and (2) that extirpation of the Gasserian ganglion through the base of the skull, though admittedly a difficult undertaking, need not endanger life, and at present holds out the best prospect in dealing with the intractable forms of trigeminal tic.

[During the lecture, which was illustrated by diagrams and microscopical specimens, Mr. Rose demonstrated the different stages of the operation on the cadaver.]

NOTES ON THE USE OF PILOCARPIN IN DERMATOLOGY.

By ROBERT M. SIMON, M.D., M.R.C.P.,
Physician to the General Hospital, Birmingham.

THOUGH G. Simon, in 1879, and Pick, in 1880, published important papers on the Therapeutical Use of Pilocarpin in Diseases of the Skin, there has been no notice of its employment in England except in alopecia areata. In November, 1890, Dr. Klotz read a short paper on Pilocarpin in Dermatology, and, though his personal experience was limited, spoke in the highest terms of its value; but it is a matter for wonderment that the American Dermatological Association, before whom the paper was read, seemed to be unable to discuss it from lack of experience of the use of the drug.

There is abundant *a priori* reason for expecting benefit from its use in cases of great thickening of the skin, such as chronic eczema or scleroderma. Of the latter disease I have had no case; and though it does not fall to the lot of a physician to a general hospital to see many cases of very chronic eczema, I have tried pilocarpin in a few with the happiest results. It has been objected that it is a drug requiring heroism to administer and great care in its administration. If, as is indeed the case, this be so, it can be replied that we want to use pilocarpin only in cases in which other remedies are useless, and our patients often in very great distress.

S. P. came under my charge after having spent much time and money at Harrogate and elsewhere in trying to get relief. For fifteen months he had had eczema, and suffered acutely from the itching and distress dependent upon it. Nothing had given him much relief. He was ordered bran baths, and a lotion containing half an ounce of liquor carbonis detergens to a pint of lime water, while liquor arsenicalis, with small doses of iodide of potassium, was given internally. When I saw him his skin was enormously thickened and pigmented by the protracted inflammation, and I held out to him no hope of improvement until this thickening had been absorbed. To effect this, ointments containing salicylic acid were tried, but without much result, so on March 5th, 1891, he was admitted into the General Hospital to try subcutaneous injections of pilocarpin. The dose employed was at first one-eighth of a grain, and subsequently one-sixth of a grain, twice daily. There was very little sweating at first, but a good deal subsequently; otherwise, beyond relief to the itching, no obvious results were noted; but gradually the skin got thinner and the irritation less. He had to leave the hospital on April 2nd for business reasons, but was readmitted on June 9th. The same treatment was adopted, and on July 8th he was again discharged as he felt so very much better. Two months ago I received a very grateful letter from him, saying that he was quite well and that his skin was normal. He had altogether 110 injections, but never suffered local or general discomfort therefrom.

Though the course of treatment may seem to have been very prolonged, and to be one requiring great patience, both on the part of the patient and the doctor, it must be remembered that we know no other remedy which could be expected to produce anything like so good, if indeed any, result.

Pachydermatous conditions are always serious, and though local thickenings may be fairly easily dealt with, a general diffuse chronic inflammation of the skin has hitherto been almost beyond the power of medicine to cure. The difficulties of applying keratolytic agents over a large surface are almost insuperable, and the advantage is not commensurate.

For the relief of prurigo senilis I have found nothing so useful as the hypodermic injection of pilocarpin, and, though the relief is only temporary, to a patient worn almost to death by itching and sleeplessness a few days' respite is a glimpse of heaven. In psoriasis I have met with no good results from the use of pilocarpin, and in subacute eczema with bad ones.

SUCCESSFUL VACCINATION.—Mr. John J. Powell, of Weybridge, has just received the Government grant of £11 19s. for successful vaccination.

REMARKS ON THE FUNCTION OF THE THYROID GLAND:

A CRITICAL AND HISTORICAL REVIEW.

By VICTOR HORSLEY, F.R.C.S., F.R.S.,
Surgeon to the National Hospital for the Paralysed and Epileptic;
Assistant-Surgeon to University College Hospital; Professor of
Pathology in University College, London.

