HISTOLOGICAL OBSERVATIONS ON THE THYROID

by

G. SCLARE

A thesis submitted to the
University of Glasgow
for the degree of Doctor of Medicine

1959

The structure, products and use of the thyroid gland are still capable of forming the subjects of interesting inquiry.

Sir Astley Cooper, 1836.

In our knowledge of the physiology and pathology of the thyroid gland, the vast territory of the unknown still dwarfs the area of certainty.

D. Hubble, 1956.

BOOK 1

CONTENTS

Page

INTRODUCTION

Our understanding of the thyroid in health and disease has taken immense strides forward in the past 15 years. The advances have been due largely to the introduction of new techniques - radioactive, biochemical, and more recently immunological - which have opened up vast new fields for study in thyroid physiology and pathology, and have elucidated many problems which would have remained insoluble by the traditional methods. Yet it is my belief that histological study of the thyroid has not been and never will be rendered obsolete by the advent of new techniques. Many investigators in recent years have been so eager to apply the newer methods that they have neglected to correlate their findings with simultaneous histological changes, and have failed to gain the maximum information from their investigations. The body of new knowledge which is now available to us should be a fresh incentive to the histologist to re-examine the microscopic structure of the thyroid.

I make no apology, therefore, twenty years after the introduction of radioactive iodine, for offering

a purely histological study of the thyroid, and hope to show that the worker who is limited to routine histological techniques has yet a part to play in the investigation of thyroid structure and function.

Perhaps because thyroid histology has in the past been the province of the surgeon rather than the pathologist, there has been a tendency for histological studies of the abnormal thyroid to be based on an insufficiently clear picture of the normal. Much of this work is devoted therefore to a study of the normal pattern of thyroid histology in different age groups, and to drawