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Concerning pathological manifestations in low-grade thyroid diseases

Nobel Lecture, December 11, 1909*

First Section

The low grades of thyroprival disorders

Pasteur's investigations, which were primarily serving purely practical aims, into the cause of the fermentation of wine, and his findings in connection with this concerning the processes of decomposition in general, have prepared the ground for the greatest, and certainly the most beneficent, advance in Medicine. From Lister's spirit of inquiry originated the idea of applying to human pathology, in a way that was as simple as it was ingenious, Pasteur's concepts about the importance of the smallest organisms in the decomposition of liquids: he studied the decomposition of urine under the influence of the dust particles in atmospheric air and established, using measures that have now been long abandoned, that the fluids in human wounds, the so-called wound exudate, was also preserved from decomposition by keeping dust away; and, as a result of this, healing of wounds took place with a hitherto unknown speed and reliability.

The results of Pasteur's and Lister's investigations, which sprang from practical requirements and purely clinical observations, have shown themselves to be more fruitful than one would have ever dreamed possible, thanks to the energetic cooperation of numerous investigators (among whom R. Koch on the theoretical side and R. Volkmann on the practical side are outstanding).

The first powerful advance was, it is true, a practical one. Surgical treatment underwent a vast expansion, as not only could the dangers be eliminated within the province of treatment for accidental wounds, which had been under the care of the surgeons till then, but also a surgical method of treatment, which was crowned by the most brilliant cures, was made possible in the great majority of the so-called internal diseases. It has become possible within less than half a century to expose all the organs of the body, brain and heart not except-

* The lecture was given in a substantially abbreviated form.

ed, without danger, and carry out the necessary surgical measures on them.

But it was just this ability to make all the organs accessible to direct observation, and to alter the conditions in which they exercise their functions, that broadened our knowledge of the *physiology* of the body extraordinarily. The physiologists have even learned from the surgeons to set up their animal experiments under the influence of narcosis and asepsis in such a way that unnecessary pain during, and disturbances after the operation do not occur, and the physiological activities of the organs can be brought to light without any distortion at all. It is only necessary to recall the amazing results concerning the function of the organs of digestion obtained by Pavlov, whose merits have also been duly acknowledged in this place.

It was also due to strict asepsis that one of the most serious, and, before Lister, most dangerous operations[1] could be undertaken without substantial risk, that is the removal of a goitrous thyroid, which so often proves urgently necessary on account of severe respiratory disturbances. We ourselves have communicated a continuous series of 300 and more goitre operations without a fatality. Important though this result has been for suffering humanity, yet it has been far exceeded by the understanding which has grown, anew on practical and clinical soil, concerning the vital *physiological* function of the thyroid. It is true that Schiff, the physiologist, had already initiated experiments into the acute ill effects of thyroid withdrawal in dogs, but they have been disregarded. They were in fact communicated merely incidently in an essay on sugar formation in the liver (1859). With the passage of time it has become clear that these effects were essentially related to the parathyroid glands, and proved that the lack of these is not compatible with life. Schiff himself only really understood the significance of his experiments and extended them further with more exhaustive investigations, after our communications had appeared. Early in 1883, at the Congress of the Deutsche Gesellschaft für Chirurgie we announced that some 30 of our first 100 patients operated on for goitre, whom we were able to follow up and reinvestigate, presented a syndrome which can be precisely characterized, and which we designated simply with the name *cachexia strumipriva.* This appeared in a well-marked form only in those patients from whom we had removed the whole thyroid, and on the other hand only with temporary manifestations in those in whom the whole goitrous structure was supposed to have been removed, but where in fact a portion had remained, which continued to grow.

Isolated observations concerning the relationship between cretinoid disturbances and alterations in the thyroid had already been made by earlier in-

vestigators. Thus Felix Platter was already familiar with sporadic cretinism; Curling, Fagge (1873), and Ord and Boumeville knew about anomalies of the thyroid in cretinous conditions; Sir W. Gull had described the latter in adult women, leaving open, however, the question as to whether disease of the thyroid might play a part in it; the two Reverdins had seen accompanying "bizarre" changes (October, 1882) in some of their patients operated on for goitre, and had published a short annotation about this in the autumn of 1882.

At the time when I described cachexia strumipriva in Berlin (April, 1883) as an *invariable* sequel to such an excision on the basis of numerous observations, and warned against total excision, because this always led to resulting states which presented cretinoid features when fully developed, a brilliant communication was given at the same Congress by a distinguished surgeon on the benefit and technique of total excision; and immediately before my communication the two Reverdins in the *Revue de la Suisse romande* (April, 1883) emphasized and sung the praises of the excellent results of their total excision.[2]

Further discoveries concerning the nature and character of the new disease soon followed in confirmation of my communication. By following up the patients they had operated on, the Reverdins realized the relationship between cachexia strumipriva and the myxoedema of the English, with which they were acquainted; and at a famous session of the Clinical Society in London (November 23, 1883), Felix Semon referred to my work in the discussion following the demonstration of a typical case of myxoedema by Drewitt, and mentioned a supporting case following total excision by Lister. Ord read out a letter which I had written to him about the aetiology of the affliction and the relation of myxoedema to cachexia thyreopriva.

With this the impulse was provided for the impressive investigations by the Committee of the Clinical Society (Vol. 21 of the *Proceedings),* which came to the conclusion that myxoedema and sporadic cretinism, and probably cachexia strumipriva too, were identical, and that there were close relationships with endemic cretinism. Sir Victor Horsley confirmed with his monkey experiments that it was the removal or destruction of the thyroid and the loss of its physiological function which lay at the root of the disease (as in Switzerland and Germany Lanz and Fuhr were also able to show). With this the doctrine of the association between cachexia strumipriva and the cessation of the physiological function of the thyroid was placed on a firm footing, so that this condition had bo be rechristened *cachexia thyreopriva.*

After the discovery, which rested on clinico-pathological observations, had been thus transferred to the sphere of physiology, there followed the attempts

to provide by *transplantation* a substitute for the thyroid's function, which was now recognized to be a vital one. Schiff had already made such attempts earlier on dogs, Sir Victor Horsley and von Eiselsberg repeated them on animals, Bircher and I made some attempts on humans with transitory, but variable success.

Murray and Howitz's finding, which seems so simple and yet is so exceedingly important, that the administration of *thyroid juice* was quite sufficient to compensate for the deficiency of thyroid function, was of great significance for the theory of thyroid function. This finding has become a corner-stone of the structure and doctrine of internal secretion and organotherapy. Only if the thyroid brings about its important action on the rest of the body through a secretion which is delivered into the blood can it be understood that the gland itself can be dispensed with, providing the juice expressed from it is incorporated in the body. We are indebted to Baumann's[3] brilliant discovery of the thyroid's *iodine content* for providing a more precise justification of this interpretation. By Baumann, by his estimable follower Roos, through the studies of the thyroid's iodine content by Oswald, A. Kocher and a great number of later observers[4] it has been established that the iodine, bound to a protein, passes into the thyroid secretion, and that this iodine-containing secretion is capable of performing the physiological function. Baumann's *iodothyrin* seems to be the most important component of the thyroid juice and of the thyroid preparations on the whole and it is capable in the majority of cases to compensate completely for certain aspects of thyroid function, as Baumann and Roos have already proved and as we can confirm with our findings in humans. Certainly, iodothyrin is not identical with the so-called thyroidin (the extract from the whole thyroid). We have seen patients who did not tolerate iodothyrin and could not ascertain any improvement with it, while improvement set in immediately with thyroidin. But reversely thyroidin now and again is not tolerated, where iodothyrin works very well.

The main point is that it could be confirmed that the thyroid cells deal with the iodine in such a way that it is delivered into the vessels in an organic compound, and displays the most important physiological effects; and that we can remove this thyroid compound from animals and supply it to a human to compensate for the defective functioning of his thyroid gland. One may hope that this complicated organic compound, for whose production at the present moment we still have to rely on the chemical activity of animal cell conglomerates, may be resolved in time into a simpler compound, which chemistry can elaborate synthetically, independently of the animal body. Indeed, Halsted

and Crile have made the important finding that the deficiency in parathyroid function can be covered not only by the administration of an extract of animal parathyroid, but by a very simple chemical preparation, calcium chloride or lactate, and so by a precisely defined substance of inorganic chemistry.[5] This is imposing evidence of the great importance of chemical processes in quantitatively quite insignificant cell conglomerates in our body, and at the same time for the justification of our efforts to influence the vital manifestations of our body with chemical compounds.

Seldom in the history of medicine has the recognition of the most effective cure followed as swiftly on the heels of the discovery of a disease, as the establishment of the complete effectiveness of iodothyrin and thyroidin followed the recognition of cachexia thyreopriva. In this way the latter has become the most important foothold in the study of the *vascular glands* and the cell conglomerates of intermediary metabolism. These are just as much genuine glands as are the glands with an excretory duct, only they transmit their secretions into the blood, instead of to the exterior. Consequently, their excretory products can also become harmful if they accumulate, and their specific products exert rapid and pronounced effects on other organs.

The substances in question are partly as far known and producible as iodothyrin and adrenalin; some, like part of Starling's hormones, can be revealed by their physiological excitatory actions. They have the most decisive significance for the normal course of the vital processes in various organs and have brought a gratifying clarity to many of the reciprocal actions of the organs on one another, which had been attributed to nervous connections but had not been made comprehensible thereby.[6]

Brown-Séquard has directed attention to the great importance of the internal secretions and has sought to turn those of the sex organs to therapeutic account. Van Mering and Minkowski have demonstrated the presence of an internal secretion for the pancreas, which exerts a controlling influence on carbohydrate metabolism. But no internal secretion exceeds that of the thyroid in importance to the *whole* organism. Are doctors now making use of the newly won province *of physiological therapeutics* to the extent that it deserves? Emphatically not. The reason for this is that, even at the present moment, the fully developed picture of cachexia thyreopriva is still not sufficiently well known to every doctor for him to recognize it immediately in every case. I see a number of patients who are treated for anaemia, chlorosis, scrofulosis, nervousness and menstrual disorders, in which the signs of thyroid insufficiency strike the practised eye at one glance.

But there is still another important reason which makes the diagnosis more difficult. In mild and limited thyroid disorders, where function is not abolished, but merely impaired, *only very rarely do the symptoms of cachexia thyreopriva stand out clearly,* and for this reason either have no attention paid to them at all or are misinterpreted. And yet only the right knowledge and the physiological therapy based on it produce real cures. For this reason I would like, on the strength of extensive observations, to undertake to draw attention to poorly defined forms of cachexia thyreopriva which are found in limited and moderate thyroid disease.

Of course, doctors' prescriptions have been influencing the thyroid with medicaments for a century now on a most extensive scale. However, this influencing was confined quite exclusively to enlargements of the thyroid gland. How could people have bothered about influencing its function as long as this was so completely unknown that it was credited with no physiological importance at all, and therefore the operative removal of the organ considered permissible? Since Coindet's discovery, iodine has been employed against goitres in the most varied forms and doses on a very large scale, without even following up this effect in the histological processes.

An important point, however, to which the discovery of iodine in the thyroid and of the effect of thyroid secretion as a substitute for glandular function has led, is the knowledge that a very important effect is exercised *on the glad* itself by both the material which is indispensable to normal thyroid activity and the secretion which is elaborated with its assistance. Iodine makes the gland smaller, and Reinhold and von Bruns have shown that thyroid juice also produces a shrinkage of the abnormally enlarged thyroid. But not only that: just as the secretion influences other organs to a considerable extent in their activity, so it reacts similarly on the organ in which it is formed. Rogers has recently directed attention to this in a very noteworthy essay.[7]

The thyroid cells take up iodine with particular avidity, and are able to store it up in great quantities. But the grade of uptake and particularly the kind of influence on the specific thyroid activity is quite different in healthy and diseased glands, and is different in the various forms of disease. While the kind of uptake and metabolism of iodine in the thyroid is dependent on the latter's histological structure, as may be concluded from the investigations of Roos, Oswald, A. Kocher, Marine and Lenhart, so on the reverse the administration of iodine is capable of influencing the histological structure quite considerably. The authors are agreed that, with the administration of iodine, a considerable increase of the colloid in the follicles takes place, according to de

Ligneris (our former assistant) in normal as well as in hyperplastic thyroids, according to Marine and Lenhart as a constant result in the latter. The investigators are agreed that colloid goitres can store up the greatest absolute quantities of iodine but that the relative content (calculated per gram of gland) is always less than in normal glands. Finally, they are agreed that as a rule in hyperplastic goitres the smallest storage of iodine is demonstrable, but that, on the administration of large doses, a very marked accumulation can take place, which is, according to Marine and Lenhart, relatively always smaller than in the normal gland, and according to A. Kocher and John, occasionally greater. Von Bruns and von Baumgarten have provided the evidence that thyroid juice from an external source also results in a marked accumulation of secretion in the follicles in goitres. If different histological structure exercises such a fundamental control over iodine metabolizing in the thyroid and if iodine and the thyroid secretion itself react and strongly influence the histological structure, then the conclusion to be drawn from this is that every anatomical-histological change in the gland must influence the internal secretion and can evoke pathological disorders. With only a moderate decrease in the secretion, at first only low-grade and sporadic symptoms of cachexia make their appearance, which blur the clinical picture to the point where it becomes unrecognizable.

This fact that illnesses occur whose symptoms vary within wide limits, but which are all capable of being favourably influenced by the same medical treatment, has already been established by the old doctors. They regarded the various manifestations of disease as being mere variations of quite well-defined *dyscrasias* or *diatheses.* We have now gained the understanding that at the bottom of these dyscrasias can lie a qualitative or a quantitative plus or minus of some internal secretion which is indispensable for the normal function of the organs. Bacteriology has demonstrated in a similar way that extraordinarily different clinical pictures essentially belong together; and that the differences are explained only by the greater or smaller quantity or effect of *the same* infecting agent and with this the larger or smaller amount of toxins. So the old doctors were not without justification in insisting on a *uniform therapy* in larger groups of illnesses on the basis of the hypothesis of dyscrasias - the conditions were merely unfulfilled yet for securing a clear conception of the word dyscrasia.