(Concluded from page 219.)

THE EFFECTS OF THYROIDECTOMY.

I have thus far been compelled to assume what is a matter of common knowledge, namely, that the extirpation of the thyroid tissue in a healthy animal will, under certain circumstances, produce a remarkable and fatal series of symptoms which have been spoken of as "cachexia strumipriva," or "cachexia thyroidectomica," etc.

These conditioning circumstances and the details of the cachexia must now be briefly recounted. Of these, the first and the most important, fundamentally, is the question of the class of the animal, inasmuch as the physiological value of the gland differs very considerably according to the species employed.

Effect of Class of Animal upon the consequences of Thyroidectomy.

Birds, Rodents, Ruminants, etc.—In the first place, it appears that thyroidectomy in birds is never accompanied by cachexia. This has been established in chickens by Allara, and very carefully by Ewald and Rockwell in pigeons. It is possible, however, that duration of life after the operation may in these animals play the important part it does in some other orders. From his earliest experiments Schiff recognised that the rodents (rats and rabbits) differed from the carnivora so far as the effects of loss of the thyroid gland were concerned, and in his first publications he drew attention to this important fact. Philipeaux also found that no effect followed thyroidectomy in albino rats. In the same year Colzi demonstrated that the rodents did not show the cachexia, as also Rogowitsch, and later Albertoni and Tizzoni. I found myself that whereas the carnivora showed the cachexia in its most marked form, it was less marked in the monkey and absent in rabbits; however, the influence of duration after the operation has never been discounted in the case of rodents. On turning my attention to the ruminants, solipedes, and suidae, I found that in the sheep in one case, after preliminary symptoms had shewed themselves, the animal survived a considerable interval of time—569 days—at the end of which exposure to cold determined the onset of the fatal symptoms.¹¹ Exactly the same was observed with a donkey, in which preliminary symptoms followed the loss of the gland for some weeks, and then, these having ameliorated, the fatal cachexia supervened after a long interval¹² of months when the animal was exposed to cold. In pigs observations by myself and by Munk have yielded negative results, but the animals were not observed for a sufficient length of time, the more especially as the gland in these animals is relatively small. Many years before von Rapp removed the thyroid from a goat, which was stated to have survived, but not watched for a long period. It has also long been known that the removal of goitres in horses and mules is ultimately fatal. It is evident that many more experiments are very requisite in these larger animals, but so far as the positive results go the conclusion is obvious that certainly in the ruminants and solipedes the operation of thyroidectomy is followed by the usual fatal cachexia after an interval of many months.

¹¹ The first sheep referred to on page 76 of the *Clinical Society Report* as surviving has since died—that is, more than three years after the thyroidectomy. Unfortunately its symptoms were very imperfectly observed. *Post-mortem* examination (without chemical examination) showed oedema of the lung, serous effusions, etc.

¹² If anything were wanting to demonstrate the fallacy in Munk's view that the cachexia thyroidectomica is due to injuries of the nerves in the neck it is the fact that in these large animals and in monkeys the symptoms are not well marked until the wound is absolutely healed, and the tissues perfectly quiescent, in some cases for months.

Man.—In man the observation of the sequence of events is, of course, not open to such accurate measurement. After the likeness of the symptoms of myxœdema to cretinism had been described by Gull, it was reserved for Ord to define clearly the existence of myxœdema, and to completely exhibit the disease in its general bearings anatomically as well as pathologically. He first determined the destructive changes in the thyroid and the profound alterations of the connective tissues. The treachery of clinical deductions is, of course, proverbial, but may naturally be less questioned in cases where persons in health, but for the inconvenience and distress of a goitre, have been subjected to complete thyroidectomy. But here also opportunity of fallacy is present, inasmuch as the object of the operator, being in every case to do no more than is absolutely necessary, it has been most usual for the extirpation to be incomplete (Wölfler, Semon, Biondi). Where total extirpation has unquestionably been performed, however, Kocher thinks that the cachexia in greater or less degree infallibly supervenes. Reverdin, who first noted and fully described the occurrence of the cachexia in man, has shown that the statements as regards non-appearance of the symptoms are often due to imperfect observation; but of greater interest is the occurrence of cachectic symptoms and their disappearance concurrently with restoration of thyroid function by means of compensation. Reverdin has termed this *myxœdeme fruste*, an expression which very fitly represents the arrest of the cachexia. Conversely several authors (Poncet, Niehans, Zesas, Schulthers, Lünig, and Occhini) have shown that partial operations on goitres may occasionally initiate cachectic symptoms. The earlier facts of all authors, carefully summed up by Semon, showed that from one-third to one-fourth of so-called total thyroidectomy operations is followed by the cachexia. Doubtless with the spread of knowledge of the disease, and with opportunities of *post-mortem* examination, the real parallel between the operation and its consequences will be soon established.¹³ Finally, it is sufficiently significant that no surgeon nowadays performs the operation of total extirpation except for malignant disease.

