way mutually exclusive. What we term a disease is not an entity but a chain of interlinked events a few of which are faintly illumined here and there by the dim and flickering light of partial understanding. It is the physician's business to break this chain at some point along its course and thus free the patient from the inexorable development of his lesion. In this connexion recent vindications of the observational method, reinforced by the revolutionary contemporary techniques of statistics and epidemiology, are surely no less dramatic than the triumphs of the laboratory. The relation of maternal rubella to developmental defects, of cigarette-smoking to lung cancer, or of parity, sexual habits, and religion to carcinoma of the cervix uteri are contributions of basic biological significance, while by illuminating causation they point the way clearly to prevention and control.

Many such aetiological factors must lie buried in the histories of our neurological patients. But the weakest link in the chain is not always at its beginning, and the clinical scientist whose studies are devoted to mechanisms of symptom-production can justifiably point to many instances in which it is his investigations which have led to the effective control of disease by interrupting the pathogenetic sequence at some later stage in its course. After all, both alkalis and gastrectomy are more generally effective in the treatment of peptic ulcer than psycho-analysis, the initial lesion of diabetes mellitus remains veiled in mystery despite the adequate control of the disease which can be achieved with insulin, and modern anticonvulsant drugs will control many cases of epilepsy in the genesis of which the respective contributions of genetic and environmental factors remain at present entirely obscure.

LYMPHADENOID GOITRE (HASHIMOTO'S DISEASE)

A CLINICO-PATHOLOGICAL STUDY

BY

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Following the pioneer work of Roitt *et al.* (1956), the pre-operative diagnosis of lymphadenoid goitre may now be made with some precision. A series of cases is presented with a view to defining with like precision the histological features of the thyroid gland in this condition. At the same time the clinical features are described and the treatment and aetiology of the disease are discussed.

Present Series

The series consists of 33 cases of lymphadenoid goitre and represents all patients with this disease operated on at the Middlesex Hospital by the surgical staff over the last twenty years. It should be pointed out that the criteria on which inclusion in this series was based were strict; consequently a further 20 cases, whose claim to inclusion was the presence of lymphocytic infiltration in the thyroid gland, have been excluded. In addition a small number of patients not operated upon, but whose diagnosis has been confirmed and who have been treated medically, are discussed.

During the period 1935-55 2,141 thyroidectomies were done at the Middlesex Hospital, which represents an incidence of lymphadenoid goitre of 1.54%. Our impression is that this figure is too low and stems probably from the fact that most of these thyroidectomies were undertaken for toxic goitre.

In 1937 McClintock and Wright were able to identify a total of only 50 cases in the world literature, while

Joll (1939) found an incidence of 0.9% in 5,650 thyroidectomies. More recently Heptinstall and Eastcott (1954) described an incidence of 2.7%. If the figures for thyroidectomy at the Middlesex Hospital be

FIG. 1.—Age distribution in 32 cases of lymphadenoid goitre.

examined over the last five years the incidence of lymphadenoid goitre rises to 2.6% in 660 thyroidectomies.

Age.—Lymphadenoid goitre characteristically affects middle-aged women. Our youngest patient was 37 years and the oldest 73, with an average of 51 years (Fig. 1). This age incidence agrees closely with that found by other authors. The disease may, however, rarely occur in childhood; for example, Statland *et al.* (1951) describe two cases in girls of 10 and 14 years, the latter having had a goitre since the age of 6.

Sex.—In all series described there is an overwhelming preponderance of female patients, the incidence being over 95%. We have only one example of lymphadenoid goitre occurring in the male, a doctor of 64. Likewise Marshall *et al.* (1948) describe only one male case in a series of 78 patients.

Symptoms

The Goitre.—A swelling in the neck has been noticed by the patient in all cases, but the duration of history varies widely from as little as one month in one case up to 35 years in another. However, the simple average in our cases is 2½ years; this is a fairly representative figure of the duration of the goitre before medical advice is sought. We have doubts, which are expressed below, whether the few patients who give a history of goitre of many years' duration have in fact had a lymphadenoid goitre during all that time.

Discomfort in Neck.—This is a common symptom, and appears to be a characteristic feature of the disease, occurring more commonly with lymphadenoid goitre than with colloid goitres of comparable or larger size. Over one-third of our patients complained of a feeling of discomfort and tightness in the neck, not amounting to pain but nevertheless a constant annoyance, particularly when lying prone. In only three cases was the onset of the goitre marked by definite pain in the neck, although seven patients had noticed pain and tenderness in the goitre at various times. Headache was not uncommon and was complained of by one-third of the patients.