Cachexia thyreopriva is also a dyscrasia in the sense used by the old doctors. We were already able to show in our first communication that, with the reliability of an experiment, on total removal of the thyroid a completely *typical*

syndrome made its appearance, which left no grounds for doubt as to the diagnosis. Of course, one should be clear that this syndrome demonstrates differences which are related to the patient's age, and equally to the associated influences of nutrition, and psychical and bodily care, etc., operating at the same time. The most serious forms fall into the same class as cretinism, which has the same basis, and only occur - as was emphasized in our first communication - if the noxious conditions (thyroid deficiency) operate in the earliest period of development; and the ugly picture of mental and bodily degeneration, which formed the basis of previous descriptions, only comes about if there has been a complete neglect of every mental and bodily care at the same time.

Classical *cretinism* is *a particular form* of cachexia thyreopriva and applying this name indiscriminately to every severe case of cachexia thyreopriva is not historically justified. It is just as little justified to apply the name of Ord's *myxoedema* indiscriminately to every case of cachexia thyreopriva. The cretinoid form affects children mostly, acquired forms of myxoedema affecting mainly adults. But if one looks at the matter properly, the main distinction lies in the fact that, until growth is completed, it is affected very severely by a deficiency in thyroid function, not only in the form of stunted growth, but also of certain skeletal deformities, such as a flattened nose, and a large angular skull, etc. In this it is chiefly a matter of simple *cessation of growth,*[8] which is the more severely marked the further back the start of the disease lies. Röntgenograms and pathological-anatomical investigations reveal the characteristic feature of the skeleton to be a state of ossification such as normally occurs in individuals a number of years younger. Seldom, irregularities are found along the lines of ossification (Läwen).[9]

Of course, this main symptom of the disease in young individuals, in the form of a cessation of the normal ossification processes at the ossification centres and epiphyseal lines, becomes quite unimportant in adults. But, in the absence of this symptom, all those bodily disfigurements which depend on defective skeletal growth and have a *big part* in the recognized cretinous type are also missing: the relatively short, fat extremities, the fat hands with short fingers, the big head with the prominent tubera, the low forehead, the turned-up nose with the sunken bridge, the short thorax, which in conjunction with a relatively small pelvis leads to a marked protuberance of the abdomen - they are all brought about by the cessation of epiphyseal growth, and must, therefore, be absent in the adult. But the not infrequent obstruction of nasal breathing with ozaena, and the adenoidal proliferations in the nasopharynx are still partly connected with the obstructed growth of the nasal skeleton.

For children, the *cessation of growth (and its results!)* is, and remains, one of the chief diagnostic signs for cachexia thyreopriva and for milder cases of *hypothyroidism.* And even if, in a child, at first nothing of note is evident other than backwardness in its growth, one must first of all investigate the thyroid to determine whether it shows deficient development. Indeed the disfigurements mentioned above can be almost completely absent, and the face and body relatively well-formed, providing the disturbance of thyroid function develops relatively late, e.g. during puberty. We saw a girl recently whose mother we operated on for an extensive colloid goitre, in whom the symptoms of hypothyroidism only showed themselves at the age of thirteen with the onset of the first menses. From then on growth had ceased, but the girl was mentally and physically well developed. On treatment with thyroid, growth was reestablished.

If one ignores the disturbance in skeletal growth and its consequences, which do not apply to adults, then one finds considerable conformity in the other symptoms of cachexia thyreopriva in both young and older individuals. What most of all caught the eye of earlier observers in adults is expressed in Ord's term myxoedema, which rejoices in great, indeed too great, popularity. The name refers to the *bloated condition* of these patients, which, however, can also be absent at certain stages; and in such a case the nature of the illness can be overlooked altogether, since one cannot diagnose a case of myxoedema in the absence of any swelling of skin and mucous membrane.

The other sign, for which Fagge, Sir William Gull and Mosler had already selected the term *sporadic cretinism* and whose use they also permitted in the case of adults, is the dullness and the mental and physical sluggishness and *incapacity,* which in fully developed cases is sufficiently striking to suggest the analogy with genuine cretinism, especially if the bloated face is added to a stupid expression. But the degree of dullness varies considerably. In general the patients do not feel really ill, but merely have the feeling of something *inhibiting* them in everything they want to undertake - the effect being greater the more mentally active and alert they used to be. With the best will in the world they can no longer perform any sort of sustained mental work, they cannot read, write nor converse for long, and hence prefer to be silent and withdraw from society. Speech becomes slow and laborious and answers have to be waited for. The decline in memory is quite especially burdensome.

Later disturbances develop in the sphere of vision, hearing and of the sense organs generally. The sharpness of the senses diminishes, subjective disorders of the senses can occur, such as seeing sparks and, in particular, hearing abuz-

zing in the ears. Diminished taste and smell spoils their pleasure in eating, and finally makes them, especially children, indifferent, if not completely averse, to the consumption of food. Parents often complain about this. It is understandable after Pavlov's demonstrations of the importance of psychical factors on digestive activities, that the appetite should be diminished in these circumstances, and digestion become sluggish, especially as the patients bother as little about regular bowel evacuation as they do about other things.

Dementia only occurs as an exception and indeed almost only when there is really early development of cachexia; and it is involved essentially as a result of the neglect of all mental and physical care and education of children of this sort. On the other hand, in individuals in whom the illness makes its appearance at a later stage and who have reached a certain level of mental development, it is on the contrary striking how clearly they can judge, how they know, that they are *inhibited* by some sort of pathological process and that the mechanism of their body does not obey the influences of the will. They are very miserable about this and in turn are extremely grateful for the great alleviation and improvement which they gain from the administration of the minute doses of thyroid which a doctor, thanks to the correct diagnosis, has prescribed them.

As a rule the incapacity and rapid exhaustion of the mind is equalled by that of the *body,* at least at the height of the illness. Exertions, especially of a sustained nature, are impossible and, should they be forced, lead to immoderate exhaustion. This is all the more striking as the musculature is very well developed in formerly powerful people, quite unlike the situation in severe cases of Basedew's disease. The powerful arm and calf musculature will not lend itself to swift or energetic movements.

So the whole being acquires a heavy, cumbersome and slow quality. If one adds to this the *bloated condition and increased corpulence* of *the body,* then the idea of a disturbance in thyroid function should occur to every doctor. In recent and severe cases in spontaneous myxoedema, as well as in operative cachexia thyreopriva, the changes in the face and the hands strike the eye at once. The patients themselves are very well aware of this swollenness; if they are under treatment and under the influence of thyroid preparations, then they find the rapid decrease in bloatedness and the associated relief at their most noticeable within a day or less. On the other hand they know that the time has come for some treatment as soon as their eye-lids, lips and cheeks, and their hands and body are a bit swollen again.

In severe cases the eyes appear oedematous, but without real oedema being

present, and if the lids, as often happens in such cases, are clear and translucent, the impression is easily formed that one is dealing with a nephritic; especially when, as happens not uncommonly, the swellings in the lids, face and hands only appear for a short while, and then disappear again. The fat, often somewhat pendulous cheeks, the fatter or somewhat puffy lips, the fat hands and feet, an increase in the waist in women and a thickening in the region of the hips and buttocks all belong to the typical case of cachexia. As a consequence of their clothing, and in particular because of corsets, it is often women who notice the deterioration in their condition - first of all in their waist and then in the hip region. With this it is, as a rule, not a question of the deposition of mucin in the tissues, but of swelling of the fatty tissue. The English Committee has already drawn attention to the fact that the demonstration of increased mucin deposition has so far only been successful in experimentally induced myxoedema following total excision of the thyroid, occurring, namely, in the skin, fibrous tissue, blood, and also in the salivary glands, so that, for example, the parotid produces mucin, and indeed in amounts which previously only the submaxillary glands used to produce. So far in our operative cases we have not been able to confirm this increase in mucin.

The swellings appear also in a circumscribed form, and not just as a more or less diffuse swelling of large sections of the skin, which is indeed how they strike one in the legs, appearing in the form of a firm, shapeless and unlovely swelling of the leg particularly in its lower part. So the doctor's attention is often drawn to supraclavicular pads, which are diagnostic of cachexia, and also to a swelling under the arms. Individual patients feel that their tongue, their gums and pharynx are more bulky, which can be confirmed objectively - particularly in the tongue, by the marked impressions of teeth at the edges. Together with this the patients have a feeling of pressure and tension which draws the attention of the more intelligent ones to a worsening of their illness. The conjunctivae can swell up oedematously and weeping of the eyes is not uncommon. Not so frequently a flow of saliva and a discharge from the nose are observed.

It is relatively rare for swelling of the joints to be observed as well. I have observed it in cases in which it seemed to me that other influences in addition to cachexia were involved, but even then the influence of thyroid therapy was really striking. Such patients readily inform the doctor that they suffer from gout or rheumatism, and especially that the swellings and pains can fluctuate. The justification for speaking of thyroprival rheumatism, which Mertoghe lays such stress on, can only be derived from the effect of the therapy, but one

must bear in mind that additional factors are often involved in such cases, particularly in older people, in order that one should not proceed uselessly with thyroid therapy in every chronic rheumatism of unknown genesis.

It is to be noticed that variation in the swellings is certainly not at all unusual, even with external changes. Thus swellings of the lids and of the whole face are specially noticed in the morning, when the patient's condition is generally at its worst; also the effect of cold increases them.

Paraesthesias, which are complained of by those patients in particular who observe themselves a good deal, and which draw the attention of the latter to the fact that a deterioration has set in again after improvement with therapy, are indeed connected with the swellings in the majority of cases. So complaints are made very frequently about the pulling sensation in the nape of the neck going down towards the shoulders, about the feeling of stiffness in the knees and in the phalangeal joints, with stiffness in the hands and feet. On the other hand I have found that complaints of a greater stiffness in the muscles, especially with an occasional sudden inadequacy of the legs so that they give way under the patients must arouse the suspicion that there is an associated hypoparathyroidism - which is of great importance for the treatment.

The bloatedness, which has the character of an oedema in the early stages and in severe cases as well, can later and in mild cases make room for simple *depositions of fat;* which deserve important consideration as isolated signs of mild cachexia. At the same time the patient's appearance, which, due to the translucency of the swollen lids, is like that of a nephritic, also changes with more marked *areas of pigmentation* making their appearance. Thus, as we see still more often as an additional feature of hyperthyroidism in its later stages, the area surrounding the lids often becomes strikingly brownish, and the complexion takes on a yellowish hue. However, this yellowish colour is also not infrequently a characteristic of mild forms, and I have also seen it in children from families in which disturbances of thyroid function were common. They look, often with a good appearance and fat, full cheeks, yellowish, like chlorotic girls.[10]

The pigmentation can become stronger and occur in the form of brownish spots both at the extremities and on the body, so that women in particular are very miserable about this change. These areas of pigmentation are very reminiscent of the similar brownish spots which one sees appear around the eyes, around the mouth and on the forehead and in other places in pregnant women whose thyroid is inadequate for the increased demands. Now and again I have seen a strikingly yellow colour in the palm of the hand. It is very noteworthy

and especially interesting theoretically to find how discolouration of this sort, especially in the form of rather large spots, regresses with thyroid therapy. For the question is whether one may not be dealing with secondary manifestations, i.e. with a reaction of the thyroid disorder on the other vascular glands, especially the adrenals and the chromaffin system. But even if it emerges that such secondary influences are at work, then the pigmented areas still are of great importance in the diagnosis and treatment as well of low grades of hypothyroidism.

With the changes in the skin and mucous membranes described so far we still have not disposed of all the evidence which we can gather from the patient's appearance in order to confirm ourselves in our suspicion of cachexia thyreopriva. Two symptoms are pre-eminent which must attract attention even in mild forms, these are namely the dryness and, on the other hand, the coldness of the skin, accompanied by further changes in the skin structures. The majority of patients know that they sweat less than others. But even if this cannot be ascertained, indeed even if damp palms are noticeable on examination, even so *dryness of the skin,* and of the hair too remains a true characteristic for the interpretation of isolated symptoms of a dubious kind as belonging to cachexia thyreopriva. The dryness of the skin is most noticeable on the fat cheeks, which feel rough, very much in contrast to the soft elastic skin of fat-cheeked healthy individuals. Often the skin peels off in small, fine scales. The rough, dry skin can be detected most easily on the fore-arm and the lower leg, since here too the solid swelling of the fatty tissue is most striking as a departure from normal conditions. On the trunk the dryness and the lack of suppleness due to the roughness of the hypodermis is also regularly present. The scalp produces abundant flakes of skin, the hair is dry and, related to this, it is often short and brittle; in severe cases the hair falls out very rapidly, so that one is surprised by the relatively bald heads of young individuals. Just as the hair becomes brittle and rough so the nails show changes too, and are cracked and rough, and show faulty, irregular growth; and the change is also marked by brownish discolouration, dryness and tearing of the nail fold. Also the teeth, as epithelial structures, suffer damage with the development of brittleness (of the enamel) and the onset of caries.

In mild cases of hypothyroidism, isolated examples of the skin changes mentioned must act as a reminder that the patients should be specially questioned and examined on this score. On the other hand, it is not permissible to classify more severe forms of skin disease without further ado under the so-called "benign" hypothyroidism of Hertoghe. For, benign, translated into intelligi-

ble language, means mild, and the severe forms of hypothyroidism are anything but mild. However, eczema, ichthyosis, sclerema and elephantiasis are not direct results of hypothyroidism, but they do develop more easily on the ground prepared by the trophic disorders of the skin which accompany this condition, as is shown by the success of a treatment with thyroid. The skin in front of and below the knee frequently shows a change in the form of a strongly pigmented, very rough thickening of the epidermis.

Dryness of the mucous membrane is also to be observed and leads to disorders such as ozaena in conjunction with mechanically disturbed nasal respiration, as has already been mentioned above.

In addition to the bloatedness and firm swelling of the skin resp. hypodermis and the dryness of the skin structures and their results, *coldness* of the skin still remains to be mentioned as a diagnostically important and regularly occurring symptom of cachexia, even in its mild forms. From time to time patients complain of coldness, and in any case the majority feel considerably worse in cold than in warm weather, in significant contrast to patients with Basedow's disease. But also where no complaint is made, the coldness of the hands and also of the face strikes the attentive observer. At first sight, indeed, patients of this sort apparently look very well, with red, fat cheeks. But it is just this ruddiness of the cheeks which can draw attention to hypothyroidism. Often, indeed, it contrasts with the strikingly white colour of the area round the eye-lids, the nose and the mouth, so that one might think of florid chlorosis. Then the red of the cheeks is much darker than in a healthy person, dark or bluish-red and, moreover, when one touches the cheeks they often feel cool despite the redness, and the rough skin is doubly striking with its fine scale formation.

