranged in Columns with intervening Vesicular Spaces (× 500). (Kohn.)

p, parathyroidal cells; *m*, mitoses.

(From Quain's "Elements of Anatomy," by permission of Longmans, Green & Co.

The Parathyroid Glands.—The use of the term "glands" in describing these structures is somewhat faulty, because in some animals the parathyroidal tissue occurs in scattered masses incorporated with the thyroid gland. In man, a pair of parathyroids is found near each lateral lobe, one, the "outer epithelial body" of Kohn, applied to the external aspect of the lateral lobe, and the other, the

"inner epithelial body," on the mesial aspect. These small masses consist of tissue quite different microscopically from thyroidal tissue: they are made up of solid masses of epithelial cells, apparently arranged in anastomosing columns, a rich capillary network being interposed between the columns. It is maintained by Prenant that the general structure and appearance of parathyroidal tissue is like that of the carotid glands. Tissue closely resembling thymus gland is also frequently found in the thyroid glands of mammals.

CHAPTER II.

PHYSIOLOGY.

The thyroid gland is one of the organs which discharge their secretion into the system without the intervention of a specialised duct. The thyrolingual duct at some earlier stage of development was the means by which this secretion reached the alimentary tract (Murray); it is probably this ancient mode of discharging its secretion into the alimentary tract which accounts for the fact that the administration of thyroid preparations by the mouth is quite as adequate as introduction hypodermically, or by any other means. Some observers, as we have seen, state that the thyroid shrinks and undergoes gradual degeneration as the individual reaches advanced age; on the other hand, both Stephen Mackenzie and Hector Mackenzie were unable to find any definite variation between the weight of the thyroid gland and the body weight in regard to age.[1] No theories have yet been put forward to explain the shrinkage of the thyroid gland beyond that possibly it is part of the general involution that takes place in other organs with increasing age. This, however, is an answer which cannot be accepted as final, for it is not a constant rule that in increasing age organs, including the thyroid, become atrophic; judging by the close associational relationships of atrophied kidneys and arterial disease, it would not be beyond probability that the thyroid suffers, as other organs do, from deficient arterial supply dependent upon arterial changes. Kocher's observation, however, that cachexia strumipriva may not result at all when the thyroid is extirpated in aged subjects, suggests that there is some unknown law at work

[1] Allbutt's "System of Medicine," vol. iv., p. 468.

which requires for the aged less activity on the part of the thyroidal tissue. Owing to the observations of Ord it is now well known that the clinical condition known as myxœdema is associated in the close connection of effect and cause with deterioration of the tissues which are known as the thyroid gland. Reverdin and Kocher showed that operative removal of the thyroid gland in man produces the symptoms of cachexia strumipriva.

Physiological Theories.—The views concerning the physiology of the thyroid and parathyroidal tissues may be summarised in the following way :

1. That the thyroid apparatus acts as a short circuiting apparatus, whereby as a result of the dilatation of the vessels of the thyroid less blood reaches the brain.[1]

2. Munk, in 1887, and later in 1897, maintained the view that the changes produced when the thyroidal tissues were removed were due, not to interference with the functions of the thyroid gland, but to disturbance of the *nervous structures* in the neighbouring part of the neck. This view would appear to be entirely negatived by the numerous reported good effects of thyroid feeding, and even of thyroid grafting, so long as the graft maintained its structure.

3. The third view is one which, with the two just mentioned, hardly recognises the important differences that exist between the effects of removal of thyroid as opposed to parathyroidal tissue. According to this view the thyroid gland, and in its absence probably the parathyroid gland, are really *excretory organs* in the sense that their function is to remove those products of metabolic tissue activities which when not so removed produce toxic symptoms. This view is supported mainly by Blum,[2] and recently again by Kishi.[3]

4. According to a fourth view, the various symptoms

[1] J. Simon, *Philosoph. Transact.*, London, 1894, p. 295; and Waldeyer, *Berl. klin. Woch.*, 1887, s. 233.

[2] Virchow's *Archiv*, 1899.

[3] Virchow's *Archiv*, 1904, Bd. 176, Hft. 2, s. 260.

of myxœdema which occur in animals and man after the extirpation, accidental or otherwise, of the parathyroidal and thyroidal tissues, are believed to be due to the want of an internal secretion elaborated by the thyroid gland alone or by the thyroid gland and the parathyroid, the latter acting as a reserve to the thyroid gland. Exophthalmic goitre is due, according to this theory, to an excessive amount of internal secretion or to qualitative changes occurring in this secretion.

5. It will be found possible, however, to divide the symptoms following thyroparathyroidectomy into two groups, and another and more plausible modification of the theory of internal secretion of the thyroid apparatus is one which, assuming two internal secretions instead of one, not only lends itself to an explanation of the variable results of experiment and clinical observation on myxœdema and cachexia strumipriva, but also provides an hypothesis for the explanation of Graves' disease. The above two groups of symptoms include those which may be considered toxic in character and those which are expressions of morphological change. The latter are represented by the swollen condition of the subcutaneous tissues, which produces the familiar characteristics of myxœdema, etc., whereas the toxic symptoms are shown in the form of tremors, convulsions, spasms, etc., met with in dogs and other animals after thyroidectomy, and in the psychical manifestations so obvious in post-operative myxœdema in man. The existence of two kinds of tissue in the thyroidal apparatus has proved highly attractive to various observers, who see in this dual anatomical picture a dual function, and a possible means of explaining the two very different groups of symptoms already referred to. The experiments of Gley, Rouxeau, and Edmunds appear to show that the parathyroids are capable of acting as a reserve store, to be called into function and even to hypertrophy, when the thyroid proper is removed. This view is, however, negatived by the observation of Maresch that the parathyroids have

been found quite normal in a cretin subjected to post-mortem examination, the thyroid alone being absent. Further, Charrin proved that cases of myxœdema which failed to respond to the administration of parathyroids

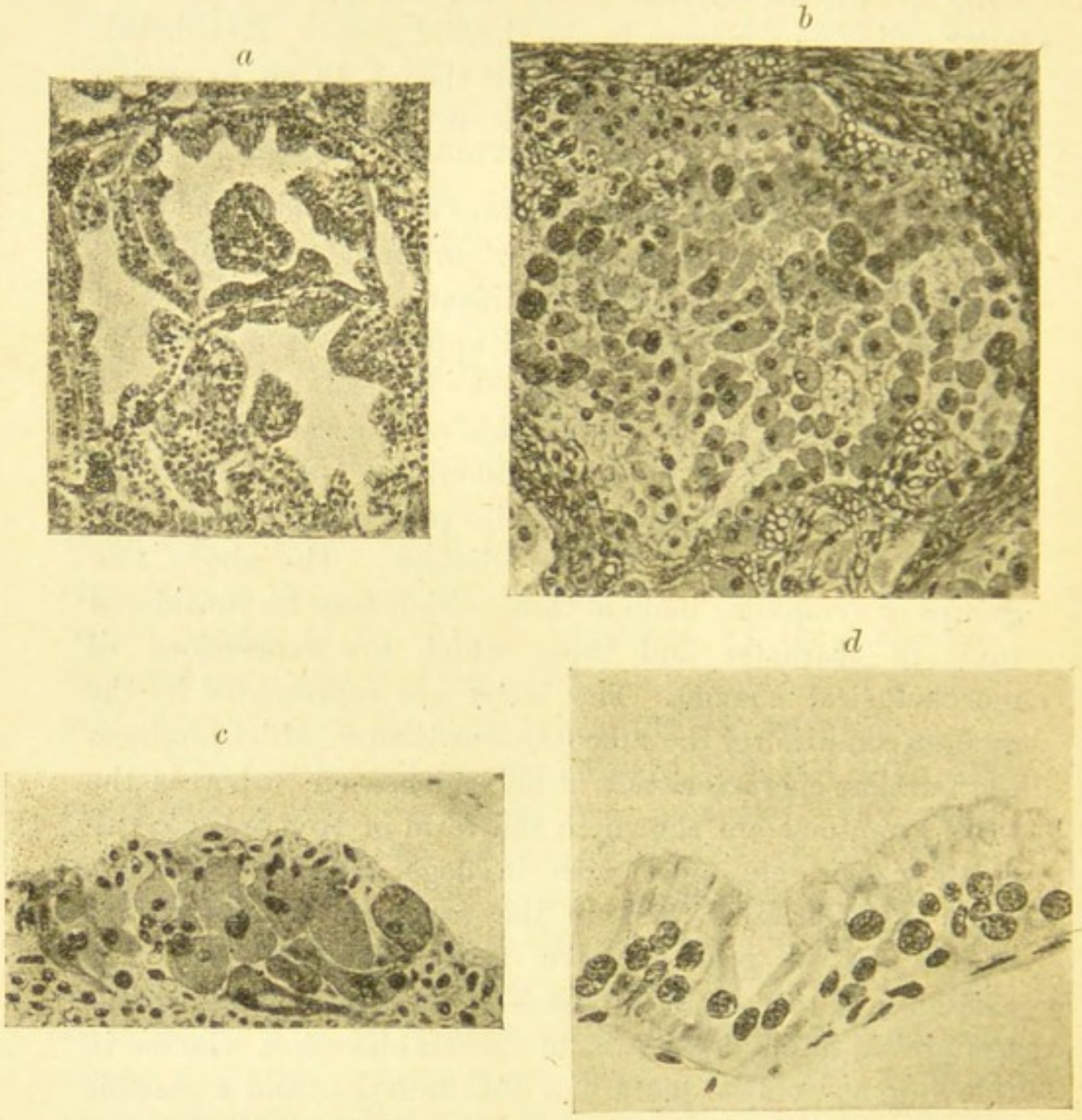


Fig. 6.—The Thyroid in Graves' Disease.

a, Section of enlarged thyroid from a severe case of Graves' Disease (×110); *b*, Section of enlarged thyroid from same case as *a* (×220); *c*, Large cells seen in the cavity of the vesicles of the same case as *a* (×220); *d*, Cells lining a vesicle of the thyroid of a woman, aet. 31, who died of Graves Disease; the cells are hypertrophied and columnar (× 600).

(Walter Edmunds, *Transact. Patholog. Soc. of London*, vol. xlvii.)

responded readily to thyroid treatment. It is therefore obvious that the function of the parathyroids is not one

of "reserve" tissue to be called up only when the thyroid gland fails. This view, however, has been again advanced by Kishi.[1]

Vassale and Generali[2] have formulated an ingenious theory which receives much support from French observers. According to these workers the thyroid proper secretes internally a substance which subserves various metabolic changes taking place in the body; in the absence of the thyroid the morphological changes met with in myxœdema and cretinism are the chief features noticed, as if the thyroidal secretion acted as a stimulus to the various metabolic processes occurring in the tegumentary and other tissues: the parathyroids, on the other hand, secrete internally a substance which appears to neutralise various products of the metabolism initiated by the thyroid: in the absence of the parathyroids, these toxic substances produce nervous phenomena—tremors, tetany, psychical disturbances, etc. Lusena[3] found that if an animal developed symptoms of tetany after the removal of the parathyroids, the subsequent removal of the thyroids led to the alleviation of the tetany, and even to its disappearance.

Brissaud found that in post-operative myxœdema resulting from the removal of both thyroidal and parathyroidal tissue not only did morphological changes occur, but also toxic symptoms, as shown by various nervous phenomena, whereas in spontaneous myxœdema of man, in which the more morphological characters are shown, the thyroid tissue alone undergoes suppression. Further, Moussu found that after producing experimental myxœdema in animals by the complete removal of thyroid and parathyroidal tissue, any symptoms of tetany caused by the circulation of thyroid toxic material not yet neutralised by parathyroid secretion were held in abeyance by the

[1] *Loc. cit.*

[2] *Arch. ital. de biol.*, 1900, vol. xxxiii., p. 154.

[3] *Fisio-patalogia dell' apparecchio tiro-paratiroideo*, 1899, vol. iii., p. 108.

injection of watery extract of parathyroids. On this last view of a dual internal secretion, Graves' disease may be attributed to a deficient power in the parathyroid tissue to neutralise the toxic material produced by activity of the thyroid proper. To express the matter briefly, it may be said (1) that the morphological changes met with in myxœdema result from the suppression of the thyroid, and (2) that probably the nervous phenomena of exophthalmic goitre and also of atypical cases of myxœdema and cases of Huchard's dysthyroidism in which there is an odd admixture of signs of exophthalmic goitre and myxœdema, depend upon inadequate function of the parathyroids. The proof of the former of these statements is given by the remarkable results obtained by giving thryoid gland to cases of myxœdema.

The therapeutic test required to substantiate the latter is not, so far, greatly developed, but Moussu[1] has shown that parathyroidal extract influences the acute symptoms following parathyroidectomy, and Lusena also obtained good results in two cases of parathyroidectomy by the ingestion of parathyroidal gland and injection of parathyroidal juice.

Experiments upon Animals.—With respect to the results of experiments upon animals, varying effects have been obtained according to the type of animals experimented upon, and according to the conditions under which the animal is kept after operation—warmth, dietary, &c. The effects produced on different animals appear also to be largely due to the particular relationship of the parathyroids to the thyroids in each species of animal, as well as to the existence of accessory thyroids. In adult cats, the thyroid consists of two separate lobes unconnected by an isthmus; the parathyroids are four in number, two connected with each lobe, one being free on the external surface of the thyroid, the internal smaller one being imbedded in the lobe towards the inner aspect. In dogs,

[1] *Soc. de biol.*, 1898, p. 867.

the external parathyroids are rarely separated from the thyroid, being usually imbedded in its substance, and the internal thyroids are still more submerged in the substance of the gland. The animals after thyroparathyroidectomy appear to die, though not in all cases, before the characteristic myxœdemic changes of the subcutaneous tissues can take place; monkeys in whom the parathyroids are imbedded in the thyroid gland survive extirpation of the thyroid and parathyroid tissues longer than dogs, and in them, according to Horsley, Murray, and Edmunds, the characteristic features of myxœdema supervene. Both dogs and monkeys develop tremors. No results comparable to those found in man follow removal of the thyroid in reptiles, and the same may be said of rodents, possibly from the fact that accessory thyroidal bodies occur removed some distance from the main thyroid gland.

Swale Vincent and Jolly[1] have recently contributed fresh observations on the functions of the thyroid and parathyroidal tissues. They find, in agreement with other observers, that not in all cases of removal of the thyroid gland or parathyroid, or both, does death result. Rats and guinea-pigs do not seem to suffer at all as a result of the extirpation of their glands. Monkeys show but transient nervous symptoms. Dogs and cats frequently, but by no means invariably, suffer severely and die; simple parathyroidectomy in the cat, the thyroid being left uninjured, is not always fatal, though Vassale and Generali affirm this; in foxes symptoms occur early, and death is rapid. Swale Vincent and Jolly were unable to produce symptoms resembling myxœdema in any animal as a result of extirpation of thyroidal tissue: in young animals extirpation of this tissue produced temporary cessation of growth, but this was not necessarily accompanied by symptoms of a cretinoid character. They go so far as to conclude that myxœdema and cretinism must be due to causes more complex than thyroid insufficiency.

[1] *Journ. of Physiol.*, 1904, vol. xxxii., No. 1, p. 65.

Many of the contradictory results are, however, probably dependent upon disturbances of the ordinary juxtaposition of the parathyroids and the thyroid masses, outlying tissue being overlooked in many cases. Gley believes that the parathyroids are of paramount importance, and that it is their removal which is more responsible for the pathological changes above noted, following upon thyroparathyroidal extirpation.[1]

Oliver and Schäfer[2] found that thyroid extract, in common with that of many other glands, causes a fall of blood pressure, the strength of the heart and the number of beats per minute being unaltered, and Oliver[3] reports that in the human being the extract causes a tendency to increase of calibre of the radial arteries.

Nicholson[4] calls attention to the observation that thyroidectomised dogs develop toxic symptoms when fed on meat, but that these symptoms entirely disappear when milk is substituted (Munk). On this observation he bases his treatment of eclampsia in pregnancy by means of milk and thyroid feeding. Dr. Chalmers Watson has also shown that the thyroid and parathyroid enlarge under a dietary consisting of raw meat.

Attempts have also been made to show that the thyroid secretion is antitoxic, serving to neutralise such toxins as are produced by bacteria. Torri[5] found that there is a hypersecretion of colloid in acute infectious diseases; that colloid material has the power of destroying organisms; further, that in acute and chronic infections there is epithelial proliferation and new formation of thyroid tissue. These results had previously been obtained by Roger and

[1] Doyon and Jouty (*Acad. des Sc.*, 1904, No. 1., p. 53) find that removal of the parathyroids in birds produces ataxia, fibrillary twitching, and death in 24-36 hours.

[2] *Journ. of Physiol.*, 1895, vol. xviii., p. 277.

[3] Croonian Lectures, 1896.

[4] *B. M. J.*, 1904, vol. i., p. 954.

[5] *Policlinico*, 1900, Nos. 6, 8, and 10.

Garnier,[1] but Kashiwamura [2] was unable to confirm them. Remedi [3] found that after injecting nuclein substance derived from the *Bacillus prodigiosus* and *B. anthracis* into the thyroid gland of dogs, epithelial proliferation occurred in the acini, as well as increased formation of colloid.

In the absence of any visible necrosis of the parenchyma of the gland and of leucocytic infiltration, Remedi argues in favour of the view of Roger, Garnier, and Torri, in which it is claimed that the colloid substance of the thyroid neutralises bacterial toxin. Cristiani,[4] besides showing a method by which successful grafts may be made under the skin of the outer sides of the ears of rabbits, guinea-pigs, and rats, the grafts being taken from the thyroid of the same animal, also proves that the new grafts have the same resistant functions as the parent tissue, for they withstand the action of streptococci and other organisms, and also survive the influence of chemical and physical irritants such as turpentine and heat: the grafts must be thoroughly established beforehand, or else exfoliation occurs as a result of the introduction of the organisms.

Inter-relationship of Secretory Glands.—A matter of very considerable interest is the alleged relationship existing between the functions of various glands possessing an internal secretion, and particular attention has been applied to the influence exerted by the thyroid on other organs, as well as the converse. Markham, Goodhart, and especially Hector Mackenzie and Marie,[5] pointed out the frequency with which exophthalmic goitre is associated with enlargement of the thymus. Another curious observation has been made viz., that enlargement of the thymus occurs in cases of myasthenia gravis; and Meyerstein [6]

Soc. de biol., 1898, p. 889.

[2] Virchow's *Arch.*, 166, s. 373.

[3] *Lo Sperimentale*, 1902, Fasc. iv., p. 500.

[4] *Soc. de biol.*, 1903, pp. 679, 713, 725, 726.

[5] *Soc. méd. des hôp.*, 1893, Feb. 17, p. 136

[6] *Neurologisch. Centralbl.*, 1904, xiii., No. 23, s. 1089.

has published a description of a young woman, *aet.* 33 years, in whom there was myasthenic weakness, shown by bilateral ptosis, incomplete paralysis of the external muscles of the right eye, and complete paralysis in the left. There were also signs of exophthalmic goitre, and Meyerstein refers to other observations in which the symptoms of the two diseases were combined.

In a certain number of cases of acromegaly the thyroid body has been found enlarged; atrophy of the internal and external genitalia has also been observed.

Benda [1] has found changes in the hypophysis in acromegaly similar to those found in the gland in myxœdema and cretinism.

Dr. Arnold Lorand, of Carlsbad, in a paper read before the Pathological Society of London, Feb. 21, 1905, advanced the view that the thyroid is partly responsible for the existence of glycæmia, the carbohydrate being derived from the colloid material; this view of the sugar-forming capacity of the thyroid is supported by the extreme rarity with which diabetes mellitus or glycosuria occurs in cases of myxœdema.

In myxœdema the genital organs show impaired development, and pregnancy is very rare in myxœdematous women. Herrgott, [2] however, observed a case of pregnancy occurring in a myxœdemic woman, aged 18 years. During delivery eclamptic manifestations occurred, the urine at the time being free from albumin. Herrgott advances this case as a proof that inadequacy of other organs than the kidney and liver is responsible in certain cases for eclamptic manifestations, and that possibly absence of the thyroid, and especially of the parathyroids, causes convulsions. Herrgott quotes the observations of Verstraeten and Vanderlinden, who describe the symptoms occurring at term in a cat which had become pregnant three years after thyroidectomy. For five days the animal was comatose and had attacks of

[1] *Deutsche med. Woch.*, 1900, V. B., s. 47 u. 288; 1901, V. B., s. 10.
[2] *Annal. de gynécol.*, 1902, lviii., p. 1.

convulsions. A macerate of sheep's thyroid was injected under the skin, and the symptoms abated in one hour. The animal aborted the following day, and the improvement continued without further treatment. Herrgott quotes this observation in support of Nicholson's views already mentioned on the dependence of eclampsia upon thyroidal deficiency.

Abrikosoff[1] describes the anatomical findings in a case of myxœdema ; a special feature was the occurrence of hypertrophy of the anterior lobe of the pituitary body ; the size of the whole organ was 2 cm. in frontal diameter, 1·5 cm. in sagittal, and 1·0 cm. in the vertical, as compared with the corresponding measurements given by Benda of a normal pituitary body : 1·4 cm. in the frontal diameter, 0 6–1·0 cm. in the sagittal, and ·5–·9 in the vertical. Microscopically there was an increase of the gland-like tubes characteristic of the normal gland, so that Abrikosoff considers that the condition was one of hypertrophy of the pituitary body similar to that which is described by Comte and Ponfinck in the pituitary body in two other cases of myxœdema. Similar results have been described by Boyce and Beadles and others. Lancereaux[2] has described a case of acromegaly and Graves' disease in which there were also symptoms of diabetes mellitus; and Magnus-Levey describes a case of acromegaly with symptoms closely allied to those of Graves' disease—marked sweating, polyuria, glycosuria, &c. It is well known that during pregnancy the thyroid gland is considerably enlarged ; Parhon and Goldstein[3] enter into a full discussion of the subject of antagonism between the thyroid and the ovary. The relationship existing between the thyroid and parathyroid has already been discussed.

[1] Virchow's *Archiv*, 1904, vol. clxxvii., s. 426.
[2] *La Semaine méd.*, 1895, p. 61.
[3] *Romania Med.*, 1904, ix., 15–18, p. 428.

CHAPTER III.

CHEMICAL PHYSIOLOGY.

Thyroiodin.—Baumann was the first to establish the existence of iodine in the thyroid gland,[1] and he and Roos were able to separate a body—*thyroiodin* or *iodothyrin*—which occurs in the gland combined with albumin and globulin. So strong is the combination of the iodine with the proteid matter, that the former can only be separated by the destruction of the proteid; the iodine may also with difficulty be split off by means of alkalies, and sodium amalgam also effects a separation, but only very gradually. The active principle of the thyroid gland is not destroyed by boiling either with or without the addition of 10 per cent. sulphuric acid even for several hours. Thyroiodin obtained from human sources contains 1·31–2·58 per cent. of iodine; it is most abundant between the ages of 25 and 55. ·3 grammes of fresh sheep's thyroid contains ·1 mg. of thyroiodin; thyroiodin obtained from sheep contains 10 per cent. of iodine and ·56 per cent. of phosphorus. Thyroiodin is also prepared from the thyroid of the calf and pig.

A. Gauthier[2] has found arsenic in the thyroid gland to the extent of 1 mg. in 127 grammes of tissue, and Baldi has shown the presence of bromine.

Baumann's thyroiodin is prepared by adding to a quantity of thyroid gland substance four times the weight of a 10 per cent. solution of sulphuric acid; the mixture is then boiled for 20 to 30 hours and cooled; a flocculent substance is formed and removed by filtration; this con-

[1] *Zeitschr. f. physiol. Chem.*, 1896, vol. xxi., s. 319 u. 418; xxii., s. 1.

[2] *Compt. rend. de l'acad. de méd.*, t. cxxix., pp. 929 and 936; t. cxxx., p. 284; and *Bull. de la soc. chem.*, 1900, No. 1., p. 2.

stitutes the crude thyroiodin; a small proportion of thyroiodin passes into the filtrate, and can be recovered by a process of neutralisation of the sulphuric acid by means of barium carbonate, by evaporation and cooling. The thyroiodin is very completely dissolved by boiling in 90 per cent. of alcohol; this solution is then evaporated in a water bath, and the residue is rubbed up with ten times the weight of milk sugar: all fat and fatty acids are then removed by means of ether and petroleum. To finally separate the thyroiodin from the milk sugar the residue is dissolved in a weak soda solution and filtered; the soda solution is now neutralised by acid, and the thyroiodin separates in flocculi, which may be recovered by filtration; this process is again repeated, with the result that though a small amount of thyroiodin is lost and some milk sugar still remains, a coloured constituent is removed. Another method (*vide infra*) used for the separation of thyroiodin is the method of artificial digestion: this process has the advantage of securing a less coloured preparation of thyroiodin than the above.

Thyroiodin is a brownish-coloured powder which is insoluble in water, chloroform, and ether, but is readily soluble in soda solution, in concentrated mineral and in glacial acetic acids. A solution of thyroiodin gives neither the biuret nor the Millon reaction. Roos has shown that thyroiodin exerts an influence on the metabolism of animals,[1] and the same has been demonstrated by Treupel in man: in large doses it produces symptoms of thyroidism, and it also exerts a specific influence on myxœdema. Quite apart, however, from the expense entailed in the separation of thyroiodin, it appears from the observations on metabolism carried out by Schiff[2] that thyroiodin is a less active agent than the gland substance, as tested by the output of nitrogen and phosphoric acid. Notwithstanding this observation it is said that cases of parenchymatous

[1] *Zeitschr. f. physiol. Chemie.*, Bd. xxi., Hft. 1. s. 19.

[2] *Wiener med. Presse*, 1897, No. 8, s. 251.

goitre are more quickly affected by means of thyroiodin than by the gland substance. O. Lanz attributed some of the symptoms of so-called thyroidism to the existence in several of the English preparations of bacterial growths, some of which he considered identical with the bacillus of malignant œdema, a possible objection which is entirely excluded by the modern methods of aseptic preparation.

Other Substances.—Fraenkel,[1] previous to Baumann's work, had separated a substance from the thyroid gland which he called *thyroantitoxin*, and which he considered to be of the nature of an alkaloid that was capable of neutralising *in situ* toxic material brought to the thyroid gland by the circulation. A macerate of the thyroid glands was prepared, then boiled and treated with acetic acid, by which means all albumins and nucleo-albumins were precipitated. The filtrate contained the active principle; to this was added acetate of lead, and the excess of lead was removed from the filtrate by adding sulphuretted hydrogen; the filtrate then obtained was evaporated to a syrup, and from this latter was obtained the active material in lamellar form; a hygroscopic crystalline form was also obtained having the formula $C_6H_{11}N_3O_5$. There is not much reason to believe that this substance has any therapeutic value: it contains no phosphorus, arsenic, or iodine. Notkin[2] separated a substance which he called *thyroproteid*; he considered that it was derived from the activity of the chemical processes of the body, and that it accumulated in the thyroid gland, where it was neutralised by an enzyme or ferment, "thyroidin," formed by the thyroid gland: in the case of failure on the part of this gland to produce this "thyroidin," the individual succumbed to auto-intoxication by the thyroproteid. Thyroproteid is considered by Notkin to be a compound albumin from which under certain

[1] *Wiener klin. Rundschau*, 1895, s. 758.

[2] *La Semaine méd.*, 1895, No. 87, p. 318.

circumstances a carbohydrate can be split off. Thyroproteid does not, however, give the ordinary reaction of proteids. Thyroproteid is analogous to the thyroprotein of Budnow and the thyronucleo-albumin of Morkotun. R. Hutchison separated proteid bodies from the thyroid gland; one, which is a nuclein-like body, resisted peptic digestion, and was probably derived from the cells of the gland; the other, described as *thyrocolloid*, is capable, in part, of being acted on by digestive juices; the non-proteid residue left after digestion of thyrocolloid is considered by Hutchison to be the more active therapeutic material, and contains most of the iodine and all the phosphorus forming part of the original colloid material—it is, in fact, the thyroiodin of Baumann. Oswald[1] isolated from the thyroid gland a substance which he called *thyroglobulin*. This body is separated from its solution in sodium chloride by a half-saturated solution of ammonium sulphate, and contains 1·50 to 1·75 per cent. of iodine, 2 per cent. of sulphur, but no phosphorus.

According to Oswald, thyroglobulin, as well as another iodine-free nucleo-proteid, are probably secreted by the glandular epithelium and are mixed with the colloid material. Oswald[2] finds that thyroglobulin in animals and man, apart from the iodine content, preserves the same elementary composition. Thyroglobulin can be obtained from healthy and diseased glands, the various samples differing only in iodine content, which is smallest in the cases of the most severely diseased thyroids and highest in the normal gland. Thyroglobulin is intimately associated with the colloid secretion of the gland, for when the colloid cannot be detected microscopically, no iodine can be shown chemically. Oswald thinks there are two thyroglobulins—one containing iodine and the other not, and a mixture of different preparations of these is responsible for the varying content of

[1] *Zeitschr. f. physiol. Chemie*, 1899, s. 14; and *Münch. med. Woch.*, 1899, No. 33, s. 1073.

[2] *Beitr. zu chem. Physiol. und Patho'.*, *Bd.* II., s. 545–556.

iodine in thyroid glands under different circumstances. Both forms of thyroglobulin are to be considered as products of secretion of the thyroid gland, and the iodisation appears to take place in the cells or follicles; the activity of the thyroglobulin depends entirely on the iodine content; thyroglobulin contains 14·3 per cent. of iodine, which is considerably more than the percentage present in thyroiodin (about 10 per cent. in sheep).

A number of other preparations have been obtained from the thyroid gland. Vermehren produced *thyroidin*, a powder which is obtained from a glycerine extract of thyroid gland by means of precipitation with alcohol. *Thyraden*, prepared by Knoll, or extractum thyroideæ, is obtained by extracting the gland with physiological salt solution; then precipitating by means of ether and alcohol; the filtrate is now evaporated to dryness and a certain amount of milk sugar is added, so that one part of the preparation corresponds to two of fresh gland, and contains ·72 milligrammes of iodine. Notkin also prepared what is known as *thyroidin depuratum*, from the substance thyroproteid which has already been mentioned. Thyroidin depuratum contains, according to Notkin, at least two proteid bodies, one a globulin-like body, the other possessed of enzyme action, and the more physiologically active. Notkin's thyroidin depuratum shows a much more toxic influence than thyroproteid, and such influence is of an opposite nature, being distinctly excitant; it is soluble in water, and can be given subcutaneously. White has also prepared a "thyroidin." Thyroid glands which have been freed from fat and connective tissue are extracted with equal parts of water and glycerine. The extract is filtered and rendered acid by adding phosphoric acid, and is then made alkaline by the addition of a solution of lime, which produces a precipitate of the colloid material from the formation of calcium phosphate; this is separated by filtration as quickly as possible, washed, and dried over sulphuric acid.

Catillon [1] prepared more simply and more expeditiously thyroidin very similar to that separated by Baumann. This substance, called by Catillon *iodothyroidin*, is prepared by digesting the thyroid gland in distilled water with pancreatine; the residue is washed with ether and petroleum and re-dissolved in dilute soda solution; the filtered solution is then precipitated by means of sulphuric acid, and the precipitate washed again and dried. Both the iodothyroidin of Catillon and the thyroiodin of Baumann (identical with the iodothyrin of Bayer) are made up with milk sugar in such strength that the proportion of active principle present is the same as in the fresh gland. Poehl has also prepared an opothyroidin. Two other substances derived from the thyroid gland are the *thyroglandin*, prepared by Stanford, and *thyrogen*, prepared by Blum. Thyroglandin is obtained by macerating the thyroid glands for twenty-four hours in water at 8–10° C; the filtrate from this macerate contains iodoglobulin, and is evaporated to dryness. The residue is boiled for an hour with soda solution; the cold filtrate is carefully neutralised with hydrochloric acid, and then this solution of sodium chloride and thyroidin is evaporated to dryness, powdered, and added to the residue of iodoglobulin above mentioned. Thyrogen is obtained by prolonged maceration of thyroid gland in water, by means of which a considerable amount of iodine is extracted; the macerate is coagulated by heat if necessary, and salt is added; the coagulum contains the iodine combined with proteid.

It has already been pointed out that probably the colloid contents of the thyroid alveoli are absorbed into the system through the lymphatics, but it has also been thought possible for some to enter by the venous system, and that the venous blood might be used for therapeutic purposes. This has been disproved by the observations of Chatin and Guinard,[2] who have shown that the veins leaving the gland contain no active material, or so

[1] *Bull. de la soc. de thérapeut.*, 1897, March 10, p. 126.
[2] *Lyon Méd.*, 1900, Sept. 30.

small an amount that it cannot be detected by physiological means; nor are the globular elements charged with this active material, for injection of the clot obtained from the blood of the thyroid veins is no more active than the serum.

Lanz has advocated the use of *äiodin*, a preparation of the thyroid gland which contains not more than ·4 to ·5 per cent. of iodine. The reasons for the introduction of this substance are that Baumann's thyroiodin, Notkin's thyroproteid, and Fraenkel's thyroantitoxin do not exert the same influence as the gland itself; further, it is stated by several observers that the therapeutic value of the thyroid gland does not depend exclusively on the iodine contained: the spleen contains relatively more iodine than the thyroid gland, and yet does not exert any beneficial influence in cases of athyrea. Lanz showed that äiodin is able to counteract tetanic symptoms and delay the fatal issue in thyroidectomised dogs.[1]

A. Gauthier has shown that the normal thyroid of man and domestic animals contains, besides iodine, a certain amount of arsenic (·85 mg. in 100 grammes of fresh gland) in the form of arsennuclein, and thyroiodin has been found to contain arsenic.[2] Treatment with thyroid preparations may produce symptoms of thyroidism (tachycardia, etc.); the interesting observation has been made that these untoward symptoms may be greatly alleviated by the use of Fowler's solution (three minims three times daily) or arsenious acid (2–6–8 milligrammes daily).[3] It thus appears possible that the symptoms of thyroidism are avoided in the normal individual owing to the natural occurrence of arsenic in the thyroid gland. It is remarkable that iodine and arsenic should have been used especially for the treatment of enlargement of

[1] For further information on the methods of derivation of other thyroid preparations, the reader should refer to Waldheim's "Serum-Backterientoxin- und Organ-Präparate."

[2] Jeandelize, "Insuffisance thyroidienne," Paris, 1903, p. 663.

[3] Mabille, "Thèse de Lille," 1898; Ewald, "Thérap. d. Gegenwart," 1899.

the thyroid gland long before these substances were known to exist in the thyroid gland. Gauthier was able to find a considerable quantity of arsenic in the thymus gland (frequently found enlarged in exophthalmic goitre), also in the brain, in the skin, and probably in the pituitary body, but nowhere else. Reference has already been made to the observation of Baldi [1] that bromine may be detected in the thyroid gland.

[1] *Arch. ital. de biol.*, 1898, t. xxix., p. 353.

CHAPTER IV.

PATHOLOGY FROM THE POINT OF VIEW OF ORGANOTHERAPY.

Those pathological conditions are alone suitable for thyroid and parathyroid treatment in which there is reason to believe that the functions of these glands are in partial or in complete abeyance; in other words, treatment by means of thyroid and parathyroid tissue is entirely "substitutional." As already explained, it is probable that when thyroid substance or preparations of the thyroid gland produce improvement in cases of athyrea, they do so (1) by supplying a substance capable of stimulating metabolism, and (2) by producing, by means of the parathyroid tissue which is present when sheep's thyroid is used, a substance which neutralises the toxic results of such metabolism. It is of importance in this connection to ascertain what is the relationship of the thyroid and parathyroid in those animals which are slaughtered for purposes of food, and which provide the great part of the thyroid preparations now in the market.

In the case of the sheep, the internal parathyroid is inserted on the internal aspect of each lateral lobe of the thyroid proper, buried in the connective tissue distributed around the blood vessels as they enter the gland; whereas the external parathyroids consist frequently of a number of nodular formations in the neighbourhood of the bifurcation of the carotid artery: they are often buried in fat lobules, and their colour varies from brown to rose colour; Schaper found them eight times in ten sheep examined, and probably in the other two animals they were present in neighbouring tissues not examined. From this it appears that the

sheep's thyroids as removed by slaughter-house methods consist of the thyroid proper and the internal parathyroid. Observations have not yet been made on the anatomy of the parathyroid gland in the adult pig; external parathyroids exist, but it is not known whether the internal parathyroids exist in the thyroid, or are not in this animal represented by the external gland. Groschuff asserts that the internal parathyroid in the pig is never developed, or, if developed, soon undergoes retrogressive changes. From this it may be concluded that thyroid preparations derived from the pig may not contain any parathyroid tissue at all. Welsh[1] describes the relationships of the parathyroids to the thyroids of cattle; the former can be readily found quite separate from the thyroid.

Of these three animals, the sheep is the one from which the majority of the preparations of thyroid gland are derived, so that their administration is capable of supplying not only deficiencies in thyroid but also in parathyroid glands.

The thyroid gland in man is subject to various forms of enlargement known as simple goitre. In the parenchymatous form, there is a simple uniform hypertrophy, each acinus containing colloid material: in the vascular form no new tissue is formed, but there is marked dilatation of the blood vessels. The thyroid is frequently the seat of tumour formation, the enlargements being in one or other lobe, or in the isthmus, or possibly affecting the whole organ. In the case of localised parenchymatous enlargement considerable difficulty is met with in diagnosing this condition from localised adenomatous or cystic formation. When symptoms of pressure are present it may be necessary to perform an exploratory operation, following this up with enucleation in the case of the tumour, or by excision in the parenchymatous form. The tumour formations which are more frequently met with are

[1] *Journ. of Anat. and Physiol.*, London, 1898, vol. xxxii., pp. 292 and 380.

adenoma and cystoma. The former is usually single, and may be localised to one or other lobe or isthmus, or may be multiple, involving the whole gland. Cystic disease may be confined to either lobe or isthmus, and may take the form of a single cyst, or there may be multiple cysts developed throughout the organ. Carcinoma and sarcoma may also occur in the thyroid gland. Cases of thyroiditis have been described in the course of acute specific illnesses. It is conceivable that in certain of the conditions of apparently simple goitre, *i.e.* those with cystic or adenomatous formation, the adjacent thyroid tissues may be rendered inadequate to the needs of the body, with the result that myxœdema occurs; or the functional relationship of the parathyroid and thyroid may be so disturbed that tetany and other allied symptoms develop; and it is probably for this reason that such cases of simple adenoma or cystic disease of the thyroid respond favourably to treatment with thyroid products. Even cases of parenchymatous goitre are improved by the use of these agents, and it is thought that the use of thyroid substance, introduced from without, leads to the shrinkage of that tissue which had undergone hypertrophy in response to an increased demand for the formation of colloid.

Myxœdema and Cretinism.—These conditions are due to the absence of the thyroid gland, the parathyroids remaining normal.[1]

Myxœdemic symptoms may, as has already been pointed out, supervene in cases of simple tumour of the thyroid; cretinism and myxœdema may be associated with enlargement of the thyroid gland. Shattock [2] describes carcinoma of the thyroid in a case of myxœdema. In some anomalous cases the signs of myxœdema and exophthalmic goitre may occur in the same individual.[3] Cases of primary myxœdema and cretinism are those in which there is no

[1] Maresch, *Zeitschr. f. Heilk.*, Berlin, 1898, Bd. xix., s. 249.

[2] *St. Thomas's Hosp. Reports*, 1887, New Series, vol. xvi., p. 255.

[3] Félix, "Thèse de Paris," 1895–1896, No. 241.

obvious cause for the atrophy of the thyroid gland. In some cases, all trace of the thyroid is lost and Bourneville has attributed the condition to arrest of development of the thyroid gland. Briquet[1] considers that in many cases of myxœdema, the amount of gland is merely insufficient for the needs of the body, implying that there may be thyroid tissue present, but in too small a quantity. Jeandelize[2] states that myxœdema follows cases of thyroiditis, or follows inflammatory disturbances near the thyroid gland. Myxœdema may be preceded by exophthalmic goitre, and the explanation given of this anomaly, as a result of the experiments of Ballett and Enriquez, is that experimental hyperthyroidism is capable of producing eventually parenchymatous and interstitial inflammatory changes in the thyroid gland, ultimately leading to atrophy and fibrosis of the organ. Plausible as the explanation may be, it does not obtain frequent support from clinical observation, for it is not *very* common to find cases of exophthalmic goitre becoming myxœdematous. Cases are reported by G. Gauthier,[3] Sollier,[4] Baldwin,[5] and L. Gauthier.[6] Jeandelize (p. 578) agrees with others that myxœdema may not only exist with exophthalmic goitre, and in some cases even follow it, but that even *myxœdema may precede exophthalmic goitre*, and quotes in support of this statement observations by Félix[7] and Jacquemet.[8] Béclère[9] and Marie[10] record cases in which excessive doses of thyroid, in cases of myxœdema, have induced symptoms of Graves' disease, including a tendency to exophthalmos.

[1] *La Presse méd.*, 1899, p. 105.
[2] *Loc. cit.*
[3] *Lyon Méd.*, 1888, May 27, p. 119.
[4] *Revue de méd.*, 1891, p. 1000.
[5] *Lancet*, 1895, i., p. 145.
[6] *Rev. méd. de la Suisse Rom.*, 1898, p. 265.
[7] *Loc. cit.*
[8] "Thèse de Montpellier," 1900, July, No. 77.
[9] *Soc. méd. des hôp.*, 1894, p. 630.
[10] *Ibid.*, 1894, p. 124.

So far as the seven cases collected by Félix are concerned, only one (Kowaleski's) can be given to support the view that myxœdema may precede and give place to exophthalmic goitre; and even in this particular case the myxœdema which occurred *with* exophthalmic goitre merely disappeared, leaving symptoms alone of exophthalmic goitre. Schrotter [1] speaks of these mixed cases as cases of dysthyroidism. This term would also describe those anomalous cases of so-called Graves' disease combined with Addison's disease, one of which is described by Moulard-Martin and Malloizel.[2]

If there is such a thing as functional defect in the thyroid apparatus or qualitative changes in the internal secretion of the thyroid and parathyroid glands without structural changes, then such mixed conditions as these are possible; in the absence of demonstrable proof of functional defect many observers refuse to accept such a possibility. It would be possible for myxœdema to precede exophthalmic goitre on the hypothesis of thyroparathyroid action enunciated by Vassale and Generali, if the vicarious overaction or hypertrophy of the anterior part of the pituitary, were accepted as proven.[3] Even then, however, such vicarious action on the part of the pituitary body would have to be considerable, and accepting the views of Tamburini and Benda that acromegaly is due to excessive activity of the pituitary body, it would rather be expected that acromegaly would develop as well as exophthalmic goitre.

Pathological Changes in the Thyroid.—The pathological examination of the thyroid in some cases of myxœdema shows that the tissue is normal in appearance, but the gland itself is considerably less in size than normal,[4]

[1] *Zeitschr. f. klin. Med.*, Bd. 48., Hft. 1 and 2., s. 1.

[2] *Revue neurol.*, 1904. xii. 20. p. 1056.

[3] For reports, *see* Mayor, *Rev. méd. de la Suisse Rom.*, 1883, p. 534; Boyce and Beadles, *Journ. of Path. and Bact.*, 1893, p. 223; Burckhardt, *Ibid.* 1895, p. 341.

[4] *See* report on an irregular type of myxœdema by Jeandelize, *loc. cit.*, p. 480.

or in other cases the thyroid is replaced by fibrous or fatty tissue, a few acini being found scattered about in these two more primitive tissues.[1]

In those cases of myxœdema and cretinism in which the size of the thyroid gland is increased, the cause of the enlargement is an excess of fibrous tissue, the presence of cysts or adenomata or even of various forms of malignant disease.

The histological changes taking place in the thyroid in exophthalmic goitre are the following: the vesicles lose their rounded or square section and become branched and stellate; the lining membrane is folded on itself; the secreting cells instead of being cubical, become columnar and the colloid material is partly or wholly replaced by a secretion which stains badly; colloid may be quite absent. In fact these changes are very similar to those met with in the thyroid when a part of this organ is experimentally removed; they suggest, therefore, compensatory hypertrophy; and Walter Edmunds,[2] though admitting that the hypertrophy may be due to parathyroid defect, does not consider that the evidence so far is sufficient to show that this is certainly the case. He found that removal of the parathyroids causes changes in the acini of the thyroid similar to those above described in exophthalmic goitre, but the thyroid did not enlarge. Reference has already been made to the increase of the thymus gland occurring in cases of exophthalmic goitre. It has also been found that the pups of thyroidless parent dogs show changes in the thyroid gland similar to those met with in exophthalmic goitre, a further suggestion that the changes in the latter disease are due to hypertrophy. It is not fully established that exophthalmic goitre is due to excessive function of the thyroid gland, for the observation that removal of a portion of the thyroid gland in exophthalmic goitre leads to

[1] *See* report on three cases of myxœdema by C. F. Beadles, *Transact. Path. Soc.*, Lond., No. xlix. p. 262.

[2] "Pathology and Diseases of the Thyroid Gland," 1901, p. 32.

improvement, is discounted by the knowledge that removal of cysts or adenomata from the thyroid will also lead to reduction of symptoms. The possibility that the convulsive and other nervous phenomena of exophthalmic goitre are due to defective or lost function of the parathyroids has already been mentioned.

Pathological Changes in the Parathyroids.—Very few observations have been made on the pathological changes occurring in the parathyroid glands. De Santi[1] describes the histology of a benign tumour occurring in a man, aged 58 years, in the cervical region of the neck; its structure was like that of parathyroidal tissue.

Garnier[2] has shown that the parathyroids undergo pathological changes in various infectious diseases, and may do so independently of any change in the thyroid, but that sometimes in the same class of infectious disease the parathyroids are not affected. Sparse as are the observations on pathological changes in the parathyroids, experimental work shows that there are definite symptoms produced as a result of their extirpation, and tetany and convulsive seizures are amongst the most marked features. Jeandelize[3] has most ingeniously supported the idea that certain convulsions in infancy are due to parathyroidal insufficiency, and gives reference to observations on infants in whom tetany and spasm of the glottis have been caused by thyroid treatment, preparations being used containing both thyroid and parathyroid substance.

Mossé[4] quotes Schultze as having relieved tetany in a goitrous girl by the use of thyroidin, a substance derived from thyroid and parathyroid tissue. Jeandelize quotes further evidence for believing that some forms of epilepsy and of eclampsia are also due to parathyroidal deficiency.

[1] *Rev. hebd. de laryng., d'otol. et de rhinol.*, 1900., tom. i., p. 103.

[2] "Thèse de Paris," 1899, No. 409, and *Gaz. des hôp.*, 1899, Oct. 3, p. 1035.

[3] *Loc. cit.*, p. 701.

[4] *Congrès français de méd.* IV. Session, Montpellier, 1898.

Lundborg[1] advances the hypothesis that tetany, myoclonus and myotonia congenita are due to different degrees of insufficiency of the parathyroids, and that periodic family paralysis is due to excessive or faulty function of the same. According to the same writer paralysis agitans is due to absence of the parathyroids, and is comparable to myxœdema following destruction of the thyroids; myasthenic paralysis is due to an excessive or faulty action of the parathyroids comparable to the excessive function of the thyroids in exophthalmic goitre. Lundborg has observed a case of myxœdema associated with paralysis agitans, the combined diseases being thought to be due to chronic progressive hypofunction of the thyroid and parathyroid respectively: a similar case was described by Luzzatto, who quite independently attributed the manifestation of Parkinson's disease to absence of the parathyroid glands. Lundborg[2] quotes Moebius, who had seen a case of Graves' disease combined with paralysis agitans. No *post-mortem* investigations are given by Lundborg to confirm his speculations.

[1] *Deutsche Zeitschr. f. Nervenheilk.*, 1904, Bd. 327, Hft. 3 u. 4, s. 217.
[2] *Ibid.*, s. 228.

CHAPTER V.

THERAPEUTIC USE OF THYROID SUBSTANCE AND ITS DERIVATIVES.

Choice of Preparation.—Of the various preparations of thyroid gland, the most important are desiccated thyroid substance, thyroiodin (Baumann), thyroglobulin (Oswald), and thyroantitoxin (Fraenkel). These substances and the others previously mentioned fall into one of two groups, those which contain iodine and those which do not. Baumann asserts that the active principle of the thyroid gland is combined with proteids and is abstracted with the latter by coagulation of the proteids and filtration. Fraenkel and others, however, state that the active principle is contained in the filtrate after the coagulated proteids have been separated. The injection of Fraenkel's thyroantitoxin is capable experimentally of slowing the pulse, of exciting the frog's heart to beat when previously poisoned by muscarine, and is able to prevent the convulsions produced in young cats following ablation of the thyroid. It therefore appears that Fraenkel's thyroantitoxin counteracts the so-called toxic or nervous phenomena. Thyroiodin, on the other hand, produces effects more comparable to the use of the gland substance; it influences the condition known as myxœdema, but does not control so markedly the convulsive symptoms of thyroparathyroidectomy.[1] Magnus-Levy[2] describes his experiences in the treatment of thirty-four cases of myxœdema and cretinism. Observations made in the case of sporadic cretins upon the influence of various preparations on the oxygen intake and CO_2 output

[1] Jeandelize, p. 612.

[2] *Zeitschr. f. klin. Med.*, 1904, lii., s. 201.

showed that dried preparations of the thyroid gland and thyroiodin caused an increase in the intake of oxygen and the output of CO_2; very slight changes or none at all were found after the use of Fraenkel's thyroantitoxin. Magnus-Levy had made no exact observations on Oswald's thyroglobulin, but expresses the view that it would have had the same effects as thyroid gland substance or thyroiodin. These two last substances are the ones most widely used, and they both contain iodine and arsenic.