Thyroid Deficiency.—Gross myxoedema is uncommon, but one-third of the patients volunteered the information that their voice had become hoarse, and this feature corresponds broadly with those who showed other signs of thyroid deficiency. In two such patients a recurrent laryngeal nerve palsy was suspected, but laryngoscopy demonstrated only

thickening of the vocal cords with a full range of movement. Lassitude is a common complaint, and a change in weight, usually but not necessarily a gain, was mentioned by 10 out of our 33 patients.

Pressure Symptoms.—Major effects due to pressure by the goitre are rare, but minor degrees of *dysphagia* are not uncommon, being manifested as a discomfort on swallowing rather than by any hold-up. In one patient the goitre was largely intrathoracic, and she complained of severe choking and breathlessness, especially on lying down. *Breathlessness* is an uncommon complaint, although moderate degrees of tracheal deviation and narrowing are often seen on the x-ray films. *Venous obstruction* is sometimes present, and occurred in three patients in this series. A useful test for unmasking early venous obstruction may be carried out in the following way. The patient is asked to hold the arms above the head; the change of posture at the thoracic inlet may then result in immediate and visible engorgement of the external jugular veins, together with congestion, flushing, and even swelling of the face if the obstruction is severe. One such patient volunteered the information that she had suffered flushing and swelling of the face, often followed by a headache, whenever she raised her arms to comb her hair.

A characteristic but inexplicable feature of the disease is the way in which all the symptoms tend to fluctuate in intensity and to vary from time to time.

Examination of the Goitre

The goitre itself is usually firm and symmetrical, with an average weight of about 100 g. As Joll (1939) points out, the enlargement affects every part of the gland, and any asymmetry is presumably due to pre-existing asymmetry of the thyroid. The pyramidal lobe invariably takes part in the enlargement when it is present, and is readily palpable, sometimes the effect being that of a trilobed goitre. The amount of fibrous tissue in these goitres varies, and so, therefore, does their consistence on palpation, a few being hard enough to suggest malignant disease. The fibrosis is responsible, when pronounced, for the characteristic bosselation of the gland surface. The enlarging lateral lobes push the carotid arteries backwards and laterally, where they may be palpated; and not infrequently these lobes pass behind the oesophagus to meet one another in the midline, forming the so-called "ring" or circular goitre. The gland moves freely on swallowing except in so far as it may be hampered by its size or shape.

Assessment of Thyroid Function

Most patients with lymphadenoid goitre have a depressed thyroid function. This amounts to frank myxoedema in about one-fifth of the cases. Of the remainder one-half can be clinically suspected of hypothyroidism, while the others are apparently in an euthyroid state.

It should be mentioned that some patients have clinical features which may lead the unwary to an erroneous diagnosis of thyrotoxicosis. Symptoms such as loss of weight, irritability, and tremor are sometimes described by the patient, but objective signs of thyrotoxicosis are lacking, with a normal pulse rate and cool hands. It should be remembered that the hypothyroid patient may be as irritable as her thyrotoxic neighbour, and that a depressed thyroid function may, by depressing appetite, particularly in the early stages, engender loss of weight.

Laboratory Investigation

Basal Metabolic Rate.—This is usually lowered or is at the lower limit of normal. For reasons discussed below we do not hold the view that lymphadenoid goitre *cannot* follow thyrotoxicosis, though it apparently rarely does so: in such a case the B.M.R. may be estimated at a time when it is falling from the hyperthyroid to the hypothyroid range (an inevitable result of the lymphadenoid reaction) and so be

found still raised above the normal. In this series the B.M.R. was determined pre-operatively in 24 patients. The Robertson-Reid scale, with a stated normal range of -15% to $+15\%$ has been used at this hospital for the past five years. The B.M.R.s of 10 patients whose rates were determined on the Robertson-Reid scale have been converted to the Aub-Du Bois standard (Fig. 2), which was in use prior to 1952.

FIG. 2.—Basal metabolic rates (Aub-Du Bois) of 24 patients with lymphadenoid goitre.

Serum Cholesterol.—This is a poor index of thyroid function, but, in the absence of concomitant conditions such as pregnancy, diabetes, renal failure, severe anaemia, etc., may be used as a rough test for myxoedema, being a less tedious, though less accurate, assessment of thyroid function than the B.M.R. The serum cholesterol was determined before operation in eight patients in this series. The values ranged from 156 to 380 mg./100 ml., four of the eight lying above the normal range (150 to 250 mg./100 ml.).

