

is followed subsequently by attacks of asthma, but which has been recently referred to by Dr. Gee in the Lumleian Lectures, and which I have myself observed, we find that once the tendency to asthma, or the susceptibility of the vagus pulmonary plexus, be established, then some other cause—indigestion, or what not—may bring on an attack. I have not given actual cases to illustrate the causes above named, for want of space, but I have notes of cases which almost cover the whole ground, and I dare say that other observers can add to my classification.

In conclusion, may I say that I feel the time ought to have arrived long ago for asthma to be relegated to its proper position and importance in medicine, and this cannot be done until it is written down as a symptom of the diseases and conditions in whose train it follows.

[*Note.*—Since writing the above, a letter has appeared in the *Lancet*, London, May 20, 1899, from Dr. De Haviland Hall, *re* a discussion at the Laryngological Society of London, in which letter he points out the necessity of regarding asthma as a symptom.]

THE ETIOLOGY OF GRAVES'S DISEASE.¹

By GODFREY CARTER, M.B., Ch.B. (Vict.), M.R.C.P.Ed., D.P.H. (Lond.), *Fellow of the Royal Institute of Public Health, Sheffield.*

I HAVE essayed to offer a few remarks on the subject of Graves's disease, as regards etiology; not because I venture to think that I can throw any fresh light upon this unsettled problem, but because the drawing into prominence of several possible causative factors, may perchance lead us to a nearer apprehension of the truth. I assume at the outset that the pathological lesions we have to account for in this disease may be considered as being connected with either—(1) An affection of the sympathetic nervous system; (2) a toxæmia from hyper- or altered secretion of the thyroid gland; or (3) the introduction into the system of a poison from without—analagous, say, to the poison which is believed, by some, to exist in "progressive pernicious anæmia" or in "Hodgkin's disease."

In order to elucidate matters, it may be as well to make a few observations, looking at the subject from each of the points of view presented by the above classification.

Considered, then, (1) as a lesion (a semi-inflammatory lesion, I presume) of the sympathetic nervous system, I grant that

¹ Read before the Sheffield Medical Society.

there is a very close likeness between Graves's disease and, say, such a picture as is presented by a person suffering from intense terror (a condition in which the somatic nervous system is, for the time being, almost paralysed, and in which the splanchnic is unmasked, and brought into full and evident play). In such a state, to use the words of Darwin and Sir Charles Bell, "the heart beats quickly and violently, so that it palpitates or knocks against the ribs; there is trembling of all the muscles of the body; the eyes start forward, and the uncovered and protruding eyeballs are fixed on the object of terror; the skin breaks out into a cold and clammy sweat, and the face and neck are flushed or pallid; the intestines are affected. Fright, intense grief, and other profound emotional disturbances, have long been recognised as immediate causes of the disease."

Ord and Mackenzie, in Allbutt's "System," remark that "we have no knowledge that the thyroid gland ordinarily becomes enlarged under the influence of fear, but it is evident that the other chief features of exophthalmic goitre temporarily result from such emotion. That occasionally Graves's disease, in a well-marked form, rapidly follows a sudden shock to the nervous system, indicates that all the symptoms may be produced in such a way."

Another argument in favour of the nervous causation is, that Graves's disease mainly affects women, and has even been known to occur in children, down to $2\frac{1}{2}$ years of age. But upon this question of the heavier incidence of the disease upon the female sex, I shall have something to say further on.

Again, it may occur in several members of the same family. It has been observed in three successive generations. "Thus," says Ord, "it has been recorded that two sisters, their father, and two of his sisters, and his mother, were subjects of the malady. There is also the well-known case where a hysterical woman had ten children, of whom eight suffered from exophthalmic goitre, and one of the latter had three children thus affected."

I will now, for a few moments, direct attention to the second of the causes named, disease of the thyroid gland itself.

On this assumption, exophthalmic goitre is an auto-intoxication, due to the presence in the blood of an excessive quantity or altered quality of thyroid secretion; and it is only right to say that this view of the causation of disease is the one which holds the field at the present time.