Notwithstanding the fact that it is very generally agreed that iodine in a combined form is the substance which is responsible for the specific effects following the ingestion of thyroid gland or thyroiodin, certain considerations point to the possibility that iodine and even arsenic are more probably passive associates of other substances so far unseparated. The following reasons are given by Gauthier.[1] The thyroid glands of cattle contain no iodine; not the least trace even can be found when large quantities of bovine thyroids are analysed, and yet the thyroid glands of oxen are capable of producing as much specific effect as the thyroid glands of other animals which contain iodine in considerable quantity. Gauthier further states, on the authority of Barbera, that iodine exercises a paralysing action upon the centres of the vagus and depressor nerves, whereas thyroiodin is an excitant. Further, some doubt is also thrown upon the view that iodine is the important constituent of the thyroid gland and thyroiodin, because there is apparently such a great variation in the content of iodine in the thyroid glands of the same species of animal at different times and with different alimentation, and there is further very considerable variation in the amount of iodine present in thyroiodin. Myxœdematous patients are not relieved by the administration of iodine compounds given instead of thyroiodin, although an ordinary dose of the latter substance contains much less iodine than an average dose of potassium

[1] "Les médications thyroidiennes," Paris, 1902, p..47.

iodide. Finally, iodine taken in the form of thyroiodin does not appear in the urine even when as much as 4 grammes (Ewald) or 15 grammes (v. Jaksch) are given in a day.

Such objections as these may well cause hesitation in the choice of thyroiodin instead of the simple gland substance. Considering, moreover, the cost of separation of thyroiodin, on commercial grounds it is obvious that the use of preparations of the simple glandular substance is to be preferred. The objection urged against the use of dried gland substance on the score of decomposition is a small one, for the preparation can with proper precautions be kept free from any bacterial decomposition. The objection that there is no means of standardising the doses of gland substance applies just as much to the substance derived from them. Richter,[1] however, insists that it is possible by using thyroiodin to administer accurate doses of the active principle, implying that there is no variability in the strength of thyroiodin.

Dosage—

Liquor thyroidei, 5–15 minims
Thyroideum siccum, 3–10 grains } British Pharmacopœia.
Tabloids of thyroid substance (Burroughs, Wellcome and Co.), 1½–5 grains.

These are the doses for adults, and may be given two or three times a day.

In children up to 4 years of age give 1 to 3 times a day one-sixth of the adult dose.
In children from 4 to 7 years of age give 1 to 3 times a day one-third of the adult dose.
In children from 7 to 14 years of age give 1 to 3 times a day one-half of the adult dose.
In children from 14 onwards give 1 to 3 times a day as in adults.

Thyroiodin or iodothyrin or thyrein.—This is made up as tabloids or powders and consists largely of milk sugar: 1 gramme of the powder or tabloid corresponds to 1 gramme of fresh gland; the iodine content is ·03 per cent. The

[1] *Berlin. Klin.*, 1900, No. 139, s. 7.

dose for an adult is ·3 grammes once, twice, or three times a day, and the dose may be increased till 2 to 4 grammes are taken daily. Children should be given doses in proportion to their age.[1] In France preparations of thyroiodin are sold under the name of *comprimés vicario*, each weighing ·25 grammes. Thyroiodin may be administered as an ointment made up in the following way:—

Thyroiodin	...	...	...	10 parts.
Ether ...	...	...	...	60 ,,
Lanoline	...	...	...	480 ,,

Other preparations may be given in the following doses :—

Thyroantitoxin, ·01 grammes to ·05 grammes daily.
Thyroidin of Vermehren, ·01 to ·03 ,, ,,
Thyraden. In tabloid form of ·25 grammes, each containing ·3 grammes of fresh gland. One to two tabloids may be given three to five times a day to adults, to children 2–5 tabloids daily.
Thyroidin depuratum, ·01 gramme doses.
White's thyroidin, 2½ grain doses.
Opothyroidin, ·1 to ·5 gramme doses.
Thyroglandin, ·18 to ·30 gramme doses.
Aiodin. For adults ·3 to ·5 grammes daily. For children, not more than ·1 gramme daily.

It must be remembered that the active principle of the thyroid when administered to suckling women is excreted in the milk and may produce symptoms in the child.

Thyroidism. — During the treatment by means of thyroid substance or its derivatives certain symptoms are apt to develop as a result of excessive doses, or possibly owing to a particular idiosyncrasy on the part of the patient. This is especially marked in cases of myxœdema. Healthy individuals have a marked tolerance for the drug. It is important to notice the earliest symptoms of thyroidism. When well developed, the following are common features: Tachycardia, with dilatation of the arteries and fall of tension in the pulse, headaches, vertigo, syncopal attacks,

[1] *Vide supra.*

delirium, tremors, insomnia, fever, nausea, vomiting, diarrhœa, and wasting : sensations of heat, pruritus, numbness, tingling of the fingers and toes, and even tetany have been observed : rashes, too, have been met with, and pain in the legs, and paresis almost amounting to paraplegia has also been noticed. Amongst the more unusual sequels of thyroid treatment in excess are optic neuritis and accommodative asthenopia. Aalbertsberg [1] reports the occurrence of double optic neuritis, followed by atrophy shortly after the commencement of treatment by means of thyroid gland in a case of myxœdema. During thyroid treatment the thyroid gland has been noticed to enlarge. Lanz and others formerly thought that the toxic symptoms of thyroidism were due to decomposition of the various forms of preparations of the thyroid gland. This belief, however, is disproved by the observation that thyroidism may be induced by the use of thyroiodin, and by the fact that owing to the more careful manipulation of the raw thyroid glands, and admixture with substances which preserve them, no decomposition can be demonstrated.

Young children as a result of excessive doses of thyroid preparations grow too rapidly, and may show signs of scoliosis and kyphoscoliosis (Bourneville and Telford-Smith). Parker, Thompson, and others have also shown that cretins under excessive treatment with thyroid preparations may develop rickets.

Indications against the use of Thyroid Derivatives.—Weakness of cardiac action is a well-recognised contraindication. If it is not very extreme, however, small doses may be ordered, or the drug be administered at intervals only. It is not advisable to prescribe the drug when albuminuria or glycosuria is present. Coincident tuberculous disease should cause hesitation, and it is also inadvisable to prescribe the drug whenever there is a suspicion of grave renal or hepatic disease.

In all cases undergoing thyroid treatment, close super-

[1] *Nederl. Tijdschr. voor Geneesk.*, ii., p. 1125.

vision is required, especially in the early stages, until observation has shown whether the patient is tolerant or not. In cases of obesity this is especially important.

Treatment by means of Thyroidal and Parathyroidal Preparations.—Thyroid gland, or thyroiodin, has served more than any other similar substance to establish the branch of practical medicine known as organotherapy upon a firm basis. *Myxœdema* in its various forms and *cretinism* are capable of being in many particulars completely cured by the use of these drugs. The condition of *obesity*, occurring independently of excess of diet, is one which so far has not received much explanation, but there is some reason for the belief that this disorder, as well as the one known as *Dercum's disease* or *Adiposis dolorosa*, may be really irregular or atypical manifestations of athyrea. Favourable results are reported of the use of thyroid preparations in these disorders, also in *sclerodermia* and *psoriasis*, more especially in the latter, and when the disorder is chronic.[1] Good effects have been reported in cases of *goitre, simple* and *exophthalmic*, as well as in *acromegaly; rheumatoid arthritis, sclerosis of the middle ear, arteriosclerosis, neurasthenia, etc.*, are also said to be improved (!).

Von Eiselsberg[2] says that thyroid gland produces transitory improvement in idiopathic tetany, and even in infantile tetany. Petretto[3] recommends thyroiodin also for certain cases of eczema, disturbances of nutrition, and in rickets.

Myxœdema.—This term, as is well known, was introduced by Ord to indicate the condition since described as athyrea, in which pronounced morphological changes occur, more especially with respect to changes in the tegumentary system, skin, mucous membranes, and subcutaneous tissue, in the skeletal system and genital organs, in metabolism and mental activity. Pronounced cases of myxœdema are comparatively readily diagnosed, but there are various degrees

[1] Radcliffe Crocker, *Lancet*, 1903.

[2] *Die Krankh. der Schilddr.*, 1901, s. 223.

[3] *Wien. klin. Rundschau*, 1903, No. 48, s. 870.

of development in which only certain features of myxœdema are developed, or in which the symptoms are all present but in slight degree. To this last group of cases Reverdin applied the name of myxœdema "fruste." To those cases in which there are only a few features of myxœdema present, the term "incomplete" has been applied, and those in which one symptom alone predominates are spoken of as "partial" myxœdema.

Reference has already been made to the puzzling cases in which myxœdema appears to be combined with exophthalmic goitre (examples of dysthyroidism).

It is hardly necessary at the present day to bring forward evidence to prove that thyroid substance or derivatives have most salutary effects upon the various morphological changes met with in this disease; nor is it necessary to enter into the details of the development of treatment. Efforts were made to graft thyroids in man and animals in whom the thyroid had spontaneously disappeared, or had been removed by operation. The result of these efforts was disappointing, for almost invariably the grafts failed to establish themselves, and only succeeded in overcoming the symptoms so long as the active thyroid substance present in the grafts was not exhausted. The isolated successes are the case described by Macpherson,[1] who successfully grafted a patient suffering from myxœdema; symptoms of myxœdema had not returned four months after the operation. Bircher also reported a case of grafting in whom there was a return of symptoms three months after the first graft and nine months after the second. These reports show that this method need not be abandoned entirely. Reference has already been made to Cristiani's more recent experimental successes in this direction (p. 23). Murray's successful use of subcutaneous injection of a glycerine extract of the thyroid gland (now the liquor thyroidei of the British Pharmacopœia),[2] marked the

[1] *Edin. Med. Journ.*, 1892, ii., p. 1021.

[2] *B. M. J.*, 1891, Oct. 10, p. 796.

next advance. Gley had failed to secure results in June of the same year because treatment had to be stopped before they could be obtained.[1] Finally simple feeding with the actual glands was advocated by Howitz,[2] by Mackenzie independently a month later,[3] and also by Fox. By this last method the thyroid secretion was made once more to enter the system by a route long ago abandoned by Nature, viz. by the alimentary tract.

Then followed the efforts already described to obtain the active principle or principles from the thyroid gland by various physical and chemical means. This step was deemed necessary for various reasons, chief amongst them being the assumed need to prepare a sterile substance, and, secondly, because of the necessity to endeavour to standardise the drug so that the variability of effect of different thyroid glands might be overcome. Judging from the experience of a number of observers, the most active preparations are the fresh gland, then gland substance dried at 60° C., and, lastly, the various albuminous extracts (v. Eiselsberg), amongst which thyroiodin is the most efficacious (Magnus-Levy). The latter writer[4] says that, usually, cases of myxœdema respond in four to eight weeks, but the rule does not always hold, and it is necessary to give the tabloids (the best form of drug) for a considerable time. If there is much cardiac weakness, this must be overcome before organic treatment can be attempted. In all cases it is well to begin with small doses, gradually increasing these during four to six weeks to the maximum. As a rule it is sufficient to allow a cessation of the use of the drug for four or five weeks, two or three times a year.

[1] *Arch. de physiol.*, 1892, p. 747.

[2] "Compt. rend. du XIV. Congrès des naturalistes scandinaves," Copenhagen, 1892, p. 517.

[3] *B. M. J.*, 1892, ii., p. 941.

[4] "Therapie der Gegenwart," 1904, Feb. and March ; also *Zeitschr. f. klin. Med.*, 1904, lii., s. 201.

Murray [1] gives instruction for the treatment of cases of myxœdema according as the cases are advanced or early. Fortunately the former group of cases is much smaller than it used to be, and the latter group relatively much larger. In advanced cases cardiac weakness is a common characteristic and is revealed by attacks of syncope, dyspnœa, and feeble irregular pulse. Such cases should be put to bed, and the treatment begun with comparatively small doses. Murray, who prefers the liquor thyroidei, advocates small doses of 3–5 minims of this preparation each night. Should the cardiac weakness be excessive, it may be necessary at the same time to administer cardiac tonics. Daily doses of 10–15 minims of the liquor thyroidei, or 2–3 grains of the dry gland are sufficient in most cases to produce satisfactory results, and when the symptoms of myxœdema have been made to disappear, the effects may be maintained by daily doses of about 10 minims of the liquor or 2 grains of the dry gland. Warning is necessary, however, in the choice of dose, for it will be found that different individuals have different degrees of susceptibility, and, further, the preparations themselves are not of constant strength. The result is that each case should be carefully studied and the effects of small initial doses carefully watched. Further it is important to remember the various grades of myxœdema already referred to, and particularly those cases spoken of as examples of dysthyroidism. In these more anomalous cases special care is required in watching the effects of the drug, more particularly in the early stages. Cases are also reported which show a variable reaction at different periods to the same drug, at one time responding to comparatively small doses, and at others requiring much larger ones. The same preparation is occasionally quite without any effect in one individual, producing little or no disturbance, whereas in another the results are marked. Young children, and especially infants, appear to be particularly

[1] "Diseases of the Thyroid Gland," London, 1900, p. 75.

susceptible to the drug, and deaths from its use are reported by various writers.

Diuresis is a common result of the treatment by means of thyroid substance, and with this there may be an increase in the perspiration; thirst also may occur. The diuresis does not appear to be due to the direct effect upon the renal substance, but is explained by a dehydration of fats leading to an increase of water and salts in the blood.

Another phenomenon which is of great interest is that in certain cases undergoing thyroid treatment, glycosuria occurs, disappearing when the treatment has ceased. Ewald has, however, reported a case in which the glycosuria persisted and even suggested the establishment of diabetes mellitus. This glycosuria is somewhat allied to that met with in Graves' disease, and may in some cases, as in this disease, be rendered evident only by the administration of 100 to 200 grammes of glucose. It is this remarkable effect of excessive thyroid feeding and the occurrence of glycosuria in exophthalmic goitre which have led Lorand and others to conclude that the colloid matter of the thyroid gland in health is broken up and yields glucose to the blood, the excess being ultimately destroyed by the internal secretion of the pancreas. It is stated that in cases of myxœdema no glycosuria occurs unless indeed it is the result of treatment by means of thyroid preparations. Transient albuminuria has also been noticed as a result of thyroid feeding.

It has already been pointed out that in accordance with the views of Moussu the parathyroid has a function independent of the thyroid; the secretion of the parathyroid appears to neutralise the toxic materials produced when the thyroid secretion influences metabolic processes; the parathyroids have been administered to cases of myxœdema, but without effect.[1] These results, besides showing that myxœdema is not due to want of parathyroid action,

[1] Hutchison, *Journ. of Physiol.*, 1898, vol. xxiii., p. 188.

prove that the thyroid and parathyroid are not interchangeable in function, and give support to Moussu's view.

The pituitary body has been described as an aberrant thyroid, and reference has already been made to a possible association of function between the two glands : there is no record of pituitary substance being successfully used in the place of thyroid gland for the cure of myxœdema.

It is of importance to remember that in certain cases of myxœdema a period is eventually reached in which the thyroid treatment is no longer efficacious ; such cases are generally elderly subjects who have reached the fifth and sixth decade : despite changes in the forms of drug administered they progressively grow worse and, as is well known, develop insanity, which is frequently of a depressed type, although sometimes there is exaltation. Ord,[1] speaking of certain cases of failure to respond to thyroid treatment, points out that those with marked symptoms of mental disorder may only show an abatement of symptoms after prolonged treatment, and in some cases the symptoms appear to be even aggravated by the use of thyroid preparations. The first case described by Magnus-Levy,[2] *æt.* 54 years, failed to respond to thyroid treatment for some time, and then appeared to improve spontaneously for a time ; two years later, on a resumption of treatment, the response was prompt. In view of the fact that some surgeons advocate the removal of the thyroid gland in part or entirely in cases of anomalous myxœdema which do not respond to thyroid treatment, believing that after the operation organotherapy will be more successful, this possibility of failure to respond to treatment in people of advancing years is of considerable importance.

Those cases of myxœdema which after a course of treatment with gland preparations appear to be able to go on satisfactorily in the absence of further treatment (*see* Case 3 of Magnus-Levy's series of myxœdema) excite

[1] Allbutt's "System of Med.," vol. iv., p. 478.

[2] *Loc. cit.*

much interest. Various explanations have been given of this curious result. It is known that if the thyroid glands are removed from animals, such as the dog or rabbit, hypertrophy occurs in the hypophysis cerebri—a veritable pituitary goitre is in fact developed. It is therefore argued that when cases of myxœdema respond permanently to a limited course of thyroid treatment, sufficient time has been given for the hypertrophy of the pituitary body to take place.[1] The obvious objection to this view is that it would be expected that many more cases would be on record of absolute cure from an abbreviated course of thyroid treatment. It is further believed that functional changes may occur in the internal secretion of the thyroid of a qualitative and quantitative character, and that possibly the latter is responsible for attacks of what may be called athyreism, which are temporarily controlled by thyroid gland treatment. Inflammatory lesions in and near the thyroid have been known to produce such temporary athyreism, and this has completely disappeared on the healing of the original lesion. Another explanation, based upon well established facts, is that frequently aberrant masses of thyroid gland occurring in other parts of the body, submaxillary region, root of tongue, larynx, pharynx, and chest, are capable after a time of undergoing hypertrophy, and so doing the work of the thyroid gland.

Special reference must be made to the results of treatment in cases of myxœdema beginning after birth in young children. In them, as in cases of cretinism or congenital myxœdema, there is very frequently an improvement of the physical characters in advance of the psychical ones. It appears that in these cases, as in the case of young animals upon whom thyroidectomy has been performed, changes take place in the cells of the nervous system, even destruction, which no subsequent thyroid treatment could be expected to adjust.

In certain anomalous cases of defective development in

[1] *Loc. cit.*, p. 365.

children, presenting swelling of the subcutaneous tissues, anæmia, mental change, etc., it may be impossible to come to a definite diagnosis, and in the absence of any of the contraindications already mentioned (p. 46), it is quite justifiable to administer thyroid gland for a short time in order to discover what is the nature of some at least of the symptoms present.

In cases of cachexia strumipriva, *i.e.* operative myxœdema, despite the occurrence occasionally of cases of spontaneous myxœdema which are quite refractory, treatment by means of thyroid is usually quite adequate. Von Eiselsberg and most surgeons agree that it is advisable, however, to leave behind if possible a portion (a quarter to one-third of the total gland) of healthy thyroid tissue, when from any reason it is desirable to remove the greater part of the gland. Such cases are frequently found to require thyroid treatment only for a time, and it appears that the thyroid left has been able to hypertrophy, even reaching the functional equivalence of the original gland. This is more probable in young subjects; in elderly subjects the part left behind may degenerate.

It is important to remember that in the periodic intermissions which are recommended in the treatment of spontaneous and operative myxœdema, and even during treatment it is advisable not to allow too highly nitrogenous a dietary, for it is found that thyroidectomised dogs die more rapidly when fed on meat than on an exclusively milk diet. A milk dietary appears to be a more satisfactory accompaniment of thyroid treatment, possibly because the milk contains, to a certain extent, the thyroid secretion of the animal from which it was drawn; this may explain an observation made by Bourneville, Lancereaux, and Raymond that children afflicted with athyrea do not reveal their symptoms till they are weaned. Rare as it is for myxœdematous women to become pregnant, it is important to remember that the administration of thyroid to the mother may be shared by the suckling infant, even to

the extent of developing symptoms of thyroidism. Byrom Bramwell describes the occurrence of thyroidism in an infant at the breast, the mother receiving thyroid tabloids for exophthalmic goitre.[1] Bang has shown that in thyroid medication of women during lactation the active principle is largely excreted in the milk.

Combe[2] states that it is advisable during thyroid treatment for the patient to abstain from alcoholic beverages. Seymour Taylor also recommends light diet and abstention from alcohol, and Buschan[3] counsels a vegetarian dietary. In view of the changes liable to take place in the heart it is advisable that the patient should rest as much as possible.

In cases requiring operation on the thyroid gland, there is always a fear lest the operation should be followed by symptoms of acute suppression of thyroidal function. In some cases even in which simple removal of an adenoma is practised, these serious symptoms have supervened. Migliacci,[4] in a paper on the pathogeny and cure of simple goitre, quotes Rebuschini and Sacchi, who insist that in all cases of operation on the thyroid gland it is advisable, for some time previously, to administer thyroid preparations, the object being not the mere reduction in size of the gland, but to aid in the removal of toxic substances which may have been accumulating in the system.

Cretinism.—This is the term applied to that form of mal-development which occurs in individuals born with an insufficiency of thyroid gland. The condition is not usually noticed till after the child is weaned, when it is observed that its growth, bodily and mental, is impaired, and that the well-known features of dry, scanty hair, dry skin, coarse lips, open mouth, protuberant tongue, flat nose, prominent abdomen, enlarged head and redundant skin, and the characteristic broad, thick, short hands

[1] *Lancet*, 1899, i., pp. 762.
[2] *Revue méd. de la Suisse Rom.*, 1897, No. 6, p. 414.
[3] *Deutsche med. Woch.*, 1895, s. 736.
[4] *Gazz. degli Ospedali et del Clin.*, 1903, No. 116, p. 1219.

gradually become more pronounced; the thyroid gland, as a rule, cannot be defined.

It is a matter of considerable misfortune that it is not possible in most cases for a diagnosis to be made sufficiently early to prevent by treatment the development of the grave disturbances of the cell elements of the cortex—a common feature in cretins. The result is that though much can be done by treatment, by means of thyroid substance, in the direction of improving the defective growth of the body and limbs, etc., there is a decided limit in most cases to the degree of improvement or the mental side. It is of the greatest importance to diagnose the condition early, for success in improving the mental condition is directly measured by the earliness with which the treatment is commenced. In very young babies the earliest and only sign very often is the protuberant tongue. The most complete and modern accounts of the treatment of cretins by means of the thyroid gland and its derivatives are those published by Magnus-Levy,[1] Kassowitz,[2] Konrad-Alt,[3] and Bourneville and Lemaire.[4]

It is important to distinguish true cretinism from other forms of imbecility met with in infants. The two maladies with which cretinism is most readily confused are the so-called mongolism and achondroplasia or fœtal rickets.

In mongol or kalmuck children there is defective mental development; in addition there are, in common with cretinism, dry thin hair, open mouth, and protuberant tongue; other distinctive features are the narrow palpebral fissures inclined to slope downwards and inwards, marked epicanthus, nystagmus, and deformity of the ears and genitalia. The bodily development is not so backward as is generally the case with cretins, nor is the skin so harsh, the limbs are much more slender, and there may

[1] *Loc. cit.*

[2] *Wien. med. Presse*, 1902, s. 1929.

[3] *Münch. med. Woch.*, 1904, No. 28, s. 1238.

[4] *Le Progrès méd.*, 1904, ser. 3, t. xx., Nos. 24, 25, 26, 28, 38 and 39.

be a curious dwarfing and curving of the small finger towards the ring finger.

Achondroplasic dwarfs, *i.e.* cases of micromelia or fœtal rickets, are characterised by a facial aspect similar to that of the cretin, but the distinguishing feature is the shortness of the limbs; although there is the same redundant crumbled skin about the hands as in cretinism, yet, as Dr. Thompson[1] points out, there is often the characteristic separation between the ring and middle fingers (Marie).

Kassowitz, whose observations were made on 22 cases of myxœdema, 75 cases of mongolism, and seven of micromelia, points out that cases of cretinism, mongolism, and micromelia may also show, in common, narrowing of the palatal arch and delay in the closure of the fontanelles, though there is complete absence of the other changes characteristic of rickets; in addition, there is a tendency to the occurrence of hernia about the umbilicus or in other parts of the abdominal wall. Cretins and mongol children are specially liable to be very constipated, and marked peristalsis of the bowels may frequently be seen through the abdominal walls; the development of the teeth is delayed, whereas in micromelia there is nothing abnormal in the dentition; further, in micromelia the intelligence is normal. Kassowitz found striking results following the treatment of cretinism by means of thyroid gland or its derivatives, much less favourable results in mongols, and none at all in cases of micromelia. The improvement effected in mongol children, though not as marked as in the case of cretins, is still important; the constipation is cured, there is a decided improvement of the hernial conditions found in the abdominal walls, and there is an improvement in the early psychical torpidity shown by drowsiness and disinclination for food. Thyroid treatment has no influence on the later psychical disturbances, on the delayed dentition, or upon the closing of the fontanelles. Cretins, as a result of thyroid treatment,

[1] "Clinical Examination and Treatment of Sick Children," 1898.

may be made to be more cleanly and to look after themselves better. Konrad Alt reports on seven well-marked cretins and five less marked ones. After a time, treatment in one of the most marked cases had to be omitted because of intense bronchitis and cardiac weakness; in the rest, good results were obtained from the use of thyroid tabloids, about $1\frac{1}{2}$ grains being given every two days at first and then daily. Alt calls especial attention to the statement that cretins cannot be very much mentally improved, and that they can never be made to develop mentally beyond the standard of a three to five years old child. Some of his cases advanced much further than this, but in none was there complete restoration of mental capacity. Magnus-Levy reports on the results of treatment of nine cases of sporadic and 14 cases of endemic cretinism. One of the cases of sporadic cretinism after three months' treatment continued to improve without further medication, an experience also recorded by Combe.[1] The results of treatment of these 23 cases were most favourable. Attention has already been drawn to the preference expressed by Magnus-Levy for tabloid preparations of the gland. Though good results were obtained with thyroiodin, Fraenkel's thyroantitoxin, preparations of the pituitary body and potassium iodide were of no use. Bayon[2] also speaks strongly in favour of the use of fresh or dry thyroid substance in all cases of athyrea. Jauregg[3] treated 72 cases of cretinism with the usual improvement in the physical characters. He makes a special point of the marked improvement in the mental weakness of some of the cases—they were able to go to school, and, with the great reduction of the macroglossia, speech became much improved. The best results were obtained in quite young cretins, aged two and two and a half years, but good results may be expected in much

[1] *Revue méd. de la Suisse Rom.*, 1895, p. 250.

[2] "Beitr. zur Diagnose vom Cretinismus," 1903, s. 93.

[3] *Wien. klin. Woch*, 1904, s. 835.

older subjects. The dosage was ½–1–2 tabloids of five grains each of thyroid substance.

Magnus-Levy recalls Virchow's description of a special type of cretinism comparable to the *partial* forms of myxœdema, in which cases the affected children show no psychical defect whatever. All the signs exhibited are physical ones. Such cases react well to organotherapeutic measures.

As in the case of treatment of myxœdema, considerable care must be taken to gauge the dose and interval between the doses. It is advisable, as in the athyrea of adults, at the beginning of the treatment, to keep the patient in bed, as syncope is apt to supervene. Children, too, are especially liable to develop pains in the limbs, and owing to the rapid growth of the bones, getting about is liable to lead to deformities in the limbs from bending of the bones. Diarrhœa and rise of temperature may also occur.

Dr. G. R. Murray recommends that small cretins should be given a dose of one to two minims of the liquor each evening, gradually increasing the dose by one minim each week or fortnight, until a maximum is reached of five, seven, or ten minims. In the case of maturer cretins, the doses to begin with may be three to five minims of the extract.

Special educational methods should also be adopted to supplement the treatment by thyroid preparation, based on the methods instituted by Guggenbühl in 1840, at Abendberg, in the Canton of Berne. These methods are now carried out in various parts of the world at special institutions, and by their means cretins are capable of being raised to a high degree of mental and moral improvement. For further reports on the satisfactory results obtained in young cretins, as opposed to older subjects, reference may be made to the papers by Roos[1] and Quincke.[2]

The treatment of spontaneous and post-operative myxœdema and cretinism by means of thyroid preparations

[1] *Münch. med. Woch.*, 1902, s. 1607.

[2] *Deutsche med. Woch.*, 1900, Nos. 49 u. 50.

is based upon very thorough experimental and clinical investigations, which show that the defects produced by absence of the thyroid gland may be remedied by the use of these preparations.

Thyroid products have, however, been used extensively in other maladies. In most of them their use is entirely an empirical one, and in some others their use is justified by the existence of cases which, though not complete examples of athyrea, yet present appearances and symptoms that to some extent recall those of myxœdema. The results obtained in many of these indirect applications of thyroid substance are contradictory; especially is this the case in the use of these substances in the treatment of exophthalmic goitre. In other cases, the drug has been known to produce very harmful results, largely owing to the fact that it may be purchased by the public directly, and be used in excess. This is notoriously the case in obesity. In suitable cases there is no doubt that results of a most satisfactory character can be obtained, but all cases of obesity are not suitable for this treatment.

Obesity.—It is well recognised that obesity may be due to excesses at the table, combined with an inefficient amount of exercise. Such cases should be treated by other means than organotherapy, though, with care, thyroid treatment may be used to supplement the dietetic treatment. There are, however, other cases in which the development of fat is a constitutional anomaly, and may be extreme; such cases occur in several members of a family, especially in young children. So, too, women, about the time of the menopause, often develop an extreme form of obesity. Cases only too frequently occur in individuals who are innocent of all dietary excesses; indeed, they may be spare eaters and of a vigorous habit. In some of the cases of excessively fat young subjects, there is a great tendency to somnolence. Owing to the scarcity of observation on Dercum's disease, or adiposis dolorosa, it is

impossible at present to say what is the pathological basis of this malady. According to Dercum,[1] this disorder is characterised by the development of irregular fatty deposits in various parts of the body, attended with pain, occurring mostly in women in middle life or later. As a rule the face, hands, and feet are not involved, and there are no mental disturbances. The thyroid gland has been found to be indurated and calcareous, a fact which has aroused the suspicion that possibly adiposis dolorosa is merely a special form of *partial* myxœdema, a sub-variety of myxœdema to which reference has already been made.

When it is remembered that thyroid treatment is liable to cause cardiac failure, and that fatty degeneration of the heart is so common an accompaniment of obesity, it is obvious that the use of thyroid preparation may readily produce catastrophes, and it is probably largely due to our inability to distinguish the cases of obesity which may be benefited by thyroid treatment from those which are unsuitable for such treatment, that so much discredit has been thrown upon this form of treatment. The effects of thyroid treatment in obesity were first pointed out in this country by Yorke-Davies,[2] and abroad by Lanz and by Mendel.[3] Various observations have been recorded on the value of the thyroid products in obesity, but it is clear from these reports that some were cases of dietetic obesity. Magnus-Levy[4] and Ebstein[5] report on the use of thyroid in such cases. The loss of weight as a result of treatment is said to be over-stated and to be very variable in amount; the treatment is considered irrational because of the want of proper pathological support for the idea of the dependency of obesity on thyroidal insufficiency and because of the dangers following upon

[1] "Twentieth Century Practice of Medicine," vol. xi., p. 554.
[2] *B. M. J.*, 1894, ii., p. 42.
[3] *Deutsche med. Woch.*, 1893, s. 173.
[4] *Zeitschr. f. klin. Med.*, 1897, Bd. 33, Hft. 304, s. 44.
[5] *Deutsche med. Woch.*, 1899, s. 1.

the use of the drug, sudden death, etc. Ebstein concludes with the statement that thyroid preparations should not be used for obesity, and Yorke-Davies[1] confirms this view. Richter[2] points out that despite the possibility of distinguishing two forms of obesity clinically—one arising from over-feeding, the other from fatty diathesis—there is no pathological basis for such separation, nor do the results of treatment differ in the two cases or in normal subjects. The introduction of thyroid products in all cases leads not only to a destruction of fatty tissues, but also of nitrogenous ones, and proteid may be lost (Andersson).[3] It is inadvisable therefore to combine thyroid treatment with dietetic management in order to get quicker results. Further, protracted treatment of obesity with thyroid substance is not to be recommended.

It is maintained by others that the dangers of the use of thyroid substance are exaggerated, and that the dosage and supervision have been at fault; it is quite certain that favourable results can be obtained, especially in those cases of young children who are afflicted with excessive formation of fat in the body, and whose appearance suggests frequently the existence of atypical myxœdema; a beginning can be made with small doses, which may be increased when it is found that no untoward symptoms arise. The dyspnœa which so often occurs in obese women at the menopause is frequently relieved by the use of thyroid preparations. Other signs of improvement are also recorded, *e.g.* loss of irregularity of heart's action, although the body weight in some cases is not reduced.[4] For other reports on the favourable influence of thyroiodin in obesity reference may be made to Grawitz,[5] Weiss,[6] and Hirsh.[7]

[1] *B. M. J.*, 1903, ii., p. 119. [2] *Loc. cit.*, s. 13.

[3] *Skandinavisch. Archiv f. Physiol.*, 1903, vol. xiv., s. 224.

[4] Schwartzbarth, *Wien. med. Presse*, 1901, No. 28, and Roos, *Münch. med. Woch*, 1902., s. 1607.

[5] *Münch. med. Woch.*, 1896, No. 14, s. 312.

[6] *Wien. med. Woch.*, 1898, No. 41, s. 1949.

[7] *Med. News*, 1900, Feb., p. 294.

Sensational accounts are published of the enormous loss of weight which may occur as a result of thyroid treatment, taking place within quite a short period of time. Rendu reports the case of a girl of 15 years of age who weighed 100 kilogrammes, and after a course of two months' treatment with thyroid gland lost 32 kilogrammes in weight; as a rule the loss of weight is much slower, and it is to be recommended to secure such slow results, as thyroidism may develop in cases in which too active treatment is carried out. Chauffard records a sudden death occurring as a result of thyroid medication in a case of hereditary obesity; 11 kilogrammes weight was lost in the first eleven days of treatment.

As a result of the treatment there is increased diuresis, loss of fat, diminished assimilation of fat, an increased output of urea, of total nitrogen, of phosphates, urates and chlorides. According to Schöndorf,[1] the output of nitrogen in cases of obesity treated by means of thyroid preparations is not so much due to oxidation of proteids as to the liberation of urea and other bodies which so frequently provoke diuresis. After a time the output of nitrogen is no longer commensurate with the amount of thyroid gland absorbed. The wasting is probably largely at the expense of the fat of the body, but, as already pointed out, proteids also appear in the urine, though to a slight extent. Widal and Javal[2] have more recently advanced evidence in support of the view that the wasting produced by the use of thyroid substance takes place at the expense of the proteids and not at all of the fats.

Definite improvement has been observed in cases of Dercum's disease as a result of thyroid treatment.

Gabriel Gauthier,[3] in summing up the method of treatment of obesity by means of thyroid products, recommends that throughout the treatment the patient should be kept

[1] Pflüger's *Arch.*, 1897, Bd. 67, s. 406.
[2] *Soc. de biol.*, 1902, April 26, p. 495.
[3] *Loc cit.*, p. 208.

under close observation. Improvement should first be sought by means of dietetic control and by exercise. When the weight has been somewhat reduced by these means, then a course of thyroid treatment should be instituted, giving the drug for a week at a time and alternating it with the use for a week of Carlsbad salts. By this method of treatment with moderate doses and over a prolonged period the effects are satisfactory.

Simple Goitre.—Organotherapy has won a most signal triumph in cases of athyrea, a comparatively rare disease. Simple goitre is much more frequent, and here, too, thyroid treatment in certain cases is very successful. Considering the number and variety of the different forms of simple goitre, great difficulty is experienced in differentiating those forms of simple goitre which are suitable for treatment by means of thyroid substance. This difficulty, however, is largely resolved by the observations made by Virchow, that all forms of simple goitre begin by an excessive development of the thyroid parenchyma and end as the fibrous, vascular, cystic or calcified forms.

The arguments advanced to justify the use of this drug in such cases are based on two distinct theories. According to one, the fibrosis and other changes occurring in the gland, *e.g.* as a result of adenomata or malignant growths, are capable of so interfering with the proper function of the rest of the gland that symptoms of athyrea are produced of a complete or incomplete form. In such cases thyroid medication is justifiable on the ground that by this means a deficiency is made good. In the case of parenchymatous goitres, however, the reason for the use of thyroid preparation is that apparently the body requires an extra supply of thyroidal secretion, and, as a result, the thyroid gland hypertrophies; by the use of thyroidal secretion, introduced from without, the gland already hypertrophied becomes much smaller and the deformity in the neck is reduced. It is, however, also stated that though there is microscopic evidence of hypertrophy of the parenchyma,

in reality the thyroid function in cases of parenchymatous goitre is depressed, and Baumann was able to show that the iodine content of such glands is less than normal. An objection may be raised on experimental grounds to the use of thyroid preparations in cases of simple goitre, for Ballet and Enriquez have shown that experimental hyperthyroidisation in dogs produces an irritative hypertrophy, followed by atrophy of the thyroid gland. The medicinal doses given in disease are, however, not so large as to produce hyperthyrea.

Parenchymatous goitre is more common in the young, and slight degrees of enlargement of the thyroid are frequently met with during the years of growth from infancy to adult age: at puberty, especially, these slight enlargements are common, and similar changes are met with at the menstrual periods, in pregnancy, parturition, lactation, and at the menopause, occasions on which considerable metabolic disturbance takes place.

The advantages of the use of thyroid preparation are more obvious in those cases of young subjects recently affected with enlargement of the thyroid gland.

It may be reasonably asked whether there is any necessity in the case of a simple goitre to apply treatment except when there are signs of pressure on adjacent structures. Quite apart from any question of the need for the removal or cure of such a disfigurement as a goitrous swelling, there is reason to believe that cases of simple goitre may ultimately develop into cases of myxœdema; it is also well known that a goitre may be the first and only sign of the onset of Graves' disease.

The evidence in favour of the view that thyroid medication can produce improvement in simple goitre is derived from both experimental and clinical observations. For many years tradition has pointed to the use of iodides in cases of simple goitre, given internally and applied locally: when Baumann discovered the specific effects of thyroiodin, an explanation was found for the beneficial results obtained

by giving thyroid glands in cases of simple goitre, and Bouchereau was able, by a comparison of the results obtained by iodine as compared with those obtained by thyroid medication, to pronounce in favour of the latter, especially with regard to recent cases of thyroid hyperplasia. Numerous other observers, including Kocher, Bruns, Marie, Roos, and Gauthier, have published records of the benefit produced in simple goitre by the use of thyroid medication. Roos[1] reports on a series of cases of endemic goitre treated with thyroiodin. The usual dose was one gramme after breakfast, often two grammes, but seldom more; after giving six to eight grammes there was a pause of two to three days. In cases in which anæmia was a prominent symptom, then the use of thyroiodin and iron gave better results than when the iron was given alone. In cases of simple goitre, with the development of a substernal tumour producing dyspnœa, this last symptom was greatly relieved by the use of thyroiodin. Bruns made observations on the effects of thyroid treatment in 350 cases of simple goitre in men and dogs. A complete result was obtained in 8 per cent., a good result in 36 per cent., a moderate result in 30 per cent., and slight effects or none in 26 per cent. Henzel found reduction in the size of the thyroid in 220 cases of simple goitre treated in the same way.

It has already been mentioned that the cases most favourable for such treatment are those of recent origin occurring in young subjects, in whom the goitre is not too voluminous—in other words, the best effects are obtained in those cases in which there is parenchymatous hypertrophy—old fibrous or cystic goitres do not respond.

Abadie found, however, that good results were to be most expected when the enlargement of the thyroid was due to connective-tissue hypertrophy, which, by its overgrowth, leads to the disintegration of the true parenchyma.

The thyroid treatment of simple goitre does not

[1] *Münch. med. Woch.*, 1902, No. 39, s. 1607.

produce permanent results, for often the goitre returns on a cessation of the treatment. The same means may be adopted as in cases of myxœdema to prevent the onset of symptoms of thyroidism, and Mabille's use of preparations of arsenic may be recommended for this purpose. In view of the numerous observations of the spontaneous transition of simple goitre into exophthalmic goitre, it is almost impossible to say whether the accounts given of the conversion of cases of simple goitre into Graves' disease as a result of thyroid medication may be accepted. Should such appear to be taking place, it is stated that a discontinuance of the treatment is followed by an abatement of the symptoms.

In some cases of simple goitre, in which there is considerable difficulty in breathing, relief of this symptom has been found to follow the use of thyroid preparations. Petretto[1] treated a man aged 51 years who was suffering from a large parenchymatous goitre which obstructed breathing. During twenty days, twenty-four tabloids of thyroiodin were given, each corresponding to ·3 grammes of fresh gland substance. Despite the limited period during which the treatment was carried out, obvious relief of the dyspnœa took place; at the same time slight symptoms of thyroidism developed, *e.g.*, giddiness, headache, and irregular heart action. Petretto concludes that thyroiodin treatment is suitable for cases of parenchymatous goitre, or at any rate it relieves the symptoms.

[1] *Wien. klin. Rundschau*, 1903, s. 870.

CHAPTER VI.

EXOPHTHALMIC GOITRE.

DESPITE the brilliant successes of the treatment of various forms of athyrea by substitution products derived from the thyroid glands of animals, practically no important advance has been made in the treatment of Graves' disease —a malady which, by reason of several of its more alarming symptoms and signs, many of them strikingly obvious to an observer, has become one of extreme importance, not only to the sufferers, but to the physician whose duty it is to secure relief.

Several modes of treatment have been introduced based upon various physiological and pathological considerations.

1. *Treatment based on the nervous theory of the causation of Graves' disease.*—Those who consider with Trousseau that Graves' disease is due to a primary disturbance of the nervous system (Munk, Jaboulay, and Abadie) seek to discover disorders especially in the sympathetic nerves, and some have advocated the destruction of various parts of this structure as a means of securing relief.

2. *Treatment based on the theory that exophthalmic goitre is due to excessive or faulty thyroid function—hyperthyrea, dysthyrea.*—Another group of observers consider, with Gabriel Gauthier and Mœbius, that Graves' disease is really due to hyperthyrea or to dysthyrea, meaning by the latter term that the thyroid secretion is qualitatively altered. Much support is given to the view of excessive formation of thyroid substance by the antithetical characters of the two diseases, chronic myxœdema and chronic Graves' disease, by the fact that suppression of part of the thyroid gland in cases of exophthalmic goitre causes a

great improvement in symptoms and signs, and, furthermore, by the fact that after flooding the system with thyroidal secretion for a considerable time, symptoms develop which are very suggestive of exophthalmic goitre. Besides tremor, nervous excitability, and tachycardia, there is a great increase of metabolic change, as shown by an increase of nitrogenous excretion and of oxidation generally, features which are especially familiar in acute forms of exophthalmic goitre. The cure of myxœdema, and the ultimate development of symptoms of exophthalmic goitre in the same patient under a course of thyroid treatment, have been described by Béclère.[1] For the same reasons that it is thought justifiable on clinical evidence to give thyroid derivatives in cases of simple goitre, it is recommended by some to give the same drug in exophthalmic goitre — either the gland is thus relieved of the necessity for extra function, and as a result involutes, or, in accordance with the experiments of Ballet and Enriquez, thyroid treatment actually causes, after an initial stimulation of the thyroid parenchyma, a retrogression and atrophy of the same.

3. *Treatment based on the theory that exophthalmic goitre is due to defective action of the parathyroidal tissue—hypoparathyrea.*—Tetany and other nervous phenomena have been observed when the parathyroids have been destroyed, and as similar phenomena are found in cases of exophthalmic goitre it has been thought that Graves' disease itself is due to insufficiency of the parathyroidal tissue (Moussu). Gley attributes exophthalmic goitre in part to functional disturbance of the parathyroid, and Jeandelize agrees that tetany, which frequently occurs in exophthalmic goitre, is due to parathyroidal insufficiency alone.

Both thyroidal and parathyroidal tissues combined, and parathyroidal substance alone, have been used for the treatment of Graves' disease, thus constituting an attempt at the direct organotherapy of this malady. The results,

[1] *Soc. méd. des hôp.*, 1894, Oct. 12, p. 631.

unfortunately, have not been satisfactory, and attention has more recently been drawn to two other modes of treatment, based on the more recently enunciated principles of immunity and cytolysis.

4. *Treatment by means of hypothyreic serum derived from thyroidectomised animals.*—It is possible that Graves' disease is due to an excessive amount of the secretion of the thyroid gland circulating in the system; this substance being in excess produces an excess of metabolites, which fail to be neutralised by parathyroidal activity, and produce poisonous effects. It is conceivable that an animal which has been deprived of its thyroidal tissue will, during its existence, as an example of operative myxœdema, accumulate in its body (also in the serum and milk) a certain excessive amount of parathyroidal products uncombined with metabolic products, as the latter, in the absence of thyroid secretion, are no longer being formed. The blood or serum or milk of such a thyroidectomised animal has been administered to cases of exophthalmic goitre with the hope that the excess of thyroid secretion may in these subjects be neutralised.

5. *Treatment by means of hyperthyreic serum.*—Still other methods have been devised based on the idea that in exophthalmic goitre the individual fails to supply substances which are capable of neutralising the effect of the excessive internal secretion of the thyroid gland. The serum of animals which have been excited to develop anti-bodies by the injection of thyroid extracts into their system, comparable to the production of diphtheria antitoxins in horses, is injected into patients suffering from exophthalmic goitre. By this means it was hoped that the patient would be enabled to neutralise the toxic agents already dominating the situation.

6. *Treatment by means of thyrolytic serum.*—If, as appears to be possible, symptoms of thyroid intoxication can be avoided in the operation of thyroidectomy, this operation produces much improvement in cases of exoph-

thalmic goitre. Much attention has, therefore, been given to the question whether a serum might be prepared which should exert a solvent action on the secreting cells of the thyroid gland, and so lead to their gradual and controllable solution and destruction, without recourse to operative treatment. Such efforts are at present in their infancy; results are discordant, and Ghedini and Cafiero's observations point to the view that cytolytic sera produced by the introduction into animals of emulsions of organs of other animals are cytolytic against the species of animals from which the organs were removed, but not in a specific sense, for not only is the homologous organ attacked, but others as well, and in the case of some cytolytic sera the action does not show itself at all on the homologous organs.

Treatment of Exophthalmic Goitre by means of Thyroparathyroid Preparations.—In discussing the treatment of athyrea by means of thyroid tabloids and other direct preparations of the whole gland removed from sheep (the animal most used), reference was made to the fact that such preparations were not purely thyroid, but thyro-parathyroid in nature. It appears, however, that the parathyroid substance does not exert any noticeable or precise influence upon cases of myxœdema. In the use of such products as thyroiodin it is probable that the more purely thyroidal secretion is being made use of. Judging from the negative observations on the effect of parathyroidal tissue as a remedial agent,[1] it may be felt that thyro-parathyroidal preparations are operative as pure thyroidal tissue.

There would appear to be very little experimental support for the use of thyroidal treatment in Graves' disease. The observations made by Ballet and Enriquez, that as a result of the use of large doses of preparations of thyroidal tissue atrophy can be induced in the parenchyma of the thyroid, alone supports such treatment; the value of

[1] Easterbrook, *Lancet*, 1898, vol. i., p. 549, and *Scot. Med. and Sur. Journ.*, 1900, pp. 297 and 495.

those observations for practical purposes is greatly discounted by the knowledge that before such a change could be effected the individual under treatment must run the risk of developing thyroidism.

Turning to the clinical observation of the success of the treatment, it is impossible to ignore the fact that many of the accounts are meagre in the extreme, that though improvements have been observed it is impossible to say that they occurred *propter hoc* rather than *post hoc*, and that many of the cases were of the more benign types which so frequently improve of themselves or as a result of the rest in bed, electrical and other treatment, which in several reports of cases are noticed to be combined with the thyroidal treatment. Gabriel Gauthier, who is an ardent supporter of the thyroidal treatment of this disease on the ground that it is due to qualitative disturbances of the internal secretion of the thyroid gland, admits that in what is considered the true form of Graves' disease by certain authors, the so-called neuroarthritic form of the French, with sudden onset, such treatment is contra-indicated. The best results are to be obtained (1) in mixed cases of exophthalmic goitre and myxœdema; (2) in cases in which a simple goitre has existed for a long time and in which some symptoms of Graves' disease can be detected; and (3) in cases of Graves' disease following infectious diseases. The improvement observed in groups (1) and (2) can hardly be advanced as an argument in favour of treating true exophthalmic goitre by means of thyroid preparations.

At the 14th Medical Congress, held at Wiesbaden in 1896, Ewald described three cases with improvement, and Schuster one case of cure. Von Noorden had found unsatisfactory results of a temporary nature followed by distinct improvement. Hoch described before the Royal Medical Society in Vienna, in 1895, a case of complete cure, and other successes are recorded, some more recently by Variot and Rendu. A long list of authors who have

reported favourable results is given by Gauthier, and he also adds an account of five cases in which he alleges that the improvement was due to various preparations of the thyroid gland. This same writer thinks the fears of inducing thyroidism are exaggerated; such symptoms appear more readily in cases of Graves' disease than in any other disease under the treatment, but they may be obviated by commencing with small doses progressively increased, the drug being omitted when any symptoms appear, to be again used at a later date. Possibly the symptoms of thyroidism may be due to impurity or decomposition of the preparations made from the thyroid gland. To obviate this, fresh glands or thyroiodin may be used. Mabille's method of combining arsenic with the thyroid treatment may also be tried.

Ehrhardt, writing on the subject of Graves' disease in v. Eiselsberg's monograph on diseases of the thyroid gland, v. Korzynski,[1] and Richter,[2] are much less convinced that any benefit follows the treatment of exophthalmic goitre by means of the thyroid gland, and Richter even sums up the whole of the results as a mere fiasco. Murray[3] also agrees that thyroid extract should not be given in Graves' disease, for he finds that it is harmful, and frequently exaggerates the symptoms.

Treatment of Exophthalmic Goitre by means of Parathyroidal Preparations.—The reports on the effects of parathyroid preparations in cases of exophthalmic goitre are extremely limited. Moussu administered eight glands for two months to a patient suffering from this malady and from tuberculosis of the lungs, pauses of two days being made every ten days; there was improvement of the palpitation, tachycardia, exophthalmia, nervous excitability, and tremors. The administration was interrupted for a

[1] "Errungenschaften und gegenwärtig Stand der Organotherapie," *Wiener Klinik*, 1902, s. 41.

[2] "Die Organotherapie," *Berlin. Klinik*, 1900, Hft. 139.