Radioactive Iodine Studies

Radioactive iodine investigation has been carried out on eight patients in this series. The results show a considerable uniformity. In most cases the 24-hour uptake level in the gland is raised to about 50% of the dose administered (Table I), a level which is generally regarded as lying at the

TABLE I.—Radioactive Iodine Studies in Eight Patients With Lymphadenoid Goitre, Showing 24-Hour Uptake as a Percentage of Test Dose

Case No.	Uptake	Case No.	Uptake
13	50.4%	22	35%
14	48%	31	57%
20	60%	32	52%
21	33%	33	42.4%

upper end of the normal range or within the lower range of overlap with toxicity. The probable explanation of this paradox is discussed below.

Urinary excretion figures are complementary to the high uptake and lie in the region of 30%.

The topographical surveys showed isodose curves evenly distributed over the goitre, corresponding accurately with the palpable enlargement; and indeed we regard a localized uptake or absence of uptake from a major part of the goitre as evidence against a diagnosis of lymphadenoid goitre (Figs. 3 and 4).

The 48-hour plasma radioactivity was determined in one patient (Case 32). The protein-bound fraction was found to be 0.66% of the administered dose per litre of serum, a figure which lies unequivocally in the toxic range (Silver *et al.*, 1955). However, clinically she was *hypothyroid*, with a B.M.R. of -25% .

The probable explanation of this apparent paradox and also of the slightly raised 24-hour uptake in the gland depends on the level of the thyroidal iodine pool, which is known to be low (Skillern *et al.*, 1956). The administered test dose of ^{131}I represents, therefore, a larger proportion of the iodine which is available for synthesis of thyroglobulin than in the normal or thyrotoxic gland. Consequently a larger proportion of the circulating thyroid hormones will

be labelled with ^{131}I . This is probably not the only explanation of these phenomena, and it seems likely that over-activity of pituitary T.S.H. also plays a part.

FIG. 3.—Topographical survey of Case 20 with outline of palpable goitre superimposed on isodose curves.

FIG. 4.—Topographical survey of Case 33 with outline of palpable goitre superimposed on isodose curves.

Precipitin Reaction and Other Tests

Though still in an experimental stage, the precipitin reaction is now being developed as a specific test for lymphadenoid goitre. Roitt *et al.* (1956) have shown in a preliminary communication that the serum of patients with lymphadenoid goitre contains a circulating antibody which will give a precipitin reaction with thyroglobulin as the antigen. The test has been performed in only three cases in this series, all showing a strongly positive result.

Other tests, less specific than the precipitin reaction, which reflect, nevertheless, the presence of a raised γ -globulin, and which may provide contributory or even diagnostic evidence, are:

1. **Plasma Protein Electrophoresis.**—The electrophoretic pattern demonstrates the presence of a raised γ -globulin level (Figs. 5 and 6).

2. **Flocculation Tests.**—The flocculation tests (thymol turbidity, zinc sulphate, and colloidal gold) show high values reflecting the alteration in the plasma protein, and typical results in four cases were (units):—Case 1: thymol turbidity, 9; zinc sulphate, 21. Case 32: thymol turbidity, 15; zinc sulphate, 19; colloidal gold, 5. Case 33: thymol turbidity, 12; zinc sulphate, 29; colloidal gold, 5. Case 13: thymol turbidity, 10; zinc sulphate, 12; colloidal gold, 4. (Normal values: thymol turbidity, 0–4 units; colloidal gold, 0–1 unit; zinc sulphate, 0–12 units.) Even if facilities for protein electrophoresis are not available the finding of abnormal flocculation tests in a hypothyroid woman with a firm symmetrical goitre is almost diagnostic of lymphadenoid goitre.

3. **Erythrocyte Sedimentation Rate.**—This is usually raised in patients with lymphadenoid goitre. However, it is so non-specific as to be of little value as a diagnostic test. Its interest lies in the fact that the raised E.S.R. is due to the presence of the abnormal γ -globulin, and it was the E.S.R.

which provided the first clue which led Roitt *et al.* (1956) to the discovery of the antigen-antibody (precipitin) reaction. Nevertheless a raised E.S.R. may be of some help in diagnosis when biochemical facilities are not available, and, conversely, we believe that a normal E.S.R. is evidence against a diagnosis of lymphadenoid goitre. The E.S.R. was determined pre-operatively in eight of our cases (Table II).