Classification.—If we now arrange the classes of animals in a line, we see that the following order is assumed:—

Consequences of Thyroidectomy.			
No Cachexia.	Slowly Devel- oped Cachexia.	Moderate but Cer- tain Cachexia.	Severest Cachexia.
Birds Rodents	Ruminants Solipedes	Man Monkeys	Carnivora

From this arrangement it is obvious that the difference of class of animal is tantamount to saying difference of nutrition and metabolism, for obviously the animals which suffer most are flesh feeders, and those which suffer least are vegetable and grain feeders, while omnivorous animals take a more or less intermediate position. This broad and important generalisation has recently received unexpected confirmation. Being apparently unaware of much of the previous work on the subject, Breisacher, a pupil of Munk's, made fresh researches on the latter's theory that the cachexia was due to the "injuries" (*Schäden*) received by the nerves in the neck. It will be remembered that Munk laid much stress on the fact that if a dog in whom thyroidectomy had been performed were given lumps of meat the characteristic symptoms commenced, whereas if it were fed on milk the symptoms were delayed a little, and at any rate not excited. Munk adapted this observation to his theory by suggesting that the lumps of meat mechanically irritated the nerves during the passage down the gullet.

Effects of Food.—Breisacher found, however, that the dogs could swallow any number of lumps of meat provided the latter was thoroughly extracted by boiling. By this means of course all the extractives, etc., were removed such as are known to be toxic to rodents¹⁴ (Kemmerich and Boguslowski), and which by this interesting observation were shown to be also toxic to carnivora whose metabolism was already disturbed by the loss of the thyroid gland. The final proof was

afforded by feeding the dogs on the bouillon instead of milk, when the cachexia rapidly appeared. Although these facts are extremely clear, it is by no means settled, as Ewald remarks, whether after thyroidectomy it is the constituents of the food which are directly toxic or whether it is the disturbance of the chemical changes in the tissues which directly gives rise to the cachexia. This is a fertile field for future research.

Other Conditioning Circumstances.—Other conditioning circumstances have already been alluded to, namely, the influence of age, existence of accessory and residual tissue, and need not be further dwelt upon. Others still to be mentioned are previous state of nutrition and temperature. It is easy to understand that the former must be very important in influencing a general metabolic condition. Hence it is that a state of low nutrition before thyroidectomy leads to early and very severe cachexia. I have found this to be particularly the case in monkeys. The influence of temperature I have already discussed fully in the report of the Clinical Society, but I will return to the question directly in considering the changes in temperature after thyroidectomy.

SYMPTOMS PRESENTED BY ALL CLASSES OF ANIMALS AFTER TOTAL THYROIDECTOMY.

I do not propose to weary my readers with a detailed account of the symptoms of the cachexia thyroidectomica found in all animals, since they are given at length in the writings of Albertoni, Alonzo, Canalis, Colzi, von Eisselsberg, Ewald, Fano, Fick, Fuhr, Herzen, Hoffs, Horsley, Loeb, Mattei, Munk, Rogowitsch, Sanguirico, Schiff, Tizzoni, Ughetti, Wagner, Weil, von Wyss. Moreover, I have already arranged, in the report to the Clinical Society, the phenomena of the cachexia, and I see no reason to alter the views expressed therein as yet. Unfortunately the investigation of this subject in monkeys has only been taken up besides myself by Munk, and although, as I showed in the report above mentioned, his experiments, though not complete, nevertheless confirmed in more than the chief points my results, it would doubtless advance the science of the subject if someone with intimate knowledge of the cachexia and of these animals would renew the examination of the questions at issue. This is rendered the more desirable since the intensity of the cachexia is so different in various species that it is probable a thorough comparative research would throw much light on the general or so-called "constitutional" changes.

