On the pathology of exophthalmic goître / by George R. Murray.

Reprinted for the Author from the BRITISH MEDICAL JOURNAL,
October 3rd, 1896.

ON THE PATHOLOGY OF EXOPHTHALMIC GOÎTRE.

SECTION OF PATHOLOGY AND BACTERIOLOGY.

At the Annual Meeting of the British Medical Association in Carlisle, July, 1896.

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THE pathology of exophthalmic goître has attracted attention, and has been a subject for discussion since the disease was first described by Graves. The importance of the subject is evident, for future advances in our methods of treating the disease will largely depend upon a clear explanation of its pathology. It will, therefore, be useful to consider the subject in the light of recent experimental research and clinical observation in order to obtain a clear expression of opinion upon the main points which require further explanation.

When we examine a typical case of exophthalmic goître we find that the most prominent symptoms are the goître, the exophthalmos, the tachycardia, the various nervous symptoms, and the condition of the skin. As a natural consequence the heart, the nervous system, and the thyroid gland have each in turn been considered to be primarily at fault, and different theories based upon some observed or suspected morbid change in one or other of these organs have from time to time been advanced in order to explain the phenomena of the disease.

Few, if any, now maintain that exophthalmic goître is primarily a disease of the heart, for it is generally allowed that the cardiac symptoms are secondary to disease of either the nervous system or thyroid gland. We thus are left to consider whether the disease is really due in the first instance to morbid changes in the nervous system or in the thyroid gland.

Many symptoms which occur clearly indicate that the normal functions of the nervous system are deranged, but this is not evidence of the existence of definite changes in the structure of any part of the nervous system, as all these symptoms may well be the result of the action of some toxic agent or of some altered state of nutrition upon the nerve centres. When we examine the records of cases in which the nervous system has been thoroughly examined, we are at once struck by the fact that in many cases no lesion has been found. On comparing the accounts of those cases in which a definite lesion has been found we find that the lesions described vary considerably in different cases, though each one may be definite enough in itself.

Some have regarded the sympathetic system as at fault, on account of the character of many of the nervous symptoms, and because a slight exophthalmos can be produced by stimulation of the sympathetic. There is, however, no anatomical basis for this theory, for the changes which have been described in the sympathetic are only those which may occur in health or in other diseases.

There is much more evidence to support the view that exophthalmic goître is due to some primary lesion of the medulla. Thus Filehne[1] found that section of the anterior fourth of the grey matter of the restiform bodies was followed by exophthalmos. In some of his experiments both enlargement of the thyroid gland and exophthalmos occurred, and in one case tachycardia as well. Bienfait[2] made bilateral transverse sections through the grey matter of both restiform bodies in rabbits. This was followed by marked alteration in the cardiac rhythm and a fine regular tremor. Exophthalmos was present in rather more than one-third of the animals used, and in one-fourth of them distinct hyperæmia of the thyroid gland appeared. These experiments show that some of the symptoms of exophthalmic goître may occur as a result of interference with the normal action of the nerve centres in the medulla. In connection with these experiments an interesting case mentioned by Mannheim[3] may be referred to in which exophthalmic goître developed a few days after the onset of a bulbar hæmorrhage and improved as absorption of the blood-clot took place.

The medulla has been carefully examined in a considerable number of cases of exophthalmic goître and in some cases definite changes have been found. Thus subserous hæmorrhages were found on the surface of the floor of the fourth ventricle by Bruhl and by Lasvènes. Numerous hæmorrhages were found by Hale White in the medulla of one case; they have also been found by other observers. It is very doubtful if these small hæmorrhages are of any pathological importance, as they are not infrequently found in cases in which no symptoms of exophthalmic goître have occurred. Mendel found atrophy of the left restiform body and of the right "solitary bundle." On the other hand, Müller and others have found no signs of disease of this part of the nervous system in the cases examined by them, and Möbius states that as a rule no lesion of the medulla is found. It is thus evident that the changes which have been described are by no means constant, and so we cannot regard them as the cause of the disease.

The thyroid gland is more obviously diseased than any organ in the body of a person suffering from exophthalmic goître, and I know of no case on record in which it has been found to be normal in structure when examined after death. We shall briefly consider the changes in structure which are found and compare them with other morbid changes, the results of which are well known. Let us compare the normal gland first with one which has been rendered almost functionless by extensive fibrosis, then with one which has undergone compensatory hypertrophy, and so is in a condition of unusual activity, and finally with a gland removed from a patient suffering from exophthalmic goître.