TABLE II.—E.S.R. (Wintrobe—correct to P.C.V. 45%) (Normal 0–10 mm.)

Case No.		Case No.		Case No.	
1	16 mm.	20	58 mm.	31	39 mm.
6	38 "	22	27 "	33	77 "
13	40 "	30	15 "		

FIG. 5.—Protein electrophoretic pattern demonstrating the raised γ -globulin level in lymphadenoid goitre.

FIG. 6.—Protein electrophoretic tracing demonstrating the raised γ -globulin level in lymphadenoid goitre.

Radiological Examination

Plain x-ray films of the thoracic inlet demonstrate that minor degrees of tracheal deviation and compression occur commonly. Radiological studies were carried out in 25 of our patients, and 15 of them showed tracheal deviation or compression. In three of these the airway appeared sufficiently obstructed radiologically to provide the reason for operation. Retro-oesophageal extension of the goitre, with mild distortion of the oesophagus on barium swallow, was seen in three patients. In only one patient was there a true intrathoracic extension of the goitre.

Reasons for Operation

(1) **Suspected Malignancy** (11 cases).—This was the most frequent reason for operation, and arose particularly when the goitre was of short duration or had increased rapidly in size of recent months. The occasional real hardness of

the gland, as opposed to mere firmness, was another factor leading to a suspicion of cancer. In addition three cases showed marked clinical enlargement of the regional lymph nodes; so great was this enlargement in one case, which showed a chain of firm, rubbery glands extending up to the angle of the jaw on one side, that a block dissection of the neck was carried out at the same time as the thyroidectomy. Section of these glands showed non-specific reactive hyperplasia only. (2) *Pressure*: on trachea in 6 cases, on oesophagus in 2, on veins in 2. (3) *Cosmetic*: 3 cases had large ugly goitres. (4) *Discomfort in neck*: 3 cases. (5) *Pain in neck*: 2 cases. (6) *Diagnosed as thyrotoxicosis*: 1 case. (7) *Undetermined*: 9 cases.

Treatment

Thyroid Extract.—Evidence is accumulating to show that lymphadenoid goitre can be effectively treated by the administration of thyroid by mouth. Thus Heptinstall and Eastcott (1954) comment on the improvement which may follow the administration of thyroid to these patients. Statland *et al.* (1951) remark on the efficacy of thyroid in preventing regrowth of lymphadenoid goitre after operation and consider that it may be a useful form of primary treatment. They describe two cases in which goitres resolved completely on thyroid treatment, following a biopsy which confirmed the diagnosis. Six patients in our present series received pre-operative treatment with thyroid extract in doses varying from $\frac{1}{2}$ to 2 gr. (32 to 130 mg.) daily. In only two of these was medication sufficiently prolonged or in dosage high enough to constitute a genuine attempt at treatment with thyroid extract. The results are interesting (Table III).

TABLE III

Case	Medication	Results
13	2 gr. (130 mg.) daily ? time	Voice became clear; gland smaller and softer; pain in neck relieved
14	1 gr. (65 mg.) daily for 6 months	Some resolution in size of gland
19	1 gr. (65 mg.) daily ? time	Gland became smaller
23	$\frac{1}{2}$ gr. (32 mg.) daily for 1 month	Gland became softer
32	2-3 gr. (130-200 mg.) daily	Goitre became much smaller and neck circumference fell from 14 $\frac{1}{2}$ to 12 in. (30 to 37 cm.) in six weeks
33	1 gr. (65 mg.) daily	Patient failed to co-operate in treatment

Cases 13 and 32, who received 2 gr. (130 mg.) of thyroid daily, responded very favourably to treatment. It may be asked, therefore, why they were operated upon. However, in Case 13 the goitre was large, and it was not then appreciated that treatment with thyroid extract, in order to prove effective, must be continued for many months. Case 32 was a psychoneurotic patient who would take her thyroid tablets only in spasmodic and brief bouts in enthusiasm.

During the last two years I have been associated with Vaughan Hudson and Doniach in the treatment of four patients with lymphadenoid goitre who have been relieved of their symptoms and whose goitres have become impalpable on the daily administration of 2-3 gr. (130-200 mg.) of thyroid extract.

Radiotherapy.—Many workers have advocated radiotherapy in the treatment of lymphadenoid goitre (Crile, 1948; Schilling, 1945). There is no doubt that irradiation will bring about a diminution in the size of the gland, mainly by its effect on the lymphoid tissue. However, in view of the apparent efficacy of thyroid treatment and the precision with which the diagnosis can now be made, we do not regard radiotherapy as the treatment of choice in this condition.