[3] *Trans. Roy. Med. and Chir. Soc.*, 1903, vol. lxxxvi., p. 159.

month, and the symptoms reappeared, but again diminished after a further period of fifteen days' administration. Moussu was disposed to attribute the good results to the parathyroid medication.[1] MacCallum[2] gave a woman suffering from exophthalmic goitre twelve parathyroids daily, taken from cows. At the time of publication he had found no improvement. The writer did not expect to get any improvement, for he had been able to demonstrate parathyroidal tissue in the fragments of thyroid tissue removed by operation from four cases of exophthalmic goitre. Gley[3] ridicules Moussu's view of parathyroidal insufficiency as being the cause of exophthalmic goitre, but considers, on the basis of Oswald's observations on the reduction of colloid and iodoproteid in exophthalmic goitre,[4] that both parathyroid and thyroid are *functionally* disturbed in exophthalmic goitre. Gley does not think that Moussu's reported cure was due to the use of parathyroidal substance.

Besides the positive results obtained by Moussu, some favourable ones are reported by Lusena[5] (quoted by Gauthier, p. 118).

Treatment of Exophthalmic Goitre by means of substances derived from Thyroidectomised Animals.— It has already been pointed out that animals injected with preparations derived from the thyroid gland develop symptoms of thyroidism which are very suggestive of exophthalmic goitre. Ballet and Enriquez,[6] acting on these experimental observations, and believing that in exophthalmic goitre an excessive amount of thyroidal secretion is being poured into the system, conceived the idea of removing the thyroid gland from animals and, when

[1] *Soc. de biol.*, 1899, p. 242.

[2] *Med. News*, 1903, p. 820.

[3] *B. M. J.*, 1901, ii., p. 771.

[4] Pflüger's *Arch.*, 1901, s. 109.

[5] *Riforma medic.*, Nov. 12, 1898, and Ferrari, "Thèse de Gèneve," 1898.

[6] *La Semaine méd.*, 1894, p. 536, and *Soc. méd. des hôp.*, 1894, t. ii., pp. 805, 941.

symptoms of tetany developed, bleeding the animal and using the blood or serum for remedial purposes in man. It was argued that this serum contained an excess of substances unneutralised by thyroid secretion, and that on injection into patients suffering from exophthalmic goitre it would serve to counteract the poisonous effects of the hypertrophied thyroid. The experimental observations required to justify this belief are unsatisfactory. It is true that although the accounts given of the hypertoxicity of the urine in thyro-parathyroidectomised animals described by Laulanie,[1] Gley,[2] and Masoin[3] are not in agreement with the observations of Verstraeten and Vanderlinden[4] and others, there is some reason to believe that the blood of thyroparathyroidecto-mised animals is toxic, because the symptoms following the removal of the thyroid and parathyroid glands can be lessened by transfusion with the blood of normal animals, or by bleeding followed by infusion of normal saline.[5] That the hypertoxicity of the urine and of the serum in these animals is due to the disturbance of the thyroid gland is shown by an observation made by Charrin that thyroid extract is capable of diminishing the toxicity of urine. Further, more direct proof of the toxicity of the serum of thyroidectomised animals is given by Gley,[6] who found various symptoms recalling those of extirpation of the gland, when the serum of a thyroidectomised animal was injected into normal animals. Sgobbo and Lamari, and Vassale and Rossi, injecting the juice-muscles of thyroi-dectomised animals, have produced fibrillary twitching and tremors in normal animals, and it will be remembered that Notkin had shown the existence in thyrocolloid of a toxic substance which he called thyroproteid. Boinet and Silbert[7]

[1] *Soc. de biol.*, 1891, p. 337, and 1894, p. 187.
[2] *Ibid.*, 1891, p. 366.
[3] *Arch. de physiol.*, 1894, p. 283, and 1895, p. 368.
[4] *Mem. de l'acad. de méd. de Belgique*, 1894, t. xiii., fasc. 7.
[5] Colzi, *Lo Sperimentale*, 1884, p. 36.
[6] *Arch. de physiol.*, 1892, p. 311, and 1895, p. 771.
[7] *Rev. de méd.*, 1892, p. 33.

demonstrated in the blood of patients suffering from Graves' disease the existence of several bodies capable of producing alterations in the action of the heart and other muscles.

It must be admitted that the experimental proof of the existence of a substance in the serum and tissues of thyroidectomised animals, capable of being neutralised by the serum of animals whose systems have been surcharged with the active principle of the thyroid gland, with the result that the symptoms of hyperthyroidisation can be inhibited, is not complete. All that can be said is that there is some evidence that there are toxic substances in the blood of cases both of athyrea and hyperthyrea, but the relationship of these toxic substances to one another is far from being clearly defined; their existence, too, is based merely on biological evidence, and not on evidence of a chemical or physical nature.

It is not a matter of great astonishment, therefore, to find that the serum treatment initiated by Ballet and Enriquez has given results as equivocal as those of other special methods applied in this disease. These two observers in 1895 published the results of treatment by means of the serum of thyroidectomised and tetanised dogs.[1] Nine cases were so treated, and these observers noticed an amelioration of the general condition in all the cases, disappearance of the tremors in almost all cases, diminution of the exophthalmos in five cases, and even reduction in the size of the thyroid gland in seven cases, a rapid reduction in the girth of the neck of 6 cm. being observed in one case. Two of the cases whilst under treatment developed tetany, and severe vomiting. Further, the dogs experimented on soon succumbed, so that it was difficult to reach the stage of tetany, at which time the serum has the most effect; by special methods of feeding, however, it was found possible to keep them alive sufficiently long for the purpose. Christensen used the milk of thyroidectomised goats in two cases of exophthalmic goitre; in one the

[1] *La Semaine méd.*, 1895, p. 329.

pulse alone improved, but in the other better results were obtained.

Lanz[1] gives an account of his own investigations in this direction, but describes the use of milk obtained from thyroidectomised goats, which apparently stand the operation well. This milk may be given fresh or preserved as a powder. Lanz gives a record of six cases treated in this way; favourable results were observed, but Lanz rightly warns against pronouncing in favour of the cure until more observations have been made. It is a strong objection against the use of such milk that the animals from which it was obtained, though thyroidectomised, were quite well and free from myxœdema. Lanz asserts that the third of his cases was one of such marked severity that, judging from his former experience of Graves' disease, he thought there could be but one issue—a fatal one; with the milk treatment this patient recovered. The treatment was carried out for periods varying from several weeks to six months, a quarter to half a litre being given daily. In one case the milk treatment produced an intensification of symptoms.

Lanz also tried the effect of administering the powdered gland of a cretin.

Burghart and Blumenthal,[2] at a later date, also developed a serum treatment of exophthalmic goitre. They report six cases treated with goat's serum and ten with *rodagen*, or milk in powder form obtained from thyroidectomised goats, and observed a reduction of sleeplessness, tremors and sweating, and a gain in body weight. To obviate any possibility of suggestion, ordinary milk powder was, unknown to one patient, substituted for rodagen. The patient had previously gained as much as 1½ lbs. a week, but now lost 7 lbs. in sixteen days, and the symptoms returned. Rodagen was again used, and in the next three

[1] *Correspondenzbl. f. Schweitz. Aerzt.*, 1899, s. 715, and *Münch. med. Woch.*, 1903, s. 146.

[2] *Deutsche med. Woch.*, 1899, s. 610 and 627; v. Leyden's *Festschr.*, 1902, Bd. ii., s. 251, and *Therap. der Gegenwart*, August, 1903.

weeks there was a gain of 4 lbs. and the symptoms once more abated. As a rule, they noticed that the exophthalmos, tachycardia, and goitre were less influenced than were other features. The writers insist that it is impossible to secure any improvement by this means of any symptoms, etc., dependent on organic changes in the heart, kidneys, etc. If there is cardiac weakness, great care is required to observe the effects of small initial doses. Some cases of Graves' disease can tolerate as much as 50 grammes of the milk daily; others improve satisfactorily with 5-30 grammes. In cases in which rapid improvement is sought, it is recommended not to use the rodagen, but to inject subcutaneously the serum of thyroidectomised animals. In ordinary cases as good results are got with milk as with serum. Burghart also tried the use of the serum of a patient suffering from myxœdema, but the results were inconclusive.

Mœbius [1] has carried out enquiries on the value of the serum of thyroidectomised sheep (*antithyroidin*) prepared by Merck. Mœbius had previously found some benefit from the use of the powdered gland of a cretin supplied by Lanz. In one case of exophthalmic goitre treated by means of antithyroidin the gland became smaller and softer. Mœbius originally intended the serum to be given by hypodermic medication, but later advocated introduction by the mouth. The serum is withdrawn from the animal's veins six weeks after thyroidectomy, is preserved by the addition of ·5 per cent. carbolic acid, and is then sealed up in 10 c.c. bottles. Five grammes (85 minims) of the serum given every second day in a dessertspoonful of wine (to hide the taste of the carbolic acid) produced reduction of swelling of the thyroid and reduction in the tachycardia and tremors; no ill effects were observed. It was thought that the flesh of sheep which had been previously thyroidectomised could be used for these patients instead of ordinary mutton. This, however, was not confirmed, nor were portions of the raw muscles found to be of any service; death occurred suddenly

[1] *Neurologisch. Centralbl.*, 1901, s. 1064.

once after the use of muscle. Mœbius prefers serum to the milk, because the latter readily becomes cheesy in taste. The high price of the serum is, however, almost prohibitive.

Schultes[1] has described the favourable results of treatment of a case by means of the antithyroid serum of Mœbius. The special feature was that the symptoms of severe exophthalmic goitre in a woman, aged 49 years, were accompanied by those of hallucinatory insanity; the patient was, during the treatment, quite unconscious of its purpose, so that the influence of suggestion could be excluded. At the end of seven weeks the psychical symptoms, and all those of exophthalmic goitre, except the proptosis, had cleared up. The dosage to begin with was ·5 grammes (8 minims) three times a day, and this was increased by 8 minims daily, until the dose reached 4·5 grammes. Goebel[2] claims to have introduced the milk treatment of exophthalmic goitre quite independently of Lanz and on an entirely different principle. Goebel considers the thyroid gland to be specially set aside for the purpose of combining iodine with organic materials, so that when an individual is fed on the milk of animals deprived of their thyroids, no iodine is ingested; that the milk of these animals was absolutely free from iodine was shown by Treue, who also was able to detect a small trace of iodine in the milk of normal animals. It is unfortunate that Goebel combined the milk treatment of his cases with the use of arsenic, galvanism of the sympathetic nerve and massage of the thyroid gland, for it is impossible to say that the good effects produced were due to the milk treatment. During the years 1903 and 1904 several reports were made on the use of antithyroid serum and milk. Rosenfeld gave antithyroidin and found improvement of nearly all the symptoms. Adam,[3] using the same preparation, reports the case of a youth aged 17 years, who had suffered for

[1] *Münch. med. Woch.*, 1902, s. 834.
[2] *Ibid.*, s. 835.
[3] *Ibid.*, 1903, s. 392.

three years with exophthalmos and goitre, which pulsated and produced narrowing of the trachea and stridor. In addition, there were von Graefe's sign, wasting, mental depression, headache, sleeplessness, but no tachycardia or palpitation, and only slight transitory tremor in the right hand. Arsenic and potassium iodide were useless, and operation was refused. On the ninth day from beginning the use of antithyroidin the thyroid gland was observed to be softer. The stock of antithyroidin was exhausted on the twenty-first day. Six days later the gland had again begun to swell; after a resumption of the treatment the symptoms had again abated, and the youth had been at work for six months when the report was made. Whether this is considered a case of Graves' disease or not, it shows the marked influence exerted on the thyroid gland. Kirnberger reports on the combined use of the sodium salt of sulphanilic acid, 10 grammes daily, with rodagen, 5-10 grammes daily; the salt is said to have a favourable influence upon the disease, increasing the appetite and weight and causing a slowing of the pulse. The results were more favourable if rodagen was also used. Rydel[1] gives a *résumé* of the cases already published, and reports the results of treatment of three other cases by means of milk. The first case showed doubtful results, the second, after eight months' treatment, showed no results whatever, and no effects had been produced in a third after three weeks' treatment.

Hallion and Carrion described at the Medical Congress at Brussels in August, 1903, a new preparation. This was made up of equal parts of glycerine and of the blood of sheep previously thyroidectomised: the mixture was allowed to stand several days, and was then filtered; to the filtrate was given the name *myhème* or *myxhème*. Hallion was able to report favourable results after the administration of this preparation.[2] Pisanté[3] describes the treatment

[1] *Charité Annalen*, 1903, s. 601. [2] *La Presse méd.*, 1903, p. 619.
[3] "Thèse de Paris," 1904, No. 52.

of eight cases with Hallion and Carrion's myxhème. Pisanté gave drachm doses three to four times a day during three or four months, allowing occasionally a week's rest. No unpleasant symptoms were recorded in any case. In early cases cure may be complete; less fortunate results will be obtained in advanced cases. Pisanté concludes by recommending that other methods of treatment should be carried out at the same time —rest, etc. (!). Lépine also tried this form of treatment, and obtained favourable results in three of his cases. Sainton and Pisanté also describe the results of treatment of three cases of Graves' disease treated with the blood and serum of thyroidectomised sheep.[1] Previous treatment had been quite useless; 6–25 drops daily of the serum was found to be more efficacious than the blood preparation in teaspoonful doses. The first case, a young subject, was cured; the second case, a man aged thirty-one years, improved as long as the serum was given; the third case was a severe one occurring in a woman *æt.* fifty-one years, but in this case, too, improvement was observed. Tachycardia and nervous disturbances were the first symptoms to be improved.

Kuhnemann[2] reports the case of a young woman nineteen years old, suffering from exophthalmic goitre; all other methods had failed until treatment by means of the milk of thyroidectomised goats was instituted, two grammes being given three times daily. Almost at once there was an increase of body weight, lowering of the pulse frequency, and reduction in the girth of the neck. The treatment was continued for five or six weeks and was then omitted for a few weeks; as a result the pulse frequency again rose and the body weight fell off, but improvement began with a resumption of the treatment. Fai also reported favourable results, but it is doubtful whether the good results were due to the antithyroidin, or to climatic influences.

[1] *Rev. neurol.*, 1904, xii., p. 1109.

[2] *Münch. med. Woch.*, 1904, No. 10, s. 438.

Josionek used antithyroidin in two cases: the first case, a man aged fifty-four years, had been ill for several months; 1–2 grammes were given daily. After 20 grammes had been administered the goitre was found to be softer; after 30 grammes the neck was found to be 6 cm. less in circumference, and the patient was able to resume work. The second patient, aged fifty-one years, had been ill longer. After the use of 50 grammes the girth of the neck was reduced 2 cm. and the general condition was much improved.

Sigel[1] reports on the effects of the use of rodagen in three patients; 10 grammes were given daily. The first patient, aged thirty-nine years, who had already been treated for three months with thyroiodin, and had lost weight and become much worse, was found not to be relieved in the least degree even when she had taken 250 grammes of the milk. The remaining two cases, belonging to Ewald's private clinic, showed no improvement whatever under the treatment.

It is impossible at the present moment to form any opinion upon the usefulness of such remedies. The absence of any harmful manifestations as a result of the treatment encourages the extension of the treatment to a larger series of cases. The doubtful character, however, of the observations on the toxicity of the serum of cases of myxœdema and exophthalmic goitre, and the discordant results already described, justify the efforts being made in quite another direction to obtain a curative serum for cases of exophthalmic goitre.

Use of Serum of Animals immunised against Thyroid Gland.—Lépine[2] attempted to immunise a goat by feeding with gradually increasing doses of the thyroid gland removed from a sheep or goat; four lobes were given by the mouth every two or three days, gradually the animal was enabled to tolerate 20–25 lobes without

[1] *Berlin. klin. Woch.*, 1904, s. 16.

[2] *Lyon Méd.*, 1903, p. 809.

suffering from any symptoms; 10-20 c.cm. of the serum of this animal injected into a dog caused loss of weight; 40 c.cm. produced somnolence and slowing of the heart. Lépine reports no cases of application of this remedy in man. Murray[1] used the serum of rabbits which had been fed on thyroid extracts. He was unable to report definite results of this treatment in human beings; probably the amounts of rabbit serum used were too small.

Use of Thyrolytic Serum. — The more modern researches carried out on the influence of sera removed from animals previously injected with extracts of cells obtained from the organs of a different species of animal have encouraged the hope that it might be possible to produce a serum in one of the lower animals which would be capable of exerting a solvent effect upon the cells of the thyroid body (thyrolytic serum).

Experimental investigations carried out with this purpose in view have revealed the fact that though such cytolysis may occur, it is not specifically thyrolytic. Ghedini[2] has reviewed the observations on specific cytolytic sera and contributed further personal observations. Ghedini made use of extracts of organs from one species of animal, injecting them into members of other species. Cafiero[3] used extracts of organs of one species and injected them into similar animals. Extracts were used of the pancreas, ovary, testicle, suprarenal body, thyroid, thymus, and of nervous tissue. The results obtained were the following: Definite changes were found in the liver and kidneys, more especially affecting the parenchyma, which showed fatty degeneration and vacuolation. Hyperplastic reaction was noticed in the spleen, and the thyroid gland showed signs of hypertrophy and also of degeneration in some cells; no changes were observed in the pancreas, ovary, or testicle.

[1] *Lancet*, 1904, ii., p. 583.

[2] *Centralbl. f. Bakt., etc.*, 1904, Original, Bd. xxxvi., No. 1, s. 33; No. 2, s. 224.

[3] *Rif. med.*, 1903.

The positive findings were in no way specific, and Ghedini concludes that the cytolytic effects observed were due to the influence of nucleoproteids derived from various organs. Similar effects can be obtained by the use of extracts of the bodies of bacilli; in no sense could it be argued that the effects were due to the development of specific cytolysins. This generalisation made by Ghedini will serve to explain the discordant results obtained by various authors in their efforts to produce a thyrolytic serum.

Mankowski [1] injected preparations of the thyroid gland of the dog into cats. The serum of the latter animals when injected into fresh dogs caused symptoms allied to those found in thyroidectomised animals. Mankowski further reports that the cells of the thyroid gland were altered. The serum retained its effects even when previously mixed with thyroid gland substance, or when injected into the veins or peritoneal cavities of the animals, the difference in effect being merely quantitative.

Gontscharukov [2] injected preparations of dog's thyroid into a sheep during a period of four weeks. The sheep died, and cytolytic changes were found in the parenchymatous cells of the thyroid similar to those described by Ballet and Enriquez under similar circumstances. Further, the serum of the sheep when injected into a dog produced symptoms of tetany just as if the dog had been thyroidectomised. The parenchymatous changes found in the thyroid of the dog so treated were such as to lead Gontscharukov to conclude that the sheep's serum was thyrolytic for the dog.

Portis [3] prepared extracts of the thyroid gland of the dog and injected them into the peritoneal cavities of goats. To exclude any hæmolytic effects, the thyroid glands were

[1] *Rousski Wratsch*, 1902, p. 215, reviewed in the *Journ. de physiol. et de pathol. générale*, 1902, p. 592.

[2] *Centralbl. f. allg. Pathol.*, 1902, Bd. 13, s. 121.

[3] *Journ. of Infectious Diseases*, Chicago, Vol. I., No. 1, 1904, p. 127.

previously washed with normal saline solution; in some cases, in order still further to exclude hæmolytic effects, the animals were injected with thyrocolloid, prepared according to the methods of Dr. Robert Hutchison. The goat's serum, when injected into fresh dogs, produced convulsions, vomiting, rapid breathing, loss of weight and even death, but Portis does not claim that the exact picture of the symptoms of thyroidectomised animals was produced. Microscopically there were seen a reduction of the amount of colloid in the acini, desquamation and disintegration of the thyroid epithelium, and in some places there was apparent restitutional change with papillary proliferation into the acini. The parathyroids and pituitary bodies were not affected. Ghedini and Cafiero's observations on the changes found under such circumstances in the liver, spleen, and kidneys were confirmed — degeneration was very marked. Portis, implying that the wasting of the thyroid glands was not complete, suggests another explanation of the changes met with in the latter organs, viz. that they were of a hæmolytic nature; when Hutchison's thyrocolloid had been used, however, instead of the gland extract, similar effects were produced. Portis found that *in vitro* the thyrolytic serum was more destructive of the thyroid cells than the serum of normal animals.

Yates[1] and MacCallum[2] endeavoured to obtain a thyrolytic and parathyrolytic serum from geese—an animal more resistant to infection than most laboratory animals, by injecting into the peritoneal cavity preparations of dog's thyroids and parathyroids. The serum obtained was found by MacCallum to have no effect upon the thyroid or parathyroid of fresh dogs. Yates quotes the observations made by Bigart and Bernard,[3] who found positive results in the development of adrenal cytolysins, and those of Abbott,[4]

[1] *University of Pennsyl. Med. Bull.*, 1903, 16, p. 195.
[2] *Med. News*, 1903, p. 820.
[3] *Soc. de biol.*, 1903, p. 161.
[4] *Journ. of Med. Research*, 1903, p. 330.

who, though unable to confirm these results, was able to find an agglutinating effect *in vitro* upon adrenal cells and a hæmolytic effect on erythrocytes. Yates proceeded to immunise geese against the suprarenal, thyroid and parathyroid glands of dogs. The thyroid serum so obtained produced enterocolitis in the fresh animal, but no macroscopic or microscopic changes were found in the thyroid, parathyroid or adrenal glands. Negative results were also obtained with the antiparathyroid serum. Yates found, however, as MacCallum had done, that *in vitro* it could be shown that these sera obtained from geese possessed agglutinative characters.

It will thus be seen that the effects reported by Mankowski and Gontscharukov were considered to be specific, owing to incomplete examination of *all* the organs of the animals experimented on, and that experimental efforts to prove the possibility of developing a thyrolytic serum for therapeutic purposes have failed.

CHAPTER VII.

OTHER APPLICATIONS OF THYROID PREPARATIONS.[1]

So far the application of thyroid derivatives has been discussed in reference to diseases which are in varying degrees closely associated with disturbances of the thyroid gland—myxœdema, spontaneous or post-operative, cretinism, simple goitre and exophthalmic goitre : reference has also been made to the treatment of those forms of obesity which may be considered as due to defective activity of the thyroid gland.

The use of thyroid preparations has, however, been extended to quite a large number of conditions which in most cases can boast, so far, of but little experimental proof of their association with thyroidal perversion.

Fracture of Bones.—One of the most interesting observations is that made by Gabriel Gauthier on the beneficial influence of the use of thyroid medication in the delayed union of fractured bones. His observations were published in 1897.[2] In one case the bones had failed to unite at the end of the 110th day, despite perfect reduction and immobilisation ; after the use of thyroid gland, during fifteen days, consolidation was obtained. Similar results were obtained in a second case, and in both the thyroid gland appeared to be normal.

Since this date, Gauthier has made further observations, and has collected the results obtained by others, numbering 37 altogether. In six cases the results were negative ; four of these were complicated by treatment by suture or by the existence of a false joint. In some of the remaining cases

[1] *See* the monographs of Gauthier and Jeandelize.

[2] *Lyon Méd.*, June 27 and July 11, pp. 296, 395.

the success could be attributed exclusively to the thyroid treatment. In Gauthier's own cases (seven) there was no discoverable cause for the delayed union. Little or no evidence can be brought forward to show that fractures are likely to be of protracted course in myxœdema, but Gauthier, quoting experimental observations,[1] says that Hanau and Steinlein have shown that in thyroidectomised animals the formation, growth and reabsorption of callus are defective. Callus formation is not hastened in normal individuals by the use of thyroid preparations, and the observations of Carrière and Vauverts confirm this statement for animals.

Bayon[2] has confirmed Gauthier's observations on the effects of thyroid medication in delayed union of fractured bones. He finds that thyroidectomy in the rabbit definitely delays the healing of fractured bones. This delay is a much earlier feature than cachexia strumipriva. Fractures in thyroidectomised animals unite better if the animals are fed with thyroid gland than if they are not so treated. In opposition to the observations of Carrière and Vauverts, Bayon found that healing of fractures even in healthy animals was hastened by the use of thyroid preparations. Bayon's results in man were obtained from an examination of the reports of 50 cases of delayed union of fractured bones. In most of the cases good results were obtained by thyroid feeding. Of 24 cases which were fully reported, eight did not appear to be benefited.

Thyroid medication has been advocated for other disturbances of the osseous system. Some improvement has been recorded in cases of **osteomalacia** and in **rickets**. Revilliod,[3] Lancereaux,[4] and Llewellyn Jones[5] have re-

[1] " Les médications thyroidiennes," p. 189.

[2] *Verhandl. der phys. med. Gesellsch. zu Würtzburg*, 1903, Bd. xxxv., No. 6.

[3] *La Semaine méd.*, 1895, p. 205.

[4] *Acad. de méd.*, 1899, Jan. 3, p. 32.

[5] *Edinb. Med. Journ.*, 1904, N.S., xv., 5, p. 425.

corded cases of improvement in **rheumatoid arthritis** following the use of thyroid substance.

The causation of **infantilism** is not completely known. There is no doubt that certain of these cases present features which stamp them at once as cases of myxœdematous infantilism. There is another type of infantilism, originally described by Lorain and Brissaud, in which the imperfect development is part of a general dystrophy specially affecting the heart and blood vessels. This form is said to be sharply defined clinically from the myxœdematous form,[1] but Hertoghe gives reasons for believing that even Lorain's form of infantilism is dependent upon dysthyroidism or perverted function of the thyroid. According to Hutinel these cases differ from myxœdematous infantilism in that the latter are due to primary atrophy of the thyroid gland, whereas the type described by Lorain may be secondary to tuberculous, syphilitic and infective processes. Delay of the onset of puberty, which often accompanies the delay of growth, may also be benefited by the use of thyroid products. The forms of infantilism described by Giffard under the title of "ateliosis"[2] are considered by him to be quite independent of defective action of the thyroid or any other organ.

By others, efforts have been made to improve the symptoms of **acromegaly** and the allied disorder, **gigantism,** by the use of thyroid preparations. The rationale of this mode of treatment has been referred to in an earlier section. If adenomatous involvment of the pituitary body is the cause of this disease, it is conceivable that the internal secretion of this organ is altered quantitatively or qualitatively, or in both directions. Despite the observations made by Rogowitsch and others on the enlargement of the pituitary body after destruction of the thyroid gland, it appears as a result of Oliver and Schäfer's observations[3]

[1] *See* Gauthier.

[2] *Practitioner*, 1903, June, p. 797.

[3] *Journ. of Phys.*, 1895, p. 277.

that extracts of the thyroid and pituitary bodies do not exert the same physiological effects, that such enlargement of the pituitary body is not compensatory.

The results of the thyroid treatment of acromegaly are so far not satisfactory; thyroid treatment has no influence upon those alterations in the extremities which appear to be due to overaction of the pituitary body. The symptoms which may be attributed to the presence of a growth in the pituitary fossa, such as headache and disturbances of vision, do, however, appear in some cases to be improved by thyroid treatment.

Of the seventeen reports, collected by Gauthier, of the treatment of acromegaly by thyroid, or by means of pituitary extract, or by both, the greater number favour the use of these substances. The results obtained by Mendel, Magnus-Levy, Schwonen, and others suggest that the improvement was very small, or none at all, or that the improvement shown was the result of suggestion. Bruns[1] and others have reported cases in which the patients expressed themselves as better, though there was decided increase in muscular weakness, as a result of thyroid treatment. Sternberg[2] sums up the use of thyroid preparations in this disease by saying that by no means ought they to be prescribed on the first consultation to a subject suffering from acromegaly; the more harmless pituitary tabloids should be preferred. Marinesco[3] and Rolleston[4] have little to say in favour of the use of pituitary substance in cases of acromegaly.

Eclampsia, Epilepsy, Tetany, etc.—Despite the existence of cases of spinal epilepsy, the larger proportion of cases of epilepsy, and conditions closely allied to epilepsy, are due to irritative lesions of the cortex of the brain. The nature of the irritant is an exceedingly varied

[1] *Neurolog. Centralbl.*, 1895, s. 1173.

[2] "Acromegaly," *New Sydenham Society*, 1899, p. 118.

[3] *La Semaine méd.*, 1895, p. 484.

[4] *Lancet*, 1896, i., p. 1137.

one; it may take a coarse form in the shape of tumour or depressed fracture, or it may be much more subtle in character, and give rise to the so-called idiopathic epilepsy, or may cause the epilepsy met with in chronic alcoholism, in lead palsy, in rickets, in general paralysis, in pregnancy, and in other conditions such as exophthalmic goitre.

Little is known of the particular agents at work in each of these diseases, but it is certain that either physical or chemical agencies, acting on cortical cells of increased susceptibility, produce those violently explosive phenomena which characterise the convulsions of epilepsy and eclampsia.

Idiopathic epilepsy does not appear to be relieved by thyroid treatment, though it is possible that in some cases of epilepsy associated with goitre such improvement may follow the use of thyroid preparation. Jeandelize, however, is inclined to think that disordered function of the parathyroidal glands is capable of producing ordinary epilepsy. So far there is no clinical support for the belief that idiopathic epilepsy can be favourably influenced either by thyroidal or parathyroidal treatment.

Considerable interest has been aroused during the last two or three years in the relationship existing between the occurrence of puerperal eclampsia and thyroidal or parathyroidal disorders. Nicholson[1] has advanced the view that eclampsia, coma, vomiting, etc., occurring during pregnancy are examples of autointoxication, and that it is necessary to make use of some substance which will overcome the vaso-constriction of the renal and other vessels. He finds that thyroid extract subserves this purpose admirably; he has administered as much as 70 to 85 grains in twenty-four hours; diuresis follows and symptoms of eclampsia subside. In the case of a primipara of eight months, suffering from headache, anuria, albuminuria and

[1] *B. M. J.*, 1902, i., p. 1214; ii, p. 1138; *Ibid.*, 1903, i., p. 1642; *Scottish Med. and Surg. Journ.*, 1901, i., p. 503, and 1903, i., p. 204.

solid œdema, treatment by thyroid was preceded by the use of morphia; the fits abated and the woman was delivered of a still-born child. This patient became again pregnant, and was treated with thyroïd substance from the onset of the pregnancy; at the seventh to eighth month she was quite well and free from fits. A second patient, aged twenty-three years, pregnant seven months, developed headache, dimness of vision, œdema, and anuria; she was sent to bed, and for ten days was treated with milk diet only, but with very slight improvement. Five grains of thyroid gland were then given three times a day, and after six days much improvement was observed; the thyroid was increased to 5 grains every three hours for seventeen days; the drug was then omitted for a fortnight, and then resumed, 5 grains only being given daily; all symptoms disappeared, and the patient was ultimately delivered of a still-born child. A fourth case is recorded by Nicholson and favourable results are given. Sturmer[1] reports that by means of thyroid extract the mortality in puerperal eclampsia can be reduced to 12·2 per cent.; unfortunately for the proof of the efficacy of the treatment, saline infusion and the injection of morphia had been practised as well.

Before any definite pronouncement can be made upon the efficacy of the thyroid treatment of eclampsia much more extended observations are required. It is, however, a rational form of treatment in that there is a marked increase in the amount of urine excreted as a result of the treatment. Further information is required too upon the influence of thyroid medication upon the life of the unborn child: it would appear to be unfavourable. Nicholson's suggestion that such manifestations occurring during pregnancy are due to thyroidal insufficiency are confirmed by the observations of Verstraeten and Vanderlinden, who by means of thyroid medication were able to check similar symptoms occurring in a thyroidectomised cat which had become pregnant.

Reference has already been made to these observations

[1] *B. M. J.*, 1904, i., p. 895.

and those of Herrgott. Herrgott observed eclampsia at the time of delivery in a myxœdemic girl, aged 18 years,[1] and considered that probably the eclampsia was due to parathyroid deficiency, this view being in harmony with that already expressed, that the deficiency of parathyroidal function led to toxic disturbances of the nervous system. Lange[2] has pointed out the frequency with which enlargement of the thyroid gland is noticed about the fifth and sixth month of pregnancy; if these cases are treated with thyroid substance or thyroiodin for about twelve to fourteen days, the functional hypertrophy subsides, but returns again after the treatment has been omitted. As a result of Lange's observations, it appears that in those cases in which the thyroid does not enlarge (22 cases out of 133 examined) there is frequently found albuminuria, and in a considerable number of these cases casts are found. Lange found that in the remaining pregnant women in whom the thyroid was enlarged, albuminuria occurred only twice, and in those two cases the mischief was of anterior date. Of the women with no enlargement of the thyroid and with albumen in the urine, six developed eclamptic symptoms. Blumreich and Zuntz conclude as a result of these observations of Lange, and from a consideration of the account given by Herrgott of his case, that the cause of the symptoms is deficiency in the thyroparathyroidal activity, and in agreement with Herrgott they conclude that the special defect is in the parathyroids. So far as can be gathered from the literature, there are no observations on the effects of parathyroidal treatment of the eclampsia of pregnancy which would support this view, but then it must be remembered that Nicholson's favourable results may be due to the parathyroidal substance contained in the commercial thyroid preparations.

It appears to be justifiable, when eclampsia develops in a woman during pregnancy, or during confinement, especially

[1] *Annal. de Gynécol.*, 1902, t. lviii., p. 1.

[2] *Zeitschr. f. Geburt. u. Gynäk.*, 1899, xl., s. 34.

if the physiological hypertrophy of the thyroid has not developed and if the urine is free from albumin, to take advantage of the thyroid medication. As Blumreich and Zuntz observe, Lange has shown that such medication in normal pregnancy is not followed by harm to either mother or child. Whether the theory of thyroidal or parathyroidal insufficiency is correct or not, it is impossible at present to say, but, at least, thyroidal treatment produces a diuretic effect, and therefore supports the more ordinary methods of treating eclampsia.

Tetany.—Tetany occurs in a variety of disorders, such as prolonged gastroenteritis in adults and children, in connection with dilated stomach, or even after specific illnesses, like typhoid fever; in children rickets is also frequently found as well, and intestinal parasites may also be present, such as Oxyuris vermicularis. In all these cases it may be considered that the tetany is due to toxic effects.

Tetany, however, is apt to occur in pregnant women or during lactation; it is known to accompany post-operative myxœdema; further, incomplete forms of tetany, *i.e.* forms in which the spasm is limited to the extremities, may be associated with puerperal eclampsia, and the final stages in exophthalmic goitre may also be ushered in by cramps and pains in the extremities, face and neck. Experimentally it has been found that when the parathyroids are removed from dogs tetany results, and Lusena has shown that when an animal has been deprived of its parathyroids, the onset of tetany may be avoided by grafting parathyroids.[1] Moussu showed that the symptoms of tetany occurring after complete extirpation of the thyroid and parathyroid could be checked by the injection of a watery extract of the parathyroids. Gottstein[2] was the first to point out the beneficial effects of thyroid treatment in cases of tetany. Favourable results have followed the use of thyroid medication at the

[1] *Rev. neurolog.*, 1900, p. 556.

[2] *Deutsche Zeitschr. f. Nervenheilk.*, 1895, No. vi., s. 177.

hands of Levy-Dorn,[1] and of Schultze. Schultze was able to relieve the tetany which occurred in a young goitrous subject, and Levy-Dorn records the case of a woman who for three years had suffered from tetany, which became much worse at her confinements: the symptoms of tetany in both cases were cured by thyroid treatment.

Ferenczi[2] reports the case of a woman aged thirty-six years. Goitre developed in her second pregnancy, and increased very considerably with each succeeding pregnancy, until it reached the size of the fist: the goitre was cystic. In the third week after her second confinement she developed tetany; this was, however, checked by temporary cessation of suckling and the use of thyroid substance. Later on the mother again suckled her child, and there was no return of tetany. Ferenczi concludes that thyroid preparations should be used in such cases.

Convulsions in Childhood.—The causation of the convulsive seizures met with in infancy and childhood has proved a source of considerable difficulty to the clinician. By some observers these convulsions are said to be true epilepsy; others consider that various forms of peripheral irritation, rickets, etc., are sufficient to cause them. It is quite certain that many children who have suffered from fits in infancy appear to grow up without further manifestations of epilepsy. It is possible that some cases of infantile convulsions are due to disturbances of the child's thyroparathyroidal apparatus, or possibly, in the case of children at the breast, from disturbance of the same tissues in the mother. Jeandelize[3] supports this view by reference to reports by Bassal and Byrom Bramwell, and to those presented at four recent medical congresses in France, dealing with the subject of infantile convulsions, viz., those of Mossé at the French Congress at Montpellier in 1898, of Bézy at the Congress in Paris, 1900, of Ausset at the

[1] *Berlin. klin. Woch.*, 1896, s. 88.
[2] *Zentralbl. f. Gynäk.*, 1904, No. 45, s. 1370.
[3] *Loc. cit.*, p. 701.

Congress at Nantes in 1901, and of d'Espine and of Moussous at the Congress held at Toulouse in 1902.

One great difficulty in the application of thyroid treatment to such cases is the diagnosis of the cases due to such thyroparathyroidal insufficiency, and therefore suitable for the treatment. Jeandelize suggests that the presence of low temperature, the increase of the convulsions by cold, and the absence of gastro-intestinal disorder will aid in the matter.

The observations of Knopfelmacher[1] and of Kalischer[2] show the complete failure of the thyroidal treatment in eleven cases of infantile convulsions.

Affections of the Skin.—Owing to the remarkable changes produced in the skin and appendages of patients suffering from athyrea, it occurred to Byrom Bramwell[3] to apply thyroid preparations in various skin diseases. The results have differed in different hands, and in different forms of skin diseases. The most marked results after the use of thyroid preparation have been noticed in cases of psoriasis, ichthyosis, lupus vulgaris, acute and chronic eczema, and in various forms of alopecia and in sclerodermia. Very favourable results were obtained by Lancereaux and Paulesco in the last-named malady, considerable improvement following on the administration of daily doses of $7\frac{1}{2}$ to 10 grains of thyroiodin. The patient had been unable to work for two years, and recovered after four months' treatment. Osler speaks less hopefully of the treatment.

Radcliffe Crocker[4] finds that the greatest benefit is derived from the use of thyroid preparations in lupus vulgaris and in other skin diseases; a five-grain tabloid should be given daily, increasing the daily dose each week

[1] *Wien. Klinik*, 1895, I. xlvii., s. 201.

[2] *Jahresb. f. Kinderheilk.*, 1897, xli., s. 181, and xlii., s. 386.

[3] Brit. Med. Assoc., 1893.

[4] "Diseases of the Skin," 1903, p. 44.

until fifteen grains are taken a day. The results of thyroid treatment of psoriasis are very variable: it appears to succeed admirably in some cases and not in others; as a general rule it is serviceable in chronic cases only, being harmful in acute ones. Radcliffe Crocker[1] gives the following additional rules for the use of thyroid preparation: it should not be given in developing psoriasis, as it may thus excite new lesions, and it is advisable when the larger doses are reached that the patient should be in bed and under supervision.

Ewald[2] was very successful in a case of diffuse psoriasis occurring in a boy nine years old who had failed to react to any other treatment. In order to avoid thyroidism, in accordance with the experience of Mabille, he combined the treatment with arsenic, giving 8–10 tabloids of thyroiodin (three grains) daily, with 2–6–8 milligrammes of arsenious acid. Similar good results were obtained in a second case of psoriasis. Gauthier[3] speaks also of the favourable results of thyroiodin combined with arsenic in the treatment of psoriasis.

Radcliffe Crocker reports[4] that great improvement may be expected in cases of ichthyosis by the use of thyroid tabloids, beginning in the case of a child of five years with doses of two grains and increasing to ten grains a day; the good results, however, only last as long as the treatment is continued.

Hæmorrhage.—The use of thyroid substance in cases of bleeding is mostly restricted to cases of hæmophilia. Successful results were obtained by Dejace, and by Combemale and Gauthier.[5]

Fuller[6] has described the good effects of thyroid extract

[1] *Loc. cit.*, p. 337.
[2] *Berlin. med. Gesellsch.*, 1900, July 18, s. 166.
[3] *Loc. cit.*, p. 215.
[4] *Loc. cit.*, p. 520.
[5] Gabriel Gauthier, *loc. cit.*, p. 223.
[6] *Med. News*, 1903, p. 385.

in three cases, giving 2½–5 grains daily. The first case was a bleeder with intractable epistaxis; a brother of this patient also developed an effusion into the knee joint; in still another case there was renal hæmorrhage. All three responded favourably. Fuller recommends that thyroid extract should only be used when other methods have failed. A severe case of epistaxis associated with purpura was greatly improved by the use of thyroid preparations. Profuse hæmorrhage, occurring at the menopause or associated with fibromata, is said to be relieved by the use of thyroid preparations. Menorrhagia, in younger women, is also beneficially affected by thyroid treatment.

Cancer of the Breast.—The observation that in many cases there appears to be an association in function between various glands of the body has led to the treatment of cancer of the breast by removal of the ovaries, and apparently with success. In some cases this operation has been successfully combined with thyroid treatment.

Blaikie Smith[1] found that thyroid treatment of cancer of the breast only produced a reduction in size of the subcutaneous nodules; the rest of the growth was unaltered. Beatson[2] gives an account of the favourable result of treatment of a case of cancer of the breast by oöphorectomy combined with thyroid treatment. This experience was confirmed by Herman, Stanley Boyd and others.

Foulerton[3] describes the results obtained by the subcutaneous injection of preparations of the thyroid and thymus glands; though a very remarkable breaking down of the growth was observed in one case, Foulerton was unable to conclude that the treatment was a cure for cancer.

Various Other Disorders.—Thyroid preparations have been found of service in a number of affections, such as paralysis agitans, progressive myopathy, and in certain

[1] *B. M. J.*, 1901, i., p. 388.
[2] *Ibid.*, 1901, ii., p. 1145.
[3] *Archives of the Middlesex Hospital*, ii., p. 144.

psychoses, more especially those associated with disturbed thyroid function. Ley, quoted by Gauthier, describes a case of asthma which occurred almost daily, and became much better with each pregnancy; the administration of thyroid substance led to a complete disappearance of the symptoms.

Capitan and Camus describe the favourable results of thyroid treatment in cases of severe chlorosis. Treatment by iron was found to be more successful when combined with thyroid treatment.

Glycosuria and Diabetes Mellitus.—There is very little support for the treatment of these disorders by means of thyroid preparations. Indeed, both experimental and clinical evidence is against it, for hyperthyroidisation is capable of producing hyperglycæmia and glycosuria: attempts have even been made, based on this fact, to endeavour to diagnose conditionns which eventually, unless carefully treated, would lead to diabetes mellitus or glycosuria. Very different views are held as to the actual method by which thyroid medication causes glycosuria. According to some the hyperglycæmia is produced by a sort of retardation of the conversion into fat of the sugar circulating in the blood; such retardation is brought about by the action of the thyroidal secretion. It is impossible on this view to find any reason for the use of thyroid preparations for the treatment of diabetes mellitus; this hypothesis further entirely neglects the recent observations on the influence of the pancreatic internal secretion. Branthomme[1] and Lépine,[2] however, report cases of successful treatment by this means.

Lorand,[3] who holds that diabetes may arise from the excessive action of the thyroid gland in the production of colloid, more proteid substance being discharged into the

[1] *Rev. de méd.*, 1897, p. 995.

[2] *La Semaine méd.*, 1897, p. 469; 1898, p. 496.

[3] "Die Entstehung der Zuckerkrankheit u. ihre Beziehungen zu den Veränderungen der Blutgefässdrusen," Berlin, 1903.

system than can be reduced into simpler bodies by the action of the internal secretion of the pancreas, has endeavoured to neutralise the excessive proteid so liberated by making use of the blood of thyroidectomised animals on much the same principle as this substance is used in exophthalmic goitre. This treatment was combined with the use of Carlsbad salts, and Lorand is able to report that he had found that the glycosuria was reduced in all cases.

Thyroid preparations have been used to correct various functional disorders of the heart, as **arrhythmia** and **tachycardia**; this application is based on the observations made by v. Cyon,[1] who found that in rabbits deprived of the thyroid gland there was a complete disorganisation of the cardiac and vasomotor nerves, especially with respect to the depressors.

Rosenblatt has observed thickening of the vessel walls with reduction of the lumen after thyroidectomy. Von Eiselsberg[2] removed the thyroid from young herbivora in the first week of life; symptoms of cachexia strumipriva developed, and after a month the animals were killed; atheroma was visible in the aorta, especially close to the valves, and the internal coat became calcified. Results of this kind have justified the efforts to relieve conditions attributable to arteriosclerosis in man by means of thyroid preparations. Roos,[3] who in one observation on advanced arteriosclerosis noticed that the pulse became softer and symptoms were abated, quotes Lancereaux and Paulesco, who obtained good results by the treatment of arteriosclerosis with 1 to 3 grammes daily of thyroiodin. These results are quite in harmony with the observations made by v. Cyon,[4] and v. Cyon and Oswald,[5] that thyroiodin and thyroglobulin cause a fall of blood pressure. Huchard

[1] *Arch. de physiol.*, 1898, p. 263.
[2] *Arch. f. klin. Chir.*, 1894, Bd. 49, s. 207.
[3] *Münch. med. Woch.*, 1902, No. 39, s. 1607.
[4] Pflüger's *Arch.*, 1898, Bd. 70, s. 161.
[5] *Ibid.*, 1901, Bd. 83, s. 199.

has advocated the use of thyroid in Stokes-Adams syndrome, and in other forms of vascular disease of which spasm and arterial hypertension are features, such as migraine, certain forms of angina pectoris, and local asphyxia of the extremities.

Peters [1] refers to the use of thyroiodin by Eitelberg in cases of sclerosis of the middle ear (!). Thyroid preparations have also been used in cases of adenoids, in Addison's disease, and in neurasthenia, but the results do not encourage such empirical applications of the remedy.

[1] *Die neuesten Arzneimittel*, 1904, s. 515.

Section II.

SUPRARENAL GLANDS.

CHAPTER VIII.

ANATOMY AND CHEMISTRY.

Until recent years only the action of the thyroid gland and of its preparations had attracted any great amount of attention; now, however, since the exact observations made by Oliver and Schäfer and by Cybulski and Szymonowicz on the action of suprarenal extract, there has been a very considerable increase in the study of the suprarenal glands.

Anatomy.—The special points of interest in connection with the anatomical consideration of these organs are largely those dealing with the afferent and efferent vessels and with the nature of the function of the cortical as opposed to the medullary cells. The suprarenal body is a ductless gland. Blood is brought to the organ direct from the aorta, from the phrenic, and also from the renal arteries; the arteries within the organ are so arranged that they surround groups of cells with a fine capillary network; the blood is then collected into venous channels which ultimately join a large emissary vein. Lymphatics are very abundant, and run along the trabeculæ; they communicate with small lymphatic sinuses placed between the various groups of cells, and even between the cells themselves. Efferent valved lymphatics are abundant, both in the fibrous coat and in the medulla; in the latter place they form an elaborate network round the suprarenal vein.

Histology.—Section of the suprarenal body shows that it is enclosed in a loose areolar and a thin fibrous envelope; the substance proper is composed of a brownish-yellow outer part, or cortex, and a smaller mass of brownish-black colour forming the inner, or medullary, portion. The cortical

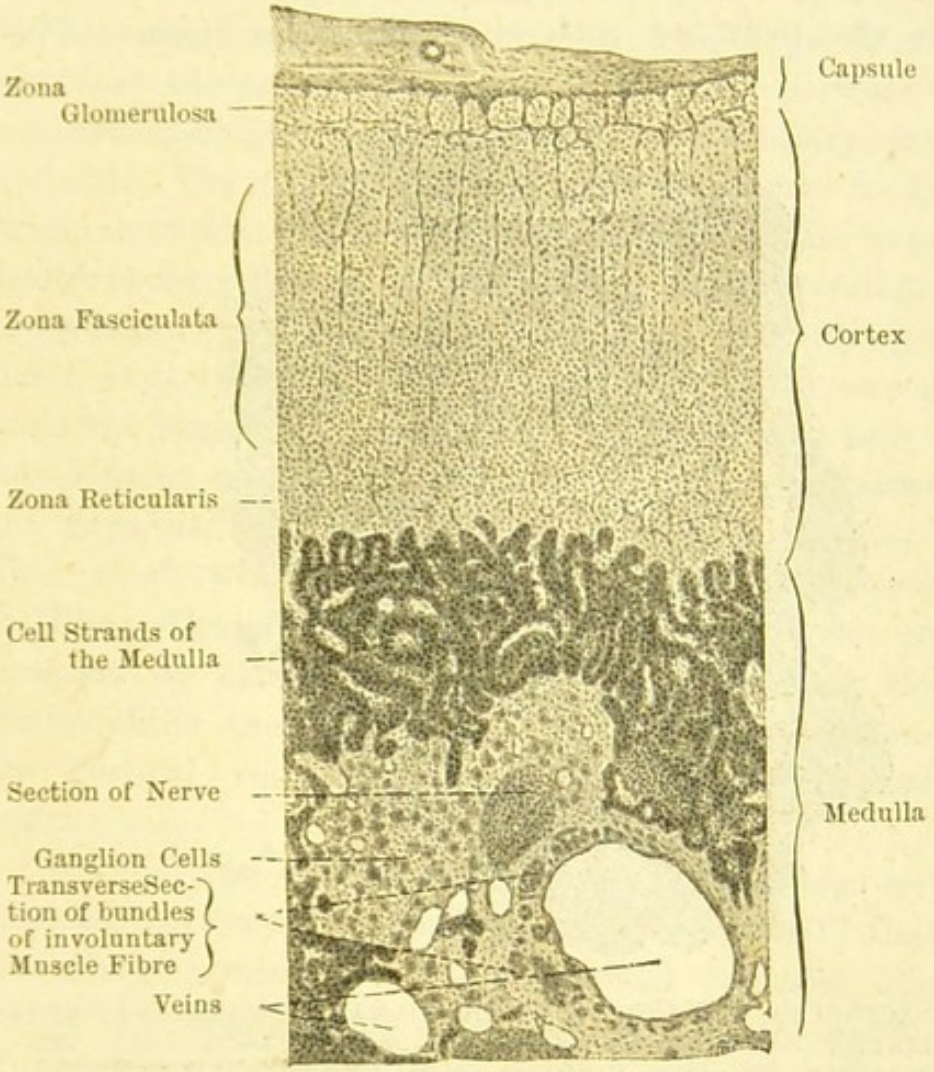


FIG. 7.—SECTION OF HUMAN SUPRARENAL GLAND (STÖHR) (× 50).

portion consists of columns of polyhedral cells seen most clearly in the intermediate part of the cortex—zona fasciculata, whereas the outer portion shows sections of masses of cells arranged in a sort of acinous form, hence the name for this part of the cortex—zona glomerulosa; the deeper portion of the cortex is known as the zona reticularis, in which the columnar arrangement of the cells is

lost, and a more or less (in man) ill-defined network appears. The zona fasciculata stains readily with eosin.