Coldness of the hands and feet is quite common. In external cold this is combined with a blue-red discolouration and in winter these individuals suffer from chilblains. Add to this the thickening of the hands and feet, and another important piece of evidence has been obtained for the diagnosis of difficult cases. Now and again these cold, fat hands seem stiff, tense or asleep to the patients and the subjective feelings of tenseness and "rheumatism" increase in the cold. The coldness is the expression of a *defective circulation,* which can manifest itself in a relatively slow, small pulse and lowered blood pressure. On the other hand, circulatory disorders in the narrow sense involving the heart and vessels, which play such a prominent role in Basedow's disease, are almost always absent. Only on exertion can the pulse speed up and are complaints occasionally made about palpitations.

Respiratory disorders as a rule are only to be seen as a result of exertions, and

these appear namely in the form of a mild or more severe degree of dyspnoea as soon as the patient goes uphill, moves quickly, or makes a physical effort in any sort of task. In this there is a very notable difference compared with hyperthyroidism, in so far as palpitations are not necessarily associated with it, while in the latter this palpitation is prominent and the patient's sensation of it gives further impetus to the feeling of oppression.

There are patients who complain of attacks of dyspnoea with a greater degree of air-hunger, and of alarming tightening sensations; however, as a result of my observations, it seems likely to me that such attacks most probably signify manifestations of endocrine deficiency involving the parathyroids. I must assume the same of the more severe attacks of dizziness and unconsciousness which particularly torment a few patients, but just those, however, who do *not* show the really typical manifestations of thyroprival deficiency.

We have already said what is necessary concerning *digestive disturbances* in the form of dryness of the mouth, a bad taste, loss of appetite, abdominal distension and obstinate constipation.

Disturbances involving the *sex organs,* whose explanation is provided by the decided effect of thyroid preparations, are not a prominent feature of mild forms of the disease. Most frequent are attacks of dysmenorrhoea and menorrhagia at the time of the menstrual flow in the form of a prolonged menstrual flow, occasionally with interruptions of the menstrual flow and a change in the nature of the blood loss (with the blood clotting in lumps). These conditions are not infrequently also accompanied by discomfort. The feeling that the breasts are becoming thicker is occasionally given manifest expression in a firm, bulky consistency of the glands, and I have even seen nodular swellings which regressed on treatment with thyroid. In a young man, who attended very irregularly to be treated for typical signs of myxoedema, pollutions were present during a deterioration in his condition, which regressed on treatment.

Changes in the blood are not always striking. In quite uncomplicated cases, in which the action of the heart is also slow and the pulse is rather small, we have found - in striking contrast to what occurs in hyperthyroidism - a reduction of the lymphocytes to 17 and 18%. and, in individual cases, a marked eosinophilia, 4% to 11 and 16%. There are indeed other cases, particularly ones which have been treated previously, in which, on the other hand, conditions occur which approach those in Basedow's disease, with a lymphocytosis of up to 40% and above. We have often seen that thyroid preparations produce a very considerable increase (up to 40-50%) in a very short time (10-14 days), especially in younger individuals showing particularly low lymphocyte counts.

We cannot yet comment on the blood picture in cachexia thyreopriva with reference to the formed elements with the same confidence as in Basedow's disease, yet some investigations undertaken on our patients are available which are very important. Dr. Kottmann, using a coagulo-viscosimeter designed by himself, has established that blood *coagulation* in cachexia thyreopriva or myxoedema is invariably *accelerated* and produces *very vigorous* clot formation - in complete contrast to the conditions in Basedow's disease. In accordance with this, Kottmann finds an increase in the fibrin content, which he ascribes to an increase in the blood fibrin content due to reduced breakdown. This is explained by the reduced supply to the blood of thyroid secretion, which is thought to activate autolytic ferments, and through them to delay coagulation. We will show that the clotting characteristics in hyperthyroidism (Basedow's disease) are just the reverse, and in this difference we have a valuable clue for the frequently difficult decision as to whether we are dealing with hypo- or hyperthyroidism.

The direct influence on blood and tissues seems to play a more important role in cachexia thyreopriva than any sort of active damage to the circulatory apparatus. The circulation of blood and lymph suffers obvious injury as a result of the cessation of the normal secretions from the thyroid. This is shown by the coldness and the bluish discolouration of the hands, and by the bloatedness and swelling of the tissues; and also by the speedy disappearance of both on the administration of thyroid extract from without.

The *cardinal symptoms of cachexia thyreopriva* are sufficiently characteristic to impress the correct diagnosis on every doctor who is familiar with them to some extent, even if only from a study of the literature. The cessation of growth is the most striking symptom in the young age-groups. Sparse growth of the hair, bloated face, dark-red cheeks with a white or yellowish complexion, fat, cold, or quite blue hands, dry skin on the face and hands, bulky body with fat deposition, flabby appearance and slow speech, these symptoms combined one way or another should make every doctor investigate the *thyroid.* He will either not feel one or will feel it to be altered in such a way that insufficiency can be inferred from the marked smallness, firmness or diffuse nodule formation.

However, individual symptoms can be lacking and then the diagnosis becomes more difficult. If any doubts do remain, then all uncertainty will be removed by the conclusion reached *ex juvantibus,* as in a few days - or with intelligent patients often after 24 hours, but certainly after 8 to 10 days - with the provision of thyroidin and thyroid preparations (the former in doses of 0.2

rising to 1.5 g) in general a quite obvious improvement sets in, which will have progressed within 4 weeks to complete well-being or at least to an improvement which seems wonderful to every lay person. Hertoghe, who is a contributor of merit to our knowledge of hypothyroidism, has shown how important inferences can be drawn in just this situation by suitable medication ex juvantibus. He has perhaps tended to overlook the fact that thyroid preparations may also improve illnesses in which other important factors are involved as well as thyroid deficiency.

But this method of supplying thyroid preparations to typically thyroprival patients also enables one to see for oneself *the various degrees of thyroid insufficiency* in their clinical manifestations with the reliability of a physiological experiment. Quite often the patients and the relatives themselves give the doctor the opportunity of following the individual stages and levels of the disease back in reverse sequence, when they neglect to continue using the remedy once they have got their health back.

In this way one gains the conviction that often only *isolated symptoms* indicate the thyroid insufficiency. With physiological medication using thyroid preparations in larger or smaller doses, and with greater or shorter interruptions, one symptom after another is, as it were, extinguished; first those which only made their appearance with a high level of thyroid secretion deficiency, and lastly those which are already apparent with a mild insufficiency. In just the same way the latter disorders can also appear spontaneously on their own as soon as thyroid function suffers partial or slight damage, or if the effects of the partial deficiency are weakened by some other suitable procedure in the form of appropriate nourishment and care.

These cases of mild *thyropenia,* as one could call this condition, are the ones which are not recognized or not correctly interpreted by the majority of doctors. But as soon as a doctor is fully conversant with the complete picture of thyroprival disorders, then he will satisfy himself that, in addition to the apparently isolated manifestations of disease for which a child or an adult is brought to the doctor, it will almost always be possible to discover traces of the typical, complete picture of cachexia thyreopriva.

We have often had children with hypothyroidism brought to us because a time had come when they failed to grow any more; others because they were always being scolded and punished by the teachers at school for their inattentiveness and apathy, and because they could not be made to do their homework by their parents; but also because they had no desire to play with their friends or to be active in any other way; others because they simply could not

be made to feed themselves properly and at the same time suffered from obstinate constipation.

Adults, especially women, have often been treated over a very long period for supposed anaemia, chlorosis and abdominal disorders, before we get to see them and establish the presence of myxoedema. Often, especially when menstruation stops, the considerable increase in fat provides the reason for consulting a doctor. There are especially good grounds for thinking of *thyropenia* if investigation of the whole body in these fat, torpid individuals, whose appearance often makes one think first of more commonly occurring illnesses, provides no adequate clue to the explanation of the illness in question : although the swollen lids with their translucent whitish colour often make one think of nephritis, the urine is found to be normal, with no trace of protein. Although the bright red cheeks in the bloated face, the cold hands, the fatigue - especially in the morning - the dyspnoea with any exertion, all direct one's thoughts to chlorosis or anaemia, yet investigation of the blood shows a completely normal erythrocyte and haemoglobin content. Despite the lack of appetite, the bad taste in the mouth, and the sluggish digestion, it is not possible to discover any anomalies of the liver, or of pancreatic and gastric function. The investigation of the genitalia in dysmenorrhoea and profuse menstrual haemorrhages provides equally little in the way of an adequate explanation. On the other hand the changes described above can be detected on examination of the blood, and, according to Leichtenstern, Magnus-Levy, Eppinger, Falta, and Rudinger (Metzner) considerable disturbances of metabolism can be detected (a reduction of fasting protein breakdown by half, etc.). In addition, the fact that the injection of adrenalin provokes no glycosuria in athyreosis even after feeding with cane-sugar, but does so after thyroid treatment (Metzner), may be of use in diagnosis.

And even if signs of disturbed activity in organs other than the thyroid are found to explain the symptoms mentioned, once again one must bear in mind that these can be of a secondary nature and may be connected with the extremely important *reciprocal actions* which *the organs with internal secretions* exercise on one another. We will return to this.

It seems certain to me that *every* deficiency of the thyroid or its function, however small it may remain, betrays itself by some symptoms, however mild and isolated they may be, which allow us to discover the reason for the changes and to make good the deficiency. We have come to understand from our numerous operations for goitre, in which the disease has varied considerably in severity and form, that *every person requires his own, quite definite quantity of*

functional thyroid substance, if he is to remain quite healthy. As the beautiful experiments by Halsted and others on animals demonstrate, when a portion of thyroid is removed, the rest of it immediately becomes hyperplastic, thus providing a replacement for the deficiency, which is adequate for the requirements; but this is not at all true of pathological conditions. Healthy and viable glandular substance is required for this. This is not always available: with diffuse colloid goitres and with multiple colloid nodules the complementary hyperplasia can be impeded by the numerous secondary tissue changes, in particular by the wide-spread occurrence of haemorrhages, fatty degeneration, calcification, cyst formation and hyaline and fibrous degeneration, and after partial excision symptoms of deficiency make their appearance. Accordingly before every goitre operation one must pay most careful attention to already existing manifestations of cachexia, the more so the older the individual[11] and the more extensive the thyroid disease is.

The activity of the thyroid can also suffer indirectly from chronic nutritional disorders, infections and intoxications. All these damaging conditions do not always produce immediate manifestations of disease, but there are a number of influences *which cause disturbed thyroid activity to move out of a latent stage and become manifest.* If someone still just possesses enough functional glandular substance for the usual requirements of his body, then only a little bit more in the way of direct or indirect impairment of its function suffices to produce clinically obvious manifestations of deficiency. We have learned to recognize the following influences as being important in this respect - so far they are still little valued for their clinical importance, but they are important for establishing correctly the indications for treatment :

1. *The development or enlargement of a colloid goitre.* We have in not a few cases seen the emergence of signs of insufficiency after an earlier unilateral excision just when the remaining parts were beginning to grow, while at the same time function was being reduced by colloid changes. We only need to consider the effect of the development of a goitrous nodule within the thyroid structure in order to satisfy ourselves how the pressure and tension due to it flatten numerous follicles, destroy the interstitial tissue and gradually bring about their atrophy. In such cases removal of the nodule by resection-enucleation can have a very favourable effect. Indeed we have been particularly struck by the way in which very extensive enucleations in apparently diffuse colloid change exerted an excellent effect on the state of the health in cases where one had been worried that insufficiency might occur or that already existing symptoms of it might be increased.

2. *Advanced years,* during which, according to Max Rubner's splendid analysis and demonstrations, slowly, but with fatal sureness every organ which has carried out a definite number of functions, is subject to a certain degeneration resulting from usage.

It happens not at all uncommonly that old people reach a particular point in time, and from then on develop flabby, yellowish skin, and their hair, teeth and nails become dry, brittle and cracked, while patches of pigmentation or even cutaneous eruptions make their appearance; and a previously non-existent fatigue where physical work and mental activity are concerned sets in, and so-called rheumatoid-arthritic manifestations assert themselves, all being symptoms which on treatment with thyroid preparations undergo an improvement which is striking and gratifying to the patients. It is to be supposed that in goitrous patients, whose thyroid enlargement perhaps originally appeared in the form of active hyperplasia as a reaction to increased demands, such influences of age assert themselves earlier and more severely.

3. In women with latent thyroid cachexia, *pregnancy* can provoke the outbreak of symptoms, and indeed in frank cachexia thyreopriva it regularly exerts a really bad influence on all the symptoms, here too in proportion to the increased need for thyroid activity for which the modified organ is inadequate. There are women who show considerable physical changes during pregnancy which are partly to be identified with symptoms of endocrine deficiency. The menstrual flow, too, can produce the first signs of cachexia or make the condition worse and more severe menstrual haemorrhages in particular are not an uncommon sign of deficient thyroid activity. This is particularly noteworthy, if one considers that in Basedow's disease the rule, on the contrary, is that the patients feel quite considerably better during the pregnancy[12] than either before or, in particular, after; and that the reappearance of the menses or their increase is a sign that improvement is setting in.

4. A really important factor, which also counts in the influence of menstruation just mentioned, is considerable *blood losses.* These too can provoke the onset of the first symptoms of cachexia or be responsible for making them worse. In such cases it is particularly desirable to avoid confusion with simple anaemia, because the appearance ofpatients with thyroid cachexia in the initial stages certainly has a striking similarity to that of chlorotic patients with their swollen face, translucent eye-lids, the translucent whitish or yellowish skin, with which bright-red cheeks often form a contrast; and also the slight swellings on the leg, and the cold hands.

5. *Chronic poisonings* cannot be too highly rated as an influence which causes

damage to the thyroid. One can confirm clinically what de Quervain had demonstrated with his histological investigations, that alcoholism and tuberculosis, and occasionally syphilis, too, damage thyroid activity and can bring out latent insufficiency like the factors mentioned above, because they incapacitate the gland's ability to adjust to greater demands. I want to draw attention even now to the fact that in this respect a very noteworthy distinction exists between the influence of *acute* infections and that of the above-mentioned and other *chronic* intoxications : If the former damage the thyroid they do not do so in the same way as the slowly-operating noxious influences. On the contrary, if the thyroid becomes the site of an attack by acutely infective substances and their products while it is a healthy and vigorously functional organ, then it is able, more so than any other organ, to protect itself to the extent that either no damage to its tissue producing deficiency symptoms occurs, or such as there is, is more than made good by reactive hyperplasia. In this way the thyroid damages itself by the excess of its defensive efforts. However, these, since they lead to active hyperplasia, do not have deficiency symptoms as their result, on the contrary they lead to hyperfunction and the disorders which are dependent on it.