Surgery.—In 1939 Joll wrote: "It is a matter of considerable doubt as to whether surgical treatment is necessary in Hashimoto's disease, assuming that pressure symptoms are slight." This statement is more than ever true to-day. Nevertheless there are circumstances in which surgical inter-

vention must be seriously considered, especially in the following conditions. (a) In the presence of major pressure symptoms which demand rapid relief, particularly should the goitre be partly intrathoracic. (b) When the diagnosis remains in doubt, and the possibility of malignant disease is still present. Few tests give 100% precise results, and cases of lymphadenoid goitre are known (Doniach, 1957, personal communication) in which the antibody titre is too low to be detected by the precipitin reaction in its present form. Furthermore, as described under the heading "Pathological Features," occasionally these goitres are accompanied by a massive lymph-node enlargement, such as would render a diagnosis of lymphadenoid goitre by biochemical methods unacceptable until the neck had been explored. (c) Failed medical treatment: it is likely that some lymphadenoid goitres will fail to respond satisfactorily or rapidly enough to medication with thyroid extract. Lack of co-operation by the patient is another cause of failure.

The Operation

Little need be said of the technique employed. No difficulty is found in delivering the relatively avascular gland from its bed, though occasionally the characteristic retro-oesophageal extension may prove troublesome, and the operation, in the absence of venous obstruction, is unusually bloodless.

The aim should be to perform a subtotal thyroidectomy rather than the conservative resection sometimes recommended. It is felt that recurrence, though uncommon, is less likely after the subtotal operation; and Ficarra (1946) believes that recurrence is always due to inadequate surgical removal. However, Statland *et al.* (1951) have shown convincingly that regrowth of the goitre is seen only in those patients who fail to take thyroid post-operatively.

It seems possible, therefore, that recurrences after the conservative excision may arise because the surgeon mistakenly considers that he has left the patient with a reasonable amount of functioning thyroid tissue. For this reason the patient may receive no thyroid, or inadequate doses thereof, after operation, and consequently the goitre recurs. It must be emphasized that the myxoedema of greater or less degree is the inevitable result of lymphadenoid goitre; surgical excision of the gland, whether partial or subtotal, hastens the onset of this state and necessitates the supply by mouth of the patient's total requirement of thyroxine.

Care should be taken to excise a pyramidal lobe, if present, and the parathyroids must be sought and safeguarded. If these are not found (and they may be particularly difficult to identify on the pale lobulated surface of the lymphadenoid gland) the "lateral leaf" of the thyroid remnant should be made thin, but longer than usual, the resection starting further forward on the surface of the lateral lobe than is usual.

Hemithyroidectomy, even when the contralateral lobe appears normal, should play no part in the surgery of lymphadenoid goitre unless the surgeon accepts the need for full post-operative thyroid medication. If this is omitted, or the need for it is not recognized, then enlargement of the remaining lobe is inevitable.

Pathological Features

The thyroid glands of the 33 patients forming this series all conformed to a similar pathological pattern, and the constancy of the cellular changes, regardless of the clinical size or length of history of the goitre, was a notable feature.

The weights of the thyroid glands varied from 50 to 350 g., with an average of 111 g. The gross appearance shows a diffuse enlargement of the thyroid which almost always involves both lateral lobes and the isthmus. The external surface of the gland shows lobulation, but the capsular surface remains intact to leave a glistening surface.

On cross-section the enlarged thyroids were replaced by pink or white homogeneous tissue involving almost all areas (Fig. 7), although a few colloid foci were discernible in some.

FIG. 7.—Showing the replacement of all lobes of the thyroid gland by white tissue (posterior view with the cleft for trachea).

Histology

The histological features are most readily described under the following headings.

Thyroid Epithelium.—There is no normal thyroid tissue in Hashimoto's disease. The thyroid epithelium shows degenerative changes, with lack of colloid production and disruption of many of the thyroid acini. The residual thyroid cells show a characteristic alteration (Ascanazi) in their cytology, with an increase in their

size due to enlargement of the cytoplasm, which stains a prominent pink colour with eosin staining, while the nuclei are vesicular in appearance. These abnormal epithelial cells either occur in clusters or are sparsely scattered among the cellular infiltrate (Figs. 8 and 10).