The medullary portion of the gland is darker than the cortex, but this is, in man, due more to the presence of blood than to any preponderance of pigment. It consists largely of venous sinuses supported in a fibrous stroma, which is also provided with much muscular tissue. The

FIG. 8.—SECTION OF THE CORTEX OF THE HUMAN SUPRARENAL GLANDS (KÖLLIKER), SHOWING CELLS OF THE ZONA FASCICULATA, CONTAINING FAT (*r*) AND PIGMENT (*r*!); VEINS (*v*); CONNECTIVE TISSUE (*b*). (× 325).

reticular stroma also contains a number of large, irregular shaped cells, which are highly vacuolated, and, unlike the cortical cells, are free from fat globules, and readily stain a dark brown colour with a solution of bichromate of potash (Henle's "chromaffine" or chromophile cells): the cortical cells show this reaction very slightly. The medullary cells, too, stain well, with iodine turning red, and with ferric

chloride turning blue (Vulpian's reaction). The medullary portion of the suprarenal bodies contains also a number of cells which recall the structure of the ganglionic cells of the sympathetic ganglia.

Development of the Suprarenal Bodies.—In view of the more recent investigations on specific cytolysins, and the attempted application of cytolysins in disease, it is important that the source of origin of the two portions of the suprarenal bodies, the cortical and the medullary, should be defined. The more widely accepted view, based on Leydig's original statement, is that the medulla of the suprarenal bodies is derived from the sympathetic nervous system, which is epiblastic in origin: the cortical portion, on the other hand, is derived from mesoblastic tissue, either as a growth from the Malpighian corpuscles of the anterior part of the fore kidney, or of the Woolfian body, or as proliferations of the germinal epithelium which covers this latter body. This view, which is supported by the observations of Kölliker, Braun, Mitsukuri, and Weldon, is not entirely accepted by other observers who consider that the real chromophilic medullary cells arise by metamorphosis of the cortical cells, and are, therefore, of mesoblastic origin.

Not only on developmental evidence, but also on histochemical grounds, it is generally conceded that the medullary portion of the suprarenal contains elements which are homologous with the ganglionic nerve cells of the ganglia of the sympathetic system. Wiesel,[1] in common with other observers, finds in the sympathetic system three microscopic elements—ganglion cells, nerve fibres, and the chromophilic cells above mentioned. The chromophilic cells occur in small clumps in all parts of the sympathetic system, and they are identical with cells found in the medullary portion of the suprarenal bodies. Kohn had formerly shown the histological similarity of parts of the sympathetic nervous system, of the medulla of the

[1] *Gesellsch. f. innere Med.*, Wien, 1903, June 4th.

suprarenals, and of the "paired bodies" of the Selachii or cartilaginous fish.[1]

Aberrant Suprarenal Bodies. — Considering the view already mentioned that the cortex of the suprarenal according to some authors is formed by outgrowths of cells from the Woolfian body, whilst other cells derived from this structure ultimately form the testicle and ovary, it is not to be wondered at that occasionally the separation of these two sets of cells is not quite regularly carried out.

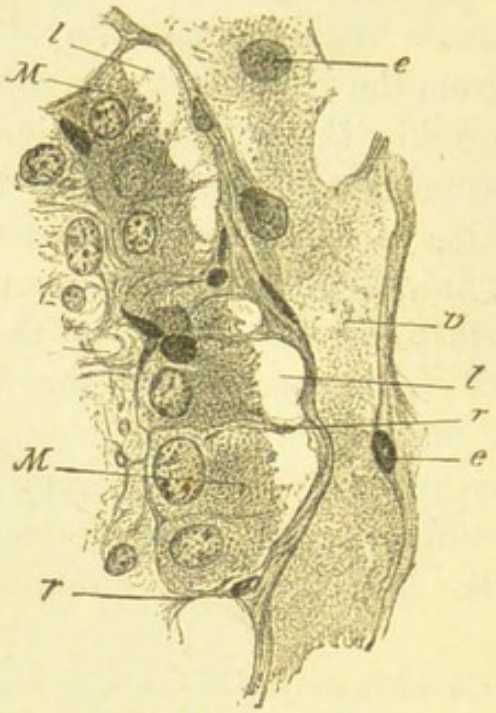


FIG. 9.—SECTION OF THE MEDULLA OF THE HUMAN SUPRARENAL GLAND (KÖLLIKER) (× 325).

M, Medullary cells; *l*, Spaces formed by shrinkage of medullary cells; *r*, reticulum connected with wall of vein (*v*); *e*, nucleus of endothelial cell of vein.

Such a possibility will account for the fact that aberrant masses of suprarenal tissue are found sometimes on the surface of the suprarenal bodies, or at the hilus of the organ, quite distinct from the main mass of the gland, or scattered about in the solar plexus or lying near the cœliac ganglia; in other cases they are found externally to or beneath the capsule of the kidney, or in the substance of the cortical

[1] *Vide* Biedl, "Innere Secretion," Berlin u. Wien, Urban u. Schwarzenberg, 1904, s. 55.

portion of the kidney; aberrant masses have also been found near the sacro-iliac joints, and along the course of the spermatic cord from the retro-peritoneal space to the epididymis. Chiari states that 96 per cent. of new-born male infants show accessory suprarenals in the globus major and globus minor of the epididymis. In women they have been found in the broad ligament in close relationship to the parovarium. Pepere[1] describes a primary malignant growth of the liver arising from aberrant masses of suprarenal tissue embedded in the liver; the cells repeated in the growth were more of the character of medullary cells; metastases occurred also in the diaphragm, lungs, and inguinal glands. Berkeley[2] observed adrenal malpositions five times in 2,000 autopsies, the aberrant masses were adherent to or infiltrated the kidney substance, or were placed in pockets on the surface of the kidneys; in one case there was bilateral infiltration of the kidneys by suprarenal tissue, and in another the aberrant mass was lying under the renal capsule. Rolleston[3] has found that the smaller accessory masses are free from medullary cells, but that larger ones may reach the size of a pea and may possess a medulla. Kohn[4] states that all accessory suprarenal bodies consist of cortical cells only. Biedl, on the other hand,[5] says that many of the structures found near the abdominal sympathetic system, and called accessory suprarenals, consist almost exclusively of medullary tissue, *i.e.* of chromophilic cells and of large and small ganglionic cells. The structures found on either side of the abdominal aorta by Zuckerkandl, and called by him "Nebenorgane," consist exclusively of chromophilic cells; extracts of these structures cause a rise of blood pressure, like that produced by the medullary part of suprarenal bodies and by adrenalin—

[1] *Arch. de méd. expér.*, 1902, xiv., p. 765.
[2] *Presbyterian Hospital Reports*, 1904, vi., p. 170.
[3] Goulstonian Lectures, 1895.
[4] *See* Swale Vincent, *J. of Anat. and Physiol.*, 1903, Oct., Pt. i., p. 34.
[5] *Loc. cit.*, s. 50.

a proof that adrenalin is derived from chromophilic cells.[1] Aschoff[2] has found chromophilic cells similar to those found in some "accessory" suprarenal bodies, in the paroöphoron and paradidymis. Mulon has found similar chromophilic cells in the carotid glands of mammals,[3] which suggests that the carotid glands are derivatives from the sympathetic system; these glands are, however, considered by other observers to arise, like the parathyroids which they simulate, from branchial clefts. Extracts of sympathetic ganglia and of the carotid glands fail to cause a rise of blood pressure, but this may possibly be due to the fact that other tissue is combined with the active cells and masks their true pressor effects (Swale Vincent).

Chemistry.—Since Oliver and Schäfer published their accounts of the rise of blood pressure, following experimental intravenous injection of suprarenal extract,[4] many efforts have been made to obtain the active principle quite pure. Bertrand,[5] Abderhalden and Bergell,[6] and Jowet[7] review the various formulas which have been considered to be chemically descriptive of the active principle, and conclude that the formula advocated by Aldrich[8]—$C_9H_{13}NO_3$ is the correct one, as compared with the one put forward by Abel, $C_{10}H_{13}NO_3$, $\frac{1}{2}H_2O$, or by Takamine, $C_{10}H_{15}NO_3$. Moore[9] described many of the solubilities and reactions of the active principle, which, however, had not so far been separated in pure form. Abel and Crauford announced in 1887[10] that they had succeeded in isolating the active principle of suprarenal extract and called it *epinephrin.*

[1] Biedl., s. 57.
[2] Orth's *Festschrift*, Berlin, August, 1903, p. 383.
[3] *Soc. de biol.*, 1904, p. 113.
[4] *Proc. Physiolog. Soc.*, March, 1894 and March, 1895.
[5] *Ann. de l'Instit. Pasteur*, 1904, No. 11, p. 673.
[6] *Münch. med. Woch.*, 1904, s. 1003.
[7] *Chem. Soc.*, 1904, vol. lxxxv., p. 192.
[8] *Americ. Journ. of Phys.*, 1901, p. 477.
[9] *Journ. of Physiol.*, xvi., p. 1; xvii., pp. 9 and 230.
[10] *Bull. of the Johns Hopkins Hosp.*, 1897.

Epirenan is the name given by Abderhalden and Bergell[1] to a crystalline form of epinephrin. Fürth[2] shortly afterwards criticised their results and showed that epinephrin was an impure body; he was able to separate a brenzcatechin-like substance, which he called *suprarelin* or *suprarenin*. Takamine in the summer of 1901 was, however, still more successful, and was able to isolate from the medulla of the suprarenal bodies a stable crystalline substance which he called adrenalin, and which possessed the active properties of suprarenal extract. Adrenalin is described by Takamine[3] as a light micro-crystalline substance, showing crystals of five or more different forms, rhomboidal, acicular, prismatic, spheroidal, or boat-shaped; it is slightly bitter, is sparingly soluble in cold water, freely in hot water, is quite stable in the dry form, has a slightly alkaline reaction, and combines with various acids. Adrenalin is a powerful reducing body, and may be used for developing photographic plates. It is not precipitated by ordinary alkaloidal reagents, and it is dialysable; it is insoluble in ether and in alcohol. Adrenalin or an accompanying chromogen gives the same colour reactions as were observed by Vulpian in the case of the juice of the suprarenal bodies,[4] viz., that it turns red on the addition of an oxidising agent such as iodine solution, and turns blue on the addition of a solution of perchloride of iron. Although adrenalin is not very soluble in cold water, its chloride salt is freely soluble; one of the best known commercial solutions is made from adrenalin hydrochloride 0·1 per cent., common salt 0·7 per cent., chloretone 0·5 per cent., and water; chloretone is a substance formed by the interaction of chloroform, acetone, and an alkali.

Such solution protected from light and air will keep

[1] *Loc. cit.*

[2] *Zeitschr. f. physiol. Chem.*, 1898, s. 142.

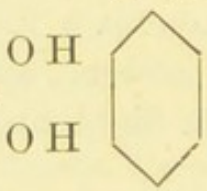
[3] *Therap. Gaz.*, 1901, p. 225; *Scottish Med. and Surg. Journ.*, 1902, x., p. 135.

[4] *Compt. rend. de l'Acad. des Sc.*, 1856, p. 663.

a considerable time; it can be sterilised without decomposing the adrenalin hydrochloride. From the reports of Lesage[1] it appears that 1,000 kilogrammes of suprarenal gland tissue obtained respectively from sheep, horses, dogs, pigs and cattle, contain of adrenalin, ·115·–121 grammes; ·081–·120 grammes; ·066–·106 grammes; ·078–·084 grammes, and ·074–·077 grammes.

Intravenous injection of adrenalin causes a rapid rise of blood pressure, but subcutaneous injection has scarcely any influence on the blood pressure. The fatal dose by intravenous injection for dogs, rabbits, and guinea-pigs is 0·1 to 0·2 milligrammes per kilogramme weight; for cats, ·5–·8 milligrammes per kilogramme.

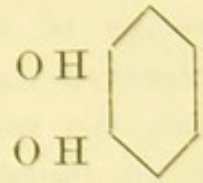
Takamine prepared adrenalin from the suprarenal bodies of oxen and sheep, by disintegrating the glands and extracting with water; the extract was treated with alcohol to precipitate the more active substances, both organic and inorganic, and the filtrate was evaporated in a vacuum and treated with alkaline reagents, which deposited the active principle in a crystalline form; this latter process was repeated in order to secure the crystals as pure as possible.

Following upon the separation of the two crystalline bodies, adrenalin and epirenan, efforts have been made to synthetise them. Friedmann,[2] by the action of methylamine on chloracetyl-brenzcatechin, obtained a substance which he called *Adrenalon*, which he was also able to derive from Fürth's Tribenzol-sulpho-adrenalin (a derivative of the natural product) by oxidation. Friedmann, on the strength of inquiries into the graphic formula of adrenalon, which he finds to be  , agrees with the graphic formula for adrenalin as established by Jowet,[3]

[1] *Arch. internat. de pharmacodyn. et de thér.*, 1904, T. 13, p. 245.

[2] Hofmeister's *Beitr. z. chem. Physiol. u. Path.*, 1904, Bd. vi, Hft. 1 and 2, s. 92.

[3] *Loc. cit.*

viz.:  The observations of Stolz[1] confirm those of Friedmann. A comparison of the effects produced on blood pressure by injection of rabbits with solutions of epirenan or of hydrochloride of adrenalon, shows that the difference between the synthetised and natural product is not a great one. Hans Meyer[2] gave an account of the synthesis of an adrenalin-like body, which, on injection into the vascular system, caused constriction of the blood vessels, contraction of the iris and glycosuria; similar reactions are shared by other compounds, such as aminoketones and ethylaminoketones.

Efforts have been made to standardise solutions containing adrenalin, based upon the reaction taking place between perchloride of iron and a chromogen, which Moore,[3] however, has shown to be quite distinct from the active principle. These efforts of standardisation, for which Batelli[4] is mainly responsible, are, therefore, based on a wrong conception, the colour reaction given with the iron salt being a measure of the amount of chromogen present rather than of the amount of active principle. Lépine[5] gives further reasons for discrediting Batelli's efforts at standardisation, because Boulard and Fayolle, working under Lépine's direction, have shown that the coloration produced on adding perchloride of iron to a solution of adrenalin is merely a measure of the acidity of the latter solution.

Guarnieri and Marino-Zucco[6] found that the activity of aqueous suprarenal extract is destroyed if the extract is rendered alkaline. Under the same conditions Oliver and

[1] *Bericht. d. deutsch. chem. Gesellsch.*, 1904, 37, 4149.
[2] *Sixth International Congress of Physiology, Brussels*, 1904.
[3] *Journ. of Phys.*, 1897, xxi., p. 382.
[4] *Soc. de biol.*, 1902, p. 571.
[5] *La Semaine méd.*, 1903, p. 53.
[6] *Arch. ital. de biol.*, 1888, x., p. 334.

Schäfer[1] were unable to produce a lowering of blood pressure. Szymonowicz and Cybulski[2] observed that if the alkaline extract were again neutralised, the specific effect returned. These observations have an important bearing upon the activity of suprarenal extract when injected subcutaneously, for contact with the alkaline fluids of the body destroys the specific effect. Batelli[3] points out that a weakly acid solution of adrenalin (·2 per cent. of HCl) retains the specific power of the adrenalin unaltered, and that alkaline solutions of adrenalin are still active so long as oxygen is excluded; this, unfortunately, does not obviate the difficulties of subcutaneous injections of adrenalin, because the tissues, besides being alkaline are abundantly supplied with oxygen.

Various other preparations have been made from the suprarenal bodies, *e.g.* Fraenkel separated a crude substance, which he called *sphygmogenine*. Other proprietary articles are *supradin*, *suprarenaden*, *suprarenin*, *atrabilin*, *rachitol*, *tonagen*, and *paragangline*. The last named substance, introduced by Vassale, is prepared from the medulla only of the suprarenal body of the calf; like other preparations of the suprarenal body, it contains lecithine.

Two other preparations have recently appeared, the *paranephrin* of Ritsert and *renoform* of Freund and Redlich; the latter, however, is merely a combination of dried suprarenal extract (0·050–·100 gramme) and an indifferent powder (5·0 grammes). Paranephrin is less toxic than other suprarenal preparations. It is made up in the strength of 1 in 1,000 with ·6 per cent. sodium chloride solution and contains no chloretone. It is claimed that it can be kept for several months without losing its active properties, and it is readily soluble in water.

[1] *Loc. cit.*

[2] *Loc. cit.*

[3] *Soc. de biol.*, 1902, p. 1435.

CHAPTER IX.

PHYSIOLOGY.

The efforts made to trace the course pursued by adrenalin in the suprarenal body have so far failed. At the present moment it is not even known whether adrenalin is merely an accumulation in the suprarenal body of adrenalin which has been circulating in the body or whether adrenalin is a substance elaborated by the parenchyma of the suprarenal body from substances brought by the blood.

In the former case the suprarenal body may be said to act as an excretory organ, the special function of which is to accumulate and destroy adrenalin ; on the other supposition adrenalin may be considered the active principle of an internal secretion. Schäfer[1] sums up in favour of the view that the suprarenal bodies act not as organs which suppress a toxic substance brought to them (the autointoxication theory), but that they supply an internal secretion which is responsible for the muscular contraction and tone of the cardiac and vascular walls and even of skeletal muscles. Schäfer found it impossible to demonstrate the existence of the active principle in the suprarenal vein, though contrary statements have been made by Cybulski, Langlois and Biedl, and Sergent and Bernard.[2] MacMunn[3] has published observations in which he shows that the spectrum of hæmochromogen occurs in solutions of the medullary substance. These observations tend to support the view that the suprarenal bodies are eliminative : further, destruction of the suprarenal bodies leads to the development of toxic

[1] "Text Book of Physiol.," vol. i., p. 958.

[2] Léauté, Paris, 1903.

[3] *Proceed. Roy. Soc., London*, vol. xxxix., p. 248.

characters in the blood, and in one to three days, as originally shown by Brown-Séquard, to the death of the animal, though exceptions to this rule have been frequently met with in white rats (Hallopeau, Boinet and others) and three times in dogs (Pal and Italian writers): in these latter cases probably accessory suprarenals have hypertrophied. Partial destruction causes little disturbance: even a remnant of one-eleventh of the total gland substance is sufficient to prevent symptoms of "decapsulation" from occurring. Biedl[1] maintains that it is not a question of how much gland is left, but what part of the gland is left, for his experiments tend to prove that though the medullary part of the gland, as shown by Oliver and Schäfer, contains the active principle, the *cortex*, and not the medulla, is essential to life. Cristiani's views[2] are opposed to those of Biedl, for he has succeeded in successfully grafting cortical cells in animals; death, however, followed in these animals on removal of the suprarenal bodies, and Cristiani concludes that the *medulla* is essential to life.

Abelous and Langlois,[3] who strongly maintain the auto-intoxication theory, have found that the blood of animals which have been deprived of their suprarenal bodies is toxic, especially to other animals which have been deprived of their suprarenal bodies. The same workers find that the transfusion of "decapsuled" animals with the blood of normal animals prolongs the survival after operation; this, however, has been denied by other workers. Myers has shown that the cortical substance is capable of neutralising snake venom. The crucial test of the whole question, as to the internal secretory action of the suprarenal bodies, would be that injection of the extract of the bodies in question should prevent the death of "decapsuled" animals. It would obviously be expecting too much of such extracts to hope that their introduction would cure cases of Addison's

[1] *Loc. cit.*, s. 56.

[2] *Journ. de physiol. et de path. génér.* iv., p. 387, and vi., p. 982.

[3] *Soc. de biol.*, 1891, p. 835; 1892, p. 388; 1893, p. 444.

disease, for Addison's disease and extirpation of the suprarenals are not identical conditions. Batelli,[1] who opposes the internal secretory view, confirms the observations of Strahl and Weiss, who found that if "decapsuled" animals are treated *continuously* with adrenalin (1 in 500,000 or 1 in 20,000) injected intravenously, they survived twenty hours, whereas the untreated "decapsuled" animals died in four to six or seven hours. Batelli has stated that even in the absence of the suprarenals, adrenalin is found to accumulate in the liver, an observation which is quite in agreement with the view that adrenalin is derived from cells found in other parts of the body than the suprarenal glands. As will be seen later, the reports on the usefulness of extracts of the suprarenal bodies in Addison's disease offer but meagre support to the internal secretory theory, though it is possible that the discouraging results are due to the impossibility of continuously injecting the patients, or because of the known effect of alkaline media in nullifying the activity of the preparations when introduced under the skin. If Biedl is right, then possibly the failure of adrenalin treatment is due to the fact that adrenalin is derived from the medulla, and the cortex, not the medulla, is essential to life. Auld [2] concludes that the cortex of the suprarenal body destroys red corpuscles, the cells of the cortex not only separating pigment but destroying the stromata as well. Lydia Felicine [3] supports the view that filtration is carried out by the cortical cells, whereby material is removed from the blood. Auld [4] and Manasse [5] have observed a colloid-like material in close relationship to the cells of the medulla, and this appearance confirms the view of a secretory activity on the part of the suprarenal body. Similar observations

[1] *Soc. de biol.*, 1902, pp. 1138 and 1180.
[2] "Selected Researches in Pathology," 1901, p. 74 *et seq.*
[3] *Arch. f. mikr. Anat.*, Bd. lxiii., s. 283.
[4] *Loc. cit.*
[5] Virchow's *Archiv*, Bd. cxxxv., Hft. 2, s. 263.

have been made by Carlier and Hultgren and Andersen. It is, therefore, possible that the suprarenal is both eliminative and secretory.

Biedl believes that the cortex abstracts a poison from the blood, and that the medulla elaborates another substance which is returned to the blood stream to exert important influences favourable to the economy. Giacomini has recently, from his observations on Petromyson, concluded that both the cortical and medullary parts of the suprarenal body have an internal secretion.

Sergent and Bernard have endeavoured to describe the symptoms of suprarenal insufficiency, maintaining that Addison's disease consists of a group of symptoms all of which are not attributable to defective action on the part of the suprarenal bodies; *e.g.* it is considered that the pigmentation of the skin is not due to suprarenal defect, but rather to the pericapsular disturbances which occur in cases of this disease. There can, however, be no doubt that some of the symptoms of Addison's disease are due to absence of the active principle of the medulla, for Oliver and Schäfer have shown that in advanced cases an extract of these organs possesses no physiological activity. Sergent and Bernard conclude that true suprarenal insufficiency is shown by asthenia and gastro-intestinal and vascular disturbances. Brown-Séquard explained the absence of pigmentation in experimental suppression of the suprarenal glands on the ground that the animals died so quickly that there was no time for it to develop. Schäfer[1] points out that if slow destruction is produced in the suprarenals, by the methods advocated by Nothnagel and the brothers Marino-Zucco, pigmentation does occur.

It is thought by some observers that the hypertension of the arterial system caused by suprarenal extract is responsible for some, at least, of the cases of atheroma occurring in man. The evidence in favour of this is based on observations

[1] "Text Book of Physiology," vol. i., p. 948.

made by Josué,[1] who found that a rabbit injected with adrenalin developed calcareous plates in the arterial system; he was unable to demonstrate arteriosclerosis. The same observer[2] showed specimens of three cases of arteriosclerosis in man; the suprarenals were enlarged and firm, and gave Vulpian's chromogenic reaction with perchloride of iron; histologically the organs showed considerable hypertrophy. Erb, junr.,[3] injected daily small doses of adrenalin into the veins of the ear of rabbits, and found as a result varying degrees of arterial atheroma, and dilatations which almost amounted to aneurysms. Casimir v. Rzentkowski[4] was able to confirm the observations made by Josué and Erb. He found that after repeated injections the heart hypertrophied and numerous calcareous areas appeared in the wall of the aorta; v. Rzentkowski hesitates to say that the changes are exactly such as are seen in atheroma occurring in man, because in the latter case a round-celled infiltration precedes the formation of atheroma, whereas in the experimental condition the reverse is the usual condition. Von Rzentkowski[5] has produced thrombosis of the aorta in rabbits by intravenous adrenalin injection. As in the case of other organs, there appears to be an association of function between the suprarenal body and the ovary. Embryological considerations would lead to this being foretold, and clinical experience confirms it. Monsters showing failure of development of the genital organs have also been found to have no suprarenal bodies (Meckl). Linser[6] has published the report of a unique case which seems to show that the suprarenal body is capable of influencing growth. A boy aged five years and seven and-a-half months suffered from a large tumour of the left suprarenal

[1] *Soc. de biol.*, 1903, p. 1374.
[2] *Bull. méd.*, 1904, xviii., p. 160.
[3] *Wien. med. Presse*, 1904, No. 18, s. 885.
[4] *Berlin klin. Woch.*, 1904, s. 830.
[5] *Gaz. lek.*, Warsaw, 1904, 2, s., xxiv., p. 524.
[6] *Bruns' Beitr. z. klin. Chir.*, 1903, Bd. 37, s. 282.

body. The ultimate microscopic picture showed that the original tumour and metastases consisted of suprarenal tissue. The boy had the size of body of a youth of thirteen to fourteen years of age, and the more manly aspect, deep voice and strong body development of a youth of fifteen to eighteen years. Radiograms showed bony development of the second decennium ; there was no enlargement of the pituitary body.

Physiological Action of Adrenalin and Allied Substances.[1]—Despite the mystery which enshrouds the problems concerning the functions of the suprarenal glands, and the degree of importance of the cortex of the body as compared with the medulla to the life of the animal, considerable unanimity is met with in the physiological action of extracts prepared from the medulla. The observations of Oliver and Schäfer and others have shown that it is from the medulla that this active principle is obtained; the existence of any active material obtained from the separated cortex is dependent upon the practical impossibility, in mammals, birds, and reptiles, of rigorously separating, by the scalpel, cortex from medulla. Swale Vincent, taking advantage of the fact that in the Selachii, these two parts of the suprarenal bodies of animals are found separate from one another, as the "interrenal body" and "paired bodies" of Balfour, has been able to show that the interrenal body, a tissue histologically identical with the cortex of mammalian suprarenals, is absolutely free from any active principle like adrenalin ; whereas the paired bodies of Balfour, also in part named by Leydig "Axillaherzen," which are histologically identical with the medullary part of mammalian suprarenals, contain an adrenalin-like principle. Swale Vincent was also able to show that the interrenal body of Teleosteans or bony fish, which is the only representative of the cortical portion of the suprarenal bodies in these animals, possesses no

[1] For much information on this subject the writer is indebted to the article by Professor Lépine, *La Sémaine méd.*, 1903, p. 53.

adrenalin action.[1] Until recently it was thought that there was no tissue present in Teleosteans representing the medulla of suprarenal bodies, but Giacomini has discovered this tissue in close relation with the walls of the cardinal vein.

Such a convenient separation of the two parts of the suprarenal body in Selachii and Teleosteans naturally suggested a means of testing the necessity of one or other of these structures for the existence of the animal. Swale Vincent[2] has found that eels will survive for several weeks the removal of the interrenal body, but Biedl[3] finds that the Selachii survive the loss of the interrenal body not longer than two to three weeks, and on these observations bases largely his opinion that it is the cortex and not the medulla of the human suprarenal body which is so essential to life.

Oliver and Schäfer found that the physiological effects of extracts of the medulla of suprarenal bodies are in the main directed towards influencing the activity of muscular tissue. The extract acts directly on the muscle wall of arteries, and this effect is quite independent of any stimulation of the vaso-motor centre, as was stated by Cybulski and Szymonowicz, who, with v. Cyon, maintain that suprarenal extract acts largely through the nerve centres. The result is a very considerable rise of arterial pressure, the contractions of the auricle are slowed and even stopped entirely, and the ventricle beats with an independent rhythm. Takamine confirms Oliver and Schäfer's view that the extract acts on the cardio-arterial muscle; Gottlieb[4] maintains that the effect is exerted on the peripheral nerve ganglia, and Boruttau and Breton[5] quote reports on

[1] *Proceed. Roy. Soc.*, 1897, vol. lxi., p. 64; vol. lxii., p. 176.

[2] Schäfer's "Text Book," vol. i., p. 957, note 3.

[3] *Loc. cit.*, s. 55.

[4] *Arch. f. exp. Path. u. Pharm.*, 1897, Bd. xxxviii., s. 99; 1900, xliii., s. 286.

[5] *Gaz. des hôp.*, 1903, p. 761.

syncopal attacks following the medicinal use of the extract, by v. Fürth, Roussel, Souques, and Morel and Michart, as proofs of the central bulbar effects exerted by the drug. Oliver has observed that a dose of suprarenal extract taken by the mouth will cause a diminution in the calibre of the arteries generally. The extract also influences the nature of the contraction of voluntary muscle, producing an effect very like that of veratria, for the contraction is more prolonged than normal. A certain amount of influence is exerted upon the bulbar centres, more especially the cardio-inhibitory and respiratory.

The effects produced by subcutaneous injection appear to vary with the species of animal: in large doses death occurred in some cases apparently from respiratory failure; quickening of the heart-beats was also noticed, and, according to some observers, fall of temperature; in most animals the limbs became paralysed, the hind ones before the fore limbs. Some observers have noticed that hypertension of the arteries is followed by hypotension, so that it is thought that the extract also contains a substance opposite in effect to adrenalin. Animals appeared also to become tolerant of large doses, after injection with smaller and non-fatal ones; the sphygmogenic effects (rise of blood pressure, etc.) are entirely absent when subcutaneous injections of suprarenal extracts are made (Cybulski, Langlois). Although the effects on blood pressure are so insignificant, it has been shown by Amberg,[1] who worked experimentally with epinephrin, that very serious toxic effects may be produced by subcutaneous injection—amongst other symptoms he noticed vomiting, great irritability and restlessness, followed by bloody diarrhœa and great prostration with feeble breathing, and in some cases death of the animal from cardiac failure. Fatal doses in dogs were produced by intravenous injection ·001 to ·002 grammes, sub-

[1] *Arch. internat. de pharmacodyn. et de thérap.*, 1902, t. ii., p. 57.

cutaneously ·006 grammes, and by the intraperitoneal route ·005–·008 grammes. So powerful is the extract of the medulla of the suprarenal body that one-millionth part of a gramme per kilo. of body weight is capable of producing distinct effects on the arteries and heart. The increase of blood pressure brought about by the use of suprarenal extract begins very soon after injection and lasts but a short time. The short duration of the effects has been ascribed to oxidation by the living blood : admixture with blood *in vitro* does not appear to destroy the specific effects. Embden and v. Fürth[1] agree that the blood alone of all the tissues exerts an oxidising effect on the active principle, but that the loss of effect on the vessel walls is possibly due to fatigue, which ultimately develops in the musculature of the artery walls ; the vessels dilate and the active principle then escapes into the tissues. Läwen[2] attributes the loss of effect to the destruction exerted by muscular tissue upon the active principle. The observations of Weiss and Harris[3] confirm those of Embden and v. Fürth in that they show that absence of effect is due to fatigue of the muscle ; a series of equal doses was administered at regular intervals, the effects produced became less and less until the effects of the last dose were nil. Dessy and Grandis[4] consider, with Salvioli, that adrenalin acts directly on involuntary muscle fibre in that it neutralises the products of contraction so that vaso-constriction is maintained ; the action on cardiac muscle is of a similar character : the influence exerted on voluntary muscle is not sufficient to affect the chemical changes. Meltzer and Auer[5] conclude from their experiments that adrenalin acts on the lining epithelium of blood vessels, causing a contraction of endothelial pores ; by this means

[1] Hofmeister's *Beitr.*, Bd. iv., s. 421.
[2] *Arch. f. Pharmak. u. Toxik.*, 1904, li., 4-6, s. 415.
[3] *Arch. f. d. ges. Physiol.*, 1904, Bd. ciii., Hft. 9, u. 10, s. 510.
[4] *Arch. ital. de biol.*, 1904, xli., Fas. 2, s. 225.
[5] *Transact. Assoc. of Amer. Phys.*, Philad., 1904, xix., p. 207.

adrenalin checks both transudation from blood vessels and absorption by them of fluids outside their walls.

It appears that when adrenalin is injected into the vessels, vaso-constriction does not occur in all the vessels. In the case of the arteries of the lungs and the arteries of the brain this is explainable on the ground that these vessels are not supplied with a nervous controlling mechanism.[1] Dixon even found that the arteries of the lungs became congested under the influence of adrenalin. Plumier[2] thinks that Brodie and Dixon failed to secure a rise of pressure in the pulmonary artery because they did not use sufficiently large doses of adrenalin. Von Cyon[3] has shown that the vessels of the dura mater, however, are influenced by extract of the suprarenal body. Carnot and Josserand[4] have shown that the active principle of the suprarenal gland on passing through the liver causes scarcely any rise of blood pressure (Langlois' antitoxic action of the liver), still less if it passes through a muscle, and least of all if it passes through the intestinal walls and the liver. The importance of the absence of constriction of the vessels of the lungs, liver, and brain is a great one, in view of the uses made of adrenalin and other preparations for hæmoptysis, apoplexy, etc.

When suprarenal extract is injected, the resulting vaso-constriction lasts considerably longer than does the rise of blood pressure; this is explained by the stimulant effect on the heart passing off more quickly than the stimulant effect (*vid* blood stream) exerted on the musculature of the arteries. Clopatt[5] has shown that suprarenal extract is capable of reviving a heart which has ceased to beat owing

[1] Dixon, *B. M. J.*, 1904, i., p. 136; Brodie and Dixon, *J. of Physiol.*, 1904, xxx., p. 476; Bayliss and Hill, *Journ. of Physiol.*, 1895, xviii., p. 334.

[2] *Journ. de phys. et de path. génér.*, Paris, 1904, t. vi., p. 655.

[3] *Arch. f. d. ges. Physiol.*, 1899, lxxiv., s. 97.

[4] *Soc. de biol.*, 1902, pp. 1346 and 1472; 1903, p. 51.

[5] Virchow's *Jahresbericht*, 1900, ii., s. 508.

to the influence of chloroform or chloral hydrate. Crile,[1] defining shock as due to exhaustion of the vaso-motor centre and collapse as mere temporary suspension of function of the centre, was able to revive animals suffering so severely from shock as to have appeared to be dead for fifteen minutes; they were resuscitated by intravenous injection of adrenalin and by artificial respiration; he also was able to keep the circulation of a decapitated dog going for ten and a half hours by the continuous injection of adrenalin.

Lépine[2] has collected reports on the action of adrenalin and similar substances upon other tissues of the body, and amongst these observations those of Doyon[3] are of special interest because of the attempts made to secure relief from asthma by use of adrenalin. Doyon found that as a result of the intravenous injection of the drug contraction took place in the muscular coat of the bronchi; in fact, a picture of asthma was produced. The blanching of the ocular conjunctiva is well known. Badano, Lewandowsky, and Radjiejewski have shown that intravenous injection of the extract causes mydriasis, but that local application fails to do this. Samberger[4] observed marked exophthalmos during continuous injection of suprarenal extract in young dogs. Local application to the bowel experimentally causes a cessation of peristaltic movements (Boruttau), an effect which would hardly have been expected, for, as a rule, at least at first, anæmia of the bowel causes increasing peristalsis. Bardier and Fraenkel have shown that intravenous injections of suprarenal extract cause a reduction in the amount of urine excreted, and even suppression, followed eventually by excessive secretion. During the oliguria Professor Lépine has shown that the proportion of phosphoric acid excreted is relatively to the urea greatly

[1] *Boston Med. and Surg. Journ.*, 1903, p. 247.
[2] *La Sémaine méd.*, 1903, p. 53.
[3] *Soc. de biol.*, 1902, p. 1477.
[4] *Wien. klin. Rundschau*, 1902, s. 577.

lowered. Langley[1] has confirmed the observation of Lewandowsky that suprarenal extract causes a diminution of the pressure exerted by the bladder on its contents. Considerable difference of opinion exists as to the effect of suprarenal preparation upon the metabolism. If suprarenal preparations are oxidised by the tissues, it would be expected that a positive nitrogen balance would occur. The published records of the influence of these preparations upon metabolism and the output of nitrogen have been drawn from the results of their use in Addison's disease. Senator[2] found that suprarenal preparations produced no changes in the output of nitrogen. Volbracht[3] and Philippen found that after treatment cases of Addison's disease put on weight, and the negative nitrogen balance which had been excessive was greatly reduced. Similar results, apparently due to a sparing of the proteid, were met with in a dog, in two other patients and in a healthy individual. Pickardt[4] found that suprarenal extract caused an increase in the output of nitrogen, and Kaufmann[5] found sometimes a negative and sometimes a positive nitrogen balance. It is possible that these variable results were expressive rather of the metabolic changes due to the disease and not to effects of the suprarenal preparations.

It appears that the great difference of opinion which exists between workers in this country and abroad upon the central nervous effects of suprarenal extract and its derivatives, as compared with the peripheral ones, is far from being resolved. Oliver and Schäfer have found that the effects are mainly peripheral, though they admit that the centres are affected. Lépine calls attention to the very interesting observation he has made upon the effect of intravenous injection of suprarenal extract upon the

[1] *Journ. of Physiol.*, 1901, p. 247.
[2] *Charité Annalen*, 1897, Jahrgang, xxii., s. 235.
[3] *Wien. klin. Woch.*, 1899, s. 757.
[4] *Berlin. klin. Woch.*, 1898, No. 33, s. 727.
[5] *Centralbl. f. Stoffwechs. u. Verdauungskr.*, 1901, s. 173.

temperature; he finds that it *always* causes a rise of temperature, and concludes that as the skin of the animal does not feel cold, such rise of temperature is not due exclusively to diminished loss of heat, but possibly to an increased central production.

One of the most interesting of modern discoveries is the connection found to exist between the occurrence of glycosuria and the introduction into the system of various glandular products; so marked is this phenomenon that glycosuria has been spoken of under various qualifications, according as its supposed cause was hepatic, renal, pancreatic, etc. Reference has already been made to the view that excessive activity of the thyroid may also lead to glycosuria. The observations made by Blum, Zuelzer and Metzger have established the fact that injection of suprarenal extract is capable of producing hyperglycæmia and glycosuria. Herter and Richards[1] found that intraperitoneal injection of adrenalin chloride was also capable of producing glycosuria. Herter and Wakeman[2] have made many observations on adrenalin glycosuria: amongst the more interesting are those which show that when the pancreas is painted with 1 c.cm. of 1 in 1,000 solution of adrenalin hydrochloride, considerable glycosuria is produced. The smallest degrees of glycosuria were those produced by giving adrenalin by the mouth, probably owing to the oxidation which goes on in the alimentary tract. Adrenalin glycosuria differs from that produced by phloridzin, because it is accompanied by a hyperglycæmia; it is quite independent of any possible increase of blood pressure due to the adrenalin, for glycosuria persists when the blood pressure is kept low by the use of nitroglycerine. Herter and Wakeman conclude that the glycosuria following the painting of the pancreas with adrenalin is due to nervous influences which, generated in the pancreas, react on the liver; solutions of potassium cyanide, when

[1] *Med. News*, 1902, pp. 201, 769, 865.

[2] *Amer. Journ. of Med. Sc.*, 1903, Jan.—June, p. 46.

applied to the pancreas, and other oxidising agents, produce the same effects; some reducing substances, like sodium salicylate, also produced glycosuria when applied to the pancreas. Judging from the fact that severer glycosuria occurred when the tail of the pancreas was treated with adrenalin than when the head of this organ was so treated, there is some justification for thinking that adrenalin has some special effect on the islands of Langerhans which Opie finds so abundant in the tail as compared with the head of the pancreas. Herter and Wakeman found that compression of the adrenals, short of destruction of these organs, was also capable of producing glycosuria, but exclusion of the glands by extirpation or ligature was followed by hypoglycæmia.

The earlier deduction made by Herter and Richards, that the adrenals are capable of an internal secretion and of influencing carbohydrate metabolism, was considerably supported by their observations that the mere compression of the adrenals caused glycosuria, for it was argued that more internal secretion was driven into the system. The same observers, however, show that the general blood pressure is not raised during these manipulations, so that the glycosuria must be due to other influences than those of the internal secretion; they invoke a nervous influence acting probably, as already stated, on the liver. Paton[1] concludes that adrenalin produces glycosuria by stimulation of liver activity, quite independently of any action of the pancreas, because in non-carnivorous birds ablation of the pancreas is not followed by glycosuria (v. Mering and Minkowski), and yet the injections of adrenalin into such animals, after removal of the pancreas, will cause glycosuria. Lœper and Cruzon[2] found that adrenalin produced a reduction of the internal secretion of the pancreas, and also reduced the amylolytic, lipolytic, and glycolytic power of the blood.

[1] *Lancet*, 1904, i., p. 654.

[2] *Arch. de méd. expérim.*, 1904, t. xvi., p. 83.

Blumenthal,[1] on the basis of work done by Cohnheim, Hirsch, Arnheim, and Rosenbaum, which points to the conclusion that the internal secretion of the pancreas activates ferments which are resident in certain cells, concludes that probably all cells, including those of the adrenal glands, are capable of producing this sugar-splitting ferment under the influence of the pancreatic internal secretion.

Arohnson,[2] whose earlier work in 1884 showed that it was possible to cause hyperthermia by irritation of the tissues near the corpus striatum, has studied the effects and influence of irritation of the heat centre upon suprarenal diabetes. It is well known clinically that in many infectious diseases such as typhoid, though not in all such cases, glycosuria, if originally present, disappears during the febrile period. Arohnson was able to show that adrenalin glycosuria behaved much as the ordinary clinical cases of glycosuria, for when hyperthermia was produced by puncture of the lateral ventricle near the corpus striatum the glycosuria was reduced, and even disappeared. This observation is hardly in agreement with that of Lépine, who found, as we have seen, that intravenous injection of suprarenal extract always caused a rise of temperature; if this were so, then according to Arohnson there should be little or no glycosuria.

[1] *Deutsche med. Woch.*, 1903, s. 961.

[2] Virchow's *Archiv*, Bd. 174, s. 383.

CHAPTER X.

EXPERIMENTAL OBSERVATIONS OF SPECIAL THERAPEUTIC IMPORTANCE.

It is to be observed that the injections of adrenalin, if given in excessive doses, are capable of leading to grave disturbances of respiration, and finally of the circulation. Livon [1] points out that when solutions of adrenalin have turned brown, though it is possible that they still retain a hypertensive character, they are also able to produce toxic effects, as shown by cessation of the action of the heart, which is probably not central, for respiration in these cases is found to persist a little after the action of the heart has ceased. Lépine, however, shows that similar abnormal effects may be noticed in preparations which are quite fresh. Mousset [2] has studied the toxic effects of over-doses of adrenalin in guinea-pigs. At first dyspnœa develops, followed by prostration; after about five minutes there is paralysis of the hind extremities. After the initial prostration a stage of irritation follows, and in the rabbit this may be accompanied by tonic and clonic movements with opisthotonus and mydriasis. A second group of symptoms recorded by Bouchard and Claude [3] includes those of pulmonary origin: respiration becomes very hurried and then slows down; the occurrence of pulmonary œdema is shown by the appearance of blood-stained foam at the mouth. Batelli attributes death to this pulmonary œdema. Mousset found post-mortem that there was regularly an intense inflammation at the seat of injection, injection of the bowel,

[1] *Soc. de biol.*, 1902, t. liv., p. 1501.

[2] *Ibid.*, p. 1471.

[3] *Compt. rend. de l'acad. des sc.*, 1902, Dec. 1, p. 928.

especially the small intestine, and hæmorrhages into the liver. In the case of animals which did not die, sloughs formed at the seat of injection, constituting, according to Mousset, a contra-indication against such mode of administration of the drug. Drummond,[1] and Drummond and Paton[2] describe the microscopic changes following the injection of adrenalin hydrochloride. The changes produced in the tissues are due partly to intestinal disturbance following the altered condition of the vascular supply, and partly to toxic causes. Besides œdema and injection of the lungs, toxic effects were noticed in the liver and kidneys, more especially in the cells at the centre of the lobules of the former and in the convoluted tubules of the latter organ.

Brodie and Dixon[3] have pointed out that experimental results strongly contra-indicate the use of adrenalin in cases of hæmoptysis.

Benno Müller[4] has published the results of an experimental inquiry into the value of the application of suprarenin to check bleeding from wounds made in various organs. By means of suprarenin he was able to operate freely on the liver, gall bladder, kidney, salivary glands, thyroid gland, subcutaneous tissues and muscle; ribs were excised and the tongue removed. In all these operations, some 74 in number, the solutions used were 1 in 1,000 to 1 in 10,000 of suprarenin hydrochloride, in normal saline solution, the stronger solution for such organs as the liver and kidney, and the weaker one for tissues which were not highly vascular. Hæmorrhage after incision was entirely checked except from the larger vessels, which required ligatures; not one of the dogs died from hæmorrhage during or after the operation; the suprarenin did not impair the health of the cells suffused with the solution, and healing

[1] *Journ. of Physiol.*, 1904, xxxi. 2, p. 81.
[2] *Ibid.*, p. 92.
[3] *Loc. cit.*
[4] *Münch. med. Woch.*, 1904, s. 199 u. 262.

occurred quite normally. No toxic symptoms were noticed. Injection of 1 c.cm. of a 1 in 10,000 or 1 in 20,000 solution into the heart muscle stimulated the action of the organ. Müller concludes that 10 c.cm. of a 1 in 1,000 solution may be applied with safety in an adult man. Very similar observations were made by Lehmann on the use of adrenalin in experimental incision of the liver with equally favourable results.[1]

Observations on the beneficial influence of combined cocaine or β-Eucaine and Adrenalin Solutions.—Koller, in 1884, showed the anæsthetic effects produced by cocaine when locally and externally applied. Corning[2] then introduced cocaine as a means of locally influencing the spinal cord, first by injecting it into extra-dural sites, and then within the dura mater. Cathelin[3] has been able to produce anæsthesia of the lower extremities by the introduction of cocaine within the sacral canal, but externally to the dura mater (epidural application). Reclus and Schleich then followed on with the introduction of "infiltration" anæsthesia, to produce which cocaine was injected subcutaneously; Schleich used solutions of cocaine in normal saline solution (·8 per cent. to ·9 per cent.), and Reclus used simply watery solutions. Then followed attempts by Oberst, Crile, and others to obtain anæsthetic effects over particular areas by the application of cocaine to large branches of peripheral nerves—a difficult operation, and not in accordance with some views of the composite nerve supply of any one particular area of the body. Bier[4] repeated Corning's observations by introducing cocaine within the dura mater by lumbar puncture, and was able to carry out six operations on the lower extremities. But in all these methods there was the risk

[1] *Münch. med. Woch.*, 1902, s. 2048.

[2] *New York Med. Journ.*, 1885, Sept. 19; *ibid.*, Oct. 31; *ibid.*, 1886, Jan. 2; and "Pain," Philadelphia, J. B. Lippincott Co., 1894.

[3] "Les Injections Épidurales," Paris, J. B. Baillière et Fils, 1903.

[4] *Deutsche Zeitschr. f. Chir.*, i., 1899, Bd. li., 361.

of general intoxication, and the problem was to devise some means by which local effects could be secured without risk to the individual. Corning pointed out that by applying a ligature to a limb, cocaine could be restricted to the extremity until it had, so to speak, spent itself in local effects.

Kossa had shown in the case of other poisons that absorption is delayed by the loss of vitality in cells which may be brought about when tissues are rendered very cold by means of ether or ethyl chloride. Braun[1] adopted Kossa's method in the use of cocaine, and found that by the combination of freezing and cocaine, local anæsthesia could be greatly prolonged. The methods of ligature of a limb and the application of cold were simply based upon the production of bloodless areas, by which means no general absorption could take place. After the discovery by Oliver and Schäfer of the specific effects of adrenalin in producing a rise of blood pressure by contraction of the muscular coat of arteries even in such small doses as those mentioned by Moore and Purinton—·000000245 to ·000024 grammes of extract per kilogramme weight of dog[2]—it was obvious that a means had been found of controlling the size of the lumen of blood vessels by infinitely small doses of suprarenal extract. But, prior to the last-named observation, Bates,[3] Dor and other ophthalmic surgeons applied suprarenal extract to the conjunctival sac to produce a bloodless field for operation. Velich noticed the anæmia produced in granulating wounds by the application of suprarenal extract. Then Braun, experimenting first upon himself, found that a subcutaneous injection of adrenalin solution (1 in 1,000,000) produced a bloodless condition of the tissues quite as readily as the method of bandaging or freezing. On account of these marked effects

[1] *Arch. f. klin. Chir.*, 1903, Bd. 69, s. 541 ; also Bd.71. ; and *Berlin. Klin.*, 1904, No. 1.

[2] *Arch. f. d. gesam. Physiol.*, 1900, Bd. 81, s. 487.

[3] *New York Med. Journ.*, 1896, p. 647.