The normal gland is composed of a number of closed follicles

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[1] *Erlanger Sitzungsberichte*, 1879.
[2] *Bulletin de l'Acad. Royale de Médecine de Belgique*, 1890.
[3] *Der Morbus Gravesii*, Berlin, 1894.

of various sizes lined by cubical epithelial cells and surrounded by connective tissue in which lie lymph spaces and blood vessels. The central part of each alveolus is filled by the colloid substance which is secreted by the epithelial cells. This secretion escapes into the lymphatic spaces, either in consequence of rupture of the wall of the alveolus or by minute channels which pass between the epithelial cells. From the lymph spaces it passes into the blood by the lymphatic vessels. The general appearance of the gland is shown in Fig. 1. Now compare this with the appearance presented by the thyroid gland of a patient suffering from myxœdema, for which I am indebted to Dr. Callcott of Gosforth. Here we see an advanced stage of fibrosis of the gland. Only three alveoli are left in the portion represented in Fig. 2, and even in them the epithelial cells have to a considerable extent

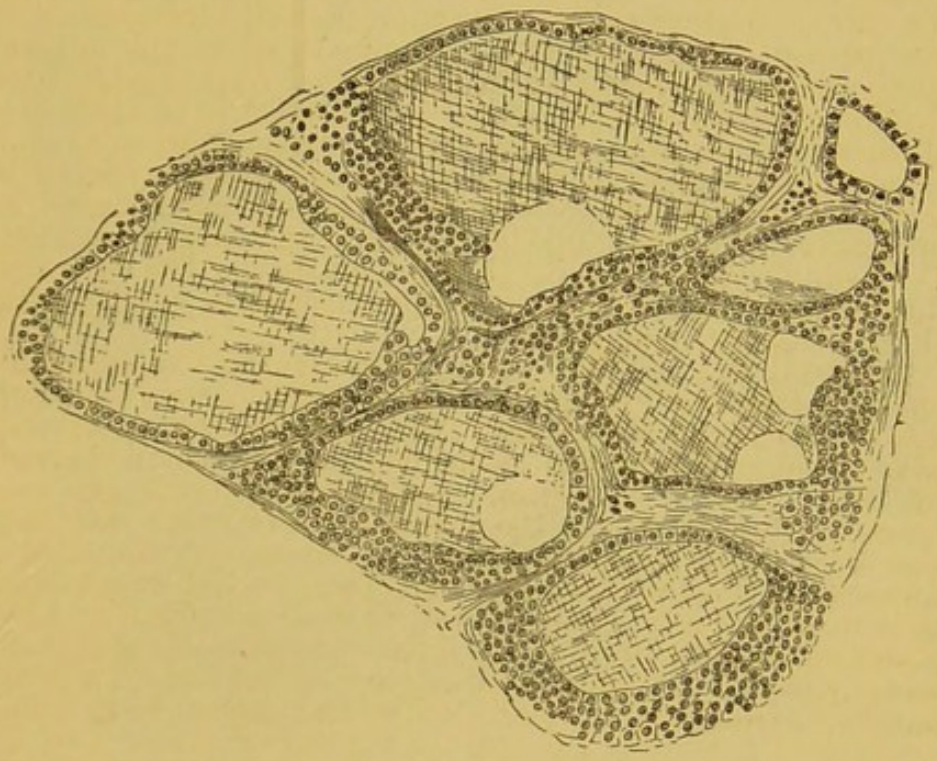

Fig 1.—Normal thyroid gland. Drawn through Zeiss obj. D. Oc. 2, with camera lucida.

either undergone partial degeneration or disappeared altogether. All the rest of the field is occupied by dense fibrous tissue and masses of small round cells. It is obvious that this gland must have been nearly functionless.

As an illustration of the changes which take place in the thyroid gland when a part of it undergoes hypertrophy so as to respond to the demand for increased secretory activity caused by the removal of the rest of the gland, we may take the following experiment[4]:—On January 5th, 1894, the thyroid gland was removed from a Rhœsus monkey while under the influence of ether. Subsequent events proved that a piece of the gland was accidentally left behind, so that instead of a complete thyroidectomy only a partial one was in reality performed.

[4] The expenses of this experiment were partly defrayed by a grant from the Scientific Grants Committee of the British Medical Association.

The wound healed by first intention, and the only changes noticed in the animal afterwards were slight hebetude, increased stupidity, and harshness of the voice. In March, 1895, fourteen months after the operation he developed general tuberculosis and was therefore killed. A piece of thyroid gland, weighing 0.42 gramme, was found on the right side, evidently a piece of the original gland which had hypertrophied. The pituitary gland weighed 0.05 gramme. Fig. 3 represents a portion of this piece of hypertrophied thyroid gland. The most important changes are: 1. The formation of new alveoli, some of which are filled by the epithelial cells. 2. Folding of the wall of the alveoli in some places so that the internal surface of the epithelium is increased in extent. 3. A change of the epithelial cells from a cubical into a columnar form. Compared with the normal thyroid gland of the monkey we have here clearly the appearances presented by a gland which

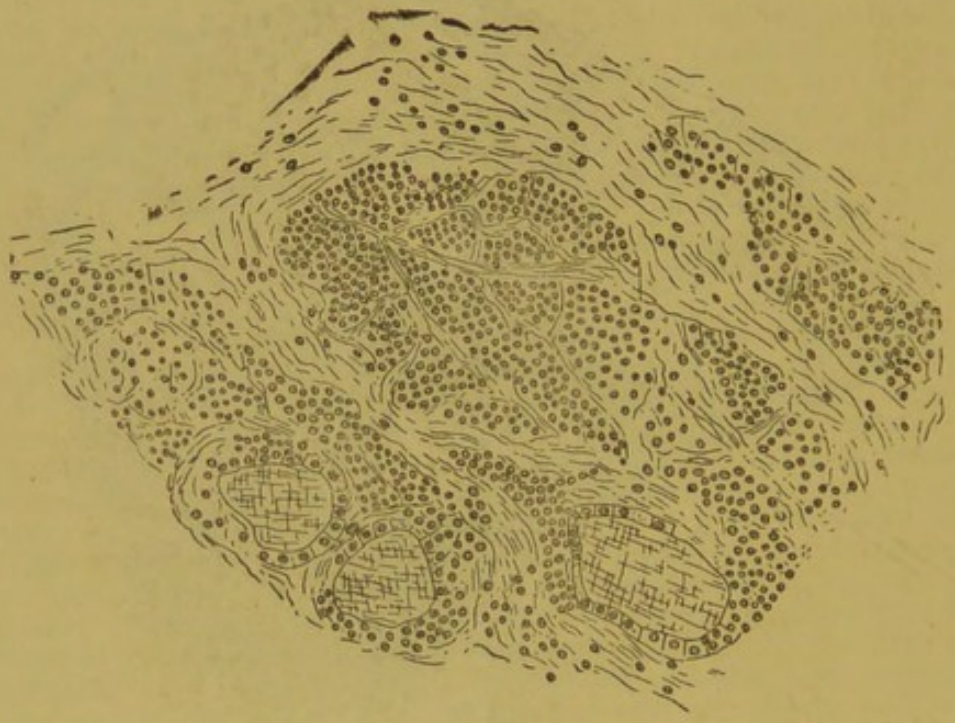

Fig. 2.—Fibrosis of thyroid gland from case of myxœdema. Zeiss obj. D., Oc. 2, camera lucida.

is working at high pressure somewhat in the same manner that the mammary gland shows signs of unusual activity during lactation.

Fig. 4 shows the changes which were present in one lobe of the gland which was removed from one of my patients by Mr. F. Page of Newcastle. There is evidently a great increase in the amount of secretory tissue as compared with that in the normal gland (Fig. 1), for the number of alveoli is increased, and in some places the alveoli are filled with epithelial cells and show no central space filled with colloid, so that in any given area of the gland there are many more secreting cells than in health. The epithelial cells themselves are also changed, for instead of being cubical they are increased in size and columnar in type. There is less colloid substance to be seen than in health; this is probably due to increased rate of removal from the gland.

On comparing these different specimens it is evident that the thyroid gland in exophthalmic goître differs greatly from the normal gland, and still more widely from the cirrhotic gland in myxœdema. On the other hand it has a strong resemblance to the portion of gland which has undergone compensatory hypertrophy and which is in a condition of over-activity. The microscopical appearances thus indicate that bulk for bulk the thyroid gland in exophthalmic goître is in a state of much greater activity than in health, and when we consider that in the great majority of cases the whole gland is considerably enlarged, it is evident that the total amount of secretion formed and absorbed may be many times greater than in health.