Cellular Infiltrate and Lymphoid Follicles.—In all examples lymphoid follicles are present and form one of the diagnostic characteristics of this type of goitre (Figs. 8 and 9). The follicles are of variable size and shape, with a central pale staining area of cells surrounded by a rim of lymphocytes. These lymphoid follicles are indistinguishable from the lymphoid aggregations found elsewhere in the body. Apart from these focal follicular formations there is a diffuse cellular infiltrate in all examples, which permeate around groups and between individual cells of the residual degenerate thyroid epithelium. This cellular infiltration is composed predominantly of two types of cell, the lymphocyte and the plasma cell. The lymphocytes are maximal in number in the areas adjacent to the lymphoid follicles, but are also present in variable numbers throughout these pathological glands. In every example plasma cells formed a constant component of the diffuse cellular infiltrate, and in more than half the cases they exceeded the lymphocytes in number (Fig. 10). These plasma cells infiltrate diffusely throughout the gland, but in areas where the thyroid epithelium has disappeared the plasma cells form confluent foci. In a few examples polymorphonuclear leucocytes were present, but they were never prominent and were always outnumbered by lymphocytes and plasma cells.

Giant Cells.—These are present in many cases. They are of two differing types; one is the large multinucleate giant cell formed by aggregation of the altered epithelial cells; in other cases giant cells of the foreign body or even Langhans type are present, surrounding residual colloid material. These giant cells appear to be formed as a reaction to this colloid (Fig. 9).

Fibrosis.—Increased fibrosis of the gland forms a constant feature of these goitres. The glands are encapsulated by a thin band of fibrous tissue, and similar fibrosis subdivides the goitre into lobules, while coarser areas of fibrosis are present in the sites of advanced epithelial degeneration. A few examples show more extensive sheets of fibrous tissue permeated by inflammatory cells, but at no point was penetration of the capsule observed and the pathological condition always remained within the gland.

FIG. 8.—Showing a lymphoid follicle with diffuse cellular infiltrate permeating the residual thyroid epithelium. (x120.)

FIG. 9.—Showing a lymphoid follicle and giant cells in the thyroid epithelium in lymphadenoid goitre. (x142.)

FIG. 10.—Showing lymphocytes and plasma cells infiltrating the residual thyroid epithelium. (x520.)

Regional Lymph Nodes.—A few cases showed marked enlargement of the cervical lymph nodes in addition to the goitre. In three examples of this lymphadenopathy was so marked that metastatic carcinoma was suspected. Histologically the enlargement of the lymph nodes was due to non-specific reactive hyperplasia.

Carcinoma and Lymphadenoid Goitre.—One case showed enlargement of the thyroid gland due to the cellular changes of lymphadenoid goitre, but in addition there was an area of primary carcinoma in the adjacent thyroid tissue (Fig. 11).

FIG. 11.—Showing a carcinoma of the thyroid with a lymphadenoid picture in the adjacent thyroid tissue. ($\times 63$.)

FIG. 12.—Showing a colloid goitre with an adjacent area of lymphadenoid tissue. ($\times 50$.)

Residual Colloid.—In three cases small areas characteristic of colloid goitre were observed. It is significant that these patients gave a history of goitre extending over 30 years, and it seems a reasonable assumption that in these the lymphadenoid reaction had occurred in a thyroid gland already the site of a colloid goitre (Fig. 12).

The Follow-up

It has already been stressed that the overwhelming majority of patients who have undergone thyroidectomy for lymphadenoid goitre will require full thyroid medication for the rest of their lives. The necessary maintenance dose varies with individuals, but the majority require between 2 and 3 gr. (130 and 200 mg.) daily of thyroid extract. This

is also the order of dosage required to bring about resolution of a lymphadenoid goitre.

After operation the onset of myxoedema is inevitable and rapid. One of our patients (Case 13), who had been away to a convalescent home after thyroidectomy, delayed her first attendance in the out-patient department until five weeks after her operation. She had in this time already become so grossly myxoedematous that she was immediately readmitted to hospital for stabilization.

Another patient (Case 7), who underwent thyroidectomy for a large retro-oesophageal lymphadenoid goitre in 1948, lost touch with her family doctor and neglected to take her thyroid pills. She died in myxoedema coma in 1954.

Discussion

The curiously constant yet unusual type of tissue response in the lymphadenoid goitre lends itself to wide speculation on the precise causation of the disease process. Thus at various times the following suggestions have all been put forward as aetiological factors in lymphadenoid goitre: inflammation (Ewing, 1928), vitamin deficiency (McCarrison, 1929), functional disorder of colloid storage and release (Hellwig, 1938), subnormal thyroid tissue with compensatory lymphoid hyperplasia (Williamson and Pearse, 1925).