Lermoyez has given to adrenalin the descriptive title "alkaloide de la bande d'Esmarch." Then followed further observations by ophthalmic surgeons, who found that if suprarenal extract was first applied to the conjunctiva, and then cocaine, atropin, eserine, etc., were applied, the latter had greater effect than if no suprarenal extract had been used. Adrenalin was seen to be a "cocaine sparer," to use a term introduced by Swain. Bukofzer and others found the same effects in the local application of suprarenal extract and cocaine in the nose and larynx, and the combination was applied in dentistry to reduce the bleeding and pain in tooth extraction. Moure and Brindel found that with the addition of adrenalin, a $3\frac{1}{2}$ per cent. solution of cocaine was sufficient to anæsthetise the larynx and nasal mucous membrane; others have used a 5 per cent. solution of cocaine. This is a great reduction in the usual 15 per cent. to 20 per cent. solution frequently used for this purpose. Braun now made use of the combination of a very small dose of adrenalin with cocaine for subcutaneous injection; he found that the local anæsthetic effect of the cocaine was increased and lasted longer. Eucaine combined with adrenalin was also found to be more serviceable than eucaine alone. Tropococaine is not suitable for combination with adrenalin because its characteristic action is soon lost. By the combination of cocaine and adrenalin, it is asserted that the toxic influence of adrenalin is reduced (Rode, Rosenberg). Dönitz [1] found experimentally that adrenalin-cocaine anæsthesia produced by injection into the spinal canal is very much more effectual than cocaine anæsthesia, and that the toxic effects of the latter are less, being reduced to one-tenth. Zeigan [2] agrees with Dönitz that the use of adrenalin reduces the toxicity of the cocaine, but, as a result of his observations on subdural injections in cats, thinks that the toxicity is reduced not to one-tenth, but

[1] *Münch. med. Woch.*, 1903, s. 1452.
[2] *Therap. Monatschr.*, 1904, s. 193.

to about one-quarter. Thies[1] gives results of the effects of the combination of adrenalin and cocaine given together and when the cocaine application succeeds the use of adrenalin. He found that the poisonous character of the cocaine was not quite destroyed by the adrenalin; amongst some of the control animals injected with cocaine and normal saline, toxic effects were less marked than when the cocaine was combined with adrenalin; in none were they worse. Some of the latter died, and some of the control animals did not. In no case did adrenalin prevent the fatal effects of cocaine. Thies goes so far as to explain the death of some of the animals on the ground that the adrenalin caused such long delay in the excretion of the cocaine that toxic effects were produced. The delay in excretion when adrenalin is injected with some substance which can be readily recognised in the urine is shown by Klapp,[2] who found that sugar is excreted by the kidneys much more slowly when it is injected subcutaneously with adrenalin than when injected alone. Braun criticises the observations of Thies, and says that the latter applied such large doses of adrenalin that considerable disturbance was set up attributable to this alone, and that in one case death even occurred, and refuses to accept his observations as disproving the statement that adrenalin reduces the toxic effects of cocaine.

It appears that the protracted stay of cocaine in the seat of injection as a result of the vaso-constrictor effect of the adrenalin does result in an increased local effect of cocaine, and, as a consequence of the activity of the cells upon cocaine, in a reduction of the amount of the latter substance, but no experiments have been made to show that adrenalin exerts a directly neutralising effect upon cocaine in the sense of toxin and antibody.

Riballier[3] has advanced another reason for the com-

[1] *Deutsche Zeitschr. f. Chir.*, 1904, Bd. lxxiv., s. 434, and "Dissertat.," Leipzig, 1903. [2] *Deutsche Zeitschr. f. Chir.*, 1904, Bd. 71, s. 187.
[3] "Thèse de Paris," 1904.

bination of adrenalin with cocaine, for he finds that cocaine alone has but small anæsthetic effect upon inflammatory tissues, whereas the combination produces much more useful results.

The dosage of adrenalin in man has been determined largely by Dönitz and Braun; the former observer, using a solution of 1 in 2,000, found that 0·5 milligramme of adrenalin may be injected into the spinal theca without producing any dangerous symptoms. Braun found that 0·5 mg. or $\frac{1}{2}$ c.cm. of 1 in 1,000 adrenalin solution injected into his forearm produced in five minutes a sensation of oppression in the chest, palpitation, hurried deeper breathing and an increase of the frequency of the pulse. These effects passed off in a minute and a half, and glycosuria did not occur. When Braun made use of a 1 in 10,000 solution of adrenalin he found that he was able to receive 1 mg. without the occurrence of any dangerous symptoms. This author concludes that adrenalin should be given in very small doses *and in great dilution;* the maximum dose should be 0·5 mg., *i.e.*, $\frac{1}{2}$ c.cm. of the solution in 1 in 1,000 adrenalin, and this should be diluted with 50 to 200 c.cm. of the cocaine solution. In minor operations $\frac{1}{6}$ c.cm. of adrenalin solution ($\frac{1}{6}$ mg.) is sufficient. Amongst other reasons against using too large a dose of adrenalin are—(1) large vessels are temporarily closed by strong solutions and so escape the necessary ligature, with the result that after the effect has passed off bleeding occurs; (2) if the tissues are strangled by a strong application of adrenalin, such changes will be produced in the vitality of the cells that subsequent healing of the wound is impaired.

CHAPTER XI.

USES OF ADRENALIN ALONE OR COMBINED WITH COCAINE OR β-EUCAINE.

Several important records of operations performed under local anæsthesia by means of adrenalin and cocaine or β-eucaine have now been reported. Braun has used local anæsthesia in over 500 cases and recommends as a modification of Schleich's solution the following: 100 c.cm. of a ·05 per cent. solution of cocaine hydrochloride, using 6 per cent. sodium chloride solution as a solvent, to which 3 to 5 drops of adrenalin hydrochloride (1 in 1,000) are added; 50 c.cm. to 100 c.cm. of the mixture may be used with safety. Braun recommends, in order to avoid the infiltration of the tissues at the actual seat of operation, that a combination should be adopted of Schleich's method of infiltration with Hackenbruch's so-called "encircling" method, by which the site of operation is surrounded by a circle of infiltrated tissue; the needle should be first inserted into deeper lying tissues of the field of operation, and then into the subcutaneous ones. In opposition to other observers, Braun does not recommend infiltration of the skin itself. Operations may be commenced as a rule about ten minutes after the infiltration. Braun finds that the lower part of the rectum can be made quite insensitive if the deeper tissues around the bowel and the subcutaneous tissues around the anus are injected with 100 c.cm. of a ·05 per cent. solution of cocaine containing 5 drops of adrenalin solution (1 in 1,000). Operation may be commenced in ten minutes. By this means operations may be performed on fistulæ and hæmorrhoids, or the mere dilatation of the sphincters may thereby be rendered quite painless.

The anæsthesia lasts one hour. For the excision of a piece of rib, the solution is introduced in such a way that the line of injection forms a rhomboid including the intercostal tissues above and below the rib to be excised. By this means an operation which is usually carried out under merely relative anæsthesia when a general narcotic is used, can be performed under absolutely anæsthetic conditions. For operations on the scalp for the removal of sebaceous cysts, etc., 10 c.cm. of a solution of 0·1 to 0·2 per cent. of cocaine and 10 drops of adrenalin (1 in 1,000) may be used. For the amputation of a finger 1 to $1\frac{1}{2}$ centigrammes of cocaine dissolved in 1 to 2 c.cm. of normal saline may be used, combined with 2 to 3 drops of adrenalin solution.

Dönitz has produced satisfactory anæsthesia in the lower extremities by injecting into the spinal canal 1 c.c. of 1 in 2,000 adrenalin solution combined with 0·0075 to 0·015 grammes of cocaine; major operations were able to be carried out and there were no toxic effects.

Honigmann[1] confirms Braun's views of the favourable influence of adrenalin upon the toxic effects produced by cocaine and its allies. Braun prefers to use cocaine, but other workers, including Honigmann, use β-eucaine. Honigmann's series of cases numbered 40, and included operations for the relief of stricture of the urethra (using 1 c.cm. of adrenalin solution and 10 c.cm. of 5 per cent. β-eucaine solution), the opening of abscesses, removal of small tumours or cervical glands, and operations for fistula in ano. For the last-named operation he used 5 c.cm. of a 1 per cent. β-eucaine solution to which were added 3 drops of adrenalin solution; for other operations he used 100 grammes of 1 per cent. β-eucaine solution to which was added 1 c.cm. of solution of adrenalin (1 in 1,000).

Foisy[2] also confirms Braun's statements as to the advantage of the combination of cocaine and adrenalin:

[1] *Centralbl. f. Chir.*, 1903, s. 665.

[2] *La Presse méd.*, 1903, p. 256; *Soc. de biol.*, 1903, Feb. 14.

and especially calls attention to the advantages of the combination for use in inflammatory affections. This writer employs three different solutions for use under different circumstances. To produce anæsthesia in inflammatory tissues ten drops of 1 per cent. solution of adrenalin hydrochloride solution are added to 10 c.cm. of a solution of cocaine to the strength of 1 in 2,000 : for large incisions or the removal of diseased tissue, *e.g.* in anthrax and suppurating glands, he recommends a solution of 10–15 drops of 1 per cent. solution of adrenalin hydrochloride and 20–25 c.cm. of 1 in 200 solution of cocaine : for furuncles or panaritia, in which cases it may be desirable not to distend the tissues with much fluid, he uses 1 c.cm. of a 1 per cent. solution of cocaine to which are added 4–5 drops of the adrenalin solution : operation may be carried out after 3–4 minutes. Foisy, in opposition to Braun, recommends that injections should be made actually into the skin, along the site of the future incision, followed by deeper injections. He advises that in all possible cases the patient should be recumbent during the operation ; after the operation, to avoid sensations of vertigo and syncope, the patient should rest recumbent for several hours.

Other favourable reports have been published by Perthes and Meisel.[1]

Gangitans[2] has applied the above combination for producing anæsthesia in 100 cases of general surgery. He uses a syringe which is capable of holding 10 c.cm. of combined solution consisting of 9 c.c. of $\frac{1}{2}$–1 per cent. cocaine solution, and 1 c.cm. of a solution of 1 per 1,000 adrenalin hydrochloride. His series includes thirty-one cases of hernia, excision of the upper jaw, gastro-enterostomy and total laryngectomy ; he also found the combination of special service in operations on the urinary tract. Great care should be taken in administration to patients suffering from

[1] *Verhandl. der Deuts. Gesellsch. f. Chir.*, 1903, i., s. 154.

[2] *Rif. med.*, 1903, Sept. 9.

arteriosclerosis or from renal disease. Gangitans had never had any occurrence of secondary hæmorrhage.

A disadvantage of cocaine, other than the toxic effects already referred to, is that, like atropine, it is readily decomposed by boiling with other substances. β-eucaine does not undergo changes in boiling, so that its solutions can be sterilised. β-eucaine—an artificial alkaloid—is less poisonous than cocaine, and acts a little less powerfully as a local anæsthetic. β eucaine is said also to differ from cocaine in that it causes no constriction of blood vessels.[1]

Mr. A. E. Barker[2] gives details of the preparation of a solution of adrenalin and β-eucaine which, in his hands, has been found to be most serviceable and almost free from unpleasant symptoms. He strongly recommends the use of β-eucaine in preference to cocaine. Powders are made up in glazed papers consisting of 0·2 grammes (3 grains) of β-eucaine, and 0·8 grammes (12 grains) of sodium chloride. The contents of one of these papers are dropped into 100 c.cm. of boiling water, and then 1 c.cm. of adrenalin solution (1 in 1,000) is added, and the whole is allowed to cool down; each 100 c.cm. (100 grammes) of this solution contains 0·8 grammes of sodium chloride, 0·2 grammes of β-eucaine, and one milligramme of adrenalin chloride; as much as 100–200 c.cm. may be injected into a patient, but as a rule 50–60 c.cm. is sufficient. The solution must be prepared at the time of operation, and it is very necessary to ensure that the adrenalin solution is fresh and free from brownish discoloration or turbidity; the adrenalin stock solution, as a rule, when properly protected from light, air, etc., will keep active for several days. The operation may be begun in about twenty minutes after the injection. The operations that have been carried out by means of this solution include eight cases of laparotomy, 23 cases of hernia, five cases of amputation, 12 cases of varicose veins, cases of operation on the thyroid gland, on

[1] Cushney, "Text Book of Pharmacology," 1903, p. 314.

[2] *Lancet*, 1903, ii., p. 203; *B. M. J.*, 1904, ii., p. 1682.

the knee joint, for fistula, for excision of rodent ulcer, for orchidectomy, and for the removal of tumours of a cystic or adenomatous character from the breast. In the case of abdominal laparotomy, it may be necessary during the stage when traction has to be made on any of the deeper lying structures, to give a general anæsthetic for a short time. Equally favourable results are published by Salecker, who uses a solution containing 0·2 grammes of β-eucaine, 0·15 grammes of sodium chloride, and 20 grammes of water; to this solution is added 0·1 c.cm. of a 1 in 1,000 solution of adrenalin or of suprarenin. Chiene[1] was able to perform an operation for the relief of an empyema by using 30 drops of a solution which contained one part of a $2\frac{1}{2}$ per cent. solution of β-eucaine, and one part of a solution of 1 in 1,000 adrenalin chloride. Simon[2] finds that adrenalin increases the effect of β-eucaine and cocaine.

Use of Adrenalin in Gynecological Operations.—Until within the last two or three years local anæsthesia has not been used in gynecological operations except in abdominal section. Freund[3] gives his experience with adrenalin combined with cocaine or with β-eucaine, and favours the latter because it is cheaper and less toxic. The cocaine solution he used was injected from a Pravatz syringe, which contained nine parts of a 1 per cent. solution of cocaine, and one part of 1 per mille solution of adrenalin; the β-eucaine solution consisted of eight parts of 1 per cent. solution of β-eucaine and two parts of 1 per mille adrenalin. Local anæsthesia was found to be useful more especially in operations for prolapsus uteri and plastic operations on the vagina; owing to the anæmia produced by these solutions they were useful also in amputations of the cervix. Less favourable results were obtained in curetting for inoperable carcinoma of the body and cervix. It is advisable, according to Freund, to inject the solutions slowly and with

[1] *Scottish Med. and Surg. Journal*, 1904, vol. xv., No. 3, p. 215.
[2] *Münch. med. Woch.*, 1904, No. 29, s. 1287.
[3] *Zeitschr. f. Gynäk.*, 1904, s. 1481.

pauses, to inject in several places, and to use moderate pressure. To avoid the risk of injecting directly into a vein it is advisable, after insertion of the needle and before injecting the solution, to withdraw the piston of the syringe; if the point of the needle lies within a vein, then blood would appear within the syringe. Peters states that adrenalin and similar preparations may be used with advantage in clearing the field of view in cases of inoperable carcinoma of the cervix; it also increases the effects of the thermo-cautery and of steaming the uterus,[1] and shortens the duration of the application of formalin when this is applied to the uterus or cervix.

Application of Adrenalin and similar preparations to mucous surfaces, etc.—Great advances in the ease with which rhinological, laryngological and ophthalmological operations and examinations can be carried out have followed the introduction of the use of suprarenal derivatives into these departments of practical medicine and surgery. In various operations on the eye, the field of operation may be kept free from blood by the use of adrenalin solution, 1–50 drops of a solution of the strength of 1 in 5,000 or 1 in 10,000. Darier[2] recommends the following solution for the purposes of removal of foreign body from the eye, cauterisation, etc.—ten drops of a solution of adrenalin hydrochloride (1 in 1,000), cocaine hydrochloride 0·1 gramme, distilled sterilised water 10 grammes. For daily instillation in glaucoma, if an operation is not indicated, the following—20 drops of adrenalin hydrochloride (1 in 1,000), cocaine hydrochloride 0·2 grammes, zinc sulphate 0·2 grammes, and distilled sterilised water 10 grammes; to be used two to eight times daily.

MacCallan[3] reported four cases of glaucoma in which adrenalin had caused a rise in tension. In certain cases of

[1] Cramer, *Deutsche med. Woch.*, 1903, No. 34, s. 609.

[2] *Merck's Bericht.*, Jan. 1903.

[3] *B. M. J.*, 1903, i. p. 1208.

scleritis and episcleritis, the application of adrenalin may be followed by increased pain.

Schnaudigel speaks favourably of the use of suprarenin in the treatment of disorders affecting the lachrymal ducts, in phlyctenular keratitis and in spring catarrh.

Macleod Yearsley was one of the first to advocate the use of suprarenal preparations in laryngology.[1] Moure and Brindel report the favourable influence of the combination of cocaine and adrenalin in curettage of the larynx for tuberculous disease; the use of cocaine alone is insufficient to check the pain. Kyle[2] advocated the use of adrenalin hydrochloride in the treatment of diseases of the nose; solutions may be used of the strength of 1 in 1,000 or 1 in 10,000. By its use considerable help is given in diagnosis, catarrhal discharge is controlled, and the field of operation may be rendered bloodless. The mucous membrane should be first rendered anæsthetic with a 2 per cent. solution of cocaine: the subsequent application of the adrenalin prolongs the effect of the cocaine. Rosenberg[3] recommends the use of Freund and Redlich's soluble suprarenal extract in 5, 10, or 30 per cent. solutions, or solution of adrenalin of the strength of 1 in 1,000 or 5 in 1,000. Rosenberger finds that local application is of greater effect than internal medication, but notes that in some cases of vasomotorial coryza and hay fever internal treatment is followed by some improvement. He gave suprarenal substance by the mouth in 0·3 gramme doses four or five times a day. The local effects of the application of soluble suprarenal extract were not of long duration, but were more protracted than those of cocaine, sometimes lasting as long as one hour. In order to secure more lasting effects of the adrenalin, a pomade may be used, made up of 1 part of 1 in 1,000 adrenalin and 2 parts of lanoline or vasoline.

[1] *Brit. Med. Assoc.*, 1889.

[2] *Therap. Gaz.*, 1902, p. 33.

[3] *Berlin. klin. Woch.*, 1902, s. 604.

Baéza [1] describes the beneficial effects of the use of adrenalin in about thirty cases of operation on the nose. It is useful also in certain cases of otitis media and in chronic ulcerative and hypertrophic rhinitis. Baéza finds that the presence of chloretone in solutions of adrenalin is disadvantageous because it causes sneezing when applied to the interior of the nose: this, however, is readily avoided if the application of adrenalin solution is not only preceded but also succeeded by the application of cocaine. Adrenalin is readily absorbed from the nose, so that it should be administered very cautiously to patients who are old or who show vascular disease. Mignon [2] also recommends the use of a pomade for prolonging the effects of adrenalin: its strength is like that of the watery solution 1 in 1,000.

Escat [3] describes the comparative ease with which in three cases of laryngeal polypi these growths were removed after the application of adrenalin, cocaine alone having failed to render this possible. Bukofzer [4] recommends, for use in affections of the nose and larynx, a solution made up of 10 grammes of a solution of adrenalin hydrochloride (1 in 1,000) and 0·5 grammes of cocaine hydrochloride. As observed by Baéza, Bukofzer noticed that the use of a solution containing chloretone may be followed by sneezing, hydrorrhœa, headache and vertigo. The occurrence of bleeding after the effects of adrenalin have passed off is as strongly asserted by some as it is denied by others, but it is generally conceded that the operation for the removal of the tonsils and adenoids should not be performed with the help of adrenalin on account of the liability to hæmorrhage when the adrenalin effects have passed off.

The use of adrenalin solution containing irritant antiseptics, as supplied in the market, may be overcome by adopting the plan of preparing a solution when required

[1] *Berlin. klin. Woch.*, 1902, s. 1217.
[2] *Arch. internat. de laryngol.*, 1903, No. 3, p. 361.
Ibid., 1904, xvii., No. 3, p. 813.
[4] *Deutsche med. Woch.*, 1903, s. 738.

from dry suprarenal extract, from adrenalin, or from suprarenalin which Hecht[1] finds as useful as adrenalin. Douglass[2] recommends the following formula for a solution to be used in the examination and treatment of disorders of the nose, larynx, etc.: to an ounce of water are added 5 grains of cocaine hydrochloride, 10 grains of sodium chloride, 5 grains of eucaine, and 30 grains of dried suprarenal gland, obtained by preference from the pig. This solution may be applied by means of sprays or by pledgets of lint; the pallor produced may last half an hour or even one hour. Douglass warns against the hæmorrhage which may follow operations carried out by means of suprarenal preparations. In such cases the bleeding can be checked by the use of iodoform gauze.

Painless extraction of teeth is rendered possible by the use of a solution of cocaine and adrenalin. A solution is prepared of 1–2 c.cm. of normal saline, containing 1–1½ centigrammes of cocaine, to which 2–3 drops of adrenalin are added. Half the solution is injected in front of the faulty tooth and half behind it, an effort being made to inject as closely as possible to the root of the tooth and to the periosteum. In five minutes the tooth may be extracted.[3]

Use of Suprarenal Derivatives in Urology.—Braun[4] points out that it is not so much the magnitude of the dose of cocaine which is introduced into the bladder as the degree of dilution which is so important. He found that the bladder could be anæsthetised preparatory to a cystoscopic examination by filling it with ·1 per cent. cocaine solution; 1–2 c.cm. of the same solution rendered the urethra anæsthetic; in the latter case, if care is taken not to allow any solution to enter the bladder, 1·0 per cent. cocaine solution may be used. These effects on the bladder can be greatly increased if 1 c.cm. of adrenalin (1 in 1,000) is added

[1] *Münch. med. Woch.* 1904, s. 202.
[2] *New York Med. Journ.*, 1903, p. 780.
[3] Läwen, *Arch. f. klin. Chir.*, Bd. 72, Hft. 2, s. 231.
[4] *Berl. Klin.*, 1904, No. 1, s. 16.

to the solution injected into the bladder or 3 drops of adrenalin solution are added to the injection for the urethra. Von Frisch[1] recommends the use of 150 c.cm. of a solution of 1 in 10,000 adrenalin solution before practising cystoscopy in cases of bleeding from the bladder, the solution being left in the bladder four minutes. A similar proceeding is recommended by Harris.[2] A solution of the strength of 1 in 1,000 may be used in suprapubic cystotomy for the removal of bladder tumours without hæmorrhage. Von Frisch also found adrenalin useful in catheterisation for urethral stricture and for prostatic enlargement and retention of urine: in the latter case a urethral injection of 2 c.cm. of adrenalin solution (1 in 1,000) is capable of removing the impediment and so permitting spontaneous micturition. Kirch[3] found that injection subcutaneously, every two hours, of four doses of 1 c.cm. of adrenalin solution (1 in 1,000) relieved bleeding occurring in the urinary tract.

Owing to the influence exerted by preparations of the suprarenal gland upon involuntary muscle fibre, it has been thought that adrenalin would be useful in cases of atony of the bladder. Moresco[4] injected 150 grammes of a solution of 1 in 50,000, and later of 1 in 25,000 of adrenal solution; the solution was left *in situ* one hour. Moresco was able to report favourable results in two cases after 4–6 injections each.

Spontaneous Hæmorrhage and various Hæmorrhagic Conditions.—Oliver first drew attention to the constricting effect of suprarenal extract when applied directly to blood vessels. Subsequent clinical experience has shown that when hæmorrhage occurs from a surface to which adrenalin may be applied, relief is prompt, and in the large majority of cases lasting; in several of the reported cases

[1] *Wien. klin. Woch.*, 1902, s. 787.
[2] *Annals of Surgery*, 1900, July.
[3] *Deutsche med. Woch.*, 1903, s. 902.
[4] *Gazz. degli Ospedali*, 1903, p. 1035.

of severe bleeding from the nose cured by the use of adrenalin, gauze has alone been used, which, however, is capable of exerting a controlling influence on the hæmorrhage. Wheeler[1] records the account of a case of epistaxis which was so severe as actually to cause faintness; by painting the mucous membrane of the nose as high up as possible the bleeding was checked at once.

Although it is probable that gauze applied to a bleeding point would in any case check bleeding, Benno Müller[2] states that it is possible to impart to gauze, tampons, etc., an extra hæmostatic power by soaking them in $\frac{1}{2}$ to 1 per mille or $\frac{1}{2}$ to 1 per cent. solutions of adrenalin. By a special process devised by Max Arnold of Chemnitz the destruction of the active properties of suprarenin by the gauze, etc., can be prevented, and the difficulty of the decomposition of solutions of suprarenin can be overcome by preparing dry sterile gauze tampons, etc., which have been previously steeped in suprarenin of the above strength. These preparations may be used to check the bleeding from a granulating wound, from the atonic uterus, and in cases of deep tears of the cervix.

Gray[3] has tried the effect of suprarenal preparations for the relief of the sanguineous expectoration of pneumonia.

Treatment of Hæmorrhoids.—Bouchard recommended the application of compresses soaked in preparations of the suprarenal gland for the relief of external piles. Le Noir[4] made further practical application of Bouchard's method. Tampons of cotton wool soaked in a solution of 1 in 1,000 adrenalin were applied to the hæmorrhoids; within an hour the congestion was greatly diminished. Mossé[5] has successfully applied adrenalin in a case of hæmorrhoids which threatened to become strangulated.

[1] *B. M. J.*, 1903, i., p. 849.
[2] *Wien. klin. Rundschau.*, 1904. s. 631.
[3] *Med. Record*, 1902, April 5, p. 527.
[4] *Soc. méd. des hôp.*, 1902, p. 980.
[5] *Ibid.*, 1903, p. 108.

He applied tampons soaked in 1 in 2,000 solution of adrenalin and some relief was obtained; the next day tampons soaked in 1 in 1,000 were applied. Although the pulse had fallen to 54, tampons were still applied for a day or so longer, when very great relief was secured. Breton [1] finds that the occurrence of bleeding from piles during relief of the bowels can be obviated by the application to the hæmorrhoids daily for five or six days of a tampon soaked in 1 in 1,000 of the extract of the suprarenal body. Demay de Cetenet [2] relieved the pain of hæmorrhoids by the use of tampons soaked in solution consisting of 30 cubic centimetres of water to which were added 30 drops of 1 in 1,000 adrenalin chloride and ·03 grammes of cocaine hydrochloride, or an ointment was made of the same quantities of adrenalin and cocaine combined with 15·0 grammes of vaseline.

Although it is known that mere contact with hydrochloric acid or pepsin does not destroy the power of the active suprarenal principle, yet, knowing the rapidity with which adrenalin and other preparations of the suprarenal body lose their activity as a result of oxidation, when brought into contact with living tissues, it is somewhat perplexing to find that very satisfactory reports occur of the influence of adrenalin, etc., when taken by the mouth, upon bleeding occurring in the stomach or intestines, a procedure recommended by O. F. F. Grünbaum.[3] Soltau Fenwick [4] recommends the administration of 10 ounces of a freshly prepared decoction, containing two grains of the desiccated gland to the ounce; the dose may be repeated in two hours, and even three such doses may be given during four hours. The best effects were obtained in acute gastric ulcer near the cardiac orifice. Half-drachm doses of adrenalin (1 in 1,000) given by the mouth have been found to check gastric

[1] *Gaz. des hôp.*, 1903, p. 761.
[2] *Journ. de méd. de Bordeaux*, 1904, p. 351.
[3] *B. M. J.*, 1900, ii., p. 1307.
[4] *Ibid.*, 1901, ii., p. 1596.

bleeding,[1] and doses of 0·5 to 3·0 milligrammes of adrenalin on injection under the skin have been said to check bleeding occurring from the mouth, nose, rectum and uterus. Carl Lewin[2] used epirenan (a pure form of epinephrin) for gastric bleeding, giving 15 drops of 1 in 1,000 solution every three hours. Graeser[3] checked severe intestinal bleeding in typhoid fever by giving three hourly doses of 30 drops of adrenalin hydrochloric solution (1 in 1,000) by the mouth ; ice, opium, bismuth and ergot had proved to be of no use. It is to be presumed in this case that the adrenalin had reached the bleeding points before it had been chemically altered. Possibly this is the explanation of the relief of cases of rectal bleeding when adrenalin is taken by the mouth.

Hæmophilia.—Reports have recently appeared on the favourable influence of suprarenal preparations in cases of hæmophilia. Thelwall Thomas[4] describes the good effects of suprarenal extract in two cases of hæmophilia. In the first case—an infant, a wound of the lip was followed by severe hæmorrhage, which yielded to packing with gauze (!) powdered with suprarenal extract, and a four-hourly dose of one grain of the extract. Similar treatment was successful in an adult hæmophiliac aged twenty-three years. Gray Duncanson[5] records a case of severe bleeding in a hæmophiliac, following upon a punctured wound of the eyelid ; this was soon checked by the local application of adrenalin. Lange,[6] in a report on severe cases of obstinate bleeding relieved by adrenalin, gives an account of a bleeder who suffered from severe hæmorrhage following upon an incision of the thumb ; plugs dipped in equal parts of a solution of adrenalin hydrochloride and normal saline were applied,

[1] Mills, *B. M. J.*, 1903, i., p. 731.
[2] *Fortsch. der Med.*, 1905, No. 1., s. 6.
[3] *Münch. med. Woch.*, 1903, s. 1294.
[4] *B. M. J.*, 1901, vol. ii., p. 1527.
[5] *Ibid.*, 1903, i., p. 421.
[6] *Münch. med. Woch.*, 1903, s. 62.

and the bleeding ceased at once. Schlesinger reports[1] the favourable effects of suprarenal preparations in a case of hæmophilia; the patient suffered from severe intestinal bleeding and 10–20 drops of adrenalin solution were administered by mouth every hour; the bleeding ceased and no untoward effects were noticed, although the patient had taken 30 grammes of the solution, or 30 milligrammes of adrenalin, in two days. A case reported by Francis[2] also appears to show that adrenalin is able to exert a very favourable influence on the bleeding of hæmophilia, although in this case the patient ultimately succumbed.

Severe Bleeding in Purpura.—These cases also are greatly benefited by the use of adrenalin chloride. Holt[3] successfully treated a new-born child suffering from hæmatemesis and purpura; twelve hours from the beginning of the treatment the hæmorrhage had ceased completely; one grain of a saccharated extract was given every hour for 6–8 hours, and then half the quantity for the remaining hours. Holt refers to cases of cure reported by Schilling, Béclère and Anderodias.

Bryan[4] was able to check severe post-partum hæmorrhage in a purpuric woman by the local application of 1 in 5,000 adrenalin solution; he admits, however, that despite the administration of 10 ♏ doses every four hours of 1 in 1,000 adrenalin solution given for the purpuric condition of the skin, a severe hæmorrhage occurred on the third day which appeared to be relieved by an ergot mixture. Tito[5] reports the cure of a case of morbus maculosus Werlhofii by the injection of 1 c.cm. of a 1 in 1,000 adrenalin solution, which was repeated; complete stoppage of the bleeding occurred. Schlesinger[6] reports a similar

[1] *Wien. klin. Woch.*, 1904, s. 317.
[2] *B. M. J.*, 1904, i., p. 1247.
[3] *Arch. of Ped.*, 1902, p. 278.
[4] *B. M. J.*, 1904, i., p. 1254.
[5] *Gazz. degli Osped.*, 1904, xxv., p. 714.
[6] *Loc. cit.*

cure. Breton [1] gives a description of a cure of a multiple hæmorrhage occurring in a case of suprarenal cancer in a man æt. fifty-nine years. The bleeding was checked by twenty drops a day of adrenalin solution, the patient dying from cachexia only, and not from loss of blood.

Treatment of Hæmoptysis.—It has already been pointed out in the section dealing with the physiological characters of adrenalin and other derivatives of suprarenal glands, that there is little support for the view that hypodermic or mouth administration of these substances can have any beneficial effects upon bleeding occurring from destructive tuberculous disease of the lungs. Notwithstanding this, some reports have been published which would seem to show that an improvement has followed the use of suprarenal preparations; in other cases no favourable results have followed. The teachings of physiology are more to be relied upon than the clinical reports which so far have been published, and in which it is impossible to say that the good results were not due to other factors. Lange found that thirty drops of solution of adrenalin (1 in 1,000) administered by mouth every two hours successfully influenced a case of hæmoptysis, and Flörsheim gave doses of 0·003 grammes of suprarenal powder with good results. Voigt,[2] in two cases of severe hæmoptysis, injected subcutaneously 1·0–1·5–2·0 c.cm. of 1 in 1,000 adrenalin solution; the hæmorrhage stopped at once. Voigt was unable to secure effects by means of mouth administration. Hedley [3] records the case of a young clergyman suffering from tuberculosis of the lungs and hæmoptysis. The ordinary remedies, such as ergot, opium (by mouth and hypodermically), dilute sulphuric acid, hazeline, terebene, the local application of ice, and absolute rest, were unable to check the bleeding; a teaspoonful dose of 1 in 5,000 solution of suprarenal repeated three times checked it,

[1] *Gaz. des hôp.*, 1903, p. 761.
[2] *Münch. med. Woch.*, 1904, s. 662.
[3] *B. M. J.*, 1904, i., p. 365.

and there was no recurrence during two months of observation; the same writer met with equally good results in a second case. Bowen[1] successfully treated a case of hæmoptysis with two five-grain tabloids of suprarenal extract; rest in bed, applications of ice, the internal use of gallic acid, ergot, hamamelis, turpentine, and morphine had entirely failed. Renon and Louste[2] have successfully used suprarenal extract in hæmoptysis, and Souques and Morel[3] also have caused a cessation of hæmoptysis by means of subcutaneous injections. They administered ½ c.cm. of 1 in 1,000 solution, and appeared to get favourable results in four out of nine cases. In agreement with Braun they say that not more than one milligramme of adrenalin should be administered subcutaneously. Duncan Macdonald[4] found that suprarenalin did no good so far as the ultimate issue of a case of hæmoptysis was concerned. He gave a drachm of 1 in 5,000 solution or 5–24 minims of 1 in 1,000 solution three or four times a day. Gray Duncanson[5] refers to a case of hæmoptysis treated with adrenalin. Although at first it appeared that the hæmoptysis was relieved by the use of adrenalin, later on it recurred under the treatment; for reasons already given he concludes that the use of adrenalin in hæmoptysis is inadvisable unless an attempt be made to reach the seat of hæmorrhage by means of an intratracheal spray.[6] Bouchard, in two cases of hæmoptysis, introduced adrenalin into the air passages by puncture of the trachea; in one case a cubic centimetre of a solution of 1 in 10,000 arrested the hæmorrhage during several hours; this was followed the next day by a similar dose, but of twice the strength; the hæmoptysis did not recur.[7]

[1] *B. M. J.*, 1904, i., p. 784.
[2] *Soc. méd. des hôp.*, 1902, p. 983.
[3] *Ibid.*, p. 975.
[4] *B. M. J.*, 1904, i., p. 1247.
[5] *Ibid.*, p. 603.
[6] *See* also *Lancet*, 1904, i., p. 369.
[7] Le Noir, *Soc. méd. des hôp.*, 1902, p. 980.

Vaquez[1] tried the effect of injecting directly into the lung substance 8–10 drops of 1 in 1,000 adrenalin solution mixed with 5 c.cm. of normal saline. The results were favourable.

Other Applications.—Suprarenal preparations have been applied for the relief of gastro-intestinal atony. Marricardi found that Vassale's preparation of the medulla of the suprarenal capsules of oxen known as *paragangline* is beneficial in cases of atony of the stomach when given by the mouth : the same mode of administration is, however, less efficacious for atony of the intestine ; in the latter case, it is advisable to administer the drug by the rectum as an enema, purgation is excited. The dose given per rectum is 30–100 drops of paragangline. In gastric atony the arrest of fermentation and the increase of body weight are probably due to the more adequate propulsion of the contents of the stomach. Baccarani and Plessi,[2] a few months previously to Marricardi, had made observations on fourteen cases of gastro-intestinal atony treated by means of paragangline. This substance does not appear to lose its activity even after twenty-four hours' contact with the stomach wall. Forty to sixty drops of the preparation were given daily in divided small doses, always, with the exception of two cases in which it was given in one large dose, without any unpleasant symptoms. The results were favourable, probably due to the increased motor activity of the stomach, and persisted after the treatment was stopped. Judging from the effects on the quantity of nitrogen lost in the urine and the stools, the use of paragangline had led to increased metabolic and digestive changes, and Baccarani and Plessi conclude that certain cases of gastro-intestinal dyspepsia are dependent upon functional insufficiency of the suprarenals.

Preparations of the suprarenal bodies have been used in other conditions in which it is to be presumed that they

[1] *Soc. méd des hôp.*, 1902, p. 981.
[2] *Die med. Woch.*, 1903, p. 393.

acted upon the muscular tissue of the organs concerned. Roy-Teissier [1] treated two patients suffering from cardiac weakness and emphysema with 0·5 milligrammes daily of adrenalin or 0·05 milligrammes every two hours. Improvement was prompt, and Roy-Teissier attributed the good results to the reduction of the cardiac dilatation and to the rise of blood pressure produced by the use of the drug; owing to the oxidation of the drug by the tissues when given subcutaneously, he considers it is more advisable to administer by the mouth. Considerable care is required in the choice of such cases for treatment by means of adrenalin, for in elderly subjects, or those the subject of grave myocardial weakness, an increase of arterial tension may be followed by disastrous results. Solis Cohen recommends the use of Abel's epinephrin, which has been placed on the market as suprarenaline, as a remedy for those cases of asthma which are associated with lowered vasomotor tone. It is best given to be absorbed from the tongue; 1½ grains may be so absorbed every hour or second hour or third hour. Similar good results are obtained in cases of hay fever with low arterial tension. Bullowa and Kaplan [2] recommend the use of adrenalin hydrochloride in the angioparetic forms of asthma, but, contrary to ordinary experience, find the best results are obtained when the drug is injected hypodermically. Doses of 3–6 minims of the 1 in 1,000 solution are recommended: the attacks are relieved in two minutes. Aronsohn recommends for asthmatical attacks dependent upon affections of the nose, a spray composed of one part of adrenalin (1 in 1,000) and two parts of liquid paraffin, or an ointment consisting of 1–5 grammes of adrenalin solution (1 in 1,000) and 5 grammes each of lanoline and vaseline.

Suprarenal extract has been found useful in functional disorders of the heart associated with lowered arterial tension. Migraine, which is generally considered to be

[1] *La méd. mod.*, 1904, p. 230.

[2] *Med. News*, 1903, p. 787.

associated with spasm of the arteries in the neighbourhood (Thoma), has also been relieved by the use of these preparations. Neurasthenia, in certain cases, is found to be associated with lowered arterial tension; Bernard and Heitz [1] in such a case found post-mortem that the only changes present were atrophic ones, affecting the medulla of the suprarenal bodies. On grounds such as these, suprarenal extract has been used with the view of increasing the arterial tension and so getting rid of the symptoms of neurasthenia. Souques and Morel refer to the satisfactory results obtained by Huchard, Dufour and Roques de Fursal in the treatment of cases of neurasthenia by means of suprarenal preparations. Galvagni reports the cure of a case of myasthenia by means of Vassale's paragangline. Crile [2] injected a patient intravenously on several occasions with 1 c.cm. of one part of adrenalin in 50,000 normal saline solution. The patient had received a very severe injury. Crile considers that the prolongation of life for nine hours was due to the use of adrenalin and a general external pressure kept up by means of a pneumatic rubber suit. Similar favourable results have been reported by Martin and Pennington,[3] who treated six cases of shock following operation. They injected 0·2 centigrammes of adrenalin in a solution of 1 in 100,000 with 100 c.cm. of normal saline. Barr [4] reports favourably on the use of adrenalin in the treatment of pleural and peritoneal effusions. He recommends the injection of a drachm of 1 in 1,000 solution into the pleural cavity and of 2–3 drachms into the peritoneal cavity after the removal of the fluid, a procedure which, however, by itself is sufficient in some cases to prevent any further effusion.

Engman and Loth [5] found that suprarenal gland is

[1] *Bull. méd.*, 1904, p. 356.
[2] *Bost. Med. and Surg. Journ.*, 1903, p. 247.
[3] Péry, *Journ. de méd. de Bordeaux*, 1904, p. 121.
[4] *B. M. J.*, 1904, i., p. 649.
[5] *New York Med. News*, 1903, p. 1023.

useful in certain skin diseases, such as general pruritus, chronic urticaria and lichen urticatus. They recommend for children doses of 0·03 to 0·06 grammes three times a day and for adults ·06 to 3·0 grammes three times a day, taken immediately after food; care must be taken lest headache, vomiting and diarrhœa are produced by the drug. On the other hand, the use of adrenalin has been found to cause urticaria. Rosenberg [1] records the case of a young girl who after the application of adrenalin to the nose developed urticaria; eight days later the drug was again applied and urticaria again developed. Beurmann has used suprarenal preparation in cases of lupus with favourable results.

Lépine suggests that adrenalin would be of service in cases of exophthalmic goitre, as a means of counteracting the dilation of the blood vessels. According, however, to the observations made by Donath [2] and by Spiethoff,[3] the blood pressure in exophthalmic goitre is very variable. Their observations, made by means of various forms of sphygmometers, prove that there is no constancy in the degree of tension in exophthalmic goitre; usually blood pressure was found to be normal or a little raised: even in severe cases only some showed a fall of blood pressure. In these latter cases adrenalin might be expected to exert a favourable influence on the tension of peripheral arteries, but even then it would be a somewhat dangerous treatment, considering the fact that in the severe cases the heart's action is so feeble. Solis Cohen has reported favourably on the use of suprarenal preparation in exophthalmic goitre, especially when combined with thymus feeding. Benedict has recommended the use of adrenalin (0·00025 gramme internally) in cases of cardiac disorder dependent on vasomotor disturbances. Clark [4] has recommended the use of

[1] *Berlin. klin. Woch.*, 1903, s. 939.

[2] *Zeitschr. f. klin. Med.*, 1903, Bd. 38, s. 203; Bd. 48, s. 65.

[3] *Centralbl. f. innere Med.*, 1902, No. 34, s. 849.

[4] *B. M. J.*, 1895, i., p. 1086.

suprarenal preparations for the relief of the hydruria of diabetes insipidus, which is considered by many observers to be a vasomotorial disturbance of the renal vessels. The urine passed by a woman, aged 39 years, was reduced from 30 pints to between 2 and 3 pints; it increased again when the treatment ceased.

The results of the treatment of rickets by means of these substances, though favourably spoken of by Stoeltzner,[1] who used rachitol, are not convincing, nor would the present-day views of the pathology of this disorder give any hope of improvement by such treatment. (*Vide* Netter [2] and Hönigsberger.[3])

Adrenalin has been found useful in cases of apparent death (asphyxia, submersion and chloroform syncope). Reichert [4] has had good experimental results in the treatment of poisoning by opium and morphine by means of the same remedies, and Exner [5] has been able to show experimentally that peritoneal injection of suprarenal preparations has retarded the absorption of toxic substances such as strychnine.

[1] *Deutsche med. Woch.*, 1899, s. 614.
[2] *Centralbl. f. Stoffwechs. u. Verdauungskr.*, 1901, s. 614.
[3] *Münch. med. Woch.*, 1901, No. 16, s. 627.
[4] *Univ. of Pennsyl. Med. Bull.*, 1901, p. 91.
[5] *Arch. f. exp. Path. u. Pharmakol.*,1903, Bd. l., Hft. v. & vi., s. 313.

CHAPTER XII.

PATHOLOGICAL CHANGES IN THE SUPRARENAL GLANDS.

Rolleston[1] has summarised the various pathological changes occurring in the suprarenal bodies; some are merely pathological curiosities and are devoid of any clinical importance, as they may be quite unassociated with any clinical manifestations. Among the more frequent changes met with are shrinkage of the gland—to such an extent in some cases that the atrophied organ may be overlooked. This atrophy may be a part of the general retrogressive changes taking place as a result of old age, or may be due to disturbances of the arterial supply. Various forms of degeneration are also met with in the suprarenal body, including cloudy swelling, fatty degeneration, hyaline and colloid changes and lardaceous transformation. Various growths may involve the suprarenal as primary or secondary manifestations; simple growths include adenomatous formations, many of which are probably of the nature of accessory suprarenal bodies. Syphilis may show itself as gummatous formations, or as a general fibrosis of the organs. Cystic formations occur within the gland, and hæmorrhages are met with, some due to injury, some to other causes. Tuberculosis may attack the suprarenal bodies as part of an acute miliary dissemination, but it may assume the chronic form; the tuberculous deposit takes place in the medullary portion first.

In accordance with the prevailing tendency to describe functional disturbances of the kidney, liver, thyroid gland etc., just as for a much longer period descriptions have been

[1] Allbutt's System of Medicine, vol. iv., p. 540 *et seq.*

given of the functional disorders of the central nervous system, *e.g.* hysteria and hypochondriasis, attempts have been made to establish a functional disturbance of the suprarenal glands (Neusser). Reference has already been made to Sergent and Bernard's efforts to associate functional disturbances of the suprarenal functions with asthenia and gastro-intestinal and vascular disturbances. The great objection to this effort is the obvious one that at present the action of the suprarenal body in health is not fully understood. Bernard and Heitz [1] also have endeavoured to show a relationship between some forms of neurasthenia—a disorder hitherto considered to be due to functional disturbance of the nervous system—as a result of atrophic and degenerative changes in the suprarenal bodies.

Addison's Disease.—The pathology of this disease remains one of the enigmas of medicine. Efforts have been made by some writers and by Addison himself to restrict this designation to those cases in which the symptoms originally described by Addison were associated with fibro-caseous and finally fibrous change of the suprarenal bodies of a tuberculous nature. It appears, however, that this is undesirable in view of the fact that symptoms identical with those of Addison's disease occur in individuals in whom it is ultimately found that the changes in the suprarenals are those of secondary (practically never of primary) malignant disease of the glands, of simple atrophy (*i.e.* independent of antecedent inflammatory changes), of atrophy associated with chronic inflammation, of hæmorrhage into the medulla, or are those associated with the development of echinococci (Bukofzer). The symptoms of Addison's disease may occur independently of any changes in the suprarenal glands—12 per cent. of all cases, according to Hansemann[2] and 30 per cent. of all cases according to Lewin,[3] the only signs of pathological changes being pressure upon

[1] *Bull. méd.*, 1904, p. 356.

[2] *Berlin. klin. Woch.*, 1896, s. 296.

[3] *See* Bukofzer, *Deutsche med. Woch.*, 1903, s. 738.

or inflammation of the semilunar ganglia and its connections with the solar plexus. Finally, as Rolleston points out, the suprarenals may be apparently completely destroyed by carcinoma, or by tuberculous disease, and yet no symptoms of Addison's disease are present; the same writer suggests that this may be due to the fact that the patient's life was cut short before the symptoms of Addison's disease had really developed. In twelve of a series of forty-nine cases of Addison's disease dependent upon tuberculous disease of the suprarenal bodies, the sympathetic system was found normal. From the point of view of the importance of the suprarenals in the causation of Addison's disease, it is an interesting fact that so far it has been found impossible to produce experimental Addison's disease by removal of the suprarenal bodies, but answers are found to this difficulty: (1) the animals die before the characteristic symptoms can develop; (2) in those cases in which the animals do not die, life is maintained by the hypertrophy of accessory suprarenal bodies which have not been removed, or by a remnant of the suprarenal body not removed at the operation.

It has already been observed that the suprarenal bodies, like the thyroid and pancreas, consist of two different tissues and that probably these two different tissues subserve different functions, the one (medulla) providing an internal secretion and the other (cortex) acting as an excreting organ. The evidence affirming that Addison's disease is due to a failure on the part of these functions is inconclusive, and the disappointing results in a large number of cases in which an attempt has been made to remedy Addison's disease by the use of suprarenal preparations lend some objection to the view that Addison's disease is due entirely to a defective supply of the internal secretion of the organ.

Very many of the difficulties met with in the explanation of the pathology of Addison's disease are removed by closer attention to the observations originally made by

Kohn and more recently by Wiesel on the similarity between the so-called chromophilic cells of the sympathetic ganglia and other parts of the sympathetic system and the chromophilic cells found in the medulla of the suprarenal body; this chromophilic tissue, which has been shown to be closely associated with the function of adrenalin production, consists thus of two parts, a "sympathetic" portion and a "suprarenal" portion; either of those alone may or may not be able to supply adrenalin as an internal secretion sufficient for the needs of the body. If one of these tissues is destroyed, then the internal secretion of adrenalin is adequate or not, according as the remaining chromophilic tissue is or is not capable of performing the work. It would thus be possible to explain the failure to produce experimental Addison's disease by assuming that though the suprarenal bodies are removed the amount of chromophilic tissue still left is sufficient for the needs of the body. The objection to this view which at once occurs is that suprarenal preparations do not cure cases of Addison's disease, but possibly this may be explained on the ground that toxic effects produced by the disease of the suprarenal bodies have proceeded so far as to have produced changes in other vital organs or tissues which cannot be remedied by the introduction of suprarenal preparations. Wiesel found in five cases of clinically manifest Addison's disease that the chromophilic cells—"sympathetic" and "suprarenal"—were absent, whilst a normal suprarenal cortex was found both in the suprarenal bodies and in the various accessory bodies present. Despite the fact that adrenalin is not destroyed by hydrochloric acid and pepsin, it is possible that mouth administration leads to considerable disturbance in the character of suprarenal extracts; unlike the thyroid gland, the suprarenal bodies have not been shown to have ever had embryological connection with the alimentary tract by means of which their secretion might reach the digestive tube.

Value of Suprarenal Extract and other derivatives in

the treatment of Addison's disease.—In comparison with the results obtained by the thyroid treatment of myxœdema, the suprarenal treatment of Addison's disease has proved of doubtful efficiency. There are various reasons why such treatment should fail, and they may be thus summarised.

1. The physiology of the suprarenal bodies is not as well understood as is the physiology of suprarenal extracts, of adrenalin obtained from the whole gland, or of Vassale's paragangline obtained almost entirely from the medulla. The medulla of the suprarenal body is relatively a small part of the whole gland, and the cortex is proportionally greater; it is probable that the cortex is of vital importance to the individual. Biedl [1] destroyed the interrenal body of Selachii, the fish died within two or three weeks and apparently with symptoms allied to those met with in mammals when the suprarenal bodies are ablated, and yet, as Swale Vincent has shown, the interrenal body contains no material which exerts an action like that of suprarenal extract. Biedl has found on six occasions that after removal of almost all the suprarenal tissue in animals, leaving behind nothing but a portion of cortex, the animal survives. On the other hand, animals in which he left nothing but the medulla, the cortex alone being removed, succumbed. As Biedl points out, this would suggest that the cortex is an important part of the suprarenal body. It is for various reasons probable that the cortex is excretory. It is not to be expected, therefore, that the suprarenal bodies or extracts, or adrenalin, or any other pure preparation would serve to take the place of a gland which in health is both secretory and excretory. As has already been pointed out, Cristiani opposes this dual action of the suprarenal gland, because animals die after removal of the suprarenal bodies, although previously they had been successfully grafted with cortical cells, and Wiesel has shown that the cortical cells may be quite healthy in individuals who have succumbed to Addison's disease.

[1] "Innere Secretion," Wien, 1904, s. 55.