6. Finally, one cannot leave unmentioned the importance of the *reciprocal action of the vascular glands or organs of internal secretion* in the onset of disturbances of function involving the thyroid. This factor is very important in the occurrence of thyroprival disorders with insufficient objective findings in the thyroid and again in clinical pictures which deviate from the typical picture of pure cachexia thyreopriva, and yet can be influenced favourably by thyroid therapy correctly combined with other remedies. The organs with internal secretions are very sensitive to stimulating substances, and it is an entirely obvious supposition to make that mild anomalies of thyroid function perceptibly affect the pituitary and adrenals, etc., earlier than they do the body as a whole, so that symptoms appear which indicate the involvement of other "vascular glands" before the symptoms due to the primarily diseased organ, i.e. to the thyroid, become evident in the rest of the body. With the proviso that I will return to this, I refer to my own observations on cases in which acromegaly was present in combination with symptoms of myxoedema, and thyroid therapy had a clearly beneficial influence. In such cases one must think of a secondary influence of the pituitary in the sense of compensatory hypertrophy due to deficient thyroid activity. According to Hooling thyroidectomy brings about compensatory cell proliferation with colloid production in the pars intermedia and in the posterior lobe of the pituitary. Clinical investigation in our cases

revealed deficient development of the thyroid. The thymus also, whose removal[13] in the earliest days of life brings about growth disorders analogous to those of thyroid excision, shows important reciprocal connections. Similarly, clinical pictures could be explained which, like infantilism, mongolism, etc. have certain features in common with cachexia thyreopriva, and are quite often improved by the administration of thyroid preparations, though not at all with the same precision as in the latter condition.

Finally, as a result of thyroid deficiency, the adrenals and the chromaffin system (if Falta's hypothesis of reciprocal facilitation holds good) can suffer damage, and signs of their defective activity make their appearance. *In the irregular clinical manifestations of cachexia thyreopriva,* myxoedema and cretinoid states one must also bear in mind that the endocrine deficiency manifestations of the thyroid have been lumped together too long with those which accompany damage and destruction of the *parathyroid glands.* Almost all the symptoms which were interpreted as a manifestation of cachexia thyreopriva in the acute form, have, after Gley's original experiments and the decisive evidence of Generali and Vassale, turned out to be due to the loss of Sandström's organs, i.e. of the minute epithelial bodies of Cohn. Schiff's original experiments, too, it can now be said, have a bearing on deficiency symptoms involving the parathyroids. Already in the days before there was more precise knowledge about the latter organs, the clinical picture of hypo- and aparathyreosis in mild and severe forms had become well known as a result of von Eiselsberg's descriptions of acute tetany after extirpation of goitres. In cases where, in contrast to our subcapsular method for the excision of goitres, no importance is attached to sparing the capsule, even now mild forms still come to notice from time to time, while we get to see them extremely rarely.

Much less well known are the incomplete and *chronic* forms of *hypoparathyroidism.* Only with the production of parathyrin in bulk at Halsted's[14] instigation, and especially with the extremely important discovery by Halsted and Crile of the replacement of this expensive medicament by a simple chemical substance, *calcium lactate* or *chloride,* has it become possible to trace back ex juvantibus certain symptoms of endocrine deficiency definitely to a disturbance of parathyroid function, because the administration of parathyroid preparations brought about a cure, after thyroidin had shown itself to be completely ineffective.

Not long ago we have had the opportunity of observing a very interesting, and pertinent, case of *hypoparathyroidism,* which we cite here briefly. The patient, a woman, had had to undergo a unilateral excision of the goitre for a

diffuse, bilateral colloid goitre, which had produced a very good result right away. The operation had taken place two years previously. Subsequently, however, some disorders made their appearance which became increasingly tiresome for the patient and could not be counteracted satisfactorily by the administration of thyroid. The doctor therefore sent the patient to me asking whether some insufficiency of the parathyroids might perhaps be involved. The patient showed a few disorders compatible with thyroid deficiency (rolls of fat over the clavicles with sensitivity to pressure, and deposition of fat on the hips), but complained primarily about *pain* in the breast, back and limbs, with considerable stiffness which fluctuated greatly in intensity, so that she often could not get up from a chair, and now and then her knees would suddenly give way beneath her and she would nearly fall, so that a sort of agoraphobia developed. Dyspnoea and tightness were also present, suddenly developing during quiet cardiac activity. At the same time, her mental functions were unimpaired, while her digestion was disturbed by short-lived diarrhoea. Her appearance was good. In this case thyroid treatment proved to be quite inadequate, using both thyroidin and iodothyrin; an improvement only resulted with the administration of large doses of parathyrin of Vassale. The complete recovery, which the patient herself called a cure, was only achieved with the administration of calcium preparations. It has been our experience that these must be administered in high doses (if such are tolerated by the digestive organs), i.e. up to 6.0 g of calcium chloride in 24 hours.

We have observed a second case of *hypoparathyroidism* which was also quite substantially improved in the same way. This case has special interest in that it illuminates the great importance of causative and cooperative factors. The patient, a woman, had had a unilateral thyroidectomy three months previously with a very good result, for typical, severe Basedow's disease. However, it seemed desirable, in order to complete the cure and ensure its permanence, to undertake another ligature of the contralateral superior thyroid artery, before the patient set out on her long journey home. The patient is said to have detected a stiffness in her legs after the operation. On the second day the symptoms of an acute appendicitis made their appearance, and this was treated expectantly. After her discharge the patient claimed to have noticed tinglings in her hands, like she had had before, after the first operation, but now both hands and feet were stiff for short periods of time.

Seven weeks later the radical operation was performed to prevent recurrence of her appendicitis. Within a few hours (with her temperature rising to 40°C) there was an attack of unconsciousness, with dyspnoea and a rapid pulse,

which lasted for two hours. The attack was repeated during the night and on the following day, with a temperature of 42.6°C and a pulse rate of 162. Muscular rigidity, cyanosis and heavy sweating appeared. These attacks were now recurring very frequently, mostly with severe respiratory disturbances, and episodes of laryngospasm, and in the severe attacks there was also spasm of the masticatory muscles and of the trunk, so that severe opisthotonus occurred. With the use of parathyrin (for whose provision in large quantities we are grateful to our friend Professor Halsted), calcium chloride and cold packs (the latter seemed to be specially valuable), the convulsions ceased after having lasted for 10 days, and the high temperature went down as well. The Chvostek phenomenon stayed behind, and so did an uncommonly great weakness of the muscles which soon became very atrophic too, especially at the lower extremities.

Not until the onset of the next menses the same convulsions appeared again in a severe form, to regress quickly with treatment.[15]

We have mentioned this case, which demonstrates the usual course of acute tetany which has become chronic, in combination with epileptoid attacks, mainly in order to illuminate the importance of causative factors: Both the effect of a relatively slight surgical operation and later of the onset of the menses were very striking.[16]

If it seems advisable to cling to a certain affinity between the clinical pictures presented by all the organs of a thyroidal character, so that, just as one speaks of the chromaffin system, one could choose a suitable name for this one, such as the *iodaffin* or *iodophile system* or something similar, yet for the present it is expedient to distinguish as sharply as possible between those symptoms which result from disease of the thyroid, parathyroids and pituitary, etc. It is not conducive to the advance of clear understanding if, as has happened, a number of the most heterogeneous disorders are assigned directly to hypothyroidism, such as adenoidal proliferations in children, nocturnal enmesis, menorrhagias, pendulous abdomen and retroversion of the uterus, rickets and chronic rheumatism.

These disorders can have a hypothyroid basis for their development, but also arise through other factors in the absence of the former.

Concerning therapy, only a few words here. When we have recognized the thyroprival basis of a disease, then the correct physiological therapy, as in syphilis for instance, makes its beneficial influence clearly felt in a very short time. But it must be the *correct* remedy, and here we have observed that in individual cases Baumann's iodothyrin does not take effect, indeed is not even

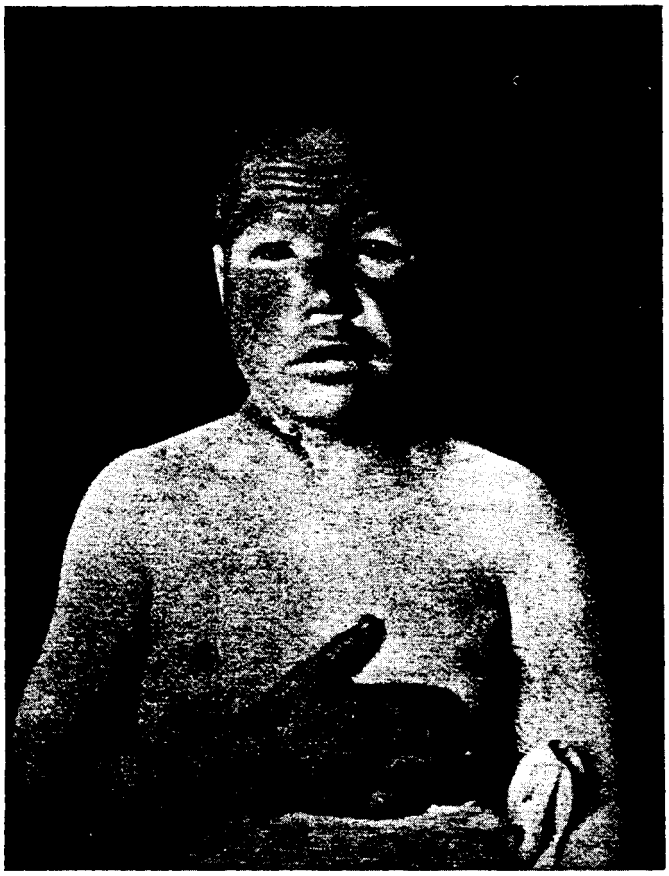

Fig. 1. A case of cachexia strumipriva 11 years after operation.

well tolerated, so that in general, where the diagnosis must be elucidated in a hurry, the usual thyroid extract, or thyreoidea sicca, is to be preferred. It is not easy to explain why it is that iodothyrin sometimes works worse than thyroidin, since it is said to represent a purer preparation. But one's first thought was that the effect is inadequate in such cases where slight symptoms of cachexia parathyreopriva are co-existent, where thyroidin is more effective because the evidence (recently from von Getzowa) is that the parathyroids are partly buried in the thyroid and parathyrin is accordingly also incorporated in the preparation.

Nonetheless there are such clear cases of operative cachexia thyreopriva which are completely well with the use of iodothyrin, that there can be no doubt that, for pure forms, a high-quality substitute for thyroid extract is

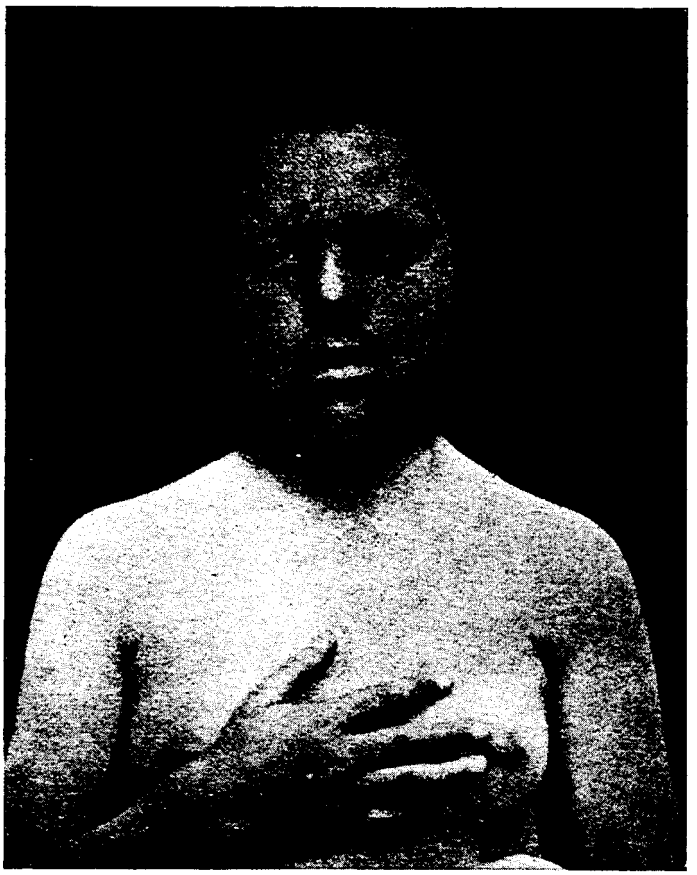

Fig. 2. The same patient as in Fig. 1, five months after administration of thyroid.

available in the Baumann preparation, as Roos has always affirmed and demonstrated. In the accompanying four photographs we have proof for this statement in a female patient who developed high-grade cachexia after total excision. She is shown 11 years after the operation in Fig. 1, then received thyroid for 5 months (Fig. 2), discontinued however the medicine again for 5 months (Fig. 3), and was cured again within 6 weeks by iodothyrin (Fig. 4). The patient, while in the state of frank cachexia strumipriva, brought a normal child into the world. With the use of pure iodothyrin as well as with the provision of thyraden and thyreoidea the pathological phenomena disappeared promptly and for a period of years, as long as the treatment went on, only to return when it was discontinued.