Levitt (1952) and others have regarded the disease as a waning hyperplasia, with progression toward thyroid fibrosis. However, it can be stated that the histology of the gland has contributed little to the solution of the aetiological puzzle, since the cellular appearances are compatible with most of the suggested causes.

The discovery by Roitt *et al.* (1956) of the presence, in the serum of patients with lymphadenoid goitre, of an antibody to the patient's own thyroglobulin suggests that the pathological changes in the gland itself are the results of an antigen-antibody reaction occurring locally, and that the cellular infiltration is secondary to this.

What remains obscure is the nature of the process which engenders this auto-sensitization. The preponderance of women in all series of lymphadenoid goitre suggests a possible linkage with pregnancy; however, no such connexion has been found, and, in any event, some other explanation would be needed of the few cases occurring in males and in children. Again, a rapid survey has failed to show any correlation between rhesus groups and this disease.

One interesting fact, however, has emerged from a study of the past medical histories in this series of patients. Previous histories were available in 27 cases, and a considerable proportion gave an antecedent history of diseases, the common denominator of which may be regarded as a pathological sensitivity on the part of the body tissues to various stimuli: thus rheumatic fever in 5 patients, rheumatoid arthritis in 3, nephritis in 2, and skin allergy in 4. In addition many gave a history of recurrent tonsillar infection, though this feature was too ill-documented to be of statistical value.

An interesting history of the onset of her goitre is given by one patient (Case 31). She had severe stomatitis following the extraction of some septic teeth: the goitre appeared suddenly, with considerable pain and tenderness of the gland itself, during the course of the stomatitis.

One may wonder, therefore, whether streptococcal infection with an allergic response may be in any way involved in this disease process. This is not suggested as a concrete theory, but merely put forward as a line for further study. We find no evidence to suggest, as Eason (1928), Vaux (1938), Levitt (1952), and others consider, that the lymphadenoid gland necessarily represents a late stage of thyrotoxicosis. On the other hand, if, as the serological evidence appears to show, the histological changes are the result of an antigen-antibody reaction taking place in the thyroid gland of a patient who has developed an auto-antibody to her own thyroglobulin, then there is no reason why such a change should not occur in the thyrotoxic patient as well as in the normal. Indeed, thyroglobulin extracted from toxic goitres

is just as satisfactory an antigen for use in the precipitin reaction as is that obtained from normal thyroids (Roitt *et al.*, 1956).

I have notes of one patient, aged 66 (Case 11), who was confidently diagnosed as thyrotoxic. The laboratory evidence did little to support this diagnosis, the B.M.R. being +13% (Aub-Du Bois). She was prepared with iodine, the B.M.R. fell to -1%, and a thyroidectomy was performed. Section of the excised gland showed a typical lymphadenoid picture. It is possible that this may have been an example of lymphadenoid reaction affecting a previously toxic gland.

It seems likely that the lymphadenoid change occurs independently of any pre-existing disease in the gland itself and, once engendered, will graft itself on whatever type of thyroid gland the patient already has. Thus, as would statistically be expected, most thyroids prior to being overtaken by the lymphadenoid change are normal. Sometimes, however, the patient already has a colloid goitre, and in Fig. 12 we illustrate a section of a typical lymphadenoid goitre in which are seen unmistakable traces of a colloid goitre. A few patients with lymphadenoid goitre give an exceptionally long history, usually terminated by a more rapid enlargement: it seems probable that these long-standing goitres have for many years been colloid in nature before being affected by the lymphadenoid reaction.

Likewise the change may affect the malignant gland, and Fig. 11 shows a carcinoma of the thyroid lying in the lymphadenoid gland. We have no evidence to suggest that malignant thyroid epithelium can or cannot be attacked by the lymphadenoid process. The carcinoma illustrated appears to be quite unaffected. Such a reaction, if it occurred, would presumably be linked to the ability of the malignant epithelial cells to elaborate thyroglobulin.

It seems, therefore, that this sensitization of the patient to her own thyroglobulin occurs as an episode in the life history of her thyroid gland: the histological changes are then imposed on the normal thyroid gland or on the toxic, colloid, or neoplastic goitre.

The lymphadenoid reaction may sometimes, I believe, be so overwhelming and complete that no functional thyroid tissue survives and the gland becomes a fibrous remnant; this may be the explanation of some cases of so-called primary myxoedema, a view already expressed by Statland *et al.* (1951). In support of this theory, Doniach (personal communication, 1957) has found a positive precipitin reaction in two such patients.