I will now review the facts ascertained concerning the chief groups of symptoms, and trace as far as possible their origin in the anatomical changes found *post mortem*.

Symptoms of Disorder of the Nervous System.

This group of symptoms has always attracted most attention, partly because the phases appear early and are well marked, but also because most research has been performed on the carnivora, which as a rule die too soon for the development of other changes. Dividing the symptoms, according to the method of Hughlings Jackson, into (1) those exhibiting over action and (2) those exhibiting want of action, the following is a brief summary of the observations:—

1. *Over-Action.*—The first symptom of over-action is fibrillar muscular tremor or twitching, resembling closely the disease called tetany (Schiff and all observers, cf. especially von Eisselsberg), and having perhaps a similar pathology. The individual contractions of the muscles I have found in monkeys to follow one another at the customary (according to Gowers and myself, see also Schäfer with myself, *Journal of Physiology*) rate of clonus, namely, 8 to 10 per second. Summation next occurs and tetanoid spasms ensue (Schiff and all observers), and finally rigidity and contracture. Similar tremors had long been known from the early observations of myxœdema, and I have seen the same in acute enlargement of the thyroid gland, while Marie with Charcot described them later in exophthalmic goitre. In man, after thyroidectomy, von Eisselsberg has shown from Billroth's cases that, while tetany occurred 12 times in 53 cases of so-called "total" extirpation of goitres, it never appeared once in 115 cases of partial extirpation.

2. *Want of Action.*—Coupled with the symptoms of over action are those of want of action, which evince themselves

¹³ See the thorough investigations of Reverdin, Kocher, Bruns, Hoffa, and Stokes.

¹⁴ In one of Billroth's cases reported by von Eisselsberg the patient from having been a meat eater experienced an unconquerable aversion to it after the operation.

as motor paralysis and anæsthesia. I have noted in the monkey that the toxæmic condition after thyroidectomy produces not infrequently functional neuroses—that is, epilepsy, hemiplegia, etc.—as does the parallel condition of anæmia.

Pathology and Morbid Anatomy.

The important question now arises, What are the pathology and morbid anatomy of these conditions?

Lower Centres Mainly Affected.—As regards pathology, Schiff showed that the tremors and spasms were not of peripheral origin, since section of the motor nerves arrested them. Peripheral changes (that is, neuritis) have been described by Albertoni and Tizzoni, but the experimental observation just referred to proved the seat of mischief to be central. After confirming the fact established by Schiff, I found that in monkeys ablation of the excitable, or so-called motor, cortex did not stop the tremors. Three years later Munk divided the spinal cord in dogs, and found that the spasms continued. These observations all tend to show that the lowest centres are the source of the muscular twitchings and spasms. Possibly the higher centres (Herzen) are also in a state of discharge, since the whole central nervous system in advanced cases shows anatomical changes. These changes, primarily anæmia and œdema (Sanguirico and Canalis, Schiff, Horsley), vary according to both the intensity and duration of the symptoms. When very marked they have been described by Weiss as hyperæmia, by Rogowitsch as "encephalitis parenchymatosa," since he found in the cortex cerebri hyperæmia, exudation of leucocytes, and vacuolation of the nerve corpuscles.

Schultze and Schwarz, while not accepting this description, describe an exudation of leucocytes into the meninges of the upper part of the spinal cord. I have found that in the carnivora the appearances thus described are sometimes, but not constantly, to be found. Herzen and Löwenthal also observed vacuolation and atrophy of the large pyramidal corpuscles of the cortex cerebri in the lower limb area. But the direct effect of the cachexia has been measured by experiment in testing the functional activity of the nervous system. Schiff was the first to approach this question, and he investigated the effect of excitation of the so-called motor region, and found the excitability diminished.