The main consideration in treatment with iodothyrin as with thyroidin in

Fig. 3. The same patient as in Fig. 2, after discontinuing the treatment for five months.

its various forms is *to find the right dose.* Since the disease is directly proportional in its severity to the amount of thyroid substance that is lacking, the effect of the remedy in one case is too strong, in another too weak, according to whether a smaller or greater remnant of functional tissue still remains. With the administration of too much (it was only in a few cases that the chemically pure preparation seemed to have a particularly powerful effect, and that it perhaps was harmful on account of this) the picture of hyperthyroidism makes its appearance with fever, sweating, dyspnoea, increased heart rate, and in severe forms even oliguria and vomiting, while otherwise thyroid preparations, iodothyrin in particular, have a very powerful diuretic effect (and as well as

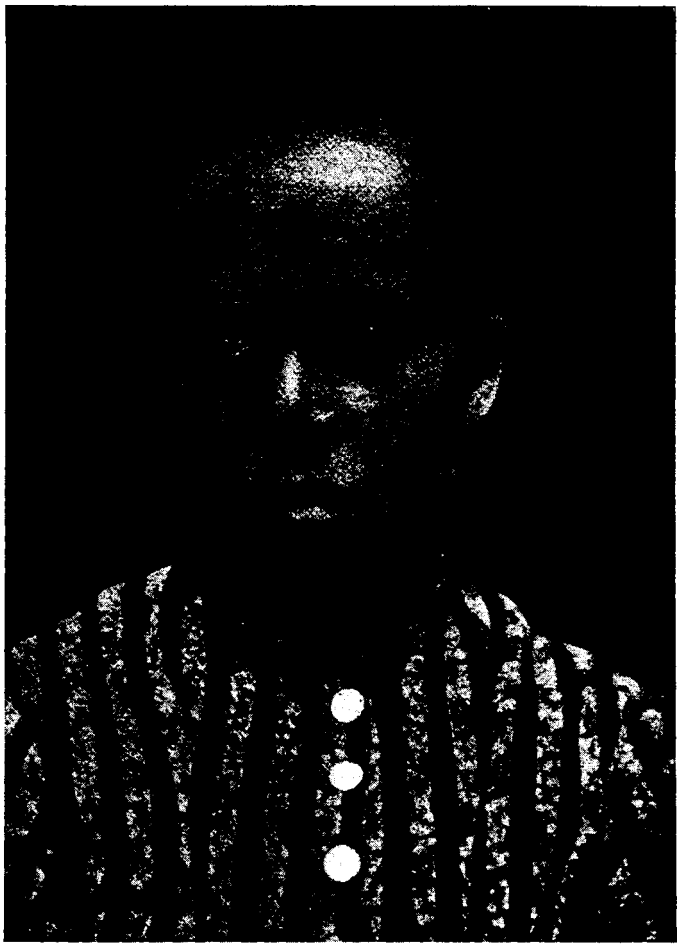

Fig. 4. The same patient as in Fig. 3, after using iodothyrin for six weeks.

the amount of urine also increase the excretion of urea, often the latter alone) and correspondingly remove the oedematous swellings in a very short time. Also a raised pulse rate can go down with iodothyrin when the correct dose has been found, as von Cyon has discovered by experiments on aminals.

Apart from the decrease in weight following regression of the oedematous swellings, the patients are most struck by the very rapid onset of an improvement in mental and physical capacity; the complexion becomes fresher, brownish spots disappear (now and then very rapidly or only with the concurrent administration of parathyroid), the pains in the nape of the neck, back and limbs disappear (with excessive doses they are increased or make their appear-

ance if they were not there before); the hair starts to grow in a way which is really striking in children, whereas before it fell out; and in children bodily growth (1½ cm in three weeks in one case) is increased quite remarkably in a short time.

With treatment employing the correct dosage it takes on average four weeks for the cure of all symptoms to be almost complete (with disappearance of coldness, dryness and difficulty in moving), and also, four weeks after discontinuing the treatment, most of the pathological symptoms have returned in the severe cases.

It may well be stressed at this stage how the sharp contrast in symptoms that exists between hypo- and hyperthyroidism makes itself felt in the treatment, too. Thyroid preparations are always useful in the former if one has worked out the correct dose, which varies between individuals; as a general rule the same medicaments are harmful in hyperthyroid conditions, and only certain cases, in particular transitional cases, tolerate the use of very small doses.

Contrariwise the phosphates, which have such a decidedly favourable effect in Basedow's disease, given in the correct combination and in large doses, are detrimental in hypothyroidism. Thus an intelligent patient, a woman with "spontaneous" myxoedema, complained of the rapid onset of an "ice cold feeling" on the administration of sodium phosphate.

The influence of cold in all forms worsens hypothyroid conditions, but has on the contrary the most beneficial effect in patients with Basedow's disease and related conditions. Thus residence in a cold climate is disadvantageous for people with cachexia, just as residence in high mountains is, while they are beneficial for hyperthyroid conditions. The opposite is the case for mild climates and staying by the sea, where to their detriment patients with Basedow's disease are often sent.

Where nutrition is concerned the two opposite conditions also diverge in many ways. We make the proviso that we will take this subject up again in detail in some other place.[17] In all cases of hypothyroidism one must bear in mind the replacement and restoration of thyroid activity by *transplantation.* If this succeeds, it has the great advantage over feeding with thyroid preparations that the body automatically regulates the quantity of secretion to be taken from the transplant, as the beautiful experiments of Cristiani and of Halsted demonstrate. The body's requirements provide the yard-stick.

Second Section

The low grades of thyrotoxic disorders

With the progressive clarification of the syndrome of cachexia thyreopriva and with the study also of the milder forms and variations of *thyroprival* disorders generally; with the consequent possibility of distinguishing the parathyroprival disorders, as well as the cases which present a more complicated symptomatology as a result of their combination with disorders of other vascular glands, and with the possibility also of distinguishing the disturbances which merely bear an indirect relationship to the deficiency symptoms on the part of the thyroid - with all this it has become ever clearer that a disease whose manifestations presented a striking contrast to cachexia thyreopriva, probably had to be related to an opposite condition of the thyroid. From the time of the first descriptions around about the forties of the last century by Graves and Basedow, attention has, in addition to the very striking symptom of exophthalmos, been paid to the swelling of the thyroid in *Basedow's disease;* indeed Flajani had already given prominence to this feature earlier on.

Now, after myxoedema and sporadic cretinism had been recognized as expressions of cachexia thyreopriva, people were also led to look for the fundamental cause of the symptoms in Basedow's disease in a primary disorder of the thyroid. Thus, from theoretical considerations arose Mobius' doctrine of the *thyrogenic* origin of Basedow's disease, in which the dependence of the symptoms on some damage to the thyroid was clearly formulated.

The proofs for this concept were derived from the striking, strict antithesis of the majority of symptoms to those of thyroprival disorders. However, success in producing a similar symptomatology in animals was achieved only with difficulty, and imperfectly. Accordingly, it was necessary to confirm by clinical observation in humans not only whether the essential basis of the clinical picture was really to be sought in a disorder of the thyroid, but also whether this alone produced the manifestations diametrically opposite to those of cachexia thyreopriva.

In contrast to cachexia, the thyroid function had to be pathologically increased, and an excess of secretion brought into the circulation.

The administration of thyroid extract, which has such a favourable influence on cases of cashexia thyreopriva had to be harmful rather than useful. The copious use of thyroidin, which followed on Murray's and Howitz's communications, not only in typical cachexia, but also in goitre (specially on Brun's

recommendation), in obesity (Leichtenstern), provided ample opportunity for observing the effects of excessive administration. An even better opportunity was provided by observing the effect of thyroidin in Basedow's disease itself, which - side by side with iodine preparations - plays an unbelievably important role, in the treatment of this disease in medical circles.

Whoever feels inclined to study the symptoms of Basedow's disease, only needs to administer thyroid preparations in large doses to predisposed individuals, or to administer iodine preparations - which comes to the same thing on account of their conversion within the thyroid. More reliably still one can rapidly convert a mild Basedow to a very severe case, if one administers thyroidin or an iodine-containing medicine. The predisposition referred to is due to the presence of certain anatomical changes in the thyroid, such as are found in families, entire local populations in cases where there is a hereditary diathesis, in puberty and pregnancy, and after infectious diseases.

Such experiments are made on people much more often than is generally imagined. In the course of years I have seen a considerable number of cases in which there has been a severe aggravation of Basedow troubles occurring under the influence of medical treatment. The relevant therapeutic attempts prove plainly enough that in contrast to cachexia thyreopriva Basedow's disease is a *hyperthyroidism,* and that it undergoes an increase in its typical symptoms as a result of a further surplus of thyroid juice. This surplus need not be administered directly from an external source in the form of thyroid juice, but can also occur as a result of an increase in the secretion in the thyroid, as it does above all with the administration of iodine, and very probably under psychic influences too.

In addition, the reciprocal proof of this fact has been provided with absolute certainty *from the surgical side,* the proof being that the diminution of the secreting substance by ligaturing arteries, and, much more directly by the excision of larger parts of the thyroid, results in a quite remarkable and rapid cure in pure, typical cases of Basedow's disease.

Rehn was the first to produce evidence in support of the advantages of operative treatment; it has been confirmed time and again by a great number of competent surgeons, and we have been able to satisfy ourselves more definitely about the excellent results of early operative treatment the longer the period of time over which we have been able to observe the patients. My son, Dr. Albert Kocher, has assembled the results of operative treatment in his great treatise on Basedow's disease.[18] Increasing experience in surmounting technical difficulties and complete asepsis always carried out with the same strict-

ness have turned the thyroid operation into one with such a safe prognosis that we have been able to label it risk-free in uncomplicated cases for a long time now. We have already reached the first quarter of our fifth thousand goitre excisions (4250) now, which does not include the great number of ligatures, which would complete the fifth thousand.

I am in a position to provide you with the *result of the fourth thousand of our operations* in the period between August 3, 1905, to July 5, 1909, i.e. in not quite four years. First of all, let it be emphasized that of those operated on with ordinary colloid goitres without serious complications, not one has died. All the same if we do count 7 fatalities out of 1,000 patients, the reason for this is that all the complicated operations without exception are included in this number too, i.e. 155 cases of *Basedow's disease,* 78 cases of totally or partially *intrathoracic goitres;* 28 cases of *malignant tumours* of the thyroid; 8 operations upon pregnant women, 3 on retro-oesophageal goitre, 4 on acute inflammations of the goitre, and 16 on recurrent goitres.

All the forms named present their particular complications; how difficult the malignant goitres are to remove at operation is self-evident in view of the adhesions and of the need for the radical removal of the adhering organs as well. Among our 28 cases we have not, however, lost a single one. On the other hand, of 78 *intrathoracic goitres* 3 died following the operation, all 3 from pneumonia, the progress of the wound being uneventful. It may be a source of surprise that we get such a relatively large number of these difficult cases for treatment. However these are referred to us preferentially, because they presuppose complete familiarity with the technique of the operation under particularly difficult conditions.

If a goitre - and this often happens on the left side, because here the inferior horn normally extends further down in any case - grows down into the thorax and undergoes most of its development there, then the pressure on neighbouring structures, i.e. the great veins and the trachea in the region of the thoracic aperture, is particularly severe; and the venous congestion and the obstructed air passage together lead to circulatory disturbances in the area supplied by the right heart and pulmonary circulation; they represent a particular form of *goitre heart,* and are very commonly associated with advanced secondary pulmonary emphysema and chronic bronchitis with retention.

It is easy to understand that a particularly marked tendency to lung complications exists in these circumstances, when one considers the longer duration of the operation and the increased difficulties of haemostasis at great depth. In addition, these are just the patients who very often only come under surgical

treatment when they are in a state of severe dyspnoea, after having been treated for a good long time, without ever being given a careful examination, as if they were suffering from asthma and bronchitis.

Finally *Basedow's disease* plays a big part in the mortality. Of the 155 cases in the fourth thousand of the goitre operations, 4 have died, which corresponds to a mortality of 2½%. This is certainly a thoroughly gratifying result already, in a disease which shows a mortality of 9-25% under medical treatment according to information from authors.

We have a recent, excellent treatise on Basedow's disease from the surgical department of our colleague, Professor Berg, in Stockholm, in which with real Swedish thoroughness and sober good sense Landström considers and contrasts the results of internal and surgical treatment. He draws attention to Mackenzie's particularly wide experience, from which the conclusion is drawn that with medical treatment the mortality amounts to 25%; where the course is acute, to 30%; that 25% pass into a state of chronic suffering; and that 50% pull through to a fairly good cure, in the latter case, as we add, mostly over the course of many years.

Among our 4 unsuccessful cases there is one fatality due to narcosis in a patient whose behaviour was so uncontrollable at operation, despite local anaesthaesia, that general narcosis was unavoidable; one case died of pneumonia (the healing of the wound was perfect) ; two patients perished as a result of previously existing toxic liver and kidney disorders. In these the operation was unquestionably too late and the attempt, urgently requested by the patients, to wrest a cure nonetheless, would have been better left unmade.

From this comparison it emerges that, with the large-scale experiments presented by the successful operative results of the surgical treatment of Basedow's disease in humans, we are now in a position to confirm, as Möbius had proposed on theoretical grounds, that the disease is related to increased thyroid function. In a report to the Congress on Internal Medicine in Munich (1904), which I had the honour of attending at the invitation of the managing committee, I procured the numerical evidence that operative treatment of Basedow goitre not only produced an improvement in every case and a cure in 72%, but I believed it was also possible to establish as a law that the regression of the symptoms of Basedow's disease occurs on a scale which is completely proportional to the amount of thyroid tissue removed. The cure is incomplete if a sufficient quantity of the diseased thyroid tissue is not taken away or removed functionally by ligature.

I was exceedingly gratified that Berg and Landström have come to con-

clusions which are fully in agreement, after their studies of operative results, namely that the cures achieved are that much better the more thyroid tissue has been taken away by excision and eliminated by ligature of arteries. Every doctor has the means of verifying this law readily available: one only needs to make a second excision or an extra ligation in cases which have not recovered completely, whereupon one will be able to confirm that there is further progress towards a cure right away. This fact has been substantiated so often by our own observations that there can no longer be any doubt about it.

In the course of a lecture Albert Kocher has compiled the operations for Basedow's disease carried out by us up to September, 1909, after he had obtained full information about their subsequent course up to the stated date. There are 376 cases. Of these 14 are excluded, because the period of observation is still too short; the same goes for those who died. The mortality for this large number of patients operated on for Basedow's disease, which goes back beyond our fourth thousand, amounts to 3.9%. Half the fatalities come under the heading of complications, i.e. asphyxia, embolism and pneumonia, the other half died as a result of disease co-existing in other organs, the heart, kidneys, liver and the lymphatic system (status lymphaticus). Of the cases, 76% are cured at this present moment. And the cases in which exophthalmos persists are *not* included among these cures. (Exophthalmos has regressed in 159 out of 203 cases.) Not cured are 10% of the cases, but in 19 patients the reason for this lies in the fact that the operation is still incomplete, but the patients cannot or will not make up their minds to submit to our recommendation of a further operation. So in reality only 20 = 5.3% have remained uncured.

So we may well affirm on the strength of the above figures that evidence has been provided that the elimination of thyroid tissue in Basedow's disease not only causes no deficiency symptoms, but, on the contrary, the more thyroid substance is removed (up to a certain point), the more reliably is the patient cured.