2. Supposing, however, that the suprarenal bodies are important merely from the point of view of their internal secretion of adrenalin, it is not at present certain that an adequate amount of adrenalin can be absorbed into the system unaltered during the passage of raw suprarenal glands, dry substance, or pure preparations, along the alimentary tract, the efficiency of the treatment of myxœdema notwithstanding, as there are developmental reasons why thyroid treatment should be successful.

Hypodermic medication is complicated because of the fact, now well established, of the rapid oxidation of adrenalin, etc., by the tissues. Even if intravenous injection of the active principle were quite safe, the practice would be impossible because of the impracticability of maintaining continuous treatment. With respect to the question whether the presence of tuberculous disease is responsible in itself for special features in the symptomatology and course of Addison's disease, it must be remembered that Addison's disease has been noticed in the entire absence of any tuberculous lesion in the suprarenals or elsewhere. It appears, however, that cases of merely atrophied suprarenals, as opposed to cases of tuberculous suprarenals, show a better reaction to organotherapeutic measures than do the tuberculous cases.

Besides the above reasons for failure, an important fact must be remembered, that in Addison's as in Graves' disease, the progress of the malady is not necessarily uninterrupted; there may be periods of quiescence and there may be periods of improvement, even in the absence of any treatment which may be considered favourably to influence the malady before organotherapy was introduced cases of cure were reported. It further appears that there is some doubt whether certain cases of cure have really been examples of Addison's disease; and in those cases in which improvement has been noted it is possible that this was restricted to those symptoms which physiological experiment has shown to be capable of receiving benefit from such treatment.

Richter,[1] in his general survey of organotherapy, sums up the curative effects of suprarenal substance in Addison's disease as nil. Huismans, in discussing the question whether the symptoms are or are not due to failure of internal secretion, says that the failure of the treatment of Addison's disease by suprarenal preparations proves that the disease is not due to absence of the internal secretion. Von Korczynski [2] concludes that there is no favourable specific influence traceable in the use of suprarenal substance in Addison's disease. He says that in a large number of cases improvement is only transitory and the disease always ends fatally; that there is no question of healing in the same sense as in the case of myxœdema by means of thyroid preparations; that at the most the suprarenal treatment of Addison's disease produces prolongation of life and that he cannot say there is any hope of cure by this treatment. Kinnicut[3] has collected the results of treatment of forty-eight cases of Addison's disease by means of suprarenal preparations; six of these were reported as cured and twenty-two improved. Owing to the remissions in the severity of the disease, scepticism prevents the acceptance of the verdict "cured" in cases observed for a short time. Deeks [4] describes a well-marked case of Addison's disease as cured by means of suprarenal extract; the observation of this case lasted merely through the months of April and May (!). Boinet,[5] however, describes a case of Addison's disease in a man aged 39 years who, during five-and-a-half years had received no less than 220 injections of suprarenal extract prepared according to the methods of Brown-Séquard and d'Arsonval. Very marked improvement took place; all treatment ceased for one year and at the end of this period there were no signs of the malady. Five other cases similarly treated

[1] *Berlin. Klin.*, 1900, Hft. 139, s. 19.
[2] *Wien. Klin.*, 1902, s. 41.
[3] *American Journ. Med. Sc.*, 1897, July, p. 1.
[4] *Montr. Med. Journ.*, 1902, p. 509.
[5] *Bull. de l'acad. de méd.*, 1903, p. 453.

showed improvement, but two others grew worse under the treatment and subsequently died. Boinet does not think good results can be expected in advanced cases. A more recent report on the effects of the results of organotherapy in Addison's disease has been made by Adams.[1] He has collected the reports of 105 cases, and has considered them in four groups divided in accordance with the results obtained. The first group includes seven cases; alarming or fatal results followed the treatment of these cases by means of grafts or injection or ingestion of suprarenal glands; there was no evidence to show, however, that the latter ordinary methods of treatment were the cause of the unfavourable results; more probably the unfavourable results depended on the disease rather than upon the treatment. The second group, numbering forty-nine cases, included those in which there was no benefit or only doubtful results. Group three includes thirty-three cases in which marked improvement occurred. Group four includes sixteen cases in which an apparent permanent cure took place as a result of organotherapy. In discussing groups three and four, Adams refers to the well-known observations of periods of spontaneous improvement and relapse which may account for some of these beneficial results, as well as to the fact that a few cases were known to get well spontaneously before the introduction of organotherapy; rest in bed and other modes of treatment may also have contributed to the favourable results, and mistaken diagnosis may have to a certain extent accounted for a number of cures.

However, as Adams points out, there are at least six cases of the series No. 59 and No. 80 (described by Anderodias), No. 70 (Dieulafoy), No. 82 (Oliver), No. 83 (Stockman), and No. 97 (Bate), which give support to organotherapy, because in them relapses occurred if the treatment was discontinued It is impossible to say how much of the improvement even in these cases was due to suggestion.

[1] *Practitioner*, 1903, vol. lxxii., No. 4, p. 473.

The deduction made by Adams from the use of suprarenal preparations in Addison's disease is that most probably disappointment will follow, that in some cases, even with very marked asthenia, real benefit will follow, but that it is unfortunately impossible to foretell which cases will respond. Despite the very cautious and extremely critical attitude adopted by Adams, it is impossible to feel that in treating Addison's disease with suprarenal preparations by doses intermittently administered by mouth or hypodermically, a rational method is being adopted. It would almost appear that unless grafting of both parts of the suprarenal body is rendered possible, all hope of cure of Addison's disease by organotherapy must be abandoned. The observations of Christiani already referred to and the recent ones of Parodi[1] show how impossible it is to secure a successful graft of medullary cells, and that the cortical cells do not survive grafting for sufficient time or in sufficient vitality to replace the normal suprarenal cortex.

Judging by the favourable results obtained by the judicious use of tuberculin against pulmonary tuberculosis, more hope would be found in an early application of this remedy to those cases of Addison's disease which, discovered in an early stage of development, are found to give a tuberculin reaction.

Vernescu[2] has described a case of the "form fruste" of Addison's disease, which responded favourably to suprarenal tabloids and extract. Adams, quoting Dieulafoy, remarks that the latter observer makes the interesting statement that sudden death is more likely to occur in the "form fruste," *i.e.* those cases in which the pigmentation of the skin is wanting, so that possibly this result was averted by organotherapy in Vernescu's case.

Reports on the use of adrenalin in Addison's disease are scanty. Raven[3] describes a most interesting case in

[1] *Lo Sperimentale*, 1904, p. 47.
[2] *Spitalul*, 1904, xxiv., 15 and 16, p. 427.
[3] *B. M. J.*, 1904, i., p. 131.

which, however, the difficulty again arises whether the symptoms abated under treatment or spontaneously. The patient was observed to develop pigmentation of the skin in 1893 after an attack of scarlet fever. During the next four years the pigmentation increased, and fainting attacks and diarrhœa and vomiting were observed. At the end of another four years she was still very weak and had fainting attacks, and at one time, when the outlook seemed hopeless, she appeared to rally under treatment with suprarenal treatment (tabloids). In 1903 she developed severe and recurring epileptiform attacks. She lay comatose for a week, and the cardinal signs of Addison's disease developed very fully; the pulse rate was 120 to 150 per minute. Consciousness returned, the pulse improved and convulsions ceased after the administration of 5 minims of adrenalin solution (1 in 1,000) three times a day. Subsequently the dose was increased to 10 minims, and at the end of a month the symptoms were greatly improved, the pulse rate being 80 to 90 per minute. The patient steadily improved under a continued treatment with adrenalin, and eleven months from the beginning of the treatment was able to be up and about, the dose given being 10 to 20 minims. A case described by Symmers[1] shows, however, that death may occur in spite of a combination of adrenalin and suprarenal treatment during 143 days. Symmers' experience and that of Raven merely confirm the opinion already expressed that Addison's disease is not amenable to the ordinary treatment by hypodermic or mouth medication, and what is said of suprarenal substance may be said of the active principle adrenalin.

Suprarenal cytolytic sera.—Studies in this direction are very limited. Abbott[2] showed that the serum of rabbits, previously injected with preparations of the suprarenal bodies of guinea-pigs, exerted no definite cytolytic effects on the suprarenal bodies of fresh guinea-pigs injected with

[1] *Med. News*, 1904, p. 502.

[2] *Transact. of the Assoc. of Americ. Physic.*, 1903.

the rabbit's serum. The animals, however, became stupefied and weak, and the temperature was noticed to fall 1°–2° C. below normal : some of the animals recovered and others died, apparently from a hæmolytic action on the part of the serum injected. Gildersleeve [1] endeavoured to settle how much the toxic effect of the serum was dependent on hæmolysis, and how much dependent on a special suprarenal effect. Gildersleeve concluded that there was a slight degree of toxic effect due to the suprarenal bodies, which, before injection, had been well washed through with saline, but admits such effects were very transient.

Even if it were proved that a cytolytic serum could be produced, there are at present no reasons for thinking there is any scope for the application of such serum, for so far there is no evidence for the belief that any group of symptoms is produced by hyperfunction of the suprarenal bodies. For the same reason, there is nothing to support any effort being made to produce a suprarenal anti-serum.

The observations made by Josué, Erb Junr., and v. Rzentkowski, point to the possibility that the artificial introduction of adrenalin, suprarenal extract etc., is capable of inducing arterial disease bearing considerable resemblance to atheroma, but so far there are no observations showing that in cases of atheroma in man, the medulla of the suprarenal bodies is hypertrophied. Indeed, the observations of Aubertin and Ambard [2] tend to show that in five out of eight cases of renal disease, associated with high arterial tension, the medullary portion of the suprarenal bodies was atrophied. The same cases even showed hypertrophy of the cortical substance. The writers do not attribute the development of arterio-sclerosis to the hypertrophy of the cortex, but consider both effects a reaction to some toxic substance at present unknown.

Toxic effects of Suprarenal Preparations. —

[1] *Univ. of Pennsylv. med. Bulletin*, 1904, xvii., 5–6, p. 183.

[2] Reviewed in *Fortschr. der Med.*, 1904, No. 13, s. 575.

Takamine[1] has made the statement that adrenalin is non-irritating and non-cumulative, an observation with which most observers would agree; but his further remark that the substance is non-poisonous is calculated to encourage carelessness in the use of a drug which is quite capable of producing symptoms of intoxication. Reference has already been made to the occurrence of headache, nausea, vomiting and diarrhœa after excessive doses of suprarenal preparations. Takamine quotes the single observation of Bloch, who states that the local application of suprarenal extract was followed in one case by markéd œdema of the soft palate and tonsil, and that eventually superficial ulcers developed. Von Fürth has observed syncope and convulsions following the use of the suprarenal preparations; Roussel has observed vertigo, mental anxiety and cardiac arrhythmia, and Souques and Morel sensations of constriction of the thorax. Le Roy des Barres[2] gives an account of the clinical manifestations following an overdose of a suprarenal preparation; his patient vomited repeatedly for one day and had some diarrhœa for two days; there were no other toxic symptoms, and recovery was complete on the fourth day. Schücking,[3] in a description of the application of suprarenal preparations in gynecological practice, refers to one case in which seven minutes after the use of $1\frac{1}{2}$ to $1\frac{3}{4}$ c.cm. of a solution of suprarenal extract (1 in 100) he observed the occurrence of extremely dark colour of the skin, recalling the appearance of Addison's disease; the pulse was still able to be felt, but respiration became very shallow and vomiting occurred throughout the next twenty-four hours; the discoloration of the skin disappeared in half-an-hour. Reference has already been made to the occurrence of urticaria after applications of adrenalin.[4] Rendu administered the fresh suprarenal

[1] *Scottish Med. and Surg. Journ.*, 1902, x., p. 135.
[2] *Arch. général. de méd.*, 1903, p. 1635.
[3] *Münch. med. Woch.*, 1904, s. 204.
[4] Rosenberg, *Berlin. klin. Woch.*, 1903, s. 939.

glands of calves to a patient suffering from Addison's disease; on the second day the urine became loaded with albumin, and the patient died suddenly after eight days; as much as 15–20 grammes (!) of the fresh gland was given daily.[1] Weakness and slowness of the pulse and collapse have been also observed, followed by death in twenty-four hours, in cases in which subcutaneous injections have been practised. Boinet[2] describes marked nervous excitability and general tremor of the upper extremities. Endelen[3] describes a fatal case after the use of 6 c.cm. of a 1 per cent. solution of cocaine and 6–8 drops of solution of adrenalin injected into a delicate patient. Braun,[4] judging from the effects produced by this particular solution on other subjects, thinks that contamination with some other substance must have occurred.

[1] *Soc. des hôp.*, 1899, p. 255.
[2] *Arch. gén. de méd.*, 1903, t. i., p. 982.
[3] *Verhandl. d. Deutsche Gesellsch. f. Chir.*, 1903, i. s. 154.
[4] *Loc. cit.*, p. 12.

Section III.

ALIMENTARY TRACT, INCLUDING THE PANCREAS AND LIVER.

CHAPTER XIII.

ANATOMY, PHYSIOLOGY, PATHOLOGY.

The applications of the enzymes derived from the stomach wall and from the substance of the pancreas in the form of pepsin, pancreatin, etc., hardly need be referred to, as their position in the list of therapeutic agents is so well assured. Considerable advance has been lately made in the study of the physiology of the intestinal mucous membrane and of the pancreas, and also in the study of the nature of the relationship which exists between the succus entericus and the pancreatic secretion.

Anatomy.—The advances which have been made are not so much in the direction of fresh anatomical discovery in the intestinal wall as in the closer observation of the morbid changes which take place in the special groups of cells in the pancreas known as the islands of Langerhans. The study of these islands of cells has received considerable impetus as a result of the suggestions made by Schäfer, Laguesse and others that they give rise to an internal secretion. The effects produced by the removal of the pancreas experimentally led v. Mering and Minkowski to conclude that the pancreas is of importance in maintaining that degree of glycæmia, something below ·3 per cent., above which glycosuria occurs. The functions of the ordinary external secretion of the pancreas, proteolytic, amylolytic and lipolytic, have been clearly defined, but it

was soon regarded as possible that removal of the pancreas caused glycosuria because of the removal of the islands of Langerhans, the individual cells of which provided a ferment that, acting on carbohydrates absorbed from the intestine or elaborated by a katalytic degradation of the proteids of the body, reduced them to simpler bodies.

The pancreas, as is well known, lies in the concavity formed by the second, third, and fourth parts of the duodenum, to which it is closely united. Its duct, the duct of Wirsung, discharges into the duodenum at the junction of the second and third parts: there may be another duct, the duct of Santorini, entering the duodenum in relationship to the main one. Opie[1] examined a hundred specimens; in 10 the ducts of Wirsung and Santorini discharged pancreatic secretion into the duodenum without anastomosing; in 90 cases anastomosis between these ducts was observed; in 84 the duct of Wirsung was the larger, and in 6 the duct of Santorini was as large or larger than the duct of Wirsung. As Opie points out, the pancreatic tissue may be considered to be a continuous mass of pancreatic lobules held together loosely by means of connective tissue; at its duodenal end it divides into two separate masses or lobes that ensheath the ducts of Santorini and Wirsung. The arteries of the pancreas are derived from the splenic and hepatic divisions of the cœliac axis and from the inferior pancreatico-duodenal branch of the superior mesenteric artery; the veins of the pancreas join the splenic and superior mesenteric veins forming part of the portal system. The nerves are derived from the solar plexus and accompany the arteries; the lymphatic drainage is into the neighbouring cœliac glands.

Accessory Pancreatic Tissue.—The head of the pancreas has been found to encircle the duodenum; scattered masses of pancreatic tissue may also be found in various parts of the neighbourhood of the pancreas; such isolated masses have been found in the tissues of the

[1] "Diseases of the Pancreas," 1903, p. 29.

stomach, duodenal and jejunal wall, and in relationship to Meckel's diverticulum. These accessory masses usually have separate ducts of their own by which they discharge pancreatic secretion into the bowel; they are, as a rule, placed in the muscularis mucosæ, though in some cases they lie in the submucous coat.

Histology.—The special point of interest in the histology of the pancreas is the fact that, unlike the simple

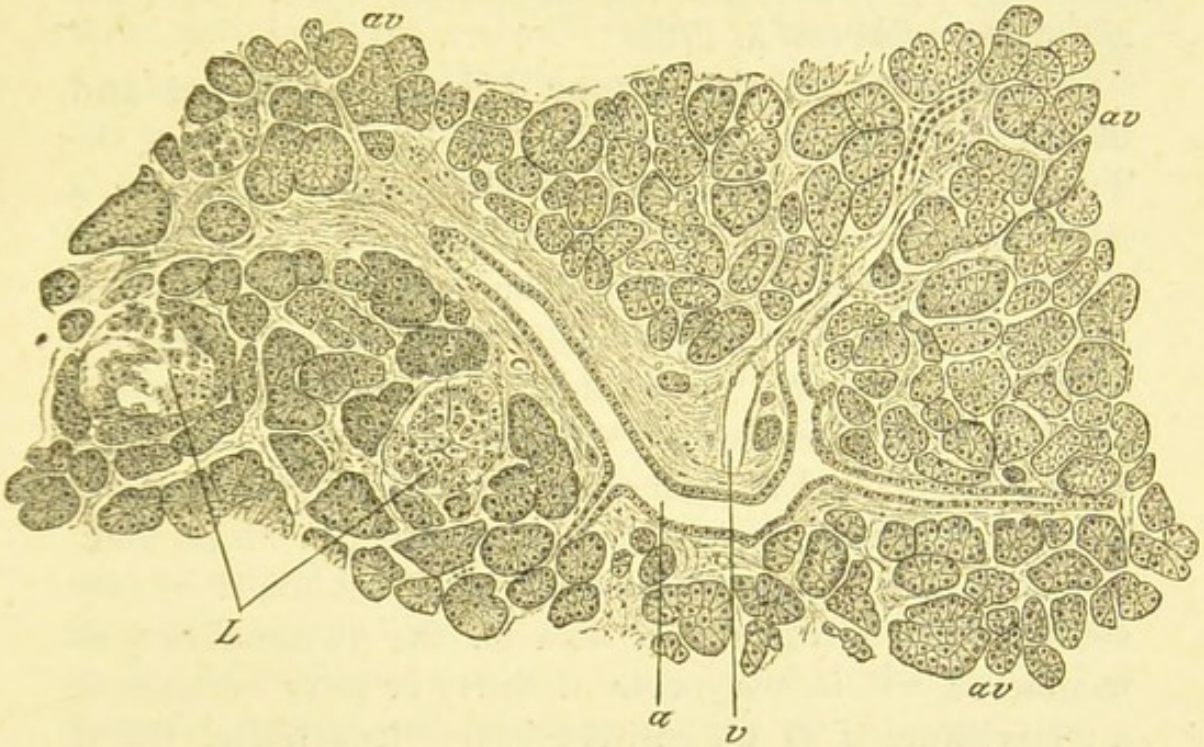


FIG. 10.—SECTION OF HUMAN PANCREAS (KÖLLIKER).

L, Islands of Langerhans; *a*, pancreatic duct and branches; *a v*, acini of pancreas; *v*, vein.

salivary glands in the mouth, the pancreas has distributed throughout its substance groups of cells differing in microscopical detail from the ordinary glandular tissue. These groups are the islands originally described by Langerhans, and now called after him. The individual cells are polygonal, and are closely beset with capillary vessels, which are larger and more abundant than the capillaries elsewhere in the gland; no ducts have been demonstrated within the cells, and there is no connection whatever, according to most observers, with the pancreatic ducts. The islands

of Langerhans, at one time considered to be lymphoid in character, have now been shown to be of epithelial origin, though it does not appear that the individual cells display any subdivision into two parts, so familiar in the other secretory cells of the pancreas and of the salivary glands. Opie has shown that in man these cells are much more numerous near the tail of the pancreas. It is believed by some that the islands of Langerhans do in certain cases discharge their contents into the ducts which drain the glandular acini (*see* p. 176).

Physiology of the Upper Alimentary Tract and of the Pancreas.—The acid gastric juice on entering the duodenum and the rest of the small intestine acts upon a body described by Bayliss and Starling[1] as "prosecretin," which is present in the epithelial cells of the mucous membrane of this part of the alimentary tract and converts it into another body, "secretin." Delezenne and Pozerski[2] explain the liberation of secretin in a different way. These workers find that an extract or macerate of intestinal mucous membrane, liver, spleen or kidney, in 0·9 per cent. normal saline, when added to secretin obtained by the action of dilute hydrochloric acid on the duodenal mucous membrane, will in the course of thirty or forty minutes, at a temperature of 39° C., entirely destroy its activity. But if the macerates before being added to the secretin are exposed to the influence of acids, or to a temperature of 70° for half an hour or 100° for some minutes, they will entirely lose their neutralising effect on secretin, showing that the macerates contain a ferment whose action is such as to restrain secretin in the intestinal mucous membrane; thus instead of hydrochloric acid converting prosecretin into secretin, what takes place is, according to these two observers, that hydrochloric acid destroys a ferment which restrains secretin, and thus allows the latter to become active. In whatever way secretin is derived it is liberated

[1] *Journ. of Physiol.*, 1902, vol. xxviii., p. 325

[2] *Soc. de. biol.*, 1904, t. lvi., p. 987.

and absorbed into the general vascular system, and carried ultimately to the cells of the pancreas, upon which it exerts a stimulant effect; such effect takes place even if nerves distributed to the pancreas along the vessels are quite destroyed.

The pancreatic cells are then stimulated to form an inactive "trypsinogen" as well as active trypsin, though the latter is very small in amount. The inactive trypsinogen reaches the bowel by means of the pancreatic duct, and is then activated by contact with a ferment known as "enterokinase," a constituent of the succus entericus, with the result that the trypsinogen, though originally incapable of acting at all on coagulated proteids,[1] and only slightly on uncoagulated proteids such as fibrin or caseinogen, becomes actively proteolytic. Enterokinase which is thus capable of activating another ferment has been also called "zymolysin." Bacteria, such as the bacillus subtilis, the Finkler-Prior bacillus, etc., have been shown by Delezenne to excrete a kinase which is also capable of activating trypsinogen. Further, the intravenous injection of a filtered acid extract of the intestinal mucous membrane is capable of producing an abundant pancreatic secretion of inactive trypsinogen, and the intravenous injection of a filtered digested stomach content will produce a flow of pancreatic juice which is actively proteolytic.[2] Until quite recently it has been believed that the conversion of insoluble proteids into soluble peptones, etc., was the final stage of digestion, and that absorption of these latter substances then takes place. Cohnheim has shown that the succus entericus contains another hitherto unknown constituent, "erepsin"; this ferment is indifferent to albumin, but is capable of splitting albumoses and peptones into substances containing still smaller molecules, thus completing their preparation for absorption into the system. Erepsin acts on syntonin, converting it into tyrosin, leucin, ammonia, arginin, lysin and

[1] Delezenne, *Soc. de biol.*, 1902, t. liv., p. 241.

[2] Camus and Gley, *Soc. de biol.*, 1902, t. liv., p. 241.

histidin.[1] Cohnheim in a further communication[2] concludes that erepsin, excreted in a Vella's intestinal loop and free from trypsin, is capable of effecting the cleavage of proteids sufficient for the needs of the animal, so that in some pathological conditions erepsin can act vicariously for trypsin, just as in other pathological conditions trypsin can perform the duties of pepsin.

Vernon[3] shows that erepsin exists in all the tissues of the body, and also in the pancreatic juice. The latter observation is supported by the discovery that when a pancreatic secretion is obtained containing trypsinogen which is unable to split into simple substances, fibrin, egg albumin and other similar proteids, it is capable of splitting albumoses into simpler bodies, which then no longer give the biuret reaction; by adding two-thirds of a volume of alcohol, the erepsin present in pancreatic juice can be precipitated, and thus separated from trypsinogen, which passes into the filtrate.

The above observations are confirmed by similar ones made in man. Hamburger and Hekma[4] obtained intestinal, juice by the introduction of a tube into an intestinal fistula; intestinal juice thus obtained, if kept antiseptically, remains active several months. It inverts cane sugar, as is well known, but does not influence milk or grape sugar It digests albumoses and casein until the biuret reaction is no longer given; it does not attack egg albumin. If the juice is heated for half an hour to 62°C. the erepsin contained will be destroyed, but the enterokinase or zymolysin will remain unaffected.

Glæssner[5] reports on the juice obtained from the pancreatic duct in man. He found, in agreement with the

[1] *Zeitschr. f. physiol. Chem.*, No. 35, s. 134.

[2] *Ibid.*, No. 36, s. 13.

[3] *Journ. of Physiol.*, 1904, vol. xxx., p. 330, and vol. xxxii., No. 2, p. 33.

[4] *Journ. de physiol. et de path. génér.*, 1904, t. vi., p. 40.

[5] *Zeitschr. f. physiol. Chem.*, 1904, s. 465.

observations of Pawlow, Chepowalnikow and Delezenne, that the secretion does not digest proteid unless intestinal juice obtained from the post-mortem room is added. From the point of view of the efforts that are being made to apply the recent investigations on the ferments of the alimentary tract to the development of new modes of treatment, it is of importance to note that Glæssner found that the intestinal juice obtained from the dog was incapable of activating the human pancreatic juice. Glæssner observed that the administration of hydrochloric acid by the mouth was followed by an increased flow of pancreatic juice, which sank again to normal in an hour; alkalies and fat, taken by the mouth, produced no such effects. The diastatic ferment present in the juice converted starch into maltose but did not convert cane sugar or maltose into simpler substances.

Reference has already been made to the observation that pepsin, trypsin and erepsin can, under certain circumstances, act the one for the other, but a still more interesting adaptability has been shown in the case of the pancreas by Bainbridge.[1] In early life, pancreatic juice contains lactase, a ferment which converts lactose into galactose and dextrose. Glæssner found this ferment absent in his patient and in adult dogs. If an adult animal, however, be fed for a few weeks on milk, the pancreatic juice will then be found to contain lactase, the lactose of the milk having acted on the mucosa of the intestine, producing a substance which, after being carried by the blood to the pancreas, is then enabled to produce lactase.

The exact nature of the relationship existing between enterokinase and trypsinogen is still *sub judice*; on the one hand, Pawlow and Bayliss and Starling[2] maintain that enterokinase is a ferment which is capable of converting trypsinogen into trypsin; on the other hand, Delezenne and Dastre have made observations which tend to show that

[1] *Journ. of Physiol.*, 1904, vol. xxxi., No. 2, p. 98.
[2] *Ibid.*, 1905, vol. xxxii., p. 129.

trypsin does not exist as a separate ferment, but is merely the combination of enterokinase (complement or amboceptor) and trypsinogen (immune body).

There is reason to believe that normal serum contains a substance (antitrypsin) which neutralises or combines with such ferments as trypsin.[1] Possibly the combination of antitrypsin and trypsin is returned to the pancreatic cells, and then by the action of secretin is once more broken up and trypsin ultimately liberated in the duodenum.

Reference has already been made to the existence of the islands of Langerhans. Gianelli and Giacomini, on the strength of their observations that in some reptiles the islands of Langerhans are arranged around a central lumen, conclude that their function is to impart some active principle to the external pancreatic secretion. The fact, however, that in higher animals no such intra-insular lumen can be demonstrated has led many observers to reject this view. It has already been mentioned that the production of hyperglycæmia and glycosuria as a result of the ablation of the pancreas has led to the surmise of Schäfer, Laguesse and others that possibly the islands of Langerhans manufacture an internal secretion. Probably this internal secretion does not act directly upon sugar circulating in the blood, but activates a glycolytic principle or principles existing in the cells of the body.

Pathological Disturbances in secretions of the upper part of the Alimentary Tract and Pancreas.—So recent are some of the physiological investigations upon these secretions that hardly sufficient time has elapsed to correlate any clinical manifestations with disturbances of secretion of such substances as enterokinase, secretin, etc. Observations, so far, merely point out some of the dangers which may be incurred if an attempt be made

[1] Glæssner, *Arch. f. Physiol.*, Leipzig, 1903, s. 389-392; and Cathcart, *Journ. of Physiol.*, 1905, vol. xxxii., No. 2, p. 497.

to introduce these substances, in excessive doses, into the system; thus, if a large amount of secretin were to gain access to the circulation, say by intravenous injection, much pancreatic juice would be formed and would enter the duodenum in a strongly alkaline condition, which, in the absence of hydrochloric acid, derived from the stomach, would remain unneutralised and would very probably, after being activated by enterokinase, exert erosive effects upon the bowel, and even produce hæmorrhages: these effects have been produced experimentally (Starling). Such warnings as these are most important, in view of the attempts being made to supplement the supposed faulty action of the mucosa of the bowel by the introduction of ferments derived from other animal sources.

The pancreas is liable to show various pathological changes, such as acute and chronic pancreatitis, tumour formation, cysts, etc. Hyaline degeneration has been described by Opie as occurring both in the excretory parenchyma of the pancreas and also in the islands of Langerhans. The same writer quotes[1] his observations on the conditions met with in the pancreas in nineteen cases of diabetes mellitus: in four cases the gland was normal, in four atrophic; in seven there was hyaline degeneration of the islands of Langerhans associated with chronic interacinar pancreatitis, and in four others there was chronic interlobular or interacinar pancreatitis. Opie concludes that considerably more than half of all cases of diabetes mellitus are due to pancreatic disease and especially to injury to the islands of Langerhans as a result of chronic interacinar inflammation. The observations of Opie have been opposed by Hansemann, and more recently by Karl Reitmann.[2] Further inquiries are necessary as to the condition of the islands of Langerhans in cases which are not examples of diabetes mellitus.

[1] *Loc. cit.*, p. 251.

[2] *Zeitschr. f. Heilk.*, 1905, Bd. xxvi., Hft. 1, s. 1.

Bramwell[1] described before the Edinburgh Medical Society a case of what he called pancreatic infantilism; delayed growth was associated with frequency of action of the bowels and fatty stools. Dr. John Thompson at the same meeting showed two similar cases.

Dr. Bramwell's patient at the end of the year 1901, although $18\frac{7}{12}$ years old, measured only 4 feet $4\frac{1}{8}$ inches in height and weighed 4 st. $7\frac{1}{2}$ lbs. The patient suffered also from diarrhœa, and Dr. Bramwell considered that the infantilism and the diarrhœa were due to pancreatic defect. After nearly two and a half years' treatment with pancreatic preparations, the height had increased by $5\frac{7}{8}$ inches, and the weight by $23\frac{3}{4}$ pounds. The sexual development had considerably increased, and the number of motions was reduced from four, five or six a day to two. (For further details of this case the reader is referred to "Clinical Studies," by Dr. Byrom Bramwell, vols. 1, 2, and 3.)

[1] *Lancet*, 1904, i., p. 725.

CHAPTER XIV.

ALIMENTARY TRACT AND PANCREAS: TREATMENT BY EXTRACTS, ETC.

The treatment of various gastric disorders by the administration of pepsin, pancreatin, etc. has so long been accepted as a rational form of treatment that special reference to them is hardly needed, nor to the beneficial effects produced by subjecting food to preliminary digestion by means of these ferments before administration to the patient.

Efforts have been made during the last few years to make use of the natural gastric secretions of living animals, more especially of the pig as being an omnivorous animal like man. This so-called gastric organotherapy has been advocated by Finkelstein[1] and by Hepp,[2] and the name *dyspeptin* has been given to the preparation by Hepp. Dyspeptin is administered in doses of two teaspoonfuls during a meal; the unpleasant odour and taste may be covered by means of beer, lemon juice, etc. Hepp finds improvement in some cases after the third or fourth dose; in other cases the treatment must be more prolonged, and in all cases careful dieting should be practised. It is most useful in cases of gastralgia and in delayed digestion; after a time the appetite improves, and a favourable influence is observed on the general nutrition in 14 to 20 days; dyspeptin is also said to act favourably on constipation or diarrhœa. Its favourable effects are of great use in the dyspepsia of pulmonary tuberculosis. Mayer confirms

[1] *Centralbl. f. Stoffwechsel. u. Verdauungskr.*, 1900, No. 9, s. 203.

[2] *Gaz. des hôp.*, 1903, pp. 621 and 708; *La Presse méd.*, 1904, No. 20, p. 156.

Hepp's opinions, and has seen good results from the use of dyspeptin in gastric catarrh, chlorosis and tuberculosis, but is careful to add that as the effects were produced in the hospital the good results obtained were possibly due to other remedies. Loeb,[1] however, has tried dyspeptin in many cases of gastric insufficiency, and in all cases has found no special benefit to be attributed to its use. He found that it did not increase the total acidity of the gastric secretion, and the preparation itself appeared to show complete absence of hydrochloric acid. *Gasterine* was formerly recommended, and, like dyspeptin, was obtained direct from the stomach of living animals, the dog being used. Its special value was considered to be due to the large amounts present of hydrochloric acid, pepsin and rennin.

Attempts have been made to apply extracts of the duodenum and small intestine as remedies for various disorders of the alimentary tract, but so far little of a convincing nature has been published. Charrin has shown that the intestinal mucosa can exert antimicrobic action, and Vidal attempted to prove experimentally that the injection of filtered fæcal matter produced death much more slowly if extract of intestinal mucous membrane was also injected. Drucbert and Dehon[2] were unable to confirm Vidal's observations, nor did they find that the stercoraceous intoxication following ligature of the intestine could be reduced by injection of intestinal extracts; the use of the latter in large doses was able to produce serious toxic symptoms. Hallion and Carrion[3] have introduced into the market *eukinase* which is an extract of the mucous membrane of the duodenum of the pig and contains enterokinase. This is recommended as an aid to pancreatic digestion in cases of intestinal dyspepsia. *Pancreatokinase* is a mixture of *eukinase* and *pancreatin*.

[1] *Deutsche med. Woch.*, 1904, s. 379.

[2] *Gaz. méd de Paris*, 1904, s. 12, iv., p. 37.

[3] *Bull. de la soc. de thérap.*, 1903, t. 145, p. 53.

Patein [1] speaks of the favourable influence of enterokinase in cases of constipation or diarrhœa, and says that the intestinal ferments may be administered by the mouth or even subcutaneously.

The hopes raised by the view that diabetes mellitus and glycosuria were due to a deficient internal secretion of the pancreas have led to the introduction of extracts of pancreas for internal use in these disorders. So far the results have not come up to expectation. The observations made by Mackenzie, Hale White and Knowsley Sibley [2] show that these preparations may cause an improvement in the general condition, but only a very few cases show a reduction of sugar. Williamson, writing on the use of pancreatic preparations in the treatment of diabetes mellitus,[3] reported that all were useless. A similar verdict has been given by Kaufmann,[4] who tried the effects of pancreatic preparations in seven cases of diabetes mellitus. In one case the raw gland was used, in two others *pancreon* was tried, and in four cases tabloids were employed. Lafitte [5] tried the use of quite fresh pancreatic substance, but the results were not encouraging. Pancreon, which is a proprietary article derived from the pancreas, was introduced by Gockel.[6] Wegele [7] describes the use of pancreon in a case of pancreatic diabetes; the patient passed fatty stools and sugar was present in the urine to the extent of ·8 per cent.; pancreon was administered three times daily in half-gramme doses. The fatty stools disappeared and the sugar was diminished, even though a carbohydrate dietary was allowed; the fatty stools recurred when pancreon was omitted. It seems quite probable from

[1] *Journ. de pharm. et de chim.*, 1903, vol. xvii., p. 430.
[2] *B. M. J.*, 1893, i., pp. 63, 452, 580.
[3] *Practitioner*, 1901, n.s. 13, p. 417.
[4] *Zeitschr. f. klin. Med.*, 1903, Bd. xlviii., s. 260 u. 436.
[5] *Soc. méd. des hôp.*, 1903, s. 3, t. xx., p. 1245.
[6] *Centralbl. f. Stoffwechsel. u. Verdauungsk.*, 1900, No. 11, s. 251.
[7] *Ibid.*, No. 14, s. 329.

the observations of Salomon,[1] of Rosenberg, and of Glæssner and Sigel[2] that the administration of preparations of the pancreas, especially when combined with alkaline treatment, is able to raise the absorption of nitrogen and carbohydrates to the normal, and of the fats to 10 or 20 per cent. of the normal; no favourable effect was noticed upon the loss of sugar. The failure on the part of preparations of the pancreas to produce a reduction of the sugar in all cases of diabetes mellitus is possibly due to the fact that not all cases of diabetes mellitus are due to pancreatic disease. So far it has not been found possible to diagnose clinically those cases of diabetes mellitus which are due to pancreatic disease from other forms of diabetes mellitus. Hirschfeld has, however, shown that cases of pancreatic diabetes may be found to run a rapid and severe course, especially in young and middle-aged subjects; the assimilation of fats is greatly interfered with, and this is readily detected by an examination of the stools. Polyuria is less common, or even absent.

Pancreatic preparations have also been used in various disorders known as intestinal dyspepsia, lienteric diarrhœa, achylia gastrica, etc., and with considerable improvement (Gockel,[3] Lenné[4] and Käppern). Käppern's patient, aged 35 years, had suffered for ten months with chronic enteritis; under treatment, the diarrhœa and constipation ceased, and there was improvement of the general condition and an increase in body weight.

Chatin and Guinard[5] have attempted to reduce the glycosuria in diabetes mellitus by injecting *per rectum* the blood obtained from the pancreatic veins of dogs. Their negative results are quite in harmony with the observations already referred to, viz. that no glycolytic ferment derived from the pancreas has, so far, been demonstrated in the blood.

[1] *Berlin. klin. Woch.*, 1902, s. 45.
[2] *Ibid.*, 1904, s. 440.
[3] *Loc. cit.*
[4] *Deutsche med. Woch.*, 1902, s. 192.
[5] *Lyon méd.*, 1900, t. xcv., p. 582.

CHAPTER XV.

THE LIVER.

In some senses the liver is one of the most marked examples of a gland which provides internal secretions for the body, for despite the want of satisfactory evidence that the blood of the hepatic veins contains an excess of sugar, it is probable that glycogen which is stored in the liver is sent on by this organ as dextrose into the general circulation, muscles, etc., where it is ultimately converted

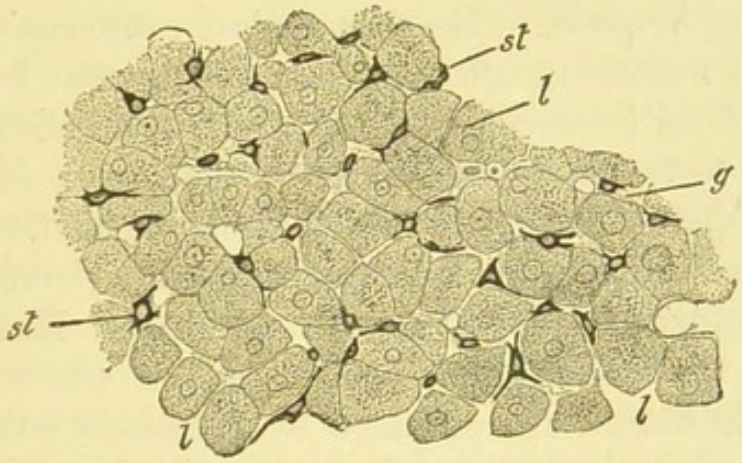


Fig. 11.—Section of the Liver of a Dog (Kölliker).

(From a gold preparation by Professor v. Kupffer.)

g, Vascular spaces; *l*, liver cells; *st*, v. Kupffer's cells.

into simpler substances; further, excretion of urea and uric acid is initiated in the liver, the final exit being by means of the kidneys. Bile, which is the external secretion of the liver, is at a certain stage reabsorbed from the intestine, so that, originally an excretion, it becomes in turn a secretion which passes again into the body. The exact significance of the circuitous courses of these secretions is so far little understood. There are reasons further for the belief that the liver acts as an organ which neutralises various toxic

substances arriving mainly by the portal vein from the alimentary tract, and it has been thought that the liver cells produce some ferment-like substance which is capable of acting as an anti-body to these various toxic substances, or of acting as an oxidising agent. There are reasons to believe also not only that the liver filters off bacteria arriving by the portal vein, but that it can also aid in their destruction.

The liver has further been shown to possess certain autolytic ferments which account for its ultimate disintegration when kept in a medium free from the influence of bacteria.

As to the existence of a ferment or ferments which are discharged as an internal secretion into the system, much as is the case with the thyroid gland, little can be said in the way of proof. The histological examination of the liver does not encourage this view, seeing that beyond the "stellate" cells described by v. Kupffer as applied in large numbers to the blood capillaries of the organ, there is no other cellular structure to which could be attributed any internal secretion other than those already referred to.

Organotherapy by means of Liver Extracts.—Most of the observations made on the effects of liver extracts in disease are provided by French observers who, not content with the use of various oils derived from the cod, seal, etc., have sought to show that other substances can be extracted from the liver capable of producing favourable effects in various pathological conditions. It is, however, possible that in some of the cases in which improvement is reported the effects have been due to the urea contained in the extracts; and it is further probable that some of the subjective improvements recorded, if not due to suggestion, are explainable by the observations of Vincent and Sheen,[1] who studied the effects produced by intravascular injection of extracts of various tissues and organs. Extracts of the liver, like extracts of the spleen,

[1] *Journ. of Physiol.*, 1903, vol. xxix., p. 242.

testis, pancreas, etc., were shown to produce a fall of blood pressure, though it was possible also to show that sometimes a pressor effect could be obtained. It is not known whether the pressor or depressor effects produced by the injections of various tissue extracts are due to any specific local agent, the liver extract producing, for example, a special dilator effect on the liver vessels as opposed to any effect on the blood vessels of other organs.

Cirrhosis of the Liver.—Of all affections attributable to disease of the liver, cirrhosis is the special one which appears to provide an admirable field for inquiry into the value of treatment by means of extracts of liver substance. Unfortunately, however, it has never been fully proved that the terminal symptoms of an affection like alcoholic cirrhosis of the liver are due to mere suppression of liver substance; the accidental discovery of high degrees of cirrhosis of the liver in patients who die of some other affection without ever having betrayed any signs of defective liver function is a common experience, and the eminently toxic manifestations which mark the closing scenes in cases of cirrhosis of the liver are quite possibly due to other causes than the absence of any hypothetical internal secretion of the liver. Many of the reports describe the treatment by means of liver extracts administered by the mouth, rectum, etc., but there is no evidence to support the view that the intestinal route is one which is favourable to the absorption into the system of the active principles present in liver extract.

Hermann[1] used liver extract in cases of cirrhosis of the liver, but beyond producing subjective signs of improvement and diuresis, which might be explained by the effect exerted by urea, no real improvement was observed. Favourable results are reported by Spillmann and Demange in alcoholic cirrhosis of the liver, but Landouzy and Dieulafoy have been unable to get favourable results in the treatment of cirrhosis of the liver,

[1] *Präg. med. Woch.*, 1897, s. 555.

jaundice, etc. More recently observations on the treatment by means of organic extracts have been published by Regnault [1] and by Créquy.[2] The latter observer describes the case of an alcoholic subject who presented all the symptoms of cirrhosis of the liver; other ordinary methods of cure failed to improve his serious condition; finally a gramme dose of watery extract of liver was administered daily, and improvement followed. Hirtz [3] demonstrated a case of cure, or, rather, of marked improvement, in the condition of a man who had been a heavy drinker and was found to be suffering from cirrhosis of the liver. By means of a milk dietary and the administration of 120 grammes daily of liver substance derived from the pig, the ascites, oliguria and the caput medusæ disappeared; there was no alteration in the condition of the shrunken liver and enlarged spleen. From what is known of the grave prognosis in cases of cirrhosis of the liver which develop ascites there is much reason to doubt the correctness of the diagnosis in this case; further, the disappearance of ascites and the increase of the urine are known to be much promoted by the diuretic effects of milk diet and the administration of urea.

Diabetes Mellitus.—Gilbert and Lereboullet [4] give a description of two forms of diabetes mellitus; in one group, which comprises cases mild in type, there is moderate glycosuria, a diminution of urea and an excess of uric acid and urobilinuria—they consider that this type is dependent upon "anhepaty," or chronic insufficiency of the liver; the other group includes the cases of severe glycosuria, and is considered to be due to "hyperhepaty" or excessive action of the liver.

In a former communication Gilbert and Carnot [5] found that gastric and pancreatic digestion disturbed the results

[1] *Rev. de thérap. méd.-chir., Paris,* 1904, t. lxxi., p. 695.
[2] *Bull. méd.*, xviii., No. 20, p. 232.
[3] *Ibid.*, 1904, p. 593.
[4] *Gaz. hebdom. de méd.*, 1901, No. 81, p. 961.
[5] *Gaz. des hôp. de Paris,* 1900, p. 995.

of the administration of liver extract by the mouth; they therefore administered it subcutaneously and by the rectum. The most active method was introduction by the latter route—100 to 150 grammes of finely minced fresh pig's liver were extracted for two hours at a temperature of 35° to 38° C. in 500 grammes of water. By means of this extract Gilbert and Lereboullet maintained it was possible to distinguish anhepaty from hyperhepaty; the liver extract excited the liver in the former case, causing a disappearance or reduction of sugar, but intensified the glycosuria in the second form of the disease. The same writers claim that other methods of treatment, *e.g.* the use of alkalies, Vichy water and milk dietary, produce equally good results in the milder forms of diabetes mellitus (simple glycosuria). Gilbert and Lereboullet tried the effects of the use of pancreatic extract in those cases of severe glycosuria which they consider dependent upon excessive activity of the liver (hyperhepaty), and got more favourable results than in the treatment of mild cases of glycosuria by means of pancreatic extract. The pancreatic extract was administered by the mouth in quarter gramme doses enclosed in capsules; by this means the effort was made to liberate the pancreatic extract, not in the stomach, but in the small intestine. They also obtained favourable results by the administration of half to one or two grammes of the extract per rectum.

Banti's Disease.—This malady is an affection of the liver and spleen; the former organ is in a condition of cirrhosis, the spleen is enlarged and ascites is apt to develop. Schiassi[1] describes a case of Banti's disease in which surgical treatment had been carried out and the ascites had subsided; as urobilin pervaded the system and the blood picture was unsatisfactory, hepatic extract (1–3 grammes) was given daily combined with 12–15 grammes of fresh bone marrow. After three months' treatment the general condition was greatly improved, and

[1] *Gazz. degli Osped.*, 1902, No. 69, p. 697.

the normal blood condition completely restored. Schiassi claimed that his operation had relieved hyperæmia of the liver, so that the liver cells were able to respond to the stimulating effect of the liver extract.

Other Applications of Liver Extracts.—Bassewitz[1] recommends the use of the reputed antitoxic power exerted by the liver in the treatment of snake bites. He recommends that the individual who has been bitten by a snake should be injected subcutaneously with a filtered extract prepared from the liver of a snake of the same species as that which attacked the individual; the contents of the gall bladder may also be administered by mouth. Bassewitz had established the neutralising effect of the snake's liver on its own venom, and by observations in poisoned animals of the antidotal effect of liver extract. Gilbert and Carnot consider that liver cells must contain a principle which prevents blood extravasation because epistaxis and purpura are common occurrences in cases of disease of the liver; the use of liver extracts has been made in cases of hæmoptysis, purpura, epistaxis, metrorrhagia, hæmatemesis, etc., and in some cases apparently with good results. Some results have also been obtained by the use of bile for the relief of gall-stone colic and of liver substance for the relief of constipation. Harmless as the administration of extracts of liver or of liver substance are when given by the mouth, subcutaneous injection of watery extracts, etc. of the liver should not be practised, seeing that it has been found that injection of watery extracts of the rabbit's liver into other rabbits is capable of producing disturbances of the circulation and respiration, cramps, depression of temperature, and even death.

The idea that the liver function, apart from anatomical change, can be at fault, not only in a quantitative, but also in a qualitative sense, is one which does not receive much support, and it must be admitted that the observations

[1] *Münch. med. Woch.*, 1904, s. 838.

above quoted require much more confirmation before they can be admitted as proofs of the efficacy of liver extracts, in the treatment of the various conditions mentioned.

It has already been pointed out that the endeavours to produce specific cytolytic sera, which should exert a solvent action on one organ alone without involving others, have ended in failure (Ghedini and Cafiero). Civray [1] also has shown that though it is possible to develop a serum capable of destroying liver cells, the cytolysis is not confined to this organ, but takes place in others as well. In the absence of satisfactory proof of excessive action of the liver, there is no practical need for the development of such a serum for curative purposes.

[1] *Centralbl. f. d. med. Wissensch.*, 1904, s. 401.

Section IV.

GENITO-URINARY ORGANS.

CHAPTER XVI.

THE TESTICLE AND OVARY.

Anatomy and Physiology of the Testicle.—Organotherapy is based upon the hypothesis that various organs of the body contribute "internal secretions," which are of importance in various directions and in various degrees. Brown-Séquard once more brought the question of internal secretion into prominence by his introduction, in the year 1889, of testicular fluid, as a means of combating the various symptoms of old age. The testicular preparations were made in accordance with the method introduced by d'Arsonval, and were injected subcutaneously. It has been known for ages that the loss of the testicles by disease or operative interference is followed by more or less well-marked specific alterations in the body and its functions—nutritional changes associated with an increase in weight, impaired vitality, loss of energy, etc. Granted the existence of an internal secretion, it was a ready solution of the changes above noticed, to attribute them to the loss of such internal secretion on the part of the testicle. The use of testicular extracts was claimed to be followed by stimulation of the whole nervous system, and of cellular proliferation; muscular power was increased, as well as the resistance of the body to microbic invasion. Unfortunately, much of the evidence adduced in favour of the beneficial effects of the extracts was derived from the interrogation of the individuals treated, and the element of "suggestion"

played so large a part that a great deal of the sensational results reported in the years following Brown-Séquard's first publication must be distrusted. Zoth and Pregl[1] were able to show by means of Mosso's ergograph that injection of testicular extract was able to produce an increase of muscular power, but Loewy and Richter[2] found that didymin (a testicular preparation) and spermin had no effect on castrated animals so far as oxygen exchange was concerned.

Testicular extract was not only applied in cases of old age, but in tabes dorsalis, Addison's disease, Graves' disease, and various infectious diseases, such as malaria, cholera, etc., and definite toxic influence was observed. Lingard[3] has recently shown that the subcutaneous injection of testicular extract into certain cattle induces a resistance to infection with rinderpest, and that the serum of these animals injected into other cattle especially susceptible to rinderpest renders them immune.

