surgical separation impracticable. The photograph represents them at the age of 18, and the showman speaks of their "health and beauty." They are intelligent, good musicians, can play the saxophone and other instruments, and they have acquired a comfortable fortune. A report more laconic and quaint would be difficult to conceive. Dr. James Rooth has furnished an excellent account of the delivery and infancy of the Brighton twins in the *British Medical Journal*, 1911, ii, 653.

Apart from the many disagreeables incidental to such unions, there is this dominating question: What will happen if one twin dies before the other?

Lazarus—Johannes Baptista Colloredò was born in Genoa in 1617. Each child was christened separately, and when

FIG. 6.—Violet-Daisy Hilton, the Brighton Twins.

they grew up were exhibited all over Europe. They were described by G. Bartholinus, professor of anatomy at Copenhagen. At that date the twins were 28. It is worth notice that Lazarus was of a just stature, courteous in deportment, and gallantly attired. He covered the body of his brother with a cloak, as presaging that when he died, he should also expire with the stink and putrefaction of his body. Lazarus therefore took the greatest care of his smaller brother. This is a good example of kindness for selfish reasons.

It is established that, as a rule, in the case of conjoined twins the death of one is quickly followed by the death of the companion. The fate of the pygopagous twins Rosa—Josepha Blazek, born at Prague and known throughout the world as the Bohemian Twins, is worth recording on account of its pathos. Josepha had pneumonia followed by catarrhal jaundice in Chicago in 1922, aged 44. Rosa refused to be separated from her sister. Josepha died first; Rosa died fifteen minutes later. Rosa's last wish was that she should be allowed to die with her sister. Rosa's son insisted on his mother's wish being respected, saying he preferred being an orphan to denying his mother's last request. At the age of 32 Rosa fell in love with the showman and conceived. She gave birth to a living child at Prague. The child was in Rosa's womb, but Josepha as well as Rosa had milk in her breasts (see *Tumours*, seventh edition, 1922, p. 502). A curious legal question arose because both women died intestate, and some relations of Josepha, the unmarried twin, claimed part of the estate.

LYMPHADENOID GOITRE AND ITS CLINICAL SIGNIFICANCE.

BY

G. SCOTT WILLIAMSON, M.D., AND INNES H. PEARSE, M.D.

(Dunn Laboratories, Professorial Units, St. Bartholomew's Hospital, London.)

WITH A NOTE ON ITS ETIOLOGY IN RATS

BY

R. McCARRISON, C.I.E., K.H.P., M.D., F.R.C.P., BREVET COLONEL I.M.S.

(Nutritional Research Laboratories, Coonoor, South India.)

(*With Special Plate.*)

WHEN working on the histology of the thyroid in 1925 we found that there were two activities carried on by the normal gland.[1] This conclusion has since been substantiated by evidence drawn from several other sources—biochemical, biological, and clinical.[2,3] The two functions we refer to are: (1) The production of secretion proper; or what for greater precision may be called "lymphogenic" secretion. This secretion contains no thyroxin. (2) The accumulation of colloid—that is, iodo-colloid, which contains the thyroxin moiety of the thyroid products.

One of the features of the normal secretory process is the conspicuous activity of the reticulo-endothelial cells[4] with the production of lymphocytes in the interfollicular lymph spaces of the thyroid gland units. It is this latter feature of the secretory process which calls for the specific designation "lymphogenic" secretion.

To the pathologist the knowledge of a specific process in the normal physiology of a gland must lead to search for the corresponding pathological condition in which undue strain falls upon that specific process. This, then, led us to look for a class of thyroid disorder in which the functional imbalance would lie in the over-production of lymphocytes during the secretory process of an otherwise normal thyroid gland. In the course of a review of about 4,000 goitres we were able to separate some glands answering to this description. These, when ranged in sequence, betrayed their own pathological sequelae—fibrosis and atrophy. Thus a pathological condition which had been obscure could now be discerned as a specific progressive disorder often associated with goitre. To this class of enlarged thyroid gland we gave the name "lymphadenoid goitre."* [5]

Goitres which essentially belong to the group of lymphadenoid goitres have been called by earlier observers "chronic inflammatory thyroiditis," "granulomatous thyroiditis," "endothelioma," "sarcoma," and also "Riedel's disease" or "woody thyroid," etc. Although these various designations fail to convey the true pathogenesis of this condition they do indicate its most striking features: (1) the lymphocytic activity which is typical of the early or progressive stages of the process, and (2) the fibrosis and atrophy which accompany its later stages.