Removal of thyroid substance could, of course, also produce its favourable effects if harmful substances, which were absorbed from it, were thus being removed from the body. The idea of such a *dysthyroidism* is still adhered to by a few, very competent, investigators. But a proof of this assumption is not available; on the contrary, from our numerous observations it seems quite certain to us that the same thyroid products which are able to make good the deficit in thyroprival disorders and do away with the pathological manifestations completely, once they are administered to individuals who already show mild, let alone more severe, symptoms of Basedow's disease, aggravate the disease,

or evoke it when they are administered in excessive quantities. We will come back to this.

But because we are convinced that on the basis of its explanation as a hyperthyroidism Basedow's disease can be cured, once it is recognized in time, there is great value in drawing attention to the initial symptoms, which are often isolated and mild.

Basedow's disease presents a quite typical picture as it was described by its discoverers, and it seems highly desirable to stick to this, even if the names vary and people speak of Graves' disease in English-speaking lands, of Basedow's disease in German countries, and of morbo di Flajani in Italy. To it belongs the triad of *exophthalmos, goitre,* and *tachycardia.* But everyone knows that not even the main symptoms are exhausted with these, and that we require other constant and important symptoms if we are speaking of Basedow's disease; thus the *tremor* has been added by Pierre Marie as a constant, principal sign (and yet one does not speak of Pierre Marie's disease), and the lid signs by Gräfe, Dalrymple, Stellwag and Mobius. Equally common or constant are the vasomotor disturbances, the warmness, the congestions, and the attacks of sweating. The principal signs of increased excitability, of the consequent perpetual nervous agitation, and almost always of sleeplessness, are constant; digestive disturbances in the form of vomiting, and much more commonly of increased bowel movements or attacks of frank diarrhoea, are seldom absent. As a rule one finds considerable emaciation, which is only partly caused by the latter disturbances (it also occurs independently of them), easily induced fatigue and weakness on mental and physical activity, so that not only are longer marches excluded, but the patients ultimately collapse if they attempt to stand up and walk.

Whenever the picture of Basedow's disease is as obvious as this, not only will a doctor be in no doubt about it, but even lay people do not mistake it any more if they have seen one or two cases. Closer examination shows many more interesting symptoms, such as changes in the skin, which is strikingly tender, smooth and hairless (while in cachexia thyreopriva an increased growth of hair is often observed in abnormal places, such as legs, back), and is much easier to cut through at operation. Loss of hair from the head, of pigmentation of the skin, particularly around the lids, white flecks on the nails and longitudinal grooves along them, are usually present.

In addition to these well-marked cases of severe exophthalmic disease with the very appropriate name exophthalmic goitre, which English and French doctors in particular prefer to use, there is a much greater number of *mild forms*

of hyperthyroidism in all stages of transition from a physiological occurrence right up to the severe and most severe conditions of Basedow's disease proper in which exophthalmos is absent; and it is very important to emphasize this, since it is the early stages especially in which these and other symptoms are not well marked and only isolated pathological symptoms are conspicuous to the patient as well as to the doctor. And yet it is so extremely desirable that the diagnosis should be made early, and the grave consequences prevented by rational therapy. In the early stages surgical therapy achieves positively brilliant successes and the protraction of so many cases because of uncertain diagnosis and groping around with inadequate attempts to cure medically bears most of the blame for the failure of later surgical intervention.

But we would like to make one reservation. Since the thyroid lesion has been recognized as the basis of Basedow's disease and it has become known that the symptoms are explicable in terms of hyperthyroidism, cases of so-called Basedow's disease have increased in a striking way, if one looks at the statistics for goitre operation. Over a very short period of time, individual surgeons get 30, 50, indeed hundreds of cases for the operation. Some moderation is definitely required here.

If the thyroid hyperplasia which can lead on to Basedow's disease is to be understood along the lines of the interpretation given by competent judges, as being in the beginning often a reaction to noxious influences affecting the body, then it is to be expected a priori that slight symptoms of hyperthyroidism should quite often be regarded as useful from the teleological point of view, and indeed even in part as healthy. In such cases *of physiological hyperthyroidism* one should not immediately intervene roughly on the strength of a diagnosis of Basedow's disease, for otherwise one runs the risk of doing harm or at least operating on cases which would never have suffered from Basedow's disease. Thus in puberty, especially in girls, increased excitability occurs often enough, with vasomotor disturbances, heat, sweating, palpitations at the slightest provocation, with shining eyes and a slight enlargement of the thyroid, without a pathological state developing from this youthful fire.

We are in complete agreement that designating such cases with the name of hyperthyroidism is justified, but the name, Basedow's disease, should most certainly not be applied to every case of hyperthyroidism, and most particularly not by surgeons, who think themselves justified in recommending early operative treatment as the most correct therapy in patients with Basedow's disease. When it comes to deciding in the individual case whether such treatment is indicated, it is no help either trying to produce an opinion using the

names, *formes frustes* or *pseuobasedow,* as if true Basedow's disease is differentiated more positively in this way. It is particularly true of these unfortunate foreign words that, where the concepts are lacking, a word appears at the right moment.

Neither were we able to interpret it as being to the benefit of hypothyroidism that Hertoghe speaks of a "benign" hypothyroidism. We have shown that these so-called benign forms are nothing other than lesser degrees of the same disease with milder, often isolated symptoms. Similarly, in the formes frustes of Basedow's disease one can only either be dealing with another disease (that would be the case according to *Stern,* since he states that *his* formes frustes never change into Basedow's disease; indeed he correctly gave them another name: goitre heart and Basedowoid, which latter term is not going to satisfy me), or the formes frustes are the same disease in essence, i.e. as regards their causality. Then one might better, because this is more comprehensible, distinguish mild and severe, or lower- and higher-grade forms, like in other diseases.

Then we will be able to decide which therapy is appropriate, and neither allow the valuable time for an early operation to pass by where it is indicated, nor subject to the operation cases which could be cured by causal treatment. In the special case it will be a matter of answering the question: are the noxious influences which have led to a change in the thyroid, i.e. to a hyperplasia of the latter with symptoms of a mild degree of hyperthyroidism, transitory and easy to eliminate, so that the prospect is that the change in the thyroid brought about by them will also regress; or are the latter not capable of spontaneous regression, either because the thyroid disorder has progressed too far, or, because the noxious influences are continuing to produce their effect?

Even those doctors who love operations will not consider an operative attack on every swelling of the thyroid in puberty and pregnancy, although the pathological-anatomical substrate shows a very considerable degree of conformity with the changes which we meet in the early stages of the true Basedow, and although we know that these swellings that have been provoked by physiological processes can constitute the prelude to Basedow's disease. We know that the noxious influences are of a fleeting nature in those cases and once they have run their course the normal state of affairs can return.

Aetiologically far more suspicious are the thyroid swellings which are initiated by diseases, because they leave more severe anatomical changes behind.

In the discussion of the hypothyreoses we have already referred to the fact that, unlike the case with these, it is not so much the chronic infections and

intoxications, as the *acute* infections (and intoxications) which produce the changes in the thyroid which lead to increased function.

It is true that there are also cases where one can obtain evidence for aetiological connections with congenital syphilis in Basedow's disease, but these form a small percentage in our register of cases. On the other hand a great number of cases of *acute infections* are known, in which Basedow's disease occurred in connection with the infection. De Quervain has drawn attention to these cases with the discussion of his "acute, non-purulent thyroiditis" and recently Landström has assembled the relevant cases in his treatise on Basedow's disease. The various forms of *influenza* and acute rheumatism are the ones in particular which do damage. Much more often still we have observed an *aggravation* in patients who previously had shown only mild symptoms of Basedow's disease, but became more seriously ill after influenza.

A part of these cases of influenza and acute rheumatoid arthritis belong to the province of the streptomycoses and this seems to us worth noting for the explanation. In our treatise on infectious diseases, which is now appearing in the second edition, Tavel and I drew attention to the fact that streptomycoses are characterized by the way they evoke severe manifestations very swiftly, but that the acute reaction of the body which underlies these also has the result that the effectiveness of the micro-organisms falls off very rapidly and they perish. One only has to think of erysipelas, where a few hours after infection a temperature of 40°C makes its appearance, with redness and swelling and painfulness of the lymph glands, and of how rapidly a falling-off of all symptoms can follow. It is infections such as these which can provoke the thyroid to hyperthyroidism with the corresponding anatomical changes. The thyroid is a very important organ of protection against intoxications and infections of acute onset. It can not only avert disease from itself, but it probably also plays a role as an organ of defence for the body as a whole. For, with thyroid deficiency, animals and humans show very little capacity for resisting infection and its consequences. Acute thyroiditis in the usual sense is the greatest rarity; real inflammation almost only occurs (as a strumitis) in the altered thyroid tissue which owes its origin to the formation of a goitre with its secondary disturbances of circulation and nutrition.

The reactive swelling, which the thyroid undergoes under the influence of infections and toxic materials suddenly supplied to it, and which can lead to a persistent hyperplasia, is not to be thought of as thyroiditis in de Quervain's sense. Analogies to such behaviour on the part of other organs in response to acute inflammations are lacking; as a result of the latter, if it does not recede

completely, the function remains impaired and reduced. Furthermore it must be remarked that the picture of Basedow's disease after an acute infectious illness often develops so swiftly to characteristic heights that there is no more doubt about the diagnosis of Basedow's disease, which also argues in favour of a merely reactive swelling. The thyroid behaves in just the same way with *violent emotions as the cause of Basedow's disease.* It is true that in these cases one can often also obtain the information that symptoms were already present before, which could be interpreted in terms of hyperthyroidism. But it is certain that great terror or anger have a very important influence on the onset and sudden aggravation of the disease, so that doubt is no longer possible about the importance of nervous influences of mental origin on the pathological increase of thyroid secretion, whether acting directly via vasomotor tropic paths or indirectly through metabolic products.

The *symptoms* from which it is possible to conclude reliably whether we are dealing with a probably transitory hyperthyreosis or with the start of a disease progressing in the direction of Basedow's disease, will best be made evident if we subject the *mild forms* of the latter to a more detailed discussion. A very sound treatise on some of the early symptoms of Basedow's disease has recently been provided by I. Holmgren from the Polyclinic at the Serafim Hospital in Stockholm (directors of the Polyclinic, Edgren and Henschen). He deals principally with a manifestation of hyperthyroidism in childhood, the *increased growth* as a result of a change in ossification. This phenomenon, to which had not previously been paid any attention, but which is particularly interesting by virtue of its contrast with the retarding of growth in hypothyroidism, is treated with great thoroughness; and the final conclusions of the author, that people with mild hyperthyroidism, and hence a disposition to Basedow's disease, constitute a particular type, is correct for many cases.

Holmgren comes to the conclusion from his studies of the literature and measurements that Basedow's disease *in childhood* most probably goes hand in hand with increased height. In fact, he finds that the increase in growth takes place before puberty, after which it slows down or stops; and, as an expression of this fact, in the skeleton of the hand an earlier synostosis of the bones occurs in individuals of large stature, progressing from the distal end proximally and from the radial side towards the ulna.

It was an obvious step to the idea, as Holmgren emphasizes, that just as deficient thyroid activity interferes with growth in early life in a striking and constant way, so should increased thyroid function result in increased growth. It is particularly interesting to see that early disappearance of the epiphysial

lines marks already on X-ray the contrast with hypothyreosis in which Langhans has first stressed the long persistence of these lines in the latter conditions. The fact that greater attention has not been paid to this feature before can be explained in terms of the relatively great rarity of cases of Basedow's disease in children before puberty. I can say that I have seen a certain number of individuals of large build, even some of a remarkable height among my adult Basedow patients, but also no inconsiderable number of relatively small individuals. However, this does no harm to the value of Holmgren's investigations. For the age at which the disease appears is decisive as regards the effect on the growth in height, just as in cachexia thyreopriva. In addition, hereditary conditions also exert an influence on the size of the body. Furthermore, the secondary involvement of other vascular glands can exercise a substantial influence in this respect. We have already emphasized with regard to the pituitary that occasional symptoms of acromegaly in cachexia thyreopriva must be ascribed to concurrent disease or complementary hyperplasia of the pituitary.

What interests us most of all in Holmgren's work - since we are collecting the essential features from which small degrees of disturbance of thyroid function may be recognized early - is his discussion of the question: Is there a Basedow type from which it might be possible to infer or predict the beginning of this illness even without typical Basedow symptoms?

The definition which Holmgren gives of the ""representative case possessing the typical features of a predisposition to Basedow's disease in girls at puberty" is, on the one hand, already adulterated far too much with the frank symptoms of Basedow's disease for us to be able to find it particularly valuable for early diagnosis, and on the other hand too comprehensive if one meant to take the other symptoms for initial signs of a Basedow, and not just as a predisposition.

"Big girls, who mature early and have an early onset of menstruation, are attractive in appearance, blonde in type, with shining eyes and rich growth of hair, lively, nervous, and often unusually intelligent" certainly belong to those people who are predisposed to Basedow's disease but yet are still to be considered healthy : but if they already have, as Homgren adds, "tachycardia, tremor and struma", then they are already right in the middle of the disease.[19]

Basedow patients (we will pay more attention later to the large build than we have done so far) thanks to their rosy complexion, to their shining eyes, cheerful temperament and mental and physical liveliness, are interesting people, who draw attention to themselves; as real sanguine persons they are of use on many occasions where a phlegmatic person with less lively thyroid activity would be out of place; as a result of the way they are brought up and of the

maternal example in particular, they are either very likeable or simply impossible to deal with or discipline, so that their relatives can barely get along with them. But from what features is one to recognize that symptoms of this sort should be ascribed to pathological influences involving the thyroid?

We can give the following information about the *very early initial symptoms* in cases where Basedow's disease later breaks out clearly: the first very noticeable, decidedly pathological sign is *a great restlessness and hastiness of the thoughts* and movements which the patients are no longer able to suppress or control, like a mild chorea. They find it impossible to sit or stand quietly for long, and so are quite unable to wait for their turn to come in the doctor's waiting room. Enclosed rooms with many people in them make them agitated, the more so the warmer the rooms are. Cool air and air at high altitudes has a calming effect. Their sleep is restless and interrupted. It is very significant that after an early operation, when the patients emerge from this state of perpetual restlessness, they know for the first time in their life, as one patient said to me, what inner peace means. In addition to this there is a *striking fatigability.* They are no longer able to bear mental or physical exertion. They can no longer execute any sustained piece of work without a feeling of exhaustion.