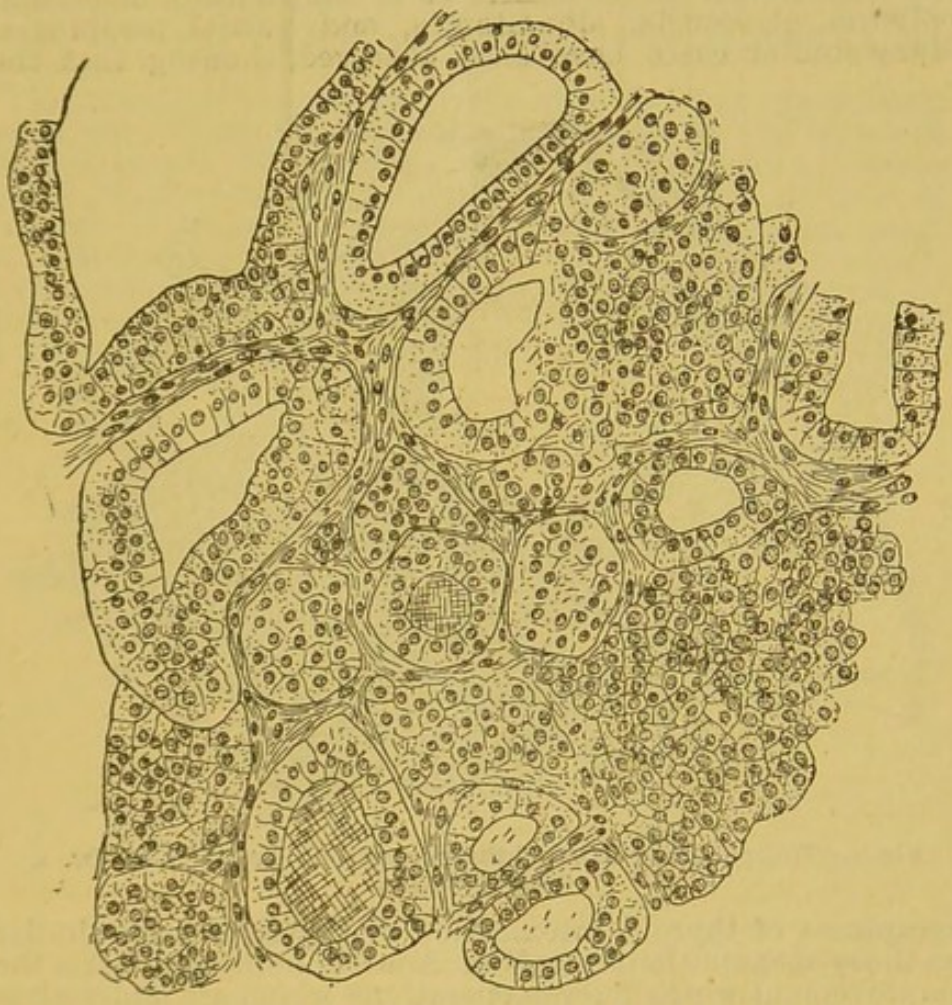

Fig. 3.—Compensatory hypertrophy of thyroid gland of monkey. Zeiss obj. D., Oc. 2, camera lucida.

We know very little about the nature of the secretion of the thyroid gland in exophthalmic goître. It is probable that it is altered in quality as well as in quantity, but this is a question which must be left for future investigation to decide. All I wish to show is that we have a satisfactory anatomical basis for the view that the symptoms of the disease are due to an over-activity of the gland. Just as the structural changes in the thyroid gland in exophthalmic goître differ as widely from the normal in one direction as those found in myxœdema do in the other, so also we find that the symptoms of the two diseases offer a striking contrast, as has

often been pointed out before by others as well as by myself.[5] The symptoms, in fact, are such as we might expect to be caused by over-activity in the gland as compared with those which we know are due to deficiency or loss of function.