Summary

Thirty-three cases of lymphadenoid goitre are presented. Based on this material, the clinical features, diagnosis, pathology, and treatment are described, and in addition the modern concept of the aetiology is discussed.

The clinical features of our cases differ little from those so ably described by Joll (1939). All patients are either euthyroid or hypothyroid, with a 95% female distribution. Symptoms are discussed under the headings of thyroid deficiency, pressure, and the goitre.

Radiologically, major tracheal or oesophageal pressure is rare; minor degrees of pressure are common.

The laboratory investigations which are discussed include the B.M.R., radioactive iodine studies, and the precipitin (antigen-antibody) reaction described by Roitt *et al.* (1956). The value and significance of less specific tests such as plasma protein electrophoresis are discussed.

Treatment should be by the oral administration of thyroid extract, though the need for surgical excision will probably arise in certain circumstances, notably for the urgent relief of pressure and for the establishment of the diagnosis. After thyroidectomy, myxoedema and/

or recurrence of the goitre will follow if the need for continued thyroid replacement is not recognized. The need for careful follow-up of both medically and surgically treated cases is emphasized.

The pathological features of the lymphadenoid gland are described and attention is drawn to the high proportion of plasma cells present in the diffuse cellular infiltrate.

Histological evidence is presented which supports the view that while the lymphadenoid reaction usually affects a thyroid gland which was previously normal this is not necessarily so; colloid goitres, thyrotoxic goitres, and malignant goitres may, it is believed, be so affected.

The immediate cause of the lymphadenoid change appears to be the result of an auto-sensitization to the patient's own thyroglobulin.

The underlying cause of this phenomenon is unknown.

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REFERENCES

- Crile, G., jun. (1948). *Arch. Surg. (Chicago)*, **57**, 443.
 Eason, J. (1928). *Trans. med.-chir. Soc. Edinb.*, **42**, 169.
 Ewing, J. (1928). *Neoplastic Diseases*, 3rd ed. Saunders, Philadelphia and London.
 Ficarra, B. J. (1946). *Arch. Surg. (Chicago)*, **52**, 729.
 Hellwig, C. A. (1938). *Arch. Path. (Chicago)*, **25**, 838.
 Hepburn, R. H., and Eastcott, H. H. G. (1954). *Brit. J. Surg.*, **41**, 471.
 Joll, C. A. (1939). *Ibid.*, **27**, 351.
 Levitt, T. (1952). *Ann. roy. Coll. Surg. Engl.*, **10**, 369.
 McCarrison, R. (1929). *Brit. med. J.*, **1**, 5.
 Marshall, S. F., Meissner, W. A., and Smith, D. C. (1948). *New Engl. J. Med.*, **238**, 758.
 Roitt, I. M., Doniach, D., Campbell, P. N., and Hudson, R. V. (1956). *Lancet*, **2**, 820.
 Schilling, J. A. (1945). *Surg. Gynec. Obstet.*, **81**, 533.
 Silver, S., Yohalem, S. B., and Newburger, R. A. (1955). *J. Amer. med. Ass.*, **159**, 1.
 Skillern, P. G., Crilet, G., McCullagh, E. P., Hazard, J. B., Lewis, L. A., and Brown, H. (1956). *J. clin. Endocr.*, **16**, 35.
 Statland, H., Wasserman, M. M., and Vickery, A. L. (1951). *Arch. intern. Med.*, **88**, 659.
 Vaux, D. M. (1938). *J. Path. Bact.*, **46**, 441.
 Williamson, G. S., and Pearse, I. H. (1925). *Ibid.*, **28**, 361.

The Standing Technical Committee on Synthetic Detergents, appointed a year ago by the Minister of Housing and Local Government, has issued a progress report (H.M.S.O., London, price 6d. net). Foam occurring on rivers, canals, and sewage works remains a common cause of complaint. In some places the foam is so extensive and deep as greatly to reduce the chances of rescuing anyone falling into the water. At such places anti-foaming agents are a necessary concomitant of lifebelts. The remedies used at sewage works against foaming are palliatives rather than cures, and manufacturers are investigating the production of synthetic detergents more readily decomposed at sewage works. The committee is also sponsoring research on this and similar problems. After the very rapid increase in the use of detergents between 1949 and 1954, the limit of consumption now appears to have been reached, or nearly so: in 1956 34,500 tons were used for domestic and 6,500 tons for industrial purposes.