If one gets to see patients of this sort, one is struck by the restless, shy quality in their glance, which is often combined with Kraus' *shining eye*. It may be that a prolific growth of hair is present in the very early stages, but soon the hair starts to fall out, though it does not become dry or brittle. The nails too become thin and brittle and develop white spots, but are long and smooth and the nail bed shines through intensely red.[20] The skin over the body retains a soft smoothness and delicacy. Exophthalmos is often still not present at all in these cases. In a lecture on Basedow's disease given before the Medical Society in London in May, 1906, we have stressed that very pronounced and severe cases of Basedow's disease exist which run their course without any exophthalmos, so that the name, *exophthalmic goitre,* of the English can indeed be used synonymously with Graves' disease and Basedow's disease, but is not at all appropriate for *many* cases of quite severe hyperthyroidism.

On the other hand, in cases in which exophthalmos is on the way, there is often already a *swelling, together with reddening of the lids,* while a *discolouration of the lids* in the form of slight yellowish-brown rings round the eyes is characteristic (especially in the later stages) of the cases in which the eye-ball is not protuberant.[21] Related to the reddening of the lids is the *congested appearance;* the cheeks, forehead and especially the lips are markedly reddened, the tongue is mostly quite clean, but bright red, and more commonly the veins of the face

are also dilated. It is really striking how very easily these individuals break out into a *sweat,* in particular they sweat profusely over their whole body with any mental excitement, especially under the arms, but also often only in the palms of the hands. In the same way excitement, and hence also medical examination provokes *tremor* very easily. The latter is best tested for in the hand with extended fingers, when the arm is stretched out unsupported. It is rapid, fine and regular. But it cannot always be found in the hand. There are cases in which the hand can still be held steadily, while on the contrary the extended, raised leg trembles and presents this same swift, short trembling. This is probably due to the fact that the weight of the raised leg, and hence the effort, is greater. The tongue can tremble too, as can the eye-lids if the command is given to close them gently. Also where there is no complaint of palpitations, *tachycardia* can be produced by exertion and excitement, and we consider it significant if this is very severe, reaches 120 or over and persists for a long time. Usually during the examination of the heart the red spots appear on the chest which are known as "taches cérébrales". It may turn out to be the case that more exact observations prove Holmgren right in stating that a greater percentage of the patients are fair-haired and of large build. However, Basedow patients of the same sort occur among nationalities with dark complexions and dark hair; and in families where the father and mother are not big, small individuals are also found who are already afflicted with Basedow's disease at a tender age. Indeed, the elegant, graceful build in contrast to the heavy, thickset habitus in hypothyroidism is present more regularly than are Holmgren's symptoms. In particular, bones and muscles appear slender, not bulky as they do in cachexia thyreopriva, and the hands, which are particularly valuable for forming an estimation, have fine, pointed, thin fingers which are striking. Their slender, pointed shape must be explained by the result of Holmgren's roentgenography, according to which the increased bone growth stops at the distal end first.

The Basedow habitus, as we have described it while considering Holmgren's investigations, certainly has its importance and is of great interest. But it is no more the full-blown disease itself than is a habitus phthisicus or apoplecticus. What is then the common factor among the manifestations described by us as early pathological symptoms which permits us to conceive of them as already being the start of the disease proper? It is the complete surrender to autonomic processes in the body, which can no longer be restrained, so that they seem removed from all voluntary control.

Tachycardia and palpitations, trembling, sweating, diarrhoea, hot flushes, hurrying and restlessness, changes and sometimes protrusion of the eyes all

certainly occur as a result of psychic excitement in healthy people as well, especially the so-called nervous people. But the results are related to the degree of excitement, they can be held in check by exertion and by strength of will, and they are of a transitory nature. In Basedow's disease they are *out of all proportion* to the cause of excitement, *are persistent* and are completely *beyond any control* by an effort of will.

It is very understandable that people should have preferred to think of a neurosis of the sympathetic nervous system in such cases. The sympathetic is the accelerator of the heart, it takes care of the vessels, and influences glandular secretion. But the theory of an abnormal sympathetic stimulation is difficult to develop in detail, because sympathetic stimulation, the physiologists assert, constricts the vessels - unless one wishes to join Metzner *(loc. cit.)* in supposing that in certain vascular fields it also produces dilation of the vessels, depending on the site of attack by the noxious material. If one accepts the latter, then it would be possible to find an explanation for the fact that the results of a psychical trauma do not pass away, in that it might produce an alteration in the thyroid together with, and perhaps by means of, sympathetic stimulation: the thyroid then maintains the sympathetic stimulation in turn with chemical damage which proceeds from it. It is easy to confirm that the vascular changes develop to a particularly marked extent in the thyroid itself. But a psychical trauma could also bring about the damage to thyroid secretion directly by break-down products of neural substance or by the effect of sympathetic stimulation.

Be this as it may, it is still certain that *the vascular changes* come to light *most clearly in the thyroid.*

The thyroid swelling can be very small in the early stages of the disease. Not only is the patient's statement, that it only appeared after some months, quite usual, but also doctors often cannot for a long time establish the existence of the swelling when they make their examination in the doubtful early stages. The size of the goitre is after all immaterial to the diagnosis, however much it should be taken into consideration for the prognosis. I have also seen cases (and misjudged them too in the past) in which the thyroid still seemed to lie within the normal range with regard to size, but in these one can still establish the presence of that symptom which parallels the vascular disturbances in the rest of the body, namely the changes in the blood vessels. Even a small thyroid can present exquisitely the signs of dilation and relaxation of the thyroid arteries in the form of a *systolic blowing sound over all the four arteries.* It is more important to examine this and confirm it early on than to look around to see if

a goitre is there or not. Now and again the blowing is accompanied by exquisite rustle, it is for obvious reasons generally stronger over the superior thyroid arteries, very often not equal over all the arteries and differing in strength from one side to another.

Blowing sounds over the arteries and heart readily occur when the circulation is considerably speeded up, and in chlorotic-anaemic conditions, but these well-marked sounds over the thyroid arteries occur, to my knowledge, in no other diseases except Basedow's and struma vasculosa. The question of the struma vasculosa has provoked many differences of opinion, because one does not connect any definite notion with this designation. If one merely understands under this heading a vascular dilation not occurring in other diseases of the thyroid, particularly colloid goitres and simple hyperplasias, which can be diagnosed clinically by palpation and by the auscultatory phenomenon described, then there can be no objection at all to the expression. On the contrary, one needs to be able to designate this quite specific characteristic with a short name.

The dilation of the vessels in Basedow's disease does not only refer to the larger arteries of the thyroid, but also to the other vessels and in particular to the smallest vessels. A Basedow goitre in the early stages often presents a dark-red colour, which is bluish-red with mild congestion; and every injury, however small, produces severe bleeding. The vessels are thin-walled and exceptionally easily torn - changes which make the operation so very difficult. The vascular phenomena are all the more striking if all the sounds are absent from the other vessels and from the heart too. That this engorgement with blood extending right into the capillary regions must exercise quite a considerable influence on the secretory activity of the parenchymatous tissue needs no further substantiation. But we would like to stress that here the dilation of the smallest vessels is of much greater importance than is that of the main arteries. For there are cases of struma vasculosa with very large murmuring arteries with marked blowing sounds, in which there are either no early symptoms of Basedow's disease present, or at the most only a suggestion of them. In Basedow's disease the occurrence of visibly pulsating, tortuous arteries with marked vibrations is rather by way of an exception. Naturally these cases are often especially difficult. A strong hearing pulsation occurs quite frequently, and now and again there is an exquisite expansive pulsation.

Vascular manifestations are therefore of quite particular value for confirming a diagnosis in cases where enlargement of the thyroid is either absent or small. They can regress in later stages but it is just in these cases that the thyroid

swelling comes to light in a way that has something quite different about it from other goitres. Above all in rapidly developing Basedow's disease the thyroid swelling can also develop remarkably rapidly and this rapid enlargement is very much to be heeded. For it only occurs exceptionally with ordinary goitres, as in small epidemics of goitres in barracks and schools, in pregnancy, and as a result of complications such as haemorrhages.

Apart from the vascular disorders, and occasionally without them, the *typical characteristics of the Basedow goitre* are as follows: no nodular-circumscribed swellings are formed; either the whole thyroid or a considerable portion of it swells uniformly, e.g. a lateral lobe, and now and then a middle portion in particular. The rule is that - with differences in size, it is true - both lateral lobes, the middle portion, the pyramidal process, and what is called by us the posterior lobules enlarge (vide elsewhere for the substantiation of this designation). It is really striking how well one nearly always feels the pyramidal process in Basedow goitres rising up from the right or the left in the form of a cone.

According to the size or stage (vascular abundance) the consistency is in toto either somewhat softer or firmer, but the typical feature is what we designate as the compactness of the tumour. It forms a uniform mass, like those we see in malignant goitres, especially in adenocarcinomas in contrast to the nodular goitres, in which the individual parts can be moved against each other. In addition to this the individual small lobules are felt projecting from the surface in the form of small, hard nodules, presenting in this way a coherent, coarse-grained mass. The most apt comparison seems to me to be with a lactating breast in a pregnant or nursing woman, and sometimes even with diffuse adenomas of the breast. But also where the tumour is soft and pulsating, the swelling is diffuse and uniform.

Finally the *sensitivity to pressure* must be added as a sign well worth noting. This is seldom absent in the progressive stage and may well direct attention to a peculiarity in special cases by contrast with the indolence of the colloid goitres. It can recede in the later stages, in which one always still finds the same hard, coarsely granular tumour, often without vascular manifestations, but of a particular firmness.

Unless it is possible to demonstrate some of the thyroid changes described, I would hesitate to accept the diagnosis of Basedow's disease. For it is just these vascular symptoms and the rest of the characteristics typical of the struma basedowiana (in the later stages also without the former) which safeguard the doctor against speaking of Basedow's disease in every combination of goitre

with nervous manifestations. There are certainly cases in which a goitre has nothing at all to do with nervous (especially hysterical) complaints, others in which mild hyperthyroid[22] troubles have supervened, often provoked by iodine, in the form of the so-called goitre heart; and others finally where one is dealing with struma basedowificata with quite frank symptoms of Basedow's disease, often of a severe kind.

In these cases the diagnosis can be confirmed in yet other ways. There are another two important checks, which are suitable for confirming the diagnosis very early on. One of these groups of symptoms again refers to a sympathetic excitation; we mean the so-called *lid symptoms.*

The earliest of the well-known, characteristic *lid symptom* to be present is Dalrymple's symptom, a permanent retraction of the upper lid, whose origin Landström has explained very satisfactorily together with that of the other eye symptoms by his beautiful investigations. Landström has demonstrated an organic muscle which runs forward from the equator oculi as a more or less complete cylindrical sheet, and radiates to the orbital septum and the conjunctival fornix: the uniform tonic contraction of this *muscle of Landström* must act in the opposite direction to the striated ocular muscles, especially the four recti. It draws the eye-ball forwards (exophthalmos), the lids backwards (Dalrymple's gaping of the palpebral fissure), and depresses blinking (Stellwag's infrequent blinking). It can also produce a unilateral effect, however, when there is unilateral stretching, as for example is produced on looking down by the predominating contraction of the medial and inferior rectus muscles, i.e. oppose the influence of the above-mentioned medial and inferior recti, with the lateral bundles of fibres of Landström's muscle pulling the bulb laterally on strong convergence (Möbius' sign of inadequacy of convergence), and, on looking down, preventing the upper lid from following the eye-ball (Gräfe's symptom of incongruence between the movements of the eye-ball and the upper lid). Thus all the lid symptoms can be explained. But in the initial stages the spasm of Landström's muscle is not so strong that widening of the orbital fissure (Dalrymple's symptom after Sattler), prominence of the eye-ball, infrequent blinking, lateral displacement of the eye-ball during convergence, or the best-known lid-symptom of Gräfe, lagging of the upper lid on looking downwards, necessarily have to occur.

We have now made the observation that the tendency of the above-mentioned muscle to spastic contraction can already be demonstrated quite early, if the patient is made to look straight ahead at an object and one then very *quickly* makes *brief* up and down movements with the object. Almost without ex-

ception a short, sudden contraction of the upper lid is successfully evoked then, which exposes the conjunctiva above the cornea. This symptom, often the earliest of all, the production of an *instantaneous* spasm of the organic levator palpebrae, we consider to be quite characteristic of Basedow's disease, but, of course, Dalrymple's symptom with its permanent widening of the palpebral fissure, which develops later on when the spasm of Landström's muscle has become permanent, leaves even less doubt as to the presence of a real case of Basedow's disease.

One final investigation, which very early makes a decision possible as to whether one is merely dealing with states of nervous exhaustion and nervousness with or without a goitre, with a non-progressive hyperthyreosis associated with compensatory processes, or really with the beginning of a case of Basedow's disease, is the *investigation of the blood.* We consider it essential, in order to establish the diagnosis of Basedow's disease, to investigate the fact ascertained by us that in genuine Basedow's disease a really considerable *lymphocytosis* is demonstrable, in excess of the normal by 25% to 50% and above, together with a leucopenia, i.e. a decrease in the neutrophils by 1/3-1/2 of the normal figure; and we are not inclined at the present moment to acknowledge cases of Basedow's disease unless they have, together with the combination of nervous disorders and swelling of the thyroid, either the characteristic features described above, or the thyroid swelling does show the typical results on palpation and auscultation, or at least the haematological investigation confirms that with a normal number of erythrocytes (even hyperglobulaemia is not infrequently present) and a normal haemoglobin content, the ratio of the white blood cells to one another shows a shift in the direction we have indicated. Our finding has subsequently been confirmed on many occasions.[24]

A further important clue for early diagnosis is the following. Kottmann[25] has established by investigation of our patients that additional important changes in the blood can be demonstrated by estimating the amount and rate of clotting, and the freezing point. It is characteristic of the genuine Basedow that the *coagulability of the blood decreases,* which is something that we have experienced for a long time during operations on Basedow goitres in the most disagreeable way. The blood clots more slowly and defectively than normal, in complete contrast to the thyroprival diseases in which the reverse is found. At the same time a *lowering of the freezing point occurs,* which is explained by the presence of abnormal substances in the blood as a result of the increased fibrinogen break-down; the thyroid secretion is said to have an activating effect on the autolytic ferments and to increase the products of autolysis.