The lymphocytic infiltration is peculiar in that it picks out the *specific* thyroid lymph spaces in a most delicate and selective fashion (Figs. 1, 4, and 5). In this manner

* The lymphadenoid process need not cause enlargement of the gland; indeed, it has been found as a progressive condition in senility.

(*By G. Scott Williamson, Innes H. Pearse, and R. McCarrison.*)

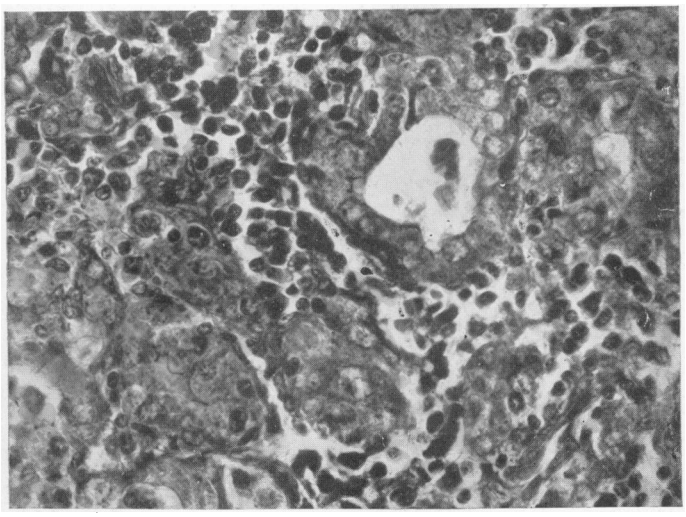

FIG. 1.—Section of a human thyroid showing the early changes in the lymphadenoid state. Lymphocytes fill the lymph sinusoids between the epithelial columns. Colloid is absent The follicle is a "secretion" follicle.

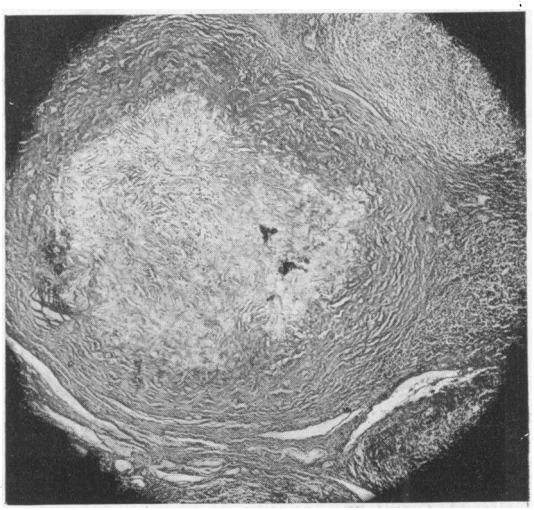

FIG. 2.—Later stage of the lymphadenoid process in a human thyroid. A whorl of fibrous tissue replaces a gland-unit.

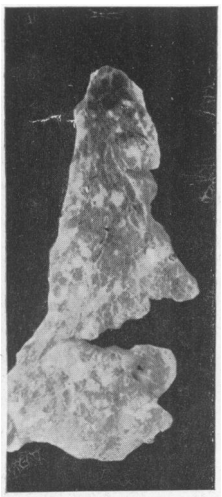

FIG. 3.—Section of a lymphadenoid thyroid of a man, aged 65, who died an accidental death and had no symptoms. The white opaque areas are foci of lymphogenesis.

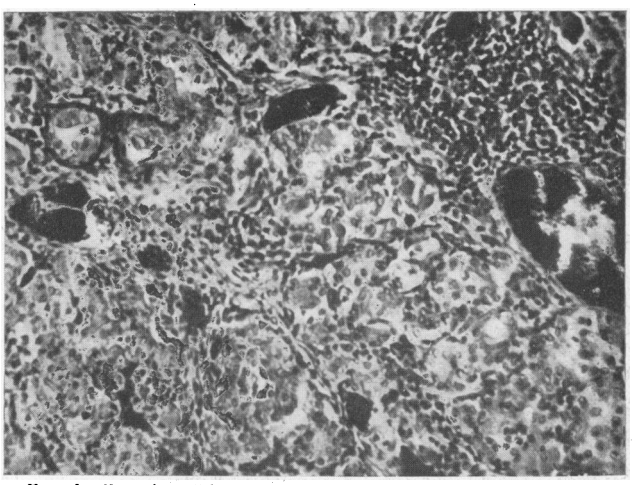

FIG. 4.—Experimentally produced lymphadenoid goitre in a rat showing invasion of the lymph sinusoids with lymphocytes and an aggregation of lymphocytes in one part of the field.