Alteration of Function of Cortex.—From a long series of experiments¹⁵ I found that the character of the cortical motor discharge was greatly altered, that is, soon exhausted, and without after-effects, and diminished until in the cretinous condition when voluntary movements became exceedingly slow and imperfect, excitation of the cortex was without appreciable result. The same thing was true for excitation of the corona radiata and spinal cord.

The point was subsequently reinvestigated by Autokratow, who found that in the height of the spasms the excitability not only of the centres but also of the peripheral nervous system was notably increased (to both the faradic and constant current), and that this persisted for some time after the conclusion of an attack. These results were confirmed by Schultze and Schwartz. This experimental demonstration of the functional failure of the higher centres ("middle level" of Jackson) is rendered complete by the clinical observation of loss of power in the highest, that is intellectual, centres, for thyroidectomy in animals produces the most exact repetition of the slowness of thought, the irritability, stupidity, and ultimately complete hebetude of the myxœdemic and cretinous human being. The one element in common is the loss of the thyroid gland.

It is thus perfectly clear that the general toxæmic state caused by loss of the thyroid gives rise to excitatory and subsequently paralytic changes in the central nervous system. It does not follow that the alteration in the blood itself is the only change required, on the contrary doubtless the connective tissues of the nerve centres undergo the same degenerative changes as the other parts of the body and the nerve protoplasm proper, that is, of the corpuscles and fibres suffers in consequence.

Symptoms of Disorder of the Blood.

Changes in Respiration.—The next most obvious set of changes are those due to the toxæmia itself. Most of these I

have already referred to under the question of hæmopoiesis, but in connection with what has just been said concerning the neuroses exhibited there come up for consideration the remarkable changes in respiration. It has already been stated that the respiratory gas exchange in the blood is greatly altered, and the proper degree of oxygenation greatly reduced. The much increased rate of respiration noted in the carnivora by Schiff and all observers obviously may be due to this asphyxial¹⁶ state of the respiratory centre. That it is so in part is shown by the observations of Schiff on the influence of artificial respiration in improving this state of affairs. But it is not the complete explanation. The accelerated respiration may be observed in spite of reoxygenation; in man indeed tracheotomy has been practised to relieve the dyspnoea in some cases of thyroid disease without result, although all mechanical obstruction was removed (Bruns), while Drobnick has found by direct inspection that the glottis was wide open during the most pronounced dyspnoea, and he concluded therefrom that there must be spasm of the bronchioles.

Further, the old view of Kocher, Lombard, and others that cachexia strumipriva and myxœdema are due to chronic asphyxia calls for remark in this connection, but may be dismissed at once, since König has shown that even repeated tracheotomy has no effect in arresting the cachexia, and it does not diminish the venosity of the blood (Albertoni and Tizzoni).

It is evident from all these facts that, as shown by Schnitzler and Seitz, there is another element at work. That element I believe to be changes in the functional ability and activity of the respiratory centre itself, due to the general lowering of metabolism as well as to the direct toxic influence of the altered blood. Proof of this bulbar failure is evidenced by other symptoms, that is, cardiac disturbance, difficulty of swallowing, and vomiting, while the well-known sensitiveness of the respiratory centre to external impressions is obviously the reason why it is the first to become disorganised. The further changes in the chemistry of the blood await research, and would greatly reward investigation.

Symptoms of General Derangement of Nutrition.

This group of symptoms is almost the most important, for, if carefully investigated, they would doubtless reveal the chemico-biological changes in the tissues which are disorganised by the loss of the thyroid's metabolic influence. So far as the gas exchanges of the blood are concerned, I have already alluded to the little that has so far been ascertained, but of course the effects and relation of such alterations to the vital activity of the tissues are quite unknown.