The study of myxœdema has demonstrated most clearly what changes take place in the system, when thyroid secretion ceases to be elaborated. The patient shows a near approach to a vegetable existence. The administration of thyroid extract rapidly transforms the state; and those who have witnessed the

effects of over-dosage, as I have done, will have observed vomiting, headache, and violent pains in the limbs, rapid pulse, and flushed skin—and, indeed, some degree of approach towards the symptoms of Graves's disease. The coarse and minute changes which are found in the thyroid, in exophthalmic goitre, are very marked and very interesting; there is enlargement in most cases, and this enlargement is not only a hyperplasia, but is associated with a true new formation of the secreting structure of the gland. In the words of Ord and Mackenzie, "on microscopic examination, the striking feature is the great increase of secreting structure. The secreting structure, moreover, is not merely increased, but it is much altered. The epithelium lining the vesicles is changed in form, from the cubical to the columnar type; there is increased proliferation also, so that the lining membrane becomes convoluted, and papillary projections into the spaces are commonly seen. The secretion contained in the vesicles is more mucous than the ordinary colloid, and stains much less deeply. Desquamation of the epithelium is not uncommon, so that the vesicles contain detached columnar cells. In addition to the changes in the vesicles, there is the production of a great number of newly formed tubular spaces, lined by a single layer of cubical epithelium." "These columns," as Greenfield points out, "closely resemble the tubules of a secretory gland. At a later period the gland may become firmer from the growth of fibrous tissue, and the proliferation changes may be obscured." "Edmunds has shown the great similarity between the gland tissue in exophthalmic goitre and that in an animal which has had a large portion of the thyroid removed by operation. From this he infers that the alteration in the thyroid gland in Graves's disease is of the nature of compensatory hypertrophy."

Greenfield has pointed out the resemblance in appearance of the goitre to a salivary gland. The goitre, according to him, "bears the same relation to a normal gland that the mammary gland during lactation bears to the quiescent gland."

Before considering the third and last view of the etiology of Graves's disease, I think it would be well to state briefly the objections which can be urged against either of the two theories, so far advanced.

As against the sympathetic nerve lesion hypothesis, it may be objected, in the words of Ord and Mackenzie, that "alterations in the sympathetic have been described by some pathologists, but it has not been shown that the changes are in any way peculiar to exophthalmic goitre. The sympathetic ganglia, it is true, in some cases, have been found diseased; but this is not a constant feature. Only some of the symptoms of exophthalmic goitre can be explained by affection of the sympathetic, and it is impossible to formulate a satisfactory theory of the malady on

this basis. The derangement of the emotional nervous system will explain a good deal, but does not account for the enlargement and over-activity of the thyroid, nor for the persistence and hypertrophy of the thymus."

I believe this hypertrophy of the thymus to be a very constant factor in Graves's disease. Osler writes: "No constant changes have been found in exophthalmic goitre. Special attention has been paid to the condition of the sympathetic nervous system, but neither in the ganglia nor in the nerves are there any changes which can be regarded as constant and peculiar. The vascular and nervous features might be due to a lesion of the nervous system, but it is difficult, on any theory, to explain all the symptoms of the disease, and to bring into line the mental and vascular phenomena, the exophthalmos, and the goitre."

Now, as to the thyroid gland theory. Under what stimulus does the gland become enlarged? Not from excessive blood supply due to vasomotor changes, because the typical symptoms may be evident before the gland has had time to enlarge; it has been shown that the increased vascularity is principally superficial; and Dr. Greenfield observes that in cases examined by him there has been no increase in vascularity of the gland itself, but rather a diminution."

Coats says: "The condition of the thyroid gland is only part of the morbid phenomena, and shows no constant lesion after death. It has been found hypertrophied, or abnormally vascular or cystic, but also, in many cases, normal." He goes on to say: "The suggestion has been made that the disease is due to a hypertrophy of the thyroid, whose excessive secretion leads to the symptoms, but this view has not been confirmed."

Ord and Mackenzie state that "we think the facts of the case suggest that the thyroid condition is, at any rate, not the primary cause of the disease"; and again (a most important consideration), "If over-activity or over-secretion of a hypertrophied thyroid gland were the whole disease, it ought to be possible to produce it by the administration of large quantities of thyroid gland. No one has yet succeeded in causing exophthalmos in this way." "It is here," continue Drs. Ord and Mackenzie, "that the hypothesis that the disease is due to over-action of the thyroid gland fails. The supporters of this hypothesis have therefore fallen back on another surmise, namely, that not merely is the gland over-active, but that its secretion, besides being increased, is also perverted. Of this we have at present no absolute proof." "No explanation has yet been given of the relation of the persistent thymus to the disease."

It will be seen from the foregoing that the pathology of

Graves's disease, and consequently the etiology, is still the subject of uncertainty, and I now pass on to the third and last hypothesis suggested, namely, that of absorption of a toxin from without, or possibly a protozoon. The only reference I can find to this view is in Allbutt's "System," where there occurs the following brief note:—"Some have looked upon Graves's disease as an intoxication."