The effects produced in various functional disorders, such as neurasthenia, hysteria, epilepsy, chorea, insanity, etc., have also been studied. The results obtained, however, have fallen far short of the hopes raised by enthusiastic supporters of Brown-Séquard's theory; and this means of treatment, for want largely also of more exact physiological support, fell into very considerable discredit. Fürbringer,[4] reviewing the observations made by French workers, reported on 18 cases of impotence treated by this method; his results were negative. Other observers came to the same opinion, and found that no specific influence was exerted on the nervous system nor upon any part of the organism.

The success of organotherapy in myxœdema, in cretinism, and in cases of artificially induced menopause, have directed attention once more to a closer study of the

[1] Pflüger's *Arch.*, 1896, Bd. 62, s. 335 u. 379.
[2] *Berlin. klin. Woch.*, 1899, s. 1095.
[3] *Centralbl. f. Bakt.*, 1904, Bd. xxxvii., Hft. 2, s. 246.
[4] *Deutsche med. Woch.*, 1891, s. 1027.

anatomy and physiology of the testicle. Out of the welter of contradiction and hasty conclusions a few facts have been rescued which are irrefutable. The extract of the testicle does exert toxic effects, and certain definite effects can be obtained from the use of spermin, which is obtained from the testicle and also from other organs. Testicular extracts are also rich in phosphorus, and their action is

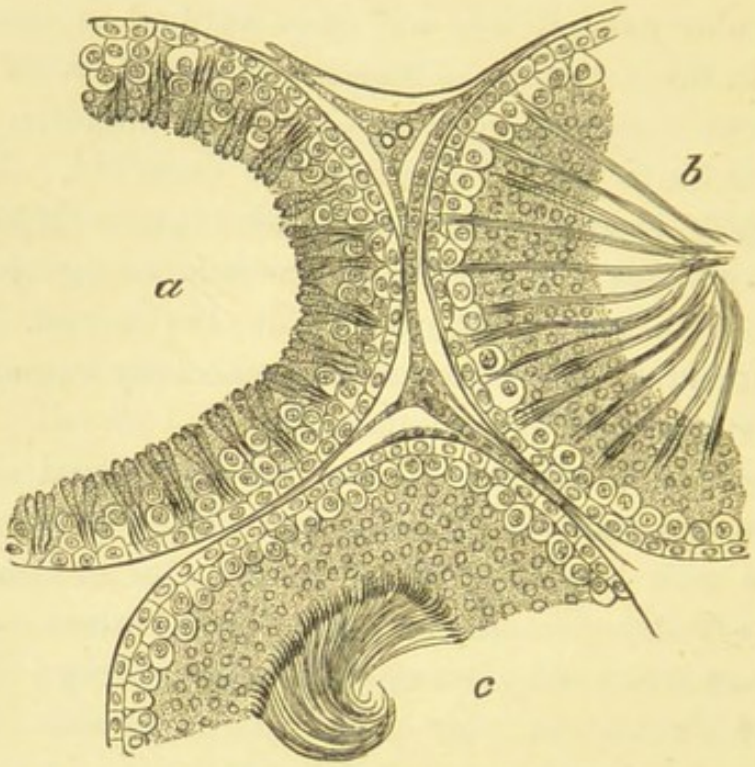


FIG. 12.—SECTION OF PARTS OF THREE SEMINIFEROUS TUBULES OF A RAT.

(E. A. Schäfer, from a preparation by Mr. A. Fraser.)

Betwen the tubules *a*, *b* and *c* are seen strands of interstitial cells, with blood vessels and lymph spaces.

(From Quain's "Anatomy," by permission of Messrs. Longmans, Green & Co.)

exactly comparable to that of the lecithins and glycero-phosphates.

The existence of the parathyroids in close relationship with the thyroid gland, of the islands of Langerhans in the pancreas, and of a more or less sharp distinction between cortical and medullary cells in the suprarenal body, has very naturally prompted an inquiry as to whether the testicle contains cells other than those whose special

function it is to secrete the constituents of the seminal fluid. The epithelium of the seminiferous tubules contains three different varieties of cells, an outer layer lying in close relationship with the basement membrane of the tubules, an intermediate layer of spermatogenic cells derived from the first layer of cells, and an innermost layer of spermatoblasts derived from the second layer; the spermatoblasts give rise to spermatozoa after having first become closely connected with special members of the outer layer of cells known as "sustentacular cells." [1] The parent cells of the tubular contents are thus seen to form the outer layer, and most important amongst these are the so-called sustentacular cells. Another group of cells, the origin and significance of which are unknown, is the group of "interstitial cells," lying outside the tubules in the spaces between individual tubules. Their appearance recalls the epithelium-like polyhedral cells seen in the cortex of the suprarenal body, which they further resemble in containing yellowish granules; similar cells are seen in the stroma of the ovary. Shattock and Seligmann [2] suggest that possibly the sustentacular cells of the testicle may contain a sort of prosecretin, which is converted into testicular secretin by chemical changes accompanying spermatogenesis, the secretin being then absorbed as an internal secretion. They also suggest that it is possible that the "interstitial cells" supply an internal secretion. The same observers (*loc. cit.*) have attacked the theory that the acquirement of secondary male characters is dependent on the discharge of sperm, metabolic changes being set up by a nervous reflex arising from the mere functional activity of the sexual mechanism. Shattock and Seligmann show that the occlusion of the vasa deferentia in the young of Herdwick sheep and of the fowl does not inhibit the full acquisition of secondary sexual characters. They were further able to show that as part result of some of their attempted

[1] Quain's "Anatomy," vol. iii., pt. iv., p. 227.

[2] *Proceedings Royal Soc.*, 1904, vol. lxxviii., No. 488., p. 49.

operations of caponisation portions of the testicle were left behind, but dislocated from the proper anatomical site. Such portions of testicle grew in the new position; they were devoid of any channels communicating externally, and consisting of tubuli only, became virtually examples of ductless glands; their natural nervous connections were also severed. The fowls in which this incomplete caponisation was practised developed male characters. The metabolic results arising from the activity of the grafts must be attributed to the elaboration of an internal secretion and its absorption into the general circulation. This important contribution to the study of internal secretion gives additional support to the alleged beneficial effects of the use of testicular substances or extracts.

That the testicle has important influence on the development of other organs of the body has been shown by Cecca and Zappi.[1] They castrated rabbits and killed them after three months. Comparisons were made between the conditions of the various organs of the mutilated animals as compared with control animals. A gain of weight took place in most of the castrated animals; the thyroid gland was found to be enlarged, and the vesicles contained more colloid than normal; the suprarenals also showed an increase of the medullary substance; no changes were found in the parathyroids, thymus or pituitary body.

Application in Disease.—Reference has already been made to the use of testicular preparations in various conditions, including those in which there is grave organic disturbance of the nervous system, as in tabes dorsalis, and in functional conditions, such as neurasthenia. It has been pointed out that, although some improvement follows the treatment, such good effects are dependent largely upon the organic phosphorus, lecithin, etc., contained in the preparations. The same explanation probably holds good for the improvement observed in cases of impotence,

[1] Epit., *B. M. J.*, 1904, ii., No. 16.

depression, melancholia and other psychoses, paralysis agitans, tuberculosis, etc.

It has been found by Burghart[1] that the use of didymin and other testicular preparations in cases of glycosuria may be followed by a reduction in the amount of sugar in the urine, and this improvement may be maintained after the drug has been discontinued. It is not at all improbable that testicular extracts, like thyroid substance, which has been shown to exert a direct oxidising effect, are capable of stimulating cellular activity and increasing the power of the cells to destroy sugar; this property is also present in ovarian substance. Didymin was found by Burghart to be of use in obesity.

Bouffé has made use of testicular extract (orchitin) in the treatment of eczema and psoriasis and obtained good results. Orchitin was administered by intramuscular injection in doses increasing from 10 to 20 c.cm. daily during the course of three months. He had treated 83 cases of psoriasis, and got cures without recurrence in 77·7 per cent. He also found that the injection of orchitin produced favourable effects in cases of irregular menstruation. Friedländer[2] describes the favourable effects of the use of testicular substance in three cases of prostatic hypertrophy. Lloyd Jones[3] recommends the use of didymin in exophthalmic goitre, 10–20 grain doses daily being given for periods of six months; he reports improvement in the pulse rate, in the tremor, nervous excitability and exophthalmos, but not in the size of the thyroid tumour.

Dosage.—Solutions can be obtained for hypodermic injections in quantities of 1–3 c.cm., or by weight 2·0–3·0 grammes up to 8 grammes. *Orchitin* may be given by the mouth in doses of 0·5, 0·8, 1·0, or 3·0 grammes in twenty-four hours. Tabloids of *didymin* (5 grains) may be given, 1 to 4, three or four times a day; dried pulverised testicular

[1] *Deutsche med. Woch.* 1899, s. 610 u. 627.
[2] *Ibid.*, 1898, Ver.-Beil., No. 38, s. 288.
[3] *B. M. J.*, 1904, i., p. 15.

substance, one part corresponding to six parts of the fresh organ, may be given in 1 to 2 gramme doses daily, and *opoörchidinum* in ·5 to ·8 gramme doses, three times a day.

The hypodermic injections are given daily for several weeks and months, the injection being made in the side of the abdomen or in the lumbar region or between the shoulders.

Anatomy and Physiology of the Ovary.—The disappointment following the introduction of testicular extract as a remedial agent in 1889 was naturally followed by considerable scepticism as to the value of organic preparations generally. Interest in the effects produced by ovarian preparations was first shown by their use in the treatment of insanity and other symptoms following operative removal of the ovaries[1]; since these observations considerable evidence has been gathered which places ovarian treatment on the same level as thyroidotherapy, for its clinical value is supported by careful physiological experiments which justify its use in certain conditions.

The symptoms noticed in women at the natural menopause are so closely simulated by those observed after removal of the ovaries that it is concluded that the menopause is associated with retrogressive changes taking place in the ovary. As in the case of the effects produced by removal of the testicle, it has also been conjectured that the symptoms, etc., produced at the menopause, natural or artificial, are in some way intimately associated with the influence of the ovary upon the body economy.

The theory of the internal secretion of various organs originated by Claude Bernard and applied by Brown-Séquard more especially to the use of testicular substance was also applied to the ovary, and it was concluded that the ovary, like the testicle, produced by an internal secretion

[1] Régis, *Soc. de méd. et de chir. de Bordeaux*, 1893, June 2, p. 279; and Landau, *Berlin. klin. Woch.*, 1896, s. 567.

the various sexual characteristics of the adult, and that when the ovary atrophied and the internal secretion ceased, obesity, flushing and various other objective, as well as many subjective phenomena of a nervous character occurring

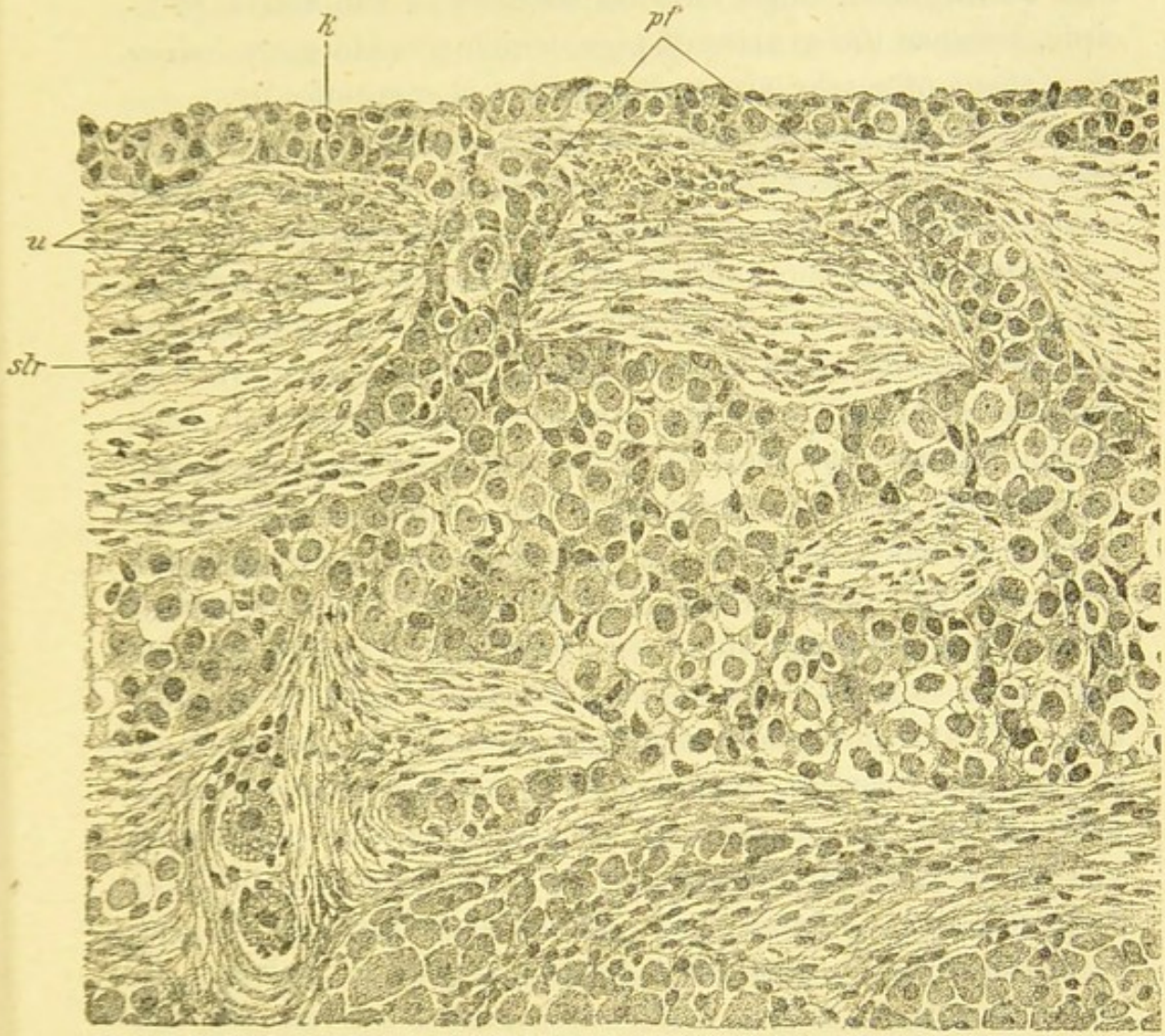


FIG. 13.—SECTION THROUGH THE OVARY OF AN EMBRYO HORSE (KÖLLIKER) (× 220).

k, Germinal epithelium; *pf*, Pflüger's egg-tubes; *str*, stroma; *u*, primitivè ova. Two small Graafian follicles below and to left; to the right and below medullary portion of ovary showing interstitial cells.

at the menopause, were developed. Certain French observers consider that *ovarin*, a preparation derived from the ovary, contains an oxidising ferment comparable to spermin (*vide infra*), and that the various abnormal phenomena observed during growth and development (*e.g.* in chlorosis), and the

phenomena following atrophy or ablation of the ovaries, are due to the occurrence of autointoxication, which in the normal individual is relieved by the menstrual flow. Iodine has been found in the ovary, and it has been thought that iodine is an important constituent of the active principle, because the ovaries of pigs, which contain more iodine than those of cattle, are more efficient therapeutically.

Histological examination of the ovary shows, as in the case of the testicle, that there are certain cells interspersed amongst the ovarian stroma cells which closely resemble the "interstitial" cells found between the tubules of the testicle. Schäfer points out that these cells are polyhedral or irregular in shape, lie in close relationship as a rule to the blood-vessels, and recall the structure of the cortical cells of the suprarenal body.[1] The similarity in appearance suggests the common source of origin which embryological considerations justify, for the testicle, ovary and suprarenal body are derived from one common source—the Woolfian body. Very curious support is supplied clinically for the view that certain parts of the Woolfian body eventually come to have an important influence on the development of adult characteristics, for not only are these characteristics inhibited by the removal of the testicles and ovaries of young animals, but cases have been described by Bulloch, Sequira and Adams[2] of carcinomata arising in the suprarenal body associated with precocious puberty in children. It is known that carcinomata can secrete the substances usually formed by the epithelial structure from which they arise. For example, colloid has been found in the metastases of thyroid carcinomata and bile in the interstices of carcinomata of the liver; it is thought that possibly in the cases described by Bulloch and others, precocious puberty was due to the excessive internal secre-

[1] For a discussion of the importance of "interstitial" cells in ovogenesis, *see* report by Janet E. Lane-Claypon, *B. M. J.*, 1905, ii., p. 18.

[2] *B. M. J.*, 1905, i., p. 775.

tion of suprarenal cells, which, like the interstitial cells of the testicle and ovary, are believed to have an important influence on the development of adult characteristics.

That removal of the ovary causes considerable disturbance in the metabolic processes of the body is shown by the observations that oöphorectomy is followed by a diminished output of phosphorus. Loewy and Richter (*loc. cit.*) castrated bitches and found alterations in the gaseous exchange which indicated a diminution (10 per cent.) of the absorption of oxygen; by the administration of oöphorin the absorption of oxygen again rose to the normal or even beyond normal. Thyroid substance administered in cases of double oöphorectomy also caused an increase of the amount of oxygen taken up, but the amount absorbed never exceeded that taken up by a normal animal. The castrated animals also became fat, and these two observers conclude that as a result of castration disturbance takes place in the combustion of fats and other non-nitrogenous substances. Thumin found that ovarian feeding exerted no influence on the output of nitrogen in a patient who had lost both ovaries. Ovarian substance has no influence on the gaseous exchange in individuals in whom the ovaries are normal, nor does its administration appear to disturb normal individuals. Parhon and Papinian confirm Senator's observations that ovarian substance increases the elimination of calcium.

It is fortunate for the purposes of physiological investigation that the ovary, unlike the thyroid, is not essential to life, for it is thus possible to sharply define all the signs which follow removal of the ovary. Further, obesity is such an obvious objective sign that improvement by the use of ovarian preparations is independent for its recognition of subjective accounts offered by the patient.

As a proof of the specific influence of ovarian substance, Skrobansky[1] describes his experiments with the serum of guinea-pigs which had been injected with

[1] *Münch. med. Woch.*, 1903, s. 1913.

ovarian substance. Two drops of the serum of a guinea-pig so injected were added to one drop of a mixture of one part of the seminal fluid of a rabbit and nineteen parts of normal saline solution. Control observations were made with the serum of normal guinea-pigs, and it was found that the serum of the injected guinea-pigs exerted a stimulating effect upon the rabbits' spermatozoa; the ova of rabbits *in situ* were unfavourably influenced by the serum, which thus appeared to possess a certain amount of specific action. Metchnikoff[1] has shown that small doses of a spermotoxic serum have an exciting action upon the movements of spermatozoa; but, showing the influence of dose in these experiments, it has also been found that larger quantities of spermotoxic serum are capable of agglutinating spermatozoa and of finally arresting them.

Use of Ovarian Preparations.—It has been pointed out that treatment with ovarian substance is one of the best examples of "substitution" treatment, closely comparable with thyroid treatment. The special value of ovarian substance is shown in cases in which the ovaries are ill developed, or have become atrophied as at the menopause, or have been removed by operation. In all these cases symptoms of the menopause may be present, *e.g.* obesity, various phenomena referable to the nervous system, such as headaches, flushings, tremors, paræsthesiæ, syncopal and anginal attacks and various psychoses, etc. Burghart[2] describes the effects of the treatment of a young woman *æt.* 20 years, in whom there was marked obesity and want of development of the uterus and ovaries. By means of the administration of oöphorin, Burghart was able to reduce the weight by 8 kilogrammes in a short time; the oöphorin was then discontinued and the obesity returned to its original degree. According to Jayle[3] the first use of ovarian substance for the relief of symptoms following re-

[1] *Ann. de l'Inst. Past.*, t. xiv., p. 1.

[2] *Deutsche med. Woch.*, 1899, s. 610 u. 627.

[3] *Rev. de gynécol. et de chir. abdom.*, Paris, 1903, p. 437.

moval of the ovaries was made by Régis,[1] the patient was suffering from insanity, and before the improvement which had commenced had been completely developed she committed suicide. In the year 1896 various observations were made by Landau, then by Mainzer, Mond, Chrobak, Muret, Jacobs, Martin and others, upon the favourable influence of various ovarian preparations on the symptoms following ovariotomy. Martin[2] treated 69 cases of ovariotomy with ovarin, and found favourable results in 31 cases. Jayle finds that ovarian preparations in post-operative menopause are most useful in checking the vasomotor phenomena, but are quite useless for the relief of neurasthenic symptoms. The treatment should be continued for fifteen days to a month, the daily dose being a full one. Bestion de Camboulas[3] reports that the symptoms of the natural menopause can be greatly improved by means of extracts of the ovary without any other treatment being practised, and finds that the mental symptoms especially can be improved in this way; the appetite also is improved and the action of the bowels becomes more regular. He prefers ovarian extract to ovarin, on the ground that the former is less likely to decompose. The subjective sensations of heat, due to vasomotor disturbances, are amongst the symptoms which are most readily relieved by the treatment. In opposition to Jayle, de Camboulas finds that neurasthenic symptoms, such as insomnia and headache, also disappear. De Camboulas warns, on experimental grounds, against administering ovarian preparation during pregnancy, as he found that in pregnant animals so treated abortion frequently occurred. Lebreton[4] finds, however, that 0·05 gramme of dried corpus luteum, given twice daily, relieves the vomiting, nausea and palpitation of pregnancy, and makes no mention of the risk of producing

[1] *Loc. cit.*

[2] *Samml. klinisch. Vortr.*, 1899, No. 255, s. 1577.

[3] "*Le suc ovarien*," Paris, 1898.

[4] *La Semaine méd.*, 1899, p. 237.

abortion. The clinical observations of de Camboulas on the effect of ovarian preparations are reliable, for all possibility of suggestion was excluded: no patient whilst being treated with ovarian substance knew the nature of the remedy. Saalfeld[1] found that ovarian preparations had a favourable influence upon the various skin disorders which occur in the natural and artificially induced menopause, such as eczema, acne, rosacea and prurigo.

Reference has been made in the section dealing with the thyroid gland to the favourable effect exerted by thyroid preparations upon certain forms of obesity which are possibly attributable to defective action of that organ. Obesity also occurs as a result of the defective internal secretion of the ovary, and seeing that ovarian substance produces, even in large doses, nothing more than a little gastric disturbance, although favourably influencing obesity, it should be given in preference to thyroid substance as a first treatment, as thyroid substance is so readily able to produce toxic symptoms, especially when continued for a long time. Loewy and Richter showed that the reduction of obesity by means of ovarian substance was at the expense of non-nitrogenous and not of proteid substances.

Geissler[2] has found that anginal attacks occurring about the menopause are soon relieved by the use of ovarian substance.

It is believed that the ovary discharges into the system an antitoxic body which neutralises certain toxic substances resulting from metabolic changes, and it is surmised that the symptoms of chlorosis are due to a want of this antitoxic substance and that until puberty sets in antitoxic substances are supplied by tissues which in the adult become atrophied, *e.g.* the thymus gland. It is also thought that the ovarian internal secretion is of importance in that it influences blood formation. Spill-

[1] *Berlin. klin. Woch.*, 1898, s. 283.

[2] *La Semaine méd.*, 1900, No. 10, p. 86.

mann and Étienne[1] and Moscucci have shown that ovarian treatment increases the number of red corpuscles, and so helps to establish the menses in cases of chlorosis.[2] Bestion de Camboulas and others also report favourably upon the use of ovarian preparations in chlorosis. Richter sounds a warning and says that theoretically the organo-therapeutics of chlorosis are not yet fully established, and in the absence of knowledge of the effects of ovarian preparations when given for a long time, enjoins caution in the use of very large quantities of such preparations.

Improvement has also been noticed in cases in which melancholia and maniacal conditions have occurred in amenorrhœa; even dysmenorrhœa and metrorrhagia have been relieved by the use of ovarian preparations. Jayle has endeavoured to establish the symptomatology of functional ovarian insufficiency, basing his diagnosis on the presence of amenorrhœa, dysmenorrhœa and metrorrhagia, associated with vasomotor and nervous disturbances. Such cases respond to treatment with ovarian preparations. Geach[3] describes a case of complete recovery in a lady, *æt.* 60 years, who was treated with ovarian extract for delusional insanity; 10 to 25 grains were given three times a day, and by the end of the tenth day improvement was so marked that the treatment was stopped. Two to three months later the improvement was complete.

Ovarian substance has been employed in the treatment of Graves' disease, with improvement in some cases and even complete cure in others. Delaunay, by means of this treatment, succeeded in curing a case of Graves' disease occurring at the climacteric. Senator[4] failed to observe any improvement in exophthalmic goitre treated with oöphorin. Epilepsy, associated with menstrual disorders,

[1] *Congrès de méd. de Nancy*, 1896, p. 453.

[2] *See* also Étienne and Demange, *Congrès de méd. de Montpellier*, 1898, p. 383.

[3] *B. M. J.*, 1904, i., p. 130.

[4] *Berlin. klin. Woch.*, 1897, s. 104 u. 143.

is said to be favourably influenced by ovarian substance. Osteomalacia fails to respond to treatment with ovarian substance, a result which would be expected seeing that ovarian medication causes an increased excretion of calcium and phosphoric acid.

Parhon and Papinian consider that the treatment of acromegaly by means of pituitary and thyroid substance is not justifiable because these substances tend to fix calcium in the body; they recommend the use of ovarian substance in acromegaly because of the elimination of calcium which these authors consider desirable in a malady in which overgrowth of bone is a feature.

Jayle, in his critical survey of the use of ovarian preparations, offers the following suggestions as to administration, etc. In order to avoid the influence of "suggestion" and dislike for the remedy, it is well to keep the patient in ignorance of the material used; liquid preparations obtained by the methods of Brown-Séquard and d'Arsonval are the best, but there are practical difficulties in the mode of preparation, so that Jayle uses ovarin, a powder prepared from the ovary; fresh glands are not to be recommended. Jayle has only once seen any unpleasant sequela as a result of the treatment—zona developed, but quite possibly this was a coincidence.

Dosage.—*Ovadin*, one or two tabloids three times a day; *ovarial* or dried ovarian substance (Merck), each tabloid containing 0·5 grammes of fresh gland, and *ovaraden* in tabloids containing the same amount of ovarian substance, 4–8 tabloids of either daily; *oöphorin* in tabloids of 0·5 grammes equal to 3·0 grammes of fresh ovary, 2–15 tabloids daily; *opoövarinum* may be given in doses of 0·2–0·8 grammes, and as much as 0·6 grammes to 3·0 grammes may be given in the day.

Spermin.—In following the accounts of the effects produced by the use of ovarian and testicular substance, it must be acknowledged that it is somewhat unsatisfactory not to be able to point to the particular substance which is

responsible for the improvement produced. The preparation of testicle contains proteids, fats, nuclein, lecithin, cholesterin, hypoxanthin, guanin, adenin, kreatin and kreatinin, and yet none of these has been shown to exert a specific effect on the metabolism of the body, nor has a specifically active substance been isolated from the ovary which can be considered responsible for those changes which the use of ovarian preparations is capable of producing.

Poehl[1] has introduced into therapeutics a substance known as *spermin*. This substance, which is a leucomaine or product of the retrogressive metamorphosis of proteids, is derived especially from nucleo-albumin and is probably contained in most of the preparations already enumerated, derived from the testicle and ovary. Spermin may be obtained as a syrupy liquid, is tasteless and colourless, is very alkaline, is insoluble in ether but very soluble in water and alcohol. Its chemical formula according to Poehl is $C_5H_{12}N_2$; as Poehl and Mendelejeff have shown, it is not identical with piperazine. Spermin forms soluble salts with hydrochloric, nitric and sulphuric acids, whereas the salt formed with phosphoric acid is insoluble. The crystals known as Charcot-Leyden crystals, found in spermatic fluid, in the blood of leucocythæmia, in asthmatic expectoration, in the pus removed from empyemata and in the dejecta obtained from individuals affected with helminthiasis, are phosphate of spermin. Poehl speaks of this salt of spermin as the "inactive" form, whereas the base spermin constitutes "active" spermin. Spermin possesses the very curious property of being an oxygen carrier, and according to Poehl is responsible for those internal oxidations which take place in the body tissues. The oxidising power of spermin is quite remarkable, for it is found that in a dilution of 1 in 10,000 it is able in the presence of a few drops of chloride of platinum solution to convert powdered magnesium instantly into gelatinous magnesium oxide,

[1] *Berlin. klin. Woch.*, 1891, s. 956.

hydrogen being given off and the odour of spermatic fluid being developed. Blood which has lost its power of oxidation through the artificial admixture of chloroform, free acids, etc., can have this power restored once more by means of spermin; spermin also increases the alkalinity of the blood. Blood acting alone on guaiacum resin produces no blue colour; if spermin be substituted for hydrogen peroxide or ozonic ether the ordinary blue colour at once appears. Tarchanoff has shown that transverse division of the spinal cord reduces the oxidation going on in the tissues of the body; this process is again restored by injection of spermin. By the introduction of spermin into the system, the relative amount of urea (an end product of the oxidation of proteid) as compared with the total nitrogen excreted is raised.

The presence of spermin prevents the phenomena of reduction which accompany the development of the cholera bacillus in cultures, and it also suppresses the production of the cholera-red reaction.

Spermin thus would appear to play the part of a catalytic ferment which regulates the tissue oxidation. In order to be able to act, spermin must exist in an alkaline medium, otherwise it is crystallised out as the well-known Charcot-Leyden crystals.

Spermin is found in the thyroid gland, in the thymus, pancreas, spleen, blood, brain and ovaries, but it is especially abundant in the testicles and prostate.

According to Poehl's theory, various substances incompletely oxidised are liable in certain diseases to be retained in the system, hence the occurrence of such auto-intoxications as gout, uræmia, diabetes mellitus, etc., and he holds that in these conditions there is an acid intoxication, or rather a reduction of the alkalinity of the fluids of the body, with the result that the spermin is rendered inactive. By the introduction therapeutically of spermin, it is possible to reinstate the oxidation processes, and at the same time to restore the blood to its normal degree of alkalinity

Spermin produces at first a fall of the number of leucocytes and then a rise.

Poehl does not advocate the use of spermin against any particular malady, but makes use of its general "tonic" influence in various diseases.

It has been objected that it is not usual to be able to demonstrate Charcot-Leyden crystals in the disorders in which spermin treatment is applied, but Poehl's answer is that in many of these cases the phosphate of spermin does not exist in a crystalline but in an amorphous form. Exceptionally this may be the case even in leucocythæmia Wegener and v. Jaksch).

Spermin has been found useful in neurasthenia, various rheumatic affections, in locomotor ataxy, diabetes mellitus, syphilis, typhoid fever, diphtheria, cholera, tuberculosis of the lungs, marasmus, psoriasis, eczema and acne, and various cachexiæ. It is useful in all cases of excessive mental or bodily fatigue and after severe operations. It is inadvisable to administer spermin in certain cases of epilepsy or of psychical conditions characterised by much excitement. Further indications for its use are given by Noé.[1] Bosse[2] used spermin in the treatment of optic atrophy of syphilitic origin. His patient was all but quite blind, and no results could be obtained by means of potassium iodide, pilocarpine or strychnine injections. A first attempt was made by means of an extract of testicle injected as a klysma; pruritus resulted. Spermin was then administered and injected 16 times. Five months after the beginning of the treatment the patient could again see the hands of a watch. This case and two other cases of pruritus senilis were relieved by the injections of spermin.

Dose.—Two preparations are in use; one, the *essentia spermini*, is administered in doses of 10 to 30 drops in warm alkaline water such as Karlsbad, Ems or Vichy; the first dose is taken fasting in the morning and others during the

[1] *Arch. génér. de méd.*, 1903, July-Dec., p. 1757.

[2] *Petersb. med. Woch.*, 1904, No. 7, s. 67.

day. The essentia spermini is a 4 per cent. solution of the sodium-spermin double chloride, and is aromatic and alkaline. Another solution, to be used hypodermically when quicker effects are required, consists of a sterile 2 per cent. solution of spermin in physiological saline solution. With aseptic precautions, no harmful results follow. The dose for injection is 1 to 2 c.cm. daily. In grave cases the dose may be repeated several times.

CHAPTER XVII.

THE KIDNEY.[1]

Anatomical and Physiological Considerations.—Probably no excretory organ has been more closely studied than the kidney, both from the physiological and from the clinical point of view. The reasons for this attention are to be found in the comparative ease with which the kidney may be attacked by the physiologist and by the surgeon, and because from the anatomical disposition of the urinary tract the excretion of the kidney in health and disease can be most readily studied. Unlike most other eliminative organs, the kidney appears to excrete (using the term in a strictly etymological sense) substances brought to it preformed elsewhere, such as water, urea, etc., and to secrete substances in the sense that the renal epithelium elaborates more complex substances from other substances which reach it by the circulation; *e.g.* it is held by some that uric acid may be elaborated by the kidney epithelium; this secretory power is shown by the experiments of Schmiedeberg and of Bunge,[2] who found that fresh kidney tissue (not extract of kidney tissue) was able to form hippuric acid from benzoic acid and glycocoll, and Jaarsveld and Stokvis[3] showed that when renal activity is impaired in man there is a loss of the power to convert benzoic into hippuric acid. It thus appears that the kidney is an excretory organ in a double

[1] The writer acknowledges his indebtedness for many of the observations and references in this chapter to Dr. J. Rose Bradford's Goulstonian and Croonian Lectures on the Kidney in 1898 and 1904.

[2] *Jahresbericht ueber d. Fortschr. der Thier. Chemie*, 1876, s. 66.

[3] *Ibid.*, 1879, s. 356.

sense, eliminating material brought to it already formed, as well as other substances which it manufactures. There then remains the question whether possibly the kidney, like the thyroid, suprarenal and pituitary bodies, and like the liver, pancreas, ovary and testicle, elaborates an internal secretion which is important to the economy. The differences in the symptoms produced in non-obstructive suppression as compared with obstructive are such as to suggest in the former case not only that the excretory power is lost, but also that the internal secretion is suppressed.

In the condition which is known as anuria there is a cessation of the excretory powers of the kidneys; anuria is met with in various conditions, and in one large group of cases in which no obstruction is discoverable in the urinary passages, uræmic manifestations quickly develop and death takes place in a few hours or a day or two (Roberts), though this period may be lengthened to as much as seven days—as, for example, in the non-obstructive suppression of urine following diphtheritic infection—by such therapeutic measures as copious daily saline infusions; Bradford and Lawrence have shown[1] that it is possible for life to be maintained for seven days even, in cases of suppression of urine following endarteritis of the renal vessels. Another group of cases differentiated by the late Sir William Roberts includes those cases of obstructive suppression of urine in which life is prolonged eight or ten days or more, and in which the ordinary symptoms of uræmia are masked (latent uræmia). Merklen, in a thesis written at a later date, drew attention to the difference in the time of survival of patients suffering from one or another form of anuria, and to the difference in the clinical symptoms; patients were found to suffer from suppression of urine and yet did not develop the usual uræmic symptoms, the only symptom being alteration in the pulse and pupil,

[1] *Journ. of Pathology and Bacteriol.*, 1898, vol. v., p. 195.

lowering of the temperature and possibly slight twitchings of the face.

The original explanation offered for the occurrence of uræmia in cases of renal disease was that it was due to loss of function of renal excretion ; part of the kidney substance might be destroyed without the onset of symptoms, but when a larger part was destroyed then uræmic manifestations occurred. Tuffier[1] showed that experimental removal of a quarter of the total kidney substance was possible without death occurring.

Brown-Séquard[2] extended his ideas on the "internal secretion" of the testicle, and endeavoured to show that uræmia was due to the suppression of the internal and external secretion of the kidney, and not to the suppression of the external secretion only, basing his opinion on the clinical observations made by Roberts, Merklen and others, and on the experimental observations he had made upon rabbits and guinea-pigs. He removed both kidneys from these animals, producing uræmia, and then injected them with a glycerine extract of kidney substance prepared in accordance with the method developed by himself and d'Arsonval. He found that nephrectomised animals thus treated lived longer than when organic extracts were not used. Such experiments were considered to support the view that part of the effects of double nephrectomy was due to loss of an internal secretion which could be replaced by the introduction of renal extracts. Bradford,[3] independently of the observations of Tuffier, published a preliminary communication on the effects of the removal of large quantities of the total kidney substance. Dogs were experimented upon, and a varying amount of one kidney was removed at a first operation ; two to six weeks later the whole of the remaining kidney

[1] *Bull. de la soc. anat.*, 1888, p. 447.

[2] *Soc. de biol.*, 1889, pp. 415, 420, 430 : and 1892, pp. 265 and 722 ; *Compt. rend. de l'acad. des sc.*, 1892, pp. 1399 and 1400.

[3] *Proceedings Physiol. Soc.*, 1891, vol. xii., p. xviii.

was removed; if by this method of experimentation three-quarters or more of the total kidney substance were removed the animal rapidly wasted, passing much water and urea, and died within two to six weeks after the second operation; if an amount of kidney substance was removed less than three-quarters of the total kidney substance, death did not occur so soon, some animals living for three months. Tuffier, quoted by Bradford,[1] had found that the limit of safety for the animal was reached when only 1·5 grammes of kidney substance per kilogramme of body-weight was left. Bradford, experimenting in a different way from Tuffier, who removed one kidney first and then parts of the other which had hypertrophied, considered that the danger limit was reached when 2 grammes of kidney substance per kilogramme weight of kidney substance, or one-third of total substance, was left behind. Paoli has stated that the minimum amount of kidney substance necessary to life is half of one kidney. Vitzou[2] failed to find that by removal of part of one kidney, followed a month after by removal of the other, there were any serious disturbances such as albuminuria, polyuria and increase in the excretion of urea.

The different estimates given by these observers on the amount of kidney substance necessary for survival after partial nephrectomy, are dependent upon the method of operation—some observers removing a part of one kidney first and others removing the whole of one kidney first—in both cases the kidney substance left after the first operation being capable of undergoing various degrees of hypertrophy before the second operation was performed.

Experimental Observations on the Value of Extracts, etc., of the Kidney.—Meyer[3] published the results of experiments on dogs and rabbits; in three different series of experiments the animals were sub-

[1] *Journ. of Physiol.*, 1898-99, vol. xxiii., p. 417.
[2] *Soc. de biol.*, 1901, p. 1167.
[3] *Arch. de physiol.*, 1893, p. 761; 1894, p. 179.

jected to double nephrectomy. Cheyne-Stokes breathing was taken as a sign of uræmia; in one group, injection into the peritoneal cavity of 20 c.cm. of glycerine extract of kidney substance caused a temporary cessation of Cheyne-Stokes breathing, although the animals ultimately died: in another series, removal of 60 c.cm. of blood and the introduction of 60 c.cm. of defibrinated blood derived from a normal animal restored the regularity of the rhythm; the same, but more permanent, effect was observed if in another series of nephrectomised animals blood obtained from the renal vein of a normal animal was used instead of defibrinated blood. Meyer concluded from his experiments that the kidney supplied an internal secretion in accordance with the view of Brown-Séquard. Chatin and Guinard[1] quote observations on the effect produced by defibrinated blood obtained from the renal veins of healthy animals; by injecting this subcutaneously or intravenously the lives of animals which had undergone double nephrectomy were prolonged. Ajello and Parascandalo,[2] using Brown-Séquard's glycerine extract of kidney substance, were also able to prolong the lives of animals subjected to double nephrectomy; they found that the albuminuria which usually follows removal of one kidney did not occur if the animals were injected with renal extract; they were quite unable to secure successful grafts of renal tissue. Chatin and Guinard tried the effects of the serum of blood drawn from the renal veins of the goat and of the dog, using the former in two series of experiments and the latter in three others; the animals before being injected with the serum had had both kidneys removed. They found that the serum had no beneficial effect upon the animals; indeed, in all cases the animals injected with the serum were made worse, and died sooner than control animals. Silvestri[3] found that extracts of renal substance injected into sound animals

[1] *Arch. de méd. expér. et d'anat. path.*, 1900, t. 12, p. 137.
[2] *Lo Sperimentale*, 1895, Sez. biolog., p. 540.
[3] *Policlin.*, Roma, 1902-3, fasc. ix., Sez. prat., p. 1665.

were able to cause anorexia, oliguria, albuminuria, hæmaturia, somnolence, coma and death, lesions being found in the viscera generally; and that in animals which had had one or both kidneys removed, the extract aggravated the symptoms. Floresco[1] found that if removal of more than half of one kidney is performed, and then 30–80 days later the other one is removed, polyuria, albuminuria and increase of urea are only slightly apparent, the increase of the urea being quite temporary; probably these more favourable results are due to the fact that the part of the first kidney left had had time to hypertrophy before the second one was removed.

Fioresco made observations on the effect of removal of the cortical substance. He states that he removed the whole of the cortical substance, and found that the medullary substance left was capable of performing the duties of the kidney (!); the occurrence of blockage of the ureter and bladder with blood was overcome by attaching the ureters to the abdominal wall. On the other hand, in the case reported by Bradford and Lawrence (*loc. cit.*), the cortices of both kidneys were necrosed by occlusive disease of the renal vessels, and the patient lived but seven days after the onset of suppression.

Brown-Séquard endeavoured to support his view of the existence of an internal secretion of the kidney by a comparison of the results obtained by ligature of both ureters with those of the double nephrectomy. He found that the former animals lived twice as long as the latter, the reason being advanced that in the case of ligature of the ureters the excretory function of the kidney alone was interfered with. It appears, however, that there is practically no difference in the results obtained (1) by removal of both kidneys, (2) ligature of both ureters, (3) ligature of one ureter and excision of the other kidney: in all cases there occurred progressive weakness, fall in temperature, dyspnœa,

[1] *Journ. de physiol. et de path. genér.*, 1903, t. v., p. 1024.

diarrhœa, wasting, occasionally vomiting, and usually death on the fourth day.[1]

The subject of the alleged beneficial effects of the introduction of renal extracts has been reinvestigated by Mlle. L. Stern,[2] who found that subcutaneous injection of renal extract did not prolong the lives of nephrectomised animals and that injection of normal saline had a more beneficial effect than injection of renal extracts.

The sum of the evidence in favour of an internal secretion of the kidney comparable to that of the thyroid appears to show that the original idea of Brown-Séquard of the existence of a renal internal secretion, based upon clinical considerations, is not borne out by experimental proof. It is quite possible that the discordant results already referred to are due to the fact that different preparations were used by different observers, or that possibly the true internal secretory activity of the kidney exists only in the living cells, and not in any extracts, so that it is impossible to prove or disprove the view of an internal secretion based upon experiments with renal extracts; reference has already been made to the fact that glycocoll and benzoic acid can only be combined to form hippuric acid by the intervention of renal epithelium, and not by renal extracts.

Anatomical investigations give little support to the view of an internal secretion, for whether the mechanical view of Ludwig of the functions of the kidney, or the vital secretory one advanced by Bowmann and Heidenhain, be accepted, practically the whole of the anatomical elements of a uriniferous tubule are devoted to the removal of material arising by the blood stream preformed or elaborated by renal epithelium before excretion. In accordance with Ludwig's view a certain amount of water is reabsorbed by the epithelium of the convoluted tubules.

[1] Bradford, Croonian Lecture, *Lancet*, 1904, vol. ii., p. 125.

[2] *Rev. méd. de la Suisse Rom.*, 1902, p. 667.

Renaut[1], basing his views on the observation made by Dubois[2] on the antitoxic secretion of the cells of the convoluted tubules and upon observations carried out by Regaud and Poligard on Ophidiæ, considers that the epithelium of the convoluted tubules contains "granules" which provide a material that is absorbed into the system—a true internal secretion. This substance may be antitoxic in character, as it has been found that animals in whom nephrectomy has been performed are more susceptible to the influence of lead poisoning and to injection with various micro-organisms; possibly this internal secretion hinders the too rapid breaking down of the muscle and other tissues into urea, which has been shown by Bradford to be such a constant phenomenon following upon suppression of large parts of the kidney tissues.

Treatment by means of Kidney Derivatives.—In view of the contradictory evidence derived from physiological inquiry, and more especially of the adverse verdicts of the more recent investigations, very little experimental justification exists for the treatment of the suppression of a hypothetical internal secretion of the kidney by means of renal preparations. Clinical reports have been published in the past, and continue to be published, in which it is stated that marked improvement has followed the use of kidney derivatives in conditions in which it is known that these particular organs are diseased. Judging from the number of reports of favourable results, it really seems that in certain cases beneficial results do follow their use, but in the present state of physiological inquiry it would be better to attribute such results to the diuretic effect of renal preparations or to their more direct physiological excitant effect upon the renal tissue still left undestroyed than to attribute them to the effects of an artificially supplied internal secretion. Possibly *nephrine* and other renal preparations provide a means of stimulating oxidation in

[1] *Bull. gén. de thérap.*, 1904, t. 147, pp. 3 and 37.

[2] *Soc. de biol.*, 1903, p. 287.

general, the kidney merely sharing in this general stimulation. Similar good results have been reported as a result of treatment by means of spermin and testicular extract.

Favourable Results of Treatment by Renal Derivatives.—Dieulafoy[1] treated a man aged 43 years who had suffered for a long time from Bright's disease and grave uræmic phenomena. The patient was treated with glycerine extracts of the kidney of the guinea-pig and of the ox (nephrine) injected subcutaneously; marked diuresis and amelioration followed, but the patient subsequently died. Teissier and Frenkel[2] gave full reports with urinary analysis of two patients, the subjects of chronic nephritis, who had been injected with 2 to 4 c.cm. of glycerine extract of sheep's kidney. The patients were considerably improved, the albumin was lessened and the urinary toxicity was increased after the injection; the output of urine, of urea or of phosphates was not notably affected. Other favourable results were obtained by Gonin,[3] by Donovan[4] in a case of nephritis and general dropsy, and by Chipérowitch,[5] who treated cases of nephritis with fresh kidney substance or extract, and found a diminution or disappearance of albumin. Léon Jacquet[6] reported on eight cases of renal disease treated with renal preparations, and noted favourable results, very similar to those of Teissier and Frenkel—improvement of the general condition, reduction of albumin and increase of the urotoxic coefficient.

Concetti obtained improvement in cases of nephritis by the subcutaneous injection of *renaden*, 1 to 3 or 4 grammes a day, or by the ingestion of large doses of kidney substance. He found progressive diminution of the albuminuria, increase of urea and of the total quantity of

[1] *Soc. méd. des hôp.*, 1892, p. 668.
[2] *Arch. de physiol.*, 1898, p. 108.
[3] *Lyon Méd.*, 1894, p. 433.
[4] *B. M. J.*, 1895, *i.*, p. 15.
[5] *Therap. Woch.*, 1895, s. 650.
[6] Quoted by Chatin and Guinard.

urine; cases of chronic nephritis failed to show any increase of the output of urine. De Lignerolles made use of serum obtained from the renal vein of goats, and injected subcutaneously doses of 20 c.cm.; he also refers to a case treated by Turbure by means of defibrinated blood obtained from the renal vein of the dog. All cases but one showed improvement in the general condition, and progressive loss of albumin; one case described by de Lignerolles, and Turbure's case, showed a diminution of the urinary toxicity. Gilbert and Carnot[1] found that renal extract, like liver extract, produced an increase of the coagulative power of the blood, and that a favourable influence followed its use in cases of hæmorrhagic Bright's disease. Obolenski[2] obtained favourable results by the subcutaneous injection of 400 grammes of lamb's or pig's kidney combined with 800 grammes of normal saline, or by the injection *per rectum* of 30 grammes of kidney substance and 50 to 60 grammes of normal saline.[3]

Dubois[4] described the cure of a case of uræmia. The patient was 69 years old and had intense albuminuria following upon exposure to cold. A macerate of two or three pigs' kidneys was given daily for ten days. Renaut communicated to the Academy of Medicine in Paris in December, 1903, a description of the results of treatment of renal disease by macerates of kidney substance as recommended by Dubois.[5] The macerate is prepared by finely mincing three pigs' kidneys, which must be obtained quite fresh; the fragments are then washed in distilled water to remove all traces of urine. As a rule, the medullary portion of the organ is not used, being useless. The

[1] "L'Opothérapie," Paris, 1898.

[2] *Wratsch*, 1899, No. 27, quoted by Casper and Lohnstein; *Monatschr. über die Krankh. des Harn. u. sexual Apparats*, 1899, iv., s. 632.

[3] *Vide* Senator, *Die Erkrank. der Nieren*, 1902, Zweite Auflage, s. 277.

[4] *Soc. de biol.*, 1903, p. 287.

[5] *Bull. génér. de thérap.*, 1904, t. 147, p. 3037.

hashed kidney substance is then crushed up in 450 grammes of normal saline (·7 per cent.), allowed to stand for four hours, and then the supernatant fluid is decanted off. The macerate is prepared daily, and is administered in three or four doses in the twenty-four hours. Treatment is continued for ten days, and an interval of four to five days elapses before it is resumed. A spoonful of concentrated bouillon may be administered with each dose. Renaut finds that this method of treatment is more efficacious than any other treatment hitherto recommended, producing diuresis, reducing the loss of albumin and counteracting the causes of arterial hypertension and the tendency to cardiac dilatation. No serious harmful effects arise from its use, but occasionally there occur pruritus, urticaria, miliary rashes, perspiration and slight gastric disturbance, such as nausea and vomiting. The treatment may be applied in all cases of renal insufficiency, in chronic nephritis, interstitial nephritis, and in cases of so-called cardiac or cyanotic kidney disease. Teissier[1] recommends the use of glycerine extracts of the kidney, or blood serum removed from the renal veins, or the macerates as prepared by Dubois and Renaut. Favourable results are obtained in some cases which appear hopeless, and Teissier considers that organotherapy may be used in all kinds of chronic nephritis, in uræmia, in temporary renal insufficiency, and also in anuria resulting from the impaction of a stone. Beneficial results are, however, only to be expected in cases in which some kidney parenchyma capable of functioning still remains, and Teissier recommends that the kidney preparations should be used in cases which threaten to develop into renal disease, before all renal substance is irremediably damaged. Capitan[2] reports the cure of a patient suffering from uræmia, who also was gouty and had myocardial degeneration. Twelve days' treatment with ordinary measures failed to secure relief, and death

[1] *Bull. méd.*, 1904, No. 53, p. 617.
[2] *Ibid.*, 1904, No. 5, p. 51.

threatened. Capitan then injected 3 c.cm. of nephrine, and the cardiac condition improved; the urine rose from 300 to 1,600 grammes, and eventually the patient was able to resume his duties.