Tissue Changes.—In experimental thyroidectomy most observers have noted as the first prominent general change emaciation in the acute form. In man and monkeys the changes in the connective tissues are most interesting. Thus, in the early well-marked myxœdematous condition Halliburton has shown that in these animals there was an increase of mucin, and this has also been found, clinically, in a man by Charles for Ord. In one of my sheep this was extremely marked, both on chemical analysis and on microscopical examination.¹⁷

If, on the contrary, the cretinic state, as shown by my second series of experiments, supervenes, then no increase of mucin can be found, but instead, fibroid changes are noted, coupled with emaciation. This is true for man as well as monkeys.¹⁸ Professor Virchow critically examined in the former the extraordinary œdema which is such a characteristic feature of the myxœdema stage, and suggests that it is a metaplasia of the subcutaneous fat into more mucous tissue, and this not with any diminution of volume, but an increase. The fact that when the disease is most acute the proportionate existence of mucin in the tissue is increased he considers to be due to some active, irritative, previous change rather than a kind of retention which apparently my publications seemed to convey. This latter idea, however, I have never held, my view being, as I stated in 1884, that the

¹⁶ Arguing from a slender basis of clinical fact, Grützner believed that there was a definite relation between the pulmonary function and that of the thyroid gland.

¹⁷ Vide drawing in Report to the Clinical Society.

¹⁸ Grundle, myself, Bourneville and Bricon.

¹⁵ Report to the Clinical Society.

thyroid gland possesses a power of metabolising certain intermediate waste products, and that if this metabolism should be interfered with, the consequence was disorganisation of the chemical changes (more especially those of the connective tissues), resulting in the imperfect development and performance of their normal processes, and consequently in their exhibiting this form of mucinoid degeneration. As regards cretinism, Professor Virchow reminds us of the two forms, first, as we should now say, the myxœdematous form, and, secondly, the atrophic form, pointing out that, in the former case, the resemblance between the so-called congenital variety of the disease and that developed in adult life is so marked as to lead us to believe they are quite identical in origin.

Occasionally the emaciation is not very marked, and is proportional to the acuteness of the cachexia. Clinically, in man, the most obvious change of nutrition is that of the skin. The skin becomes tough, coarse, and dry, from absence of secretion, the subcutaneous tissue thickened and inelastic, the hair falls out and becomes thin and grey, and profound alterations in the appearance are established. The same is observable in monkeys, though to a less degree, according as the skin is concealed or not by the hair. Conjunctivitis has been seen by several (Fuhr, Sanguirico with Canalis, Albertoni and Tizzoni, Ewald?) and is possibly due to the bulbar paresis referred to above. The chemical changes in the tissues, though disorganised, do not appear to lead to the excretion of any toxic substances in the kidneys, since Alonzo has found that in the carnivora subcutaneous injection of the urine secreted during the height of the cachexia produces no more effect than that produced by the kidneys under ordinary circumstances.

This group of symptoms thus indicates a grave disturbance of the basis of nutrition, namely, the active change of material in the tissues. What is most needed at the present time is the analysis of these changes compared with those observed in the blood.

The Disorder of the Heat Changes.—We will next glance at a most important symptom, which, though doubtless intimately connected with those just described, nevertheless deserves special consideration. Most noteworthy in the description of the phenomena following loss of the thyroid gland is the question of heat exchange. Briefly, the case may be considered (a) so far as intrinsic changes are concerned; (b) so far as extrinsic changes have to be dealt with.

(a) By intrinsic changes I mean the modifications which are introduced into the normal heat balance of the individual subject of experiment after elimination of any traumatic pyrexia due to the wound. These may be further subdivided as "early" and "late." Early changes in the temperature of the body are those which accompany the onset of the spasms and tetany. Thus during the acme of the muscular twitchings the temperature has been observed (Herzen, Ughetti, Alonzo, Rogowitsch, myself) to rise to 4° or 5° above the normal (to 43.4° C. in the dog, Herzen). The coincidence of this pyrexia with the general nerve disturbance suggests that the rise of temperature is dependent as much upon derangements of the heat-controlling centres of the nervous system as due to the chemical changes in the muscles, etc. After this commencing pyrexia the temperature begins to fall steadily until for days before death it is subnormal, sometimes even falling 4° C. or in monkeys to 92° F. (Schiff, Horsley, Sanguirico with Canalis, Ughetti, Alonzo, Rogowitsch, Herzen). It is thus clear that the fall of metabolism is indicated, not merely by degenerative changes in the tissues, but also by this remarkable fall in the temperature. Exact confirmation of the same phenomenon is derived from clinical records, since in the myxœdematous state in man the subnormality of the temperature is one of the most constant features of the disease. This latter point introduces us to the effect of extrinsic changes.