"Progressive pernicious anæmia" is now classed by such great pathologists as Coats, for instance, as being probably due to the absorption of an intestinal toxin, and Hodgkin's disease is classified amongst the "infective tumours," yet the actual infective agent has never been demonstrated.

Leukæmia is linked with the last named in causation; and note some of the secondary changes found in these diseases.

In addition to involvement of the spleen (which under the present line of argument would be held as analogous to the enlargement of the thyroid in Graves's disease), there are enlargements of lymphatic glands of the liver, of the closed follicles of the intestine, and round-celled infiltration of the kidneys. Hodgkin's disease is spoken of as "an infective disease, having some analogies with tuberculosis, but limiting itself much more to the lymphatic system" (Coats). In it metastatic new formations are found in many organs, and possessing the structure of lymphadenomata.

Coming nearer, we find *simple* goitre now spoken of by Coats and others as "ascribed to an unknown miasm." Whitelegge, in his work on "Hygiene," says "that the agency of some organic material is necessary." Prof. Grasset has communicated the results of a study, extending over ten years, of persons suffering from goitre in one department of France alone. In that region there are places where the disease is endemic, and others where it is entirely unknown.

The affection is observed to develop after menstruation, childbirth, emotional disturbance, or a chill; often it appears consecutively to a slight fever or an attack of gastritis. From these facts Grasset concludes that goitre is a general disease with a dominant local symptom, to wit, the enlargement of the thyroid gland. This feature of the affection he regards as analogous to the enlargement of the spleen characteristic of malaria. He points out that both diseases have a special geographical distribution, both affect a gland with internal secretion, and both end in cachexia. In the blood of eight patients suffering from recent goitre (ten to fifteen days), Grasset found special parasitic elements. He describes these as spherical bodies, larger than blood corpuscles, having no nucleus and containing red pigment. Each has a free flagellum four times as long as a red blood corpuscle. There are also segmented bodies, agglomerated or separate; and, lastly, there is a body of irregular contour containing red pigment but no nucleus.

These elements recall the hæmatozoa of Laveran, from which, however, they differ by the presence of the pigment, and the absence of crescentic bodies. None of the goitrous patients whose blood was examined was the subject of malaria, or has since become affected with that disease. All this is a great change from the teaching of a little while ago, when goitre was described as being due to an excess of calcic and magnesian salts, iron pyrites, etc., in drinking water. And I am by no means certain that simple goitre is the simple local disorder it is generally supposed to be. Coats says: "The lesion is primarily an increase of the normal gland. In other cases the new formed tissue is discontinuous, occurring in the form of isolable tumours, in the midst of the gland. To this form the name of adenoma is given. In both forms the tissue is liable to colloid degeneration. A few cases are on record in which secondary tumours developed, chiefly in the bones. In a case observed by Coats there were several such tumours in the bones of the skull, which presented the typical structure of the thyroid gland."

Exophthalmic goitre shows some very wide circles of diffusion, which suggest its being a general disease. Urticaria is a prominent symptom in acute cases, and so sometimes is mania; then epistaxis, œdema of conjunctivæ, fleeting œdemas, or even general anasarca with effusion into serous cavities, diplopia on lateral movement of the eyes, pulmonary, intestinal, meningeal, and cerebral hæmorrhages have been recorded by Trousseau. Anæmia is a marked feature, and points to some grave blood deterioration. Often there is cough and dyspnœa. "Acetonæmia has been observed" by Dreschfeld "in connection with the attacks of persistent vomiting." "With vomiting also may be intense prostration and restlessness, and the dyspnœa or air hunger observed in diabetic coma" (Allbutt). "Such latter symptoms generally forebode a fatal issue." Intermittent albuminuria has been noted by Begbie and others. Then headache, cramps, and feebleness of the lower extremities, almost amounting to paraplegia, have been noted in some aggravated cases of the disease. If we add to these occasional manifestations, the history of some of the very acute cases of Graves's disease which have been recorded, I think it must be borne in upon all of us, that it is at least possible that we have to do with an infective disorder of external origin. Osler says: "Two rapidly fatal cases occurred at the Philadelphia Hospital, one of which had marked cerebral symptoms. A patient of Mr. Lloyd's, a woman, æt. 39, who had been considered perfectly healthy, was suddenly seized with intense vomiting and diarrhœa, rapid action of the heart, and great throbbing of the arteries. The eyes were prominent and staring, and the thyroid gland was found much enlarged and soft. The gastro-intestinal symptoms continued, the pulse became more rapid, the vomiting was incessant, and the patient died on the third day of the illness." This at least is a picture of acute