Unfavourable Results of Treatment. – Leyrol (quoted by Chatin and Guinard) reports that death occurred from severe anæmia in a patient suffering from renal disease who had been treated with renal extracts. In another case, in which by the same means an effort was made to relieve a mild uræmic attack, unfavourable symptoms appeared to arise as a result of the treatment. Mori also was unable to find any benefit from the renal substance itself, and certainly no harmful results, though he was of opinion that the glycerine used for extraction was capable of producing hæmoglobinuria and albuminuria in guinea-pigs. Senator (*loc. cit.*) failed to obtain any satisfactory results from the use of kidney preparations. Fornaroli reviews the whole subject of renal opotherapy, and describes his own experiences in four cases. One case was long convalescent from acute parenchymatous nephritis, another patient had had hæmorrhagic nephritis for six months, and the other two were cases of chronic nephritis which did not improve under any form of treatment. Fornaroli injected daily 5 c.cm. of a glycerine or watery extract of pig's kidney, similar in preparation to that successfully used by Dieulafoy and others. His results were uniformly unfavourable; there was no diuretic effect, and no diminution of arterial tension. One case suffered from a return of albumin, and in the other three there was an increase of the albuminuria.

Dosage.—Fresh kidney substance may be given in doses of 5·0 to 15·0 grammes daily. Dried kidney substance (1 part representing 6 parts of fresh substance) may be given in doses of 0·8 to 2·5 grammes daily. *Operenünum*, 1·5 to 3·0 grammes daily. The dosage of other special preparations is indicated above.

Section V.

OTHER ORGANS AND TISSUES.

CHAPTER XVIII.

THE PITUITARY BODY.

Anatomy.—The pituitary body or hypophysis cerebri is a glandular structure lying at the base of the brain, in the sella turcica. It consists of two lobes, a large anterior one or orohypophysis, which has a structure recalling the appearance of the thyroid and suprarenal glands, and a small posterior one, neurohypophysis, which, though probably originally composed of nervous tissue, becomes in the most highly developed mammals little more than a mass of fibro-vascular tissue connected by a cord of similar tissue with the floor of the third ventricle where the latter forms the infundibulum. The stalk-like structure connecting the posterior lobe with the infundibulum consists in part of a process derived from the anterior lobe of the pituitary body; the stalk of the pituitary body is usually quite solid, but occasionally it is found to be hollow, due to the persistence of the original canal which connected the interior of the posterior lobe with the third ventricle.

The anterior lobe is like the posterior lobe in that it is originally derived from epiblastic tissue; the anterior lobe, however, is derived from that part of the epiblast which lines the buccal cavity. A saccular prolongation of the buccal epiblast extends towards the posterior lobe and gradually applies itself to the anterior surface of that

body; gradually the sacculus is cut off from its connection with the mouth, and gives rise to what is known as the anterior lobe of the pituitary body. Both anterior and posterior lobes are ensheathed in a capsule derived from the dura mater.

Histology.—The anterior lobe or glandular part of the pituitary body resembles a secreting gland, and consists largely of a number of convoluted cords of cells as well as

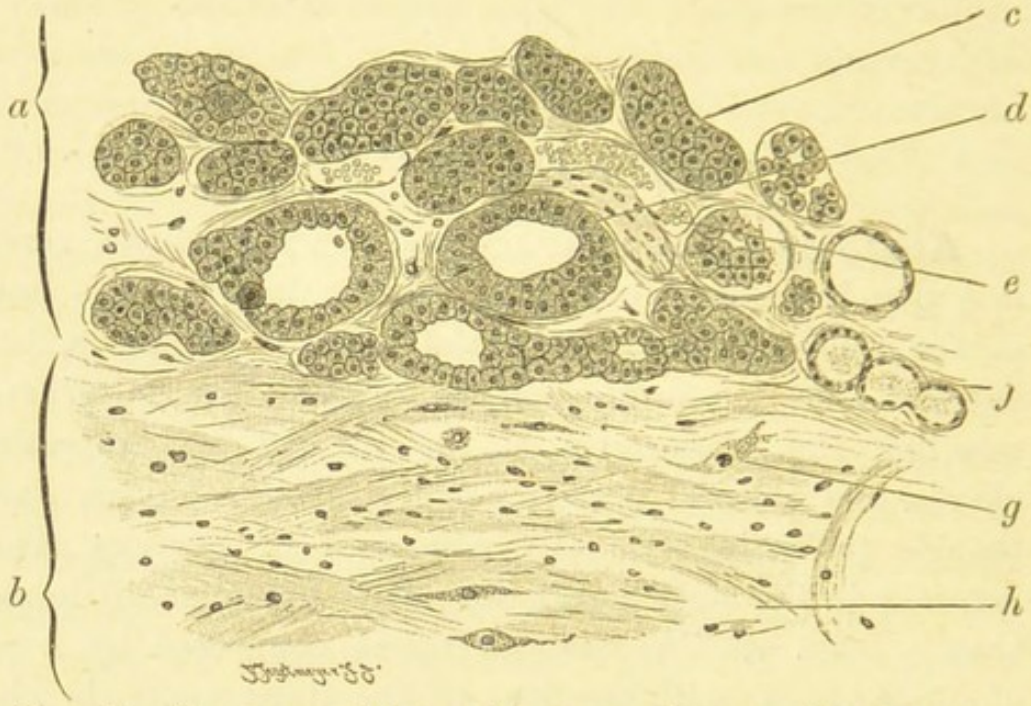


FIG. 14.—SECTION OF HUMAN PITUITARY BODY AT JUNCTION OF ANTERIOR AND POSTERIOR LOBES (STÖHR) (× 220).

a, Anterior lobe; *b*, posterior lobe; *c*, solid masses of cells; *d*, hollow masses of cells; *e*, blood vessel; *f*, colloid; *g*, multipolar cells; *h*, connective tissue cells.

of a number of cells arranged in a tubular fashion, recalling the structure of the suprarenal bodies; blood vessels, lymphatic spaces and connective tissue lie between these tubules, and the latter tissue is continuous with the connective tissue which forms the major part of the posterior lobe. It occasionally happens that some of the tubes of the anterior lobe are cut off from the main mass and form acini, which resemble very closely the acini of the thyroid gland, even to the extent of showing colloid contents.

A remarkable feature of the special cells of the pituitary body is that they show granulations; the granular cells are

present in the greatest number in the anterior lobe of the pituitary body, but a few are found scattered in the posterior lobe. Scaffidi [1] finds that there are two fundamental types of cells in the pituitary body which may be sharply differentiated from one another by the colour reactions of the granules contained within their substance. The granules within one set of cells stain most readily with orange G, the others with acid fuchsin. Besides these cells, however, other structures are seen, but Scaffidi considers them merely different stages of activity of the two above-mentioned types of cells; *e.g.* when all the granules have been shed little is left but a fragmentary cell body disposed around a nucleus (probably the "mother cells" described by Stieda); in cases where the destruction of the cell body is not so complete less deformed cells appear, some of them representing the cells described by Schönemann as "cyanophile" cells.

Physiology.—The anterior lobe of the pituitary body is so very glandular in appearance and so readily recalls the appearance of the thyroid gland that there is much excuse for the supposition that the anterior lobe at least is of importance to the economy and functions as an accessory thyroid body, hence the name pituitary goitre which has been given to any enlargement of the pituitary body. Both the pituitary and thyroid body contain iodine in the form of thyroiodin.

It has further been observed that the pituitary body undergoes changes when other glands, such as the thyroid, suprarenal, etc., are diseased or removed; the experiments made by Rogowitsch show that, after the removal of the thyroid gland in dogs and rabbits, the pituitary cells undergo a numerical increase. Although Stieda was unable to show a numerical increase, he was able to observe an increase in the size of the cells which accounted for the total enlargement of the pituitary body after thyroidectomy. Marenghi has shown that after the removal of the suprarenal bodies

[1] *Arch. f. mikr. Anat.*, 1904, Bd 64., s. 235.

in rabbits and cats there is a numerical increase of the cells of the hypophysis. Whether this increase in size of the pituitary body after removal of the thyroid and suprarenal bodies is vicarious or not is at present unsettled. Total removal of the pituitary body usually causes the death of the animal within a fortnight, more particularly in the case of young animals. Narbut [1] finds that adult animals resist the loss much more easily.

Amongst the symptoms noticed in fatal experimental cases are loss of weight, fall of temperature, and various nervous phenomena such as twitchings which recall the symptoms following thyroidectomy.

There appears to be no doubt that the pituitary body contains a substance or substances which exert considerable influence over the metabolism and on the cardio-vascular system. Experiment, however, shows that the pituitary and thyroid bodies are not vicarious in action, because an extract of the pituitary body causes a rise of blood pressure on intravenous injection and extract of thyroid tissue causes a fall.[2] Pituitary extract causes a rise of blood pressure, not only because it acts directly upon the heart-muscle and intrinsic nervous apparatus, strengthening the contraction of the heart, but also by acting directly on the neuromuscular mechanism of the blood vessels. Howell [3] found that the demonstrably active part of the pituitary body is the posterior or infundibular portion. From the observations of Schäfer, Swale Vincent and Osborne,[4] it appears that the posterior lobe contains two active substances, one which produces a pressor effect, the blood pressure being raised for some time, the other causing a lowering of the blood pressure of a much more temporary character. Herring,[5] from observations made

[1] "Inaug. Dissert.," St. Petersburg, 1903.

[2] Oliver and Schäfer, *Journ. of Physiol.*, 1895, vol. xviii., p. 277.

[3] *Journ. of Exp. Med.*, 1898, vol. iii., p. 245.

[4] *B. M. J.*, 1903, i., p. 502.

[5] *Journ. of Physiol.*, 1904, p. 429.

on the frog's heart, through which extracts of the infundibular part of the pituitary body were perfused, concludes that the infundibular portion of the pituitary body contains a substance or substances which act on the intrinsic inhibitory nervous mechanism of the heart, producing acceleration, and also on the peripheral vessels, causing constriction of them. This effect of pituitary extract upon vessels can be abolished by the use of apocodeine, which Dixon has shown paralyses the vaso-motor nerve endings.[1] Johnston[2] has studied the effects upon the nitrogenous metabolism of a dietary of pituitary bodies obtained from the calf. A dog was experimented upon, and it was found that the pituitary diet increased nitrogenous metabolism, leading to an increased output of nitrogen, urea and phosphates; at the same time the animal lost weight. Schiff was able to deduce reasons for the view that the pituitary body presides over the nutrition of the osseous system, because he found that the administration of pituitary substance to elderly men and to cases of acromegaly caused an excessive loss of phosphorus, while the nitrogen was but moderately altered. Bony tissue is rich in phosphorus and poor in nitrogen.[3]

The similarity which exists at least in microscopical characters between pituitary tissue and the thyroid gland has suggested further that possibly the pituitary body discharges its active principles into the system as an internal secretion. So far no active internal secretion has been isolated, and the evidence for the existence of this secretion is largely indirect.

Pathology.—Of all the glandular changes that are met with in acromegaly, enlargement or tumour-formation in the pituitary body is the most common, and the symptoms characteristic of acromegaly are such as can best be explained by disturbance of this organ. Several views are

[1] *Journ. of Physiol.*, 1903, xxx., p. 97.

[2] *Transact. Roy. Acad. of Med.*, Ireland, 1904, vol. xxii., p. 429.

[3] *Zeitschr. f. klin. Med.*, 1897, supp. Hft., s. 282.

held as to the relationship existing between acromegaly and disease of the pituitary body. Benda[1] maintains with Tamburini that acromegaly is due to over-action on the part of the pituitary body. Marie on the other hand thinks that acromegaly is due to deficient action on the part of the pituitary body. Mendel, taking a broad view of the subject, considers that the enlargement occurring in the thyroid, pituitary and other glands is responsible for the occurrence of acromegaly, although it is possible that the pituitary body takes a more active share than the others. Finally Strümpell, Vassale, Arnold and Cagnetto[2] look upon the pituitary enlargement and the other features of acromegaly as being all the results of some unknown disturbance of metabolism.

Much of this confusion is due to observations such as the following: it is said that acromegaly can occur without any apparent change in the pituitary body, that gross changes due to the development of tumours in the pituitary body may occur and yet acromegaly does not develop, as for example in the case described by Cagnetto,[3] Rosenhaupt,[4] and others; Friedmann and Maas have shown that removal of the pituitary body is not followed by disturbances of the growth of the limbs, and Sir Victor Horsley has shown that extirpation of the hypophysis may be followed by no symptoms, nervous or otherwise. On the other hand Vassale and Sacchi find as sequelæ—apathy, somnolence, feeble gait, dyspnœa, anæmia, lowering of temperature, emaciation, tonic and clonic muscular spasms and fibrillary twitchings.[5]

Another difficulty which requires solution is the nature of the various tumours occurring in the pituitary body; an interesting feature is the fact that metastases occurring in

[1] *Deutsche med. Woch.*, 1901, s. 513, 536, u. 564.

[2] Virchow's *Archiv*, 1904, Bd. 176, Hft. 1., s. 115.

[3] *Loc. cit.*

[4] *Berlin. klin. Woch.*, 1903, s. 893.

[5] *Rev. sperim. di fren.*, 1892, vol. xviii, p. 525; 1894, vol. xx., p. 83.

other parts of the body as a result of a malignant tumour of the pituitary body have never been described; further, pituitary tumours almost always originate in the anterior lobe. The tumour formations are largely of the nature of simple hyperplasia, or at most of adenomatous formation.[1] This was certainly the case in two of the four cases described by Benda, Fraenkel and Stadelmann; in the other two the suspicion of malignancy had to be entertained. It is quite a question therefore whether the cases of so-called malignant disease of the pituitary body are not really examples of hyperplasia, and Benda's view that acromegaly is due to an over-activity of the pituitary body is confirmed by his finding in three of the cases he examined a considerable increase of the cells peculiar to the healthy pituitary body, as if indeed the gland was in a condition of hyperplasia. The view that acromegaly is due to over-action of the pituitary body is the one which most easily meets objections; nor is it impossible to hold this view in face of the fact that removal of the hypophysis does not cause acromegaly experimentally, or that mouth feeding with pituitary substance does not cause acromegaly; in the latter case sufficiently long treatment may not have been carried out, and it is possible that pituitary extract given by the mouth becomes altered in the alimentary tract and can no longer exert any influence.

The occurrence of myxœdema and acromegaly in the same individual has been advanced as a further proof of the functional relationship of the thyroid and the hypophysis, atrophy of the former being associated with hyperfunction of the latter. Richter quotes a case of myxœdema described by Ponfinck, who found complete absence of the glandular part of the hypophysis cerebri. Symptoms of Graves' disease have also been known to be associated with acromegaly as well as with glycosuria. Glycosuria occurs in a certain proportion of cases of acromegaly.

[1] For a full discussion of this subject, *see* contribution by J. and T. W. P. Lawrence, *Trans. Path. Soc.*, 1899, p. 202.

Another disease which has been associated with excessive action of the pituitary body is gigantism, Sternberg [1] finding that 40 per cent. of all giants are also the subjects of acromegaly. According to some observers infantilism may in certain cases be due to deficient action of the pituitary body. Cestan and Halberstadt[2] have approached the question of the influence of age upon the results occurring from disturbed function. They describe two distinct groups of symptoms, one in which there are psychical changes—mental torpor, somnolence and loss of memory; in the other the alterations are more physical, producing gigantism in some cases, but in more extreme ones acromegaly. Mental symptoms are apt to occur at any period of life in which there is disturbance of the pituitary gland, but gigantism is mostly restricted to infant life, and acromegaly to young adult life; in middle and adult age mental symptoms alone are developed.

Treatment.—For want of more certain knowledge of the function of the pituitary body, and of the part it plays in the production of acromegaly, little can be expected in the direction of a causal treatment of the malady. If acromegaly and gigantism are due to diminished action on the part of the hypophysis, then there would be some reason in attempting to supplement this diminished action by means of pituitary feeding. Such attempts have been made, but the results as described by Sternberg [3] show that the substitutional treatment of acromegaly by means of preparations made from the thyroid or pituitary body has produced no confirmation of the view that acromegaly is due to diminished action of the pituitary body, supposing, of course, that the extract of this organ can be absorbed unaltered from the alimentary tract. Some improvement, however, has been noticed after use of the thyroid gland in acromegaly, also after pituitary feeding and after feeding

[1] "Acromegaly," *Sydenham Soc.*, 1899, p. 90.

[2] *Rev. neurologique*, 1903, p. 1180.

[3] *Loc. cit.*, p. 118.

with both thyroid and pituitary substance. On the other hand, some cases have been reported in which no improvement at all followed upon the use of pituitary substance, and unfavourable objective results were observed sometimes, even though the subjective evidence pointed to an improvement. The same warning has to be sounded in the treatment of acromegaly as of cases of exophthalmic goitre and Addison's disease, namely, that periodically the disease tends to undergo spontaneous improvement quite independently of any form of treatment. Some observers have found that headache and paræsthesia, both of which are marked symptoms in acromegaly, the latter taking the form of numbness and tingling of the extremities, are definitely relieved by the internal administration of the gland; no reduction can be secured in the size of the extremities by this treatment.[1] Magnus-Levy[2] records a case of acromegaly treated with pituitary substance. Symptoms arose which recalled features of Graves' disease—marked perspiration, polyuria and alimentary glycosuria.

The only possible way to counteract the effects of the increased activity of the pituitary body, which, as already pointed out, gives the most satisfactory explanation of acromegaly, would be to extirpate the hypophysis cerebri as suggested by Sir Victor Horsley. Had the hopes of investigators been fully realised as to the possibility of developing specific cytolytic sera, it would have been possible to develop a serum which would have a solvent action upon an over-active pituitary body.

So far such developments have not been made, nor have any attempts been made to employ the serum of animals repeatedly injected with doses of pituitary substance, or of animals from which the pituitary body has been removed.

Pituitary substance has been administered by mouth

[1] Marinesco, *La Semaine méd.*, 1895, p. 484; v. Cyon, Pflüger's *Archiv*, 1898, lxxii., s. 635.

[2] *Münch. med. Woch.*, 1897, s. 400.

and by subcutaneous injection for the treatment of epilepsy; the results, however, were negative, and the treatment in some cases produced serious disturbances, such as thrombosis, etc., and even intensified the fits.[1] Von Cyon has produced improvement of various cardiopathies by the use of pituitary substance.

Preparations and Doses.—Pituitary gland may be obtained as a dried substance, one part of which represents 6·5 parts of fresh gland. In acromegaly as much as 0·1 gramme (1½ grains) of dried substance may be given three times daily and may be increased to three times that amount. Opohypophysinum should be given in 0·05 gramme doses (¾ grain).

[1] Mairet and Bosc, *Arch. de phys. norm. et path.*, 1896, p. 600.

CHAPTER XIX.

THE THYMUS.

Anatomy and Physiology.—Reference has already been made to the association of changes in the anterior lobe of the hypophysis cerebri and in the thyroid, and it has been pointed out that such associations were made explainable by reference to the common origin of the thyroid body and anterior lobe of the pituitary body—namely, from the buccal mucous membrane, the latter from epiblast and the former from hypoblast.

The thymus gland, developmentally, is still more closely related to the thyroid body; for whilst the thyroid body is developed from the pharyngeal hypoblast opposite the ventral ends of the second visceral clefts, the thymus is developed from bilateral growths of the hypoblast near the third visceral cleft, as well as possibly in part from the fourth cleft.

Further association is shown from the clinical point of view. It is well known that the thymus is constantly enlarged in cases of exophthalmic goitre (Ord and Mackenzie), and it is found enlarged in cases of acromegaly. From the fact that the thymus becomes much atrophied at puberty, being replaced by fatty tissue, and that at this stage the ovaries begin to become active, speculations have been made that the thymus and ovary have somewhat similar effects upon the body from the point of view of supplying a similar internal secretion. Henderson has shown that in young cattle castration causes delay in the atrophy of the thymus, and Paton[1] has shown that removal of the thymus is followed by a rapid growth of the testicles in young guinea-

[1] *Journ. of Physiol.*, 1904, xxxii., No. 1, p. 28.

pigs weighing not more than 300 grammes. There are also observations which show that in some cases the thymus persists or hypertrophies, when for various reasons the thyroid has atrophied or become functionally insufficient. The clinical observation that treatment of simple goitre may succeed almost as well by means of thymus feeding as by ingestion of thyroid substance, and the experimental inquiry of Treupel [1] that cramps produced in dogs by removal of the thyroid can be relieved by feeding with thymus substance, may be quite well explained on purely chemical grounds by the fact that Baumann has found iodine present in the thymus, and, as in the case of the thyroid, Gauthier has found arsenic. Swale Vincent [2] found that extract of fresh calf's thymus prepared with ·9 per cent. sodium chloride solution appeared to exert no specific effect when injected subcutaneously or intravenously into animals; the same depressor effect was observed as occurs when extracts of other tissues, nervous, muscular, etc., are injected. Svehla had proved the absence of pressor effects in extracts of the thymus obtained from the human embryo.

The microscopic examination of the thymus shows that the epithelial character of the tissue is almost quite lost, the only representative being Hassall's corpuscles. The original epithelial outgrowths from the hypoblast are invaded by connective tissue and lymphoid cells, and the latter are eventually found to preponderate, being especially rich in the cortical part of the follicle, and less so in the medulla. Nucleated red corpuscles, polymorpho-nuclear neutrophile cells and coarse granular oxyphile cells, are also found in the thymus.[3] Bezançon and Labbé [4] describe in addition the occurrence of small numbers of myelocytes and

[1] *Münch. med. Woch.*, 1896, s. 885.

[2] *Proceed. of Physiol. Soc.*, 1903, xxx., p. xvii.

[3] Dudgeon, "Contrib. to the Pathology of the Thymus Gland," *Journ. of Path. and Bacteriol.*, 1905, p. 173.

[4] "Traité d'Hæmatologie," 1904, p. 881.

epithelioid cells and exceptionally of mast cells. Judging by the fact that the thymus appears in the third month of fœtal life at a time when leucocytes are first observed, there is some support for Beard's view that the thymus, like other lymphatic tissues, gives origin to leucocytes.[1] The microscopic picture, in part, closely resembles that of ordinary lymphoid tissue as found in lymphatic glands and spleen. It is impossible to define any cells which may be considered to act as internal secretory cells in the same sense as those of the thyroid, etc.

Treatment by Means of Thymus Substance.—Thymus substance has been used in the treatment of simple goitre. The advantage over thyroid substance is that improvement can be secured without running the risk of producing symptoms of thyroidism—palpitation, loss of weight, etc. ; in some cases even, the thymus has produced improvement in the goitre when thyroid substance had failed or produced unfavourable results.

Mikulicz[2] was the first to employ thymus substance for simple goitre. He treated eleven cases, and five were favourably influenced, so that meditated operations were abandoned. Dyspnœa improved and the circumference of the neck was lessened. Reinbach was able to confirm the good results obtained by Mikulicz.

Mikulicz also noticed good results following the treatment of two marked cases of Graves' disease by means of thymus gland, but reserved his opinion as to whether the thymus substance was responsible for the change. Subsequent trial has shown that exophthalmic goitre is but little improved, if at all, by the treatment. Mackenzie[3] found that out of fifteen reports collected from the literature fourteen were favourable, but in twenty cases observed by himself there was no improvement in seven, and he was unable to attribute the improvement occurring in the

[1] *Lancet*, 1899, i., p. 144.

[2] *Berlin. klin. Woch.*, 1895, s. 343.

[3] *Amer. Journ. of the Med. Sc.*, 1897, p. 132.

remaining thirteen to the thymus treatment. Henton White [1] found that the nervous symptoms in one case were improved, but the exophthalmos and goitre remained unaltered. The results published by Rushton Parker were equally inconclusive.[2] One patient took 2,000 tabloids of 5·0 grains weight, and yet no change was noticed; another patient was relieved of subjective symptoms, but the objective signs remained unaltered; a third patient was improving before the thymus treatment was begun; a fourth distinctly improved during the treatment.

Improvement following upon the use of thymus has been recorded in marasmus of children. It had long been known that in this condition the thymus gland atrophies very considerably. Improvement has also been recorded in the treatment of chlorosis as a result of thymus feeding, as well as in rickets. Mendel [3] published his results on the treatment of rickets in accordance with the observations of Friedleben [4] and Mettenheimer,[5] who considered that the thymus was of importance to growing children; they found that young animals from whom the thymus was removed developed manifestations of rickets. Mendel gave doses of 6–12 grammes of fresh calf's thymus. Over a hundred observations were made. In many cases favourable influence was observed, especially in the nervous symptoms such as spasm of the glottis; the splenic enlargement was reduced. No harmful effects were noticed.

Dose.—·05 grammes of dry substance is equivalent to ·30 grammes of fresh gland, and 12 to 20 tabloids of ·05 to ·1 gramme of dried substance may be given daily.

[1] *B. M. J.*, 1899, i., p. 786.
[2] *Ibid.*, 1899, i., p 12.
[3] *Münch. med. Woch.*, 1902, s. 134.
[4] *Die Physiol. der Thymusdrüse*, 1858.
[5] *Jahrb. f. Kinderheilk.*, 1897, Bd. xlvi., s. 55.

CHAPTER XX.

THE SPLEEN, HÆMAL LYMPHATIC GLANDS, LYMPHATIC GLANDS, MARROW.

These four groups of tissues may be considered together, for there is good reason to believe that there is much in common amongst them in histological appearance and physiological action. It is well known that the largest of these representatives of hæmopoietic tissues, viz. the spleen, is not of vital importance: the spleen may be removed without producing any serious disturbance. In all these tissues "mother cells" exist which are capable, under suitable stimulus, of producing, by the process described by Virchow as metaplasia, cells of different histological character (Pappenheim). Thus the "mother cells" of the marrow ordinarily give rise mostly to erythroblasts and granular and non-granular leucoblasts. The "mother cells" of lymphatic glands give origin mostly to small lymphocytes, and possibly the splenic "mother cells" give rise mostly to large lymphocytes. Erythroblasts may, however, be formed in the spleen and in the hæmal lymphatic glands.

Thus, with the exception of lymphatic glands, erythroblastic formation occurs in all these tissues, and leucoblastic formation in all of them without any exception. It is further possible that in the spleen, hæmal lymphatic glands and lymphatic glands, destruction of leucoblasts also occurs.[1] Destruction of red corpuscles takes place in the spleen and hæmal lymphatic glands.

Treatment by Splenic Pulp. — Extracts and decoctions of splenic pulp do not appear to have any

[1] T. Lewis, *Internat. Monatschr. für Anat. u. Physiol.*, 1902, Bd. xx., Hft. 182.

specific action, whether injected intravenously or subcutaneously, beyond causing leucopœnia, which is ultimately followed by hyperleucocytosis, due to the effects of nuclein derived from the splenic pulp. An increase of red corpuscles and of the hæmoglobin also takes place after the use of splenic substance.

Hedin[1] has shown that there exists in the spleen, lymphatic glands, kidney and liver, but especially in the spleen, proteolytic enzymes. One, which he styled lieno-β-protease, acts only in an acid medium, but another ferment, lieno-α-protease, acts only in an alkaline medium. Flexner[2] has shown that definite irritative hyperplasia can be developed by the injection into animals of preparations of spleen, lymphatic glands and bone marrow. Injection of spleen toxins was followed by marked hyperplasia of lymphatic glands, intestinal lymphoid tissue and spleen; injection of lymphatic gland toxin and marrow toxin was followed by the same effect. He was further able to show that the bone marrow under the influence of lymphatic gland toxin responded with a production of mononuclear non-granular cells, and under the influence of marrow toxin with a production of granular cells.

Treatment by Substances Derived from Lymphatic Tissues. — Splenic substance has been used in various forms of secondary anæmia, in chlorosis, pernicious anæmia, lymphadenoma, malaria, Graves' disease and leucocythæmia. The results of this treatment are, however, not encouraging. Landau and Hirsch[3] describe a substance which they call *stagnin* which is obtained by autolysis of splenic substance. Stagnin appears to produce, according to these authors, an increase of the clotting power of the blood, so that capillary oozing is checked. It does not act as adrenalin does by contracting the blood-vessels. Stagnin is administered by injection into the glutei.

[1] *Journ. of Physiol.*, 1904, vol. xxx., p. 155.
[2] *Univ. of Pennsylv. Med. Bull.*, 1902, vol. xv., p. 287.
[3] *Berlin. klin. Woch.*, 1904, s. 577.

Preparations of lymphatic glands have been used in cases of carcinoma; beyond the activity of lymphatic glands in the genesis of certain white blood corpuscles, and of their action in retaining metastatic developments of carcinoma, there is no other function known, so that there appears to be no good reason for the use of gland extracts against carcinomatous disease. Silberstein,[1] guided by the frequency with which the glands are enlarged in various infectious diseases of the respiratory tract as if to supply antibacterial agents, made use of an extract of the bronchial glands of sheep (glandulin); nine out of twelve cases of tuberculosis of the lungs are said to have been improved by this treatment—the fever and cough abated, there was a reduction in the number of bacilli in the sputum, and the appetite and weight increased. The number of other reports on this substance is, however, scanty, and the results are contradictory.

Lucatello and Malon[2] report the effects produced in cases of leucocythæmia by the use of leucolytic serum obtained from rabbits and sheep which had been treated for a long time with injections of leucocytes; 1 to 5 c.cm. of the serum were injected in one case on twenty-six occasions, and in another case on twenty-eight occasions. In the first case there was a fall of total leucocytes from 560,190 per c.cm. to 375,720; in the second case the reduction was less marked—from 500,960 to 493,300; reduction in the size of the spleen was also noticed. Franke has made observations on the effects of leucolytic serum *in vitro* upon the leucocytes withdrawn from a case of leucocythæmia. A number of axillary glands were removed from a patient suffering from lymphatic leucocythæmia; these glands were washed in sodium chloride solution and rubbed down in a capsule; this pulpy substance was then diluted and filtered through sterilised gauze; 5 to 8 or 10 c.cm. of this fluid were injected on five occasions into the peritoneal

[1] *Wien. med. Presse*, 1902, s. 1179.

[2] *Gazz. degli Osped.*, 1903, p. 108.

cavity of rabbits at intervals of three days. The serum obtained by defibrinisation of the blood of these animals was mixed with a drop of the patient's blood and kept at a temperature of 37° C. The following changes were observed—the leucocytes gradually lost their contour, and became transparent and then shrank, until finally they were converted into a granular mass, the small leucocytes taking 6–8 hours, the larger ones 12 hours, to undergo this change. Control observations were made on the patient's blood without using any leucotoxic serum, and also on mixtures of the patient's blood and normal rabbit's serum; in the controls the leucocytes after 12–14 hours were noticed to have maintained their original condition. The patient from whom the glands were removed was, however, too ill for observations to be made on the effects of this leucolytic serum by injection.

Widal attempted to produce an antiserum for lymphatic leucocythæmia by injecting animals with preparations of the lymphatic glands obtained from individuals who died of accidents; although the serum subsequently obtained from these animals was cytolytic for the leucocytes of man, it did not produce any favourable effects upon the progress of leucocythæmia. Metchnikoff,[1] considering that senility was due to the phagocytic action of mononuclear leucocytes upon various organs, endeavoured to produce a leucolytic serum which should check the development of these mononuclear cells. He injected guinea-pigs with an emulsion prepared from the spleen of the rat and found that the serum of the guinea-pigs was capable, *in vitro*, of immobilising, agglutinating and dissolving the leucocytes of the rat. Unfortunately this serum was not specific in action, and besides destroying mononuclear leucocytes, also attacked the other leucocytes present in the blood, especially the polymorphonuclear leucocytes. Besredka has shown that

[1] "Année biologique," t. viii., p. 249.

the destruction of leucocytes by antileucocytic sera is followed by the death of the animal in a few hours when given in large doses, and in smaller doses exposes the animal to invasion by saprophytes, existing naturally in various centres of the body, analogous to the invasion of the system which takes place as terminal infections in various disorders. It appears, therefore, as a result of this observation, that any attempts to produce improvement in cases of leucocythæmia by means of leucolytic sera would be accompanied by considerable risk of endangering the life of the individual.

The serum of blood has been used as a means of introducing nourishment in cases of cholera infantum and other conditions in which for various reasons it is impossible to maintain nutrition by feeding; the sterile serum of horses and cattle has been used by Reinach; 10 to 20 c.cm. may in the case of infants be injected under the skin. Salter[1] has found that the experimental injection of small quantities of normal serum into animals was followed by an increase of urinary nitrogen and a loss of weight, but that when large quantities were introduced the serum was used up as a food to such an extent as to counterbalance the loss due to increased katabolism. The injection of remedial sera obtained from animals has been noticed to produce usually within a fortnight or three weeks a rash, joint pains and rise of temperature. Salter has been able to show that if the normal serum before injection is heated to 65°, then toxic effects are removed and, as well, the substances producing increased nitrogenous metabolism are destroyed. He recommends doses of 30 to 40 c.cm. of horse or sheep serum for infants, 60 to 80 c.cm. for children, and 100 to 120 c.cm. for adults; these doses may be repeated at varying intervals according to the severity of the case, the site of injection being the subcutaneous tissues of the loin, axilla and interscapular region.

[1] *Guy's Hosp. Reports*, vol. liii., p. 241.

Ceni[1] has obtained variable results by the injection of epileptics with serum previously obtained from themselves or other epileptics after an epileptic attack. Gerhartz[2] has found improvement after this treatment, as shown by a prolongation of the interval between the fits; the best results were obtained from serum obtained from other epileptics. Favourable results are also reported by Wende[3] and by Mazzei,[4] the former finding the majority of twelve cases improved by the treatment, and the latter obtaining good results in four other cases.

Treatment by Marrow.—Marrow obtained from the long bones and the ribs has been used in a variety of diseases in which the blood shows pathological changes. In view of the investigations more recently carried out on the effects capable of being produced experimentally by the use of marrow, it must be conceded that the marrow is capable of exerting specific effects, though, as already pointed out, some of these effects are such as apparently to exclude the use of marrow in certain of the blood diseases. So far the idea that the marrow possesses an internal secretion has not been proved by experimental inquiry, although it is admitted that the marrow, like other lymphoid tissues, pours into the blood stream fresh supplies of red and white corpuscles. Injection of marrow preparations into healthy animals has not been found to exert any influence upon the number of red corpuscles per cubic millimetre, nor upon the content of hæmoglobin, but various observations have been made which tend to show that in cases in which the content of red corpuscles and of hæmoglobin is below normal, marrow extract on injection produced an improvement in both directions. Von Korczynski[5] considers that good results are obtained experi-

[1] *Neurologisch. Centralbl.*, 1903, s. 338.
[2] *Ibid.*, 1904, s. 835.
[3] *Psychiatrisch. neurolog. Wochenschr.*, 1903, Nos. 35 and 36.
[4] *Rif. Med.*, 1904, p. 432.
[5] *Wien. Klin.*, 1902, s. 41.

mentally by the use of marrow; young pups develop much more quickly if fed with red marrow.

Von Korczynski made observations in two young subjects on the effect produced by the use of *medulladen*, a preparation of the marrow of the long bones of calves. In both cases the positive nitrogen balance was greater during the period in which the marrow preparation was given than before or after that period; more carbonic acid gas was also noticed to be excreted during the period of treatment.

Discordant reports have been published on the value of medullary preparations in the treatment of various forms of blood disease, rickets, etc. Frazer[1] describes very favourable results from the use of large doses of marrow in a case of severe pernicious anæmia, but salol had also been used. Favourable results are reported by Bozzolo in leucocythæmia and lymphadenoma and by Dixon Mann in two cases of chlorosis and in the anæmia associated with hæmophilia. Combe[2] reports on the favourable effects in chlorosis, rickets and infantile lymphadenoma; improvement in cases of insanity even has been recorded by the use of medullary substances. Goldscheider, on the other hand,[3] found no improvement either in the blood picture or in the general condition. Hunt,[4] for the treatment of pernicious anæmia, gave two ounces every twenty-four hours of bone marrow obtained from the ribs of oxen. His results were not favourable, and he concludes that the treatment with arsenic was more satisfactory. Charrin and Chassevant[5] found that marrow did not show any special energetic influence upon cases of anæmia.

Watson and Thompson[6] have used *myelocene*, a pre-

[1] *B. M. J.*, 1894, i., p. 1172.
[2] *Le Semaine méd.*, 1895, p. 205.
[3] *Deutsche med. Woch.*, 1894, s. 376.
[4] *Lancet*, 1896, i, p. 282.
[5] *La Presse méd.*, 1897, p. 45.
[6] *Lancet*, 1902, ii., p. 1033.

paration of marrow, in five cases of extensive and very chronic psoriasis and have noticed improvement; it is applied in a strength of 50 per cent. solution, which is rubbed into the forearm.

Dosage.—A teaspoonful of fresh marrow obtained from the bones of the ox or calf may be given to children daily: 50 to 100 grammes to adults. Powdered medullary substance may be given in tabloids of 3 grain doses three times daily; Medulladen may be given to the extent of 6–9 grammes daily, and opomedullinum—a preparation of red marrow—6 grammes daily.

CHAPTER XXI.

MUSCLE, NERVE TISSUE, PLACENTA.

Muscle.—The muscles of the body, like other tissues may in a sense be considered to have an internal secretion —some of the material being an end product like urea, which is ultimately removed by the kidney. There is, however, no proof of any specific substance secreted by the muscles in the same sense as the thyroid secretion, which is of service in controlling metabolic and other processes. The flesh of animals forming one of the elements of the dietary of man and other flesh-eating animals, it has been thought that the comparatively high resistant powers of carnivora against tuberculosis, as compared with herbivora, was possibly due to some antitoxic property present in meat. Héricourt and Richet[1] found that dogs which were fed daily with 12·0 grammes of raw meat per kilogramme weight were able to resist the effects of intravenous injection of a culture of tubercle bacilli, whereas animals not so fed soon emaciated after the injection. The meat juice was found to be as efficacious as meat itself; cooked meat was valueless. Héricourt and Richet therefore recommend the treatment of human tuberculosis by means of raw meat juice (zomotherapy). Josias and Roux[2] found that zomotherapy was very efficacious in the early stages of tuberculosis before the invasion of the body by other organisms had occurred. Corneil and Chantemesse[3] have confirmed the observations of Héricourt and Richet, but Lawrason Brown[4] found that raw meat juice

[1] *Compt. rend. de l'acad. des sc.*, 1900, t. cxxx., p. 605.

[2] *Trans. British Congress for Tubercul.*, 1901, vol. iii., p. 312.

[3] *Ibid.*

[4] *Amer. Journ. of Med. Sc.*, 1903, p. 1071.

had no effect on the experimental tuberculosis of dogs, even if the bacilli were attenuated, so long as large doses were given; he also found that animals experimented on and fed on mixed diet may live longer than those treated with meat juice. Fraenkel and Sobernheim[1] have also failed to confirm the observations of Héricourt and Richet. Philip[2] speaks most favourably of the effects of zomotherapy in cases of pulmonary tuberculosis—the general aspect and the weight increasing, the myotatic irritability so frequently met with in tuberculosis tends to lessen and even disappears, the pulse rate becomes less frequent, the temperature tends to improve, the gastro-intestinal functions are rendered easier and more effective, the hæmoglobin increases and there is a remarkable increase in the digestion leucocytosis; finally the local lesions are distinctly improved. Lawrason Brown[3] is less enthusiastic about the special value of raw meat juice, considering the advantages mainly those of the kitchen, for it forms an agreeable addition to jellies, etc.; further there are the disadvantages of preparation.

That it is possible that meat juice exerts special influences is shown in other directions by Chalmers Watson,[4] who found that enlargement of the thyroid and parathyroid bodies was produced in fowls by the administration of raw lean meat and water, but the question whether raw meat juice possesses any special ferment which is not present in other raw animal-proteids, and which exerts a special action upon the tubercle bacilli or stimulates the system specially affected with tuberculous disease, is probably to be answered in the negative; possibly the influence of spermin, nucleinic acid and other derivatives of animal tissues is responsible for the improvement produced in an individual attacked with tuberculosis or any other infective agent.

[1] *Berlin. klin. Woch.*, 1901, s. 733.
[2] *Practitioner*, 1905, Jan., p. 14.
[3] *Loc. cit.*
[4] *Proceedings of Physiol. Soc.*, 1904, vol. xxxi., p. v.

Héricourt [1] recommends the following method of preparation: fresh beef freed from fat is minced, and is then macerated for a couple of hours in one-fifth of its weight of sterilised cold water; the meat juice is then extracted by pressure. In early tuberculosis 200 to 400 grammes of the liquid should be given daily; in the second stage 400 to 800 grammes, and in advanced tuberculosis 800 to 1,200 grammes should be given. It is best to give the juice half an hour before food; if necessary it may be flavoured with salt, etc. The treatment should be continued for six months. Other authorities recommend smaller doses because of the digestive and other disorders that may be produced by such large doses.

Croftan,[2] making use of the observation that extract of muscle, or of almost any other tissue, is capable of activating pancreatic preparations in the destruction of sugar, has sought to improve the condition of diabetic patients by the administration of a mixture of pancreatic and muscle tissues: reduction in the output of sugar was observed as a result of this form of treatment.

Nerve tissue.—There is no support for the view that nervous tissue possesses an internal secretion. The one fragment of physiological evidence that can be advanced in favour of the use of nervous tissue in such disorders as neurasthenia, melancholia, epilepsy, etc. is that which was proclaimed by Brown-Séquard when he stated that he considered that testicular substance exerted a favourable influence on the body by acting through the nervous system. Various observers, affirming their recommendations of the use of nervous substance for the treatment of various nervous disorders, do so on the assumption that these disorders are due to a want in the nervous tissue of the particular substances referred to by Brown-Séquard. The accounts given by Babes, Paul, Dauriac, Hammond, Ryan, Robertson and Burghart show by their want of agreement

[1] *Rev. de la Tuberculose*, 1900–1, t. viii., p. 1.

[2] *Philadelph. Med. Journ.*, 1904, vol. lxxix., p. 882.

that the results of treatment by brain substance of locomotor ataxy, epilepsy, various psychoses, neuralgia and other disorders of the brain and spinal cord, offer no encouragement for the use of such a remedy. The effects produced are much the same as those obtained by the use of testicular extract. No special physiological effects have been noticed on the injection of preparations of brain substance into animals. Swale Vincent[1] has shown that there are two groups of substances present in watery extract of brain substance which on intravenous injection are capable of lowering blood pressure. The same effect is produced by the intravenous injection of alcoholic extracts of brain substance.

Considerable interest, however, has been evinced as to the value of nervous substance since Wasserman and Takaki[2] showed that tetanus toxin could be neutralised by contact with extract of nervous tissue. One cubic centimetre of an emulsion of brain substance which contained about a third part of the brain substance of various species of animals susceptible to tetanus poison, was found able to neutralise ten fatal doses of tetanus toxin, so that when a mixture of the two substances was injected no poisonous result followed. Further, a fatal dose of tetanus toxin introduced alone after the first injection was not fatal. These observations were confirmed by Courmont and Doyen. Marie's experiments appear to show that the previous injection subcutaneously of cerebral substance is unable to counteract the toxic effects of tetanus poison subsequently injected directly into the brain; apparently it is necessary for the two substances to be mixed before injection. Krokiewicz[3] succeeded, however, on three occasions in successfully treating three cases of tetanus by repeated injection, begun on the ninth day of disease, of an emulsion composed of 5·0 grammes of fresh brain substance

[1] *Journ. of Physiol.*, 1904, vol. xxx., p. 143.
[2] *Berl. klin. Woch.*, 1898, s. 5.
[3] *La Semaine méd.*, 1898, No. 5, p. 178.

and 15 c.cm. of physiological salt solution. The cramps definitely abated, and on the seventeenth day of the illness the patient was cured.

Observations have been made by Babes[1] which show that hydrophobia produced in dogs by injection of virus from rabbits can be successfully antagonised by the injection of macerate of the medulla oblongata of healthy sheep provided that the virus was not too active, and the amount of brain substance used was relatively large. It has also been found that brain substance is capable of rendering strychnine and morphine non-toxic (Widal and Nobècourt).

Of recent years various observers, especially Italian, have published a considerable number of reports on the use of brain substance in epilepsy, eclampsia, chorea and other convulsive disorders which originate in the cortex of the brain. Lion[2] describes the results of treatment of epilepsy by means of various preparations of brain substance, more especially Pœhl's *cerebrinum* and *opocerebrin.* Nervous tissue derived from the grey matter of the cortex was dried and administered in 2–4 gramme doses; opocerebrin, or dried extract, in 0·2 to 0·3 gramme doses given twice daily. The treatment should be continued until cure results, short intervals being allowed to elapse during which no treatment is carried out. Lion states that acute alcoholism responds more quickly to the use of cerebrin than by means of cardiac remedies, chloral hydrate, strychnine, bromides, etc. More recently Lion advocates the administration of 1·8 grammes of cerebrin in one dose in the morning of every third day; then if the attack persists, the dose is given every other day and even every day. In some cases of severe repeated attacks of epilepsy Lion has found it advantageous to combine organotherapy with Balint's "bromopan" or "bromine" diet.[3] This diet

[1] *La Semaine méd.*, 1898, p. 147.

[2] *Berlin. klin. Woch.*, 1901, s., 1292; *Deutsche med. Woch.*, 1902, s. 905.

[3] *Berlin. klin. Woch.*, 1901, s. 617.

consists of 1–1½ litres of milk, 40–50 grammes of butter, three eggs (unsalted) and 300–400 grammes of bread and fruit; the whole yielding 2,300 to 2,400 calories, and containing not more than two grammes of sodium chloride; the deficiency of this salt is made up by means of three grammes of sodium bromide, which is incorporated with the food. Eulenberg[1] gives a much more cautious verdict than Lion; he tried the treatment by cerebral substance in six cases of epilepsy, five females and one male, the ages varying from fourteen to thirty-one years; they had resisted treatment by bromides and by Balint's bromopan dietary. Eulenberg was inclined to think that cerebrin has some effect in certain cases of epilepsy. Meyers[2] describes the results of treatment of ten cases of epilepsy by means of cerebrin: three showed no improvement and one was made worse; amongst the remainder, a reduction of the number of attacks was observed in three, and in all the psychical invigoration was a marked contrast to the depression produced by bromide treatment. Zenoni of Genoa[3] introduced a new preparation of brain substance, which he also called *cerebrin*; it is made from fresh sheeps' brains in the form of a permanent preparation; it is used subcutaneously for the treatment of grave forms of epilepsy, also for insomnia, tics and various indefinite convulsions. Muzzarelli[4] found more favourable results with Zenoni's cerebrin than with any other mode of treatment in epilepsy, in eclampsia in children, in chorea, hysteria and neurasthenia. Sciallero,[5] thinking that much of the failure of brain preparations in the relief of the above conditions was due to the harmful influence exercised by glycerine upon brain substance, introduced a new preparation, *cephalopin*, which is a preparation of brain substance and olive oil, and

[1] *Deutsche med. Woch.*, 1902, s. 907.
[2] *Nederl. Tijdschr. v. Geneesk.*, 1902, ii., s. 1189.
[3] *Gazz. degli Osped.*, 1902, p. 1461.
[4] *Ibid.*, 1903, p. 238.
[5] *Ibid.*, 1904, p. 70.

is quite free from proteid: 1 c.cm. of cephalopin is able to neutralise the toxic effects of a fatal dose of strychnine when injected with the strychnine into a guinea-pig. Sciallero recommends its use in much the same class of cases in which cerebrin has been used. Cephalopin is sold in flasks containing 2–3 c.cm., and the dose for injection is 5 c.cm. for an adult. Soleri[1] confirms the experience of Sciallero and finds that cephalopin has an anti-convulsant action. He obtained favourable results from the use of cephalopin injected in 2–5 c.cm. doses on alternate days. Montagnini[2] reports on the favourable influence of Zenoni's cerebrin in two cases of epilepsy; one was treated by subcutaneous injection and the other by administration by the mouth. These clinical reports are to some extent so much in agreement with the experimental discoveries of Babes, and Babes and Riegler, and of Widal and Nobècourt, that it is impossible to consider them as *post hoc* fallacies. The silver nitrate treatment of epilepsy introduced by Heine and Romberg, the potassium bromide and atropine treatment of Niemeyer, the valerian treatment of Cantani, and the borax treatment instituted by Sir William Gowers, have been found inadequate in a certain group of epileptic cases which obstinately resist the most excessive doses of these remedies. Organotherapy offers another remedy for such cases.

Dosage.—Besides the doses above mentioned, glycerine extract of brain substance may be injected hypodermically in quantities of from 4–5 grammes of a 1 in 10 extract, once a week or every third day.

Placenta.—The placenta of sheep has been administered in doses of 25 grammes of the fresh substance, and apparently with success, in the treatment of various forms of metritis and uterine subinvolution. Bouchacourt[3] has recommended the use of placental extract, 8 grammes daily,

[1] *Gazz. delgi Osped*, 1904, p. 1286.
[2] *Ibid.*, 1904, p. 170.
[3] *Bull. méd.*, 1903, t. xvii., p. 805.

as a galactogogue. Fieux [1] was unable, however, to obtain the slightest effect in this direction, even by the administration of 100 grammes daily for several days.

Efforts have been made to employ preparations of mammary gland, lung, parotid gland, retina, prostate and nasal mucous membrane, in order to relieve various conditions depending upon diseases of these structures. So far there is nothing of an experimental nature to justify the application of these preparations, and the reports on therapeutic effects do not encourage their extended application.

[1] *Bull Méd.*, 1903, t. xvii., p. 725.

INDEX.

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