It should follow from our analysis that the certainty of avoiding fatal mistakes in the differential diagnosis of Basedow's disease from related conditions has increased considerably thanks to recent research. But in order to profit from these innovations it is necessary to free oneself from the habit of wanting to diagnose Basedow's disease from the *exophthalmos.* The name, exophthalmic disease, which like so many other names is derived from a particular notable feature in the external appearance (which is not by any means constant), continues to produce an after-effect, less so perhaps in Germany than in French and English countries, where the designation of the disease as goitre exophthalmique and exophthalmic goitre is still generally in use.

Of course, it is easy to diagnose Basedow's disease in a person whose eyes are both protruding from their sockets, if he has palpitations, and a goitre as well. But he does not need a doctor to do this and even then mistakes are still possible with severe congestion of the veins. But as regards the present viewpoint concerning the early operation as therapy for progressive cases of genuine Basedow's disease, it is a question of not treating the cases in which no exophthalmos has appeared yet or where it is altogether absent, as long as possible with remedies which are partly ineffective, and partly harmful.

Tonics, mountain air and bed-rest, and carbon-dioxide baths are still relatively the most innocent methods of treatment, and often indeed the most suitable as regards preparation. On the other hand the frequently prescribed cardiac remedies help very little or not at all, staying by the sea is harmful, and iodine in the usual doses is questionable. And with all this, precious time is being lost, and the effects of the more prolonged toxic influence of the abnormal, copious flow of thyroid secretion on the organs assert themselves in a way which can no longer be put right.

Where *exophthalmos is absent,* then very often the diagnosis is, in fact, not made. And yet there are cases which progress to the most severe disturbances, and finally to death, in which at no stage is exophthalmos observed. So it is then absolutely urgent to appreciate the other symptoms properly. *Tachycardia* is perhaps never completely absent, and is on the contrary generally more strongly marked than in the majority of the other diseases with which a differential diagnosis is concerned ; and it is to be noted that the heart with a pulse rate of 120-140 for so long shows no change which might provide an explanation for this rapid action. This in particular must direct one's thoughts to Basedow's disease.

If one adds to this the *goitre* or the characteristic changes in the thyroid which we have described, and the peculiarity of the nervous and vasomotor disor-

ders, then one will seldom go wrong in the diagnosis in the long run. But it is quite especially important that lid symptoms can be present, particularly our symptom, in cases where exophthalmos never appears, and in the early stages in which the latter is not yet well marked. Why it is, that in certain cases exophthalmos is absent during the whole course of the disease, I am unable to say. It is conceivable that it was present in the early stages, but was not noticed, and that it has regressed. On the other hand the cases in which exophthalmos is absent have characteristics which make one think that they are not quite uncomplicated. I have been particularly struck by how pronounced the pigmented areas of the skin are, quite particularly the eye-lids and the area around them, so that brown rings make their appearance. As to whether special influences on the chromaffin system and the adrenals are then involved, further investigations will have to say.[26]

On the other hand one must remember the fact that the exophthalmos can be unilateral, from which one must conclude that the sympathetic is not always suffering in toto and to the same extent under the influence of the hyperthyroidism. As can happen on one side, in certain cases the stimulation of the sympathetic nerves can also fail to appear on both sides; and if we accept that Landström's muscle with its increased tone explains the exophthalmos, as it does the lid symptoms, then we understand that the former as well as the latter can fail to appear in these Basedow patients, while there can be a high degree of tachycardia, and irregularities of the pulse can occur very early, due to myocarditis, which makes any operation a questionable procedure.

It may be mentioned here that, according to Metmer's analysis, rather large doses of adrenalin provoke an arterial disorder by the destruction of smooth muscle fibres, and that they also produce *glycosuria.* We have frequently recorded the glycosuria in our case histories of these severe Basedow cases. The secretion of adrenalin is increased by the stimulation of the sympathetic nerves, and since the administration of thyroid preparations can also produce glycosuria, it was concluded by Metner that stimulation of the sympathetic nerves of the adrenals is brought about by the thyroid. In athyroid dogs adrenalin produces no glycosuria, but does so if they are fed with thyroid.

Landström's discovery that the eye symptoms are to be understood as due to the tonic contraction of a smooth muscle resulting from stimulation of sympathetic nerve fibres, gives again more prominence to the *theory of the excitation of the sympathetic system;* however, this excitation, in contrast to earlier vague views, should not be conceived of as a primary chronic neurosis, but might at the most develop as such acutely with psychical trauma in individual

cases, it would, however, principally be maintained or turned into a lasting and progressive illness by a tangible chemical substance, thyroidin, for which reason Ehrmann also speaks of *neurochemism.* The latter conception provides the most simple explanation for the most constant of all the symptoms of Basedow's disease - even when elicited experimentally (by the administration of large doses of thyroid) - *tachycardia,* for whose explanation no change can be found in the heart. How the vasomotor disturbances, which are also seldom completely absent but on the contrary play an important role, and the flushes, the outbreaks of sweating, and the inexplicable attacks of diarrhoea in the absence of other intestinal disorders can all be related to sympathetic stimulation, is something that must be clarified by physiological investigations.

Whether or not his new version of the sympathetic theory will get stronger support as the explanation of the symptomatology of Basedow's disease from further research and observations, we are still abundantly justified in asserting that lasting injury and excitation of the sympathetic system is mainly a secondary factor, and is maintained by a hormone in the thyroid secretion, which is acting in abnormal strength.[27] By basing our therapeutic efforts on the latter point, we have progressed to the stage where we prevent the grave results of pathological hyperthyroidism with almost the same great reliability with which, a quarter of a century after the cretinoid states were ascribed to hypothyroidism, we now control the improvement and cure of this disease by providing a substitute for the missing thyroid substance and thyroid secretion.[28]

However, in practice these gains will only demonstrate their good effects in full measure if doctors everywhere are able to estimate and diagnose the early stages of hypo- as well as hyper-thyroidism. This is particularly important in hyperthyroidism, because at the present time we are only able to achieve the ends reliably and quickly by operative measures, and we can only carry out this decisive therapy without danger in the early stages. The evidence for the successes of operative diminution of the secretory thyroid parenchyma in Basedow's disease has been furnished by numerous surgeons, with Rehn leading the others, especially in Germany, and recently by the Americans, Halsted, the Mayos, and Crile, and by Berg (Landström) in his latest publication; and we have already reproduced above our register of cases which includes the greatest numbers. We do not need to go into this again, but merely stress that the later the operation, the more imperfect and slow the outcome : the tachycardia regresses more slowly, and it takes much longer for a prolonged and severe exophthalmos to regress, while at an early stage the lid symptoms often

disappear rapidly. The blood picture when the disease has lasted for a long time often still shows the same anomalies a considerable time after the operation, and they may even increase for a while; but it finally returns to the normal state too when the other symptoms have been fully cured.

A few words may still be devoted prophylaxis. We have explained above in connection with Holmgren's arguments that certain individuals are undoubtedly *predisposed* to pathological disorders due to changes in the thyroid. Individuals of a phlegmatic constitution are without doubt more likely than others to fall ill with hypothyroidism; likewise people of a markedly sanguine nature are liable to be afflicted with hyperthyroidism more easily - for a simple reason, because there is reason to believe that in many cases a phlegmatic and a sanguine temperament already indicate in one case that the thyroid develops a moderate, and in the other a very lively activity. A mental and physical decrease in interest and efficiency in chronic afflictions and after a certain age is certainly sometimes related to thyroid damage, as on the other hand many forms of nervousness after psychical trauma, prolonged exhaustion of the nervous system, excessive sexual excitement, or acute illnesses are produced by an abnormally increased activity of the thyroid. Reduction of thyroid function is connected especially with telluric influences, and with the kind of nutrition; it leads to goitre, and, coupled with this, to manifestations of insufficiency.[29] On the other hand hyperactivity of the thyroid seems more connected with social influences, with political and business excitements, and, of course, with an inappropriate way of life, late nights, and affected social demands. There are quiet nations and excited nations. In our country, cases of Basedow's disease are relatively rare among the very numerous goitres, while nations without endemic goitre often produce cases of severe Basedow's disease. The modern way of life has reduced the number of cretinoid diseases and increased the number of pathological hyperthyreoses.

The significance of these *predispositions,* which are not to be considered at all pathological, may well be developed further in an interesting way with regard to individuals and nations. We will forego this and merely mention that it is to be hoped that progress in our knowledge of the great role which the thyroid plays in the development and normal existence of the body may direct the attention of wider circles to the necessity for opposing with prophylactic measures all the effects which thyroid diseases can produce. Among many imposing schemes for improving the human lot through the advances of science the magnanimous founder of the Nobel Prize also had the eradication of endemic goitre in mind. May these efforts also find on the part of the gov-

ernments and rulers of the peoples that understanding which is necessary if the requisite sacrifices are to be made.[30]

1. In my student days it was still the *exception* for a goitre operation to meet with success, so that even very skilled surgeons fully rejected it.
2. It is evident how completely unjustified was the later claim by the two Reverdins, which the French accept, that they discovered cachexia strumipriva.
3. I had previously asked for the iodine content of the thyroid on theoretical grounds, but had not been able to get a proficient chemist to produce the information.
4. Very recently Marine and Lenhart have carried out some unusually thorough studies in this field, and published them in the *Johns Hopkins Hosp. Bull.,* (1909) and *Arch. Internal Med.,* Nov.(1909).
5. Fromm *(Compt. Rend. Acad. Sci.,* 1909) claims to have been able to postpone for months with calcium and magnesium salts not only the results of parathyroidectomy, but also those of thyroidectomy, i.e. the cachexia.
6. Metzner in Bâle has produced an excellent survey of the "internal secretions" in the physiology text-book by Zuntz and Loewy.
7. Rogers, *Ann. Surg.,* Feb. (1901).
8. The investigations of Langhans and Hofmeister along these lines have been confirmed by von Wyss and Bircher Jr.
9. *Deut.* Z. *Chir.,* 101 (1909) 454.
10. One can even entertain the suspicion that a part of supposed chloroses is due to hypothyroidism.
11. Marine and Lenhart *(Johns Hopkins Hosp. Bull.,* May, 1909) also found with partial excision of the thyroid in dogs that there was not only the compensatory, active hyperplasia in the remaining half (Halsted), but that there was also occasionally a retrogressive change to colloidal glands as the animals became fat.
12. We will show elsewhere how unjustified for this reason is the procedure of a few gynaecologists of interrupting every pregnancy immediately in patients with Basedow's disease.
13. See the *Verhandl. Deut. Ges. Chir.,* (1910).
14. Halsted in Baltimore and his school (especially Crile, Gushing and McCallum) have earned special merits in the elucidation of the picture of chronic operative hypoparathyreosis. Important work in this field has been recently produced by the active assistants of the famous Viennese internists and pathologists von Noorden, Neusser, von Frankl-Hochwart, von Eiselberg and Weichselbaum, by Erdheim, Eppinger, Falta and Rudinger, and similarly by Iselin from Wilms' Clinic in Bâle, and by Fehr in Heidelberg.
15. A detailed description of the cases of hypoparathyroidism described here will follow elsewhere.
16. Thompson and Leighton have studied the results ofligature with gradual, slow destruction of the parathyroids *(J. Med. Sci.,* Vol. 19, 1908), and have made the impor-

tant finding that the symptoms of cramp do not appear, and the animals lose weight, and finally perish in a stupor.

17. For a more detailed presentation of cachexia thyreopriva, we refer the reader to the distinguished piece of work by Ewald, which appeared in the 2nd edition of Nothnagel's *Handbuch der Pathologie und Therapie,* 1909.
18. *Grenzgebiete.*
19. Holmgren could have admitted to this definition the high forehead as well, which is presumably also connected with the more vigorous growth of the skull bones and affords a contrast to the low forehead of the cretin.
20. The difference in the nails and the hair compared with hypothyroidism is often really striking: in the latter the nails are broad and short and more often curved forwards while in Basedow's disease the curve on the thin, pointed fingers is more pronounced from side to side.
21. We must reserve the occasion for discussing what differences there are between these two categories of cases, in which the participation of other vascular glands may play a role.
22. Cf. my communications concerning iodine-induced Basedow's disease, in March, 1910, at the Congress of the Deutsche Gesellschaft für Chirurgie.
23. Morbus Basedowii, Stockholm, 1907.
24. Thus by Caro *(Berlin. Klin. Wochschr.,* Vol. 39, 1908) and by Gordon and Jagic *(Wien. Klin. Wochschr.,* Vol. 46, 1908).
25. Kottmann, *Schweiz. Rundschau Med.,* Febr. (1910).
26. In view of the importance of the thyroid secretion for the level of adrenalin production in the adrenals mention can well be made also of Lewandowsky's findings which Metzner has emphasized, according to which adrenalin, in addition to producing a dilation of the pupil on intravenous injection (cats and rabbits), also produces a protrusion of the eye-ball and maximal dilation of the pupil; but that according to other authors, especially Langley, actions also make their appearance with the administration of adrenalin which indicate a stimulation of the thoraco-lumber segment of the autonomic system. These actions on organs with smooth musculature and the smooth muscle of vessels make themselves felt, sometimes as inhibitory (relaxation) and sometimes as facilitatory (contraction) effects, so that as well dilatation as relaxation of the vessels may be explained by sympathetic stimulation, may it come about as the direct effect of the hyperthyroidism or on the roundabout way of another organ with internal secretion.
27. If this interpretation should be confirmed by further research then the question might arise as to whether not a good part of the hypothyroid symptoms come about as a result of defective stimulation of the autonomic system, resp. of the sympathetic, so that the blood and lymphatic circulations as well as the secretory cells are no longer able to meet the varying requirements.
28. According to Falta, Eppinger and Rudinger it should be particularly emphasized that hyperthyroidism leads to inhibition of the internal pancreatic secretion and to activation of adrenalin production on the part of the adrenals, and that increased sympathetic tone comes about as a result of these secondary influences.

29. We refer to a work by Dr. Isenschmid, which is shortly to appear, which shows that the composition resp. histological structure of the thyroid in Alpine goitre areas already deviates in little children from that of goitre-free regions (by the sea).
30. For further information about *Basedow's disease* in the light of recent results, I draw the reader's attention to the classically thorough book by Sattler, which is just appearing in the second edition. Our own findings are assembled in the treatise by Albert Kocher. Further publications will follow presently.