Still further physiological evidence in favour of this view is afforded by the effects which are produced by overdoses of thyroid extract in cases of myxœdema and in healthy persons. Many illustrations of this have been given, so that it will be sufficient to take the remarkable case recorded by Béclère[6] as an illustration. A woman aged 31, suffering from myxœdema, took by mistake 92 grammes of thyroid gland in eleven days. The symptoms which developed were tachycardia, rapid respiration, exophthalmos, brilliancy of the eye, transient tremor of the arms, rise of temperature, insomnia, polyuria, glycosuria, albuminuria, and partial paraplegia. Many similar cases have been observed, showing that the

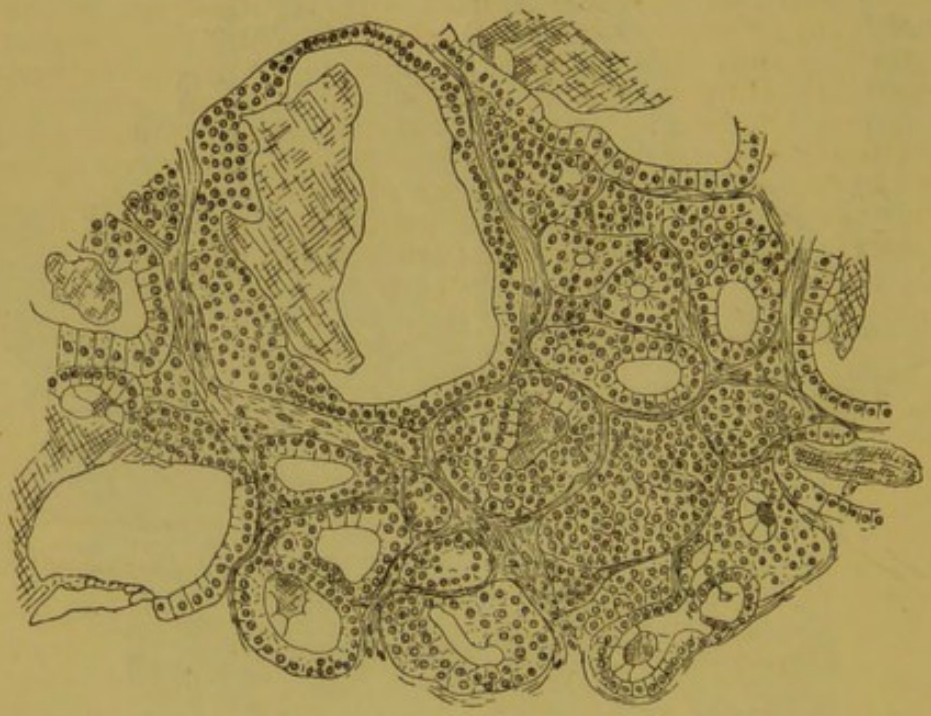

Fig. 4.—Thyroid gland in exophthalmic goître. Zeiss obj. D., Oc. 2, camera lucida.

symptoms of thyroid intoxication or thyroidism are similar to those of exophthalmic goître. Another important fact is the improvement which follows operations which are undertaken in order to diminish the secretory activity of the enlarged gland either by actual removal of a part of it or by ligation of some of the arteries which supply it. Great improvement has followed in some cases and recovery in others. I have recently seen a case which has been cured by iodine injections, a fibrosis having been set up by the iodine, which has cured the disease.

Still further evidence is afforded by those cases of exophthalmic goître, a considerable number of which have now been recorded, in which, owing to the development of fibrosis, gradually leading to loss of the function of the gland, the symptoms of exophthalmic goître have been replaced by those

[5] *Twentieth Century Practice of Medicine*. vol. iv.
[6] *La Semaine Medicale*, 1894, p. 462.

of myxœdema. In such cases the symptoms of exophthalmic goître first disappear, and it is only at a later stage that myxœdema is developed. It appears then that the progressing fibrosis is at first really curative in nature, as it lessens the activity of the thyroid gland, and the exophthalmic goître disappears. If the fibrosis progresses too far the functions of the gland become too much impaired, and more or less myxœdema is developed, according to the amount of injury done to the secreting tissue by the fibrosis.

In conclusion I would maintain that in exophthalmic goître there is an excessive formation and absorption of thyroid secretion, which may or may not be normal in character, and that the symptoms of the disease are due to the presence of this excess of secretion in the blood, and to its action upon the tissues and especially upon the nerve centres in the medulla.

The practical conclusion from this is that we should endeavour to improve our methods of treating the diseased thyroid gland. We want to be able to induce a moderate degree of fibrosis, and so imitate the natural process of recovery. Removal of a portion of the gland, though most successful in some cases, has proved to be a dangerous operation in others. Possibly injections of iodine, electrolysis, or some similar means of starting a limited fibrosis, may help us to attain the object we have in view without danger.