poisoning, and it was a case of Graves's disease. As I have drawn an endemic disease like simple goitre somewhat pointedly into my remarks, and have, moreover, insisted upon its organic miasmatic origin, it may be pertinently asked, Do we see any parallelism between the two? "Is exophthalmic goitre also predominant in certain localities?" Yes, it certainly is; although the disease, being a comparatively rare one, is not so easily dealt with for purposes of localisation geographically. Ord and Mackenzie say, "It appears that some localities furnish more cases than others." Thus certain parts of Kent, Surrey, Wiltshire, and the Thames valley have produced a relatively large proportion of cases under our observation (the writers are London men). But they add, "In districts where ordinary goitre prevails, the exophthalmic form is also met with." If this be so, we should naturally expect that in the northern midlands it would be not infrequent. Sheffield borders close upon Derbyshire, and is a centre towards which obstinate medical cases from that county would tend, in some measure, to gravitate for advice.

I therefore asked some of my colleagues if they found the disease coming up for treatment frequently here. The answer was, "Yes, frequently." Personally, I was first set thinking about this matter by observing, some years ago, that in a certain valley in the West Riding, where the inhabitants on one side of the river drank water from hills to the south, and those on the other side water from uplands to the north, that the latter suffered a good deal from goitre, while the former escaped. This was very noticeable, and what was more, from the affected side (as I will call it) came several cases to me of Graves's disease.

I believe it is by no means an unknown thing for a person to begin with simple endemic goitre, to persist with it for a considerable time, and then to drift into the exophthalmic form.

I have only one more point to touch upon.

A strong argument in favour of the sympathetic nervous causation of exophthalmic goitre, is its undoubted greater frequency in women. If due to an external agency infecting the system, why should not men suffer equally? But why do women show by far the greater incidence of cases of simple goitre, which all agree results from an imbibed miasm? Pugin Thornton¹ notes this and offers an explanation.

He says: "Women in this country are much more liable to suffer from bronchocele than men;" and he adds, "Perhaps it is on account of their being more frequently water-drinkers, for in India it has been noticed that both sexes suffer alike." Certainly in Britain we see more cases of Graves's disease in women than in men. Ord and Mackenzie put down the proportion as 5 to 1. But in France, Charcot speaks of the disease as being only a

¹ Quain's "Dictionary of Medicine."

little less frequent in men than in women, and in Germany Eulenburg gives the proportion "as one male to two females." I should be extremely interested to hear if any partiality for sex has been observed in those rare cases where exophthalmic goitre has been found in children.

I have myself only had three cases of Graves's disease altogether of late years. Two were in women, one in a man. And I may add that, in this latter, which was a very severe case, there never was, nor is now, the slightest observable enlargement of the thyroid gland.

I would not have it to be inferred for one moment, that I am writing in the capacity of an exponent of some but slightly hitherto considered view of the causation of Graves's disease. I do not wish and I do not feel competent to do that. I have had no special facilities for investigation.

No doubt all the hypotheses touched upon have been well and fully considered by those most competent to judge.

All have hitherto been found wanting; and so remain. I have endeavoured to state impartially and fairly the different arguments pro and con, according to whichever view I have been discussing. The object of my remarks is to draw attention somewhat from the stereotyped acceptance of views as regards the etiology of Graves's disease, which have found their way into all text-books, but which have only been tentatively accepted by the profession, and to ask your readers to keep open minds upon the aspects of this problem, and consider if there is any likelihood of truth in the third and less accepted view as to the causation of Graves's disease which I have placed somewhat in detail before them.

CLINICAL RECORDS.

AN UNUSUAL CASE OF ASCITES.

By JOHN DOUGALL, M.D., F.F.P.S.G., *Professor of Materia Medica, St. Mungo's College; Physician and Lecturer on Clinical Medicine, Royal Infirmary, Glasgow.*

CASE.—W. W., æt. 30, sett maker, *i.e.* dresser of stones for street causewaying, was admitted to Ward 1 of Glasgow Royal Infirmary on 14th October 1898, complaining of pain and swelling of his abdomen of six months' duration.

Family history is unimportant. His father died of enteric fever, æt. 58; his mother is alive and well, æt. 51. Patient is the eldest of a family of six—three brothers and two sisters, all living and healthy. He is ruddy featured, fairly well nourished, and has no appearance of one suffering from any organic disease. He had enteric fever when 8 years old, and frequent bilious attacks during the following ten years.