(b) By extrinsic changes of temperature a remarkable and serious influence is exerted upon the cachexia, greatly exaggerating the symptoms when the outside temperature is lowered, and, on the contrary, producing amelioration when warmth is applied (myself). Munk states that no such effects are produced by temperature. The beneficial effect of heat and the depressant action of cold, however, is very well known to patients suffering from myxœdema, cachexia strumipriva,

and cretinism, and heat plays a very important part in the treatment of these disease conditions. Doubtless the extrinsic action of a rise of temperature is owing to its importance in aiding the already hampered chemico-biological processes.

CONCLUSIONS.

Such summaries of the leading symptoms in the cachexia as the space at my disposal enables me to give I have now made. I desire only to point out that the differences in the various classes of animals and in individuals of the same class when investigated will infallibly be found to demonstrate the universal application of the results of experiment, and that, like all complex and far-reaching processes, the cachexia is a compound of several factors. Under these circumstances it will vary in phases according to the special predominance of one or other factor. I would venture, therefore, to repeat here the classification of the symptoms which I published elsewhere as follows:—Stage I. Neurotic. Stage II. Myxœdematous. Stage III. Cretinic. According to the virulence of the cachexia death may occur in any of these stages, but given any case of total disease of the thyroid gland the symptoms of the cachexia will invariably be found to follow the order just given, and any set of symptoms can be selected and referred to their proper position in the evolution¹⁹ of the cachexia in each particular individual.

Summing up the foregoing pages, it seems to me that the thoughts and method of reasoning of Hofrichter on this subject have not been sufficiently before the minds of those who have taken up the question of the function of the thyroid. Hofrichter early in this century objected to the anatomical theories which regarded the gland as a mere diverticulum of the cerebral circulation, and his objection was logically founded on the simple fact that no experimental proof of such theories existed. From thence he proceeded to discuss the relations of the gland, and by the procedure of exclusion arrived at the definite opinion that it acted on the blood, deoxydising it, and in other ways chemically changing it. The same line of thought was pursued by Vest, who argued that the thyroid altered the blood, but he was led to believe that this alteration increased the assimilation of the chyle, for the support of which belief of course no facts are available.

The broad views expressed in the writings of these early writers find confirmation in every fresh investigation of modern research, for, with the mass of facts now at our disposal, it can be scarcely gainsaid that in the first place the thyroid gland does play a definite part in the economy, and that the cachexia which follows its removal is not due, as has been alleged, to injuries of the nerves in the neck.

Further, the more careful examination of the structure of the gland has shown that it is a secreting structure, and consequently operates by influencing the metabolism of the blood and therefore of the other tissues.

The behaviour of the tissue in responding by hypertrophy, when a part of the gland is lost, the fact that a certain proportion must be maintained for the purpose of health, that its (metabolic) importance varies directly with the activity of the vital processes, and is consequently greater in early life and diminishes with age—all demonstrates indirectly the worth of the gland and in fact its indispensability.

Crucial evidence upon these latter points is afforded by the remarkable results of transplantation of thyroid tissue in animals.

Finally, the array of symptoms evoked by extirpation of the gland, the constancy of their appearance and the remarkable differences exhibited in the rapidity and extent of their development according to the special metabolism of the class of animal under observation establishes clearly the position which the gland occupies in the economy of the body.

So definite and pronounced is the cachexia thyroidectomica that few subjects in the range of pathology offer a more fruitful and inviting field of research. That others may be tempted to enter upon it and extend our knowledge of this matter is the object of these remarks.

¹⁹ An interesting confirmation of my views as to the sequence of events evoked by loss of the thyroid is afforded by a case in which the true symptoms of myxœdema were preceded by tetany, and which is reported by Stewart, who, however, refers the condition to a hypothetical lesion of the sympathetic.