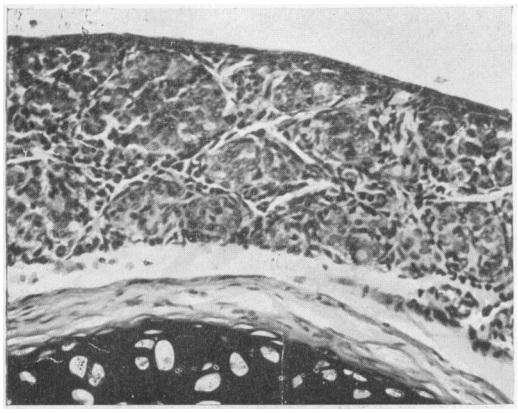

FIG. 5.—Isthmus of lymphadenoid goitre in rat, showing invasion of the lymph spaces with lymphocytes and the absence of both secretion and colloid follicles.

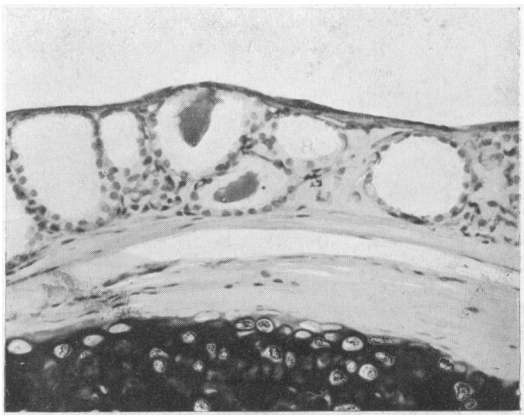

FIG. 6.—Isthmus of normal thyroid in "control" rat, for comparison with Fig. 5.

it affords a beautiful picture of natural injection of the thyroid lymph sinusoid, and lends further confirmation to our conception of the essential nature of the thyroid gland units.

As the disease progresses the lymphogenesis becomes more and more active; lymphocytes begin to collect at the hilum of the gland-unit and to range themselves in a circular fashion around its circumference as they crowd in the perivascular lymph spaces about the capsule of the gland-units. With the increasingly active lymphogenesis the parenchyma, which is producing the lymphogenic secretion, becomes hyperplastic, and active mitosis appears in the epithelium. The overgrowth of the parenchyma is so great that, in some cases, islands of solid epithelial tissue fill the follicular spaces, from which by this time all secretion has been drained away. It is noteworthy that lymphocytes only accumulate in and about those gland-units wherein lymphogenic secretion is being formed. In the follicles where colloid is accumulating there is no perifollicular lymphocytosis. This characteristic feature of the condition can, of course, only be observed in earlier cases in the human subject and in the experimentally produced condition in rats; for, as the process advances, the abnormal lymphogenic activity claims the whole field, and colloid storage becomes inconsiderable. Exhaustion of the epithelium eventually ensues, and now, no longer able to produce secretion, it becomes atrophic.

Meanwhile the cells of the reticulo-endothelial system, so actively concerned in the lymphogenic process, also suffer; an insidious fibrosis invades this tissue, creeping along its course from the periphery of the lymph sinusoid towards the centre, until there ultimately appears a complete fibrous skeleton replacing the reticulo-endothelium of the affected gland-unit (Fig. 2). The process is not that of scar formation. It is one of replacement fibrosis beginning in the reticulo-endothelial system, which is the region of functional "strain," and finally involving also the isolated islands of exhausted epithelium. The picture produced by the end-result of this process is a characteristic and peculiar one, for the gland-unit is entirely replaced by fibrous tissue. An ever-increasing number of complete fibrous whorls are ultimately formed throughout the thyroid, each whorl representing what was originally an active gland-unit of thyroid tissue. This is the "woody" thyroid of Riedel's disease. Area after area of these whorled fibrous nodules become linked together by the late progressive fibrosis of the interlobular lymph channels, and the once much enlarged thyroid tends finally to shrink into a small knot of fibrous tissue, unrecognizable as a thyroid gland except for its position. This gland is the gland of myxoedema.

It is clear from the progressive and ordered chain of events in the pathology of lymphadenoid goitre that there was justification for postulating the association of this type of thyroid with some general, as yet undifferentiated, constitutional disorder, the terminal phase of which was myxoedema.[5]

The sequence of events which thus leads up to the gland of myxoedema had been already noted by Simmonds.[6] He also emphasized the fact that this sequence of events was to be found apart from myxoedema, but in evident association with hypothyroidism. A further survey by Simmonds showed conclusively that this was not a secondary event in infectious disease, but a very specific condition of the thyroid. The lymphogenesis, as he points out, is the cause of the fibrosis and atrophy, and not a reaction following primary atrophy of the gland. Tebbutt, in a study of the condition, confirms Simmonds's main conclusion, and definitely links the pathological process to a progressive hypothyroidism and ultimate myxoedema.[7] Carrying this a step further we have shown that lymphogenesis is a function of the normal thyroid, so that lymphadenoid goitre becomes an expression of a disturbance of the lymphogenic function of the gland. We may conclude that there is some specific general disturbance which expresses itself in the thyroid gland as lymphadenoid goitre. The general condition has as its clinical sequelae hypothyroidism and finally myxoedema. Spontaneous myxoedema is thus the termination of a general disease rather than the sequel of a local thyroiditis.

Clinicians have recently begun to recognize the condition, with the result that during the last eighteen months four out of the seven lymphadenoid goitres we have received from the operating theatre were diagnosed as such before operation. It is not for us to speak, however, of the full clinical syndrome; suffice it only to say that the tendency for lesser or greater degrees of myxoedema to accompany the goitre is already well recognized by the surgeons familiar with these cases. It is, indeed, likely that many cases exist in which no symptoms occur until the insidious fibrous atrophy induces a spontaneous myxoedema. Thyroid glands are occasionally found *post mortem* in which the early stages of the lymphadenoid condition are observable in the gland histology, but where there is no record of any coexisting symptoms (see also Simmonds). A figure is shown of one such gland taken from a man, aged 65, who died an accidental death (Fig. 3). It is certainly true that the typical gland attributed by the pathologist to myxoedema is identical with the gland of the terminal stage of lymphadenoid goitre.

Let us now turn to a consideration of the etiology of the condition. McCarrison has for many years been concerned to demonstrate that the thyroid gland plays an important part in the general metabolism and, further, that other workers, by confining their attention exclusively to the metabolism of iodine, have been taking too narrow a view of the thyroid function. He therefore set out to cause a goitre on a diet which contained iodine. He was guided in his choice of diet by the experience of his previous work, which showed the overwhelming influence of vitamins in the functional turnover of the lymphocytes in the intestine—or intestinal lymphogenesis.[8] He ultimately found a diet, containing an abundance of iodine, which gave rise to a disturbance of the lymphogenic function of the thyroid gland. In other words, McCarrison has produced experimentally a lymphadenoid goitre.

There is no room for doubt that the goitre produced in the rat and the goitre of the natural disease in man represent the same condition (Compare Fig. 1 with Figs. 4 and 5). The rat goitres represent the earlier stages, the greater number of human lymphadenoid glands encountered represent both the early and the later stages of an identical pathological process in the thyroid. Unless the human glands are completely replaced by fibrous tissue, areas can always be found somewhere in them in which the condition is still progressive; if the rat goitres are selected some will be found in which the characteristic fibrosis is already beginning to show. In the human subject the age at which the progressive symptoms show themselves is rarely before 45 years, while myxoedema, of course, occurs on an average a decade later. We have, then, every reason to expect that the terminal phase of lymphadenoid goitre can also be produced in rats, provided they can be kept alive sufficiently long under suitable experimental conditions.

NOTE ON THE EXPERIMENTAL PRODUCTION OF LYMPHADENOID GOITRE IN RATS.

BY

COLONEL R. McCARRISON, I.M.S.

The composition of the diets used in the experimental production of lymphadenoid goitre[9 10] in rats is as follows: American white flour, 72 to 82 parts; meat residue, 5 to 15 parts; olive oil, 8 parts; salt mixture, containing 0.45 per cent. of potassium iodide, 5 parts; distilled water *ad lib.* Various modifications of this diet, containing greater or lesser amounts of white flour, or having certain proportions of the white flour replaced by starch, have also been used.

Approximately 25 per cent. of young rats fed on diets of this composition, and confined in separate cages under conditions of the most scrupulous cleanliness, have exhibited goitres of various sizes at *post-mortem* examination. The goitres have been found in rats killed, or dying, as early as 75 days from the initiation of the experiments and as late as 165 days. They have occurred more frequently in females than in males. Macroscopically they are of glistening, fleshy appearance, bright or darkish red in colour, and vary in size from twice to five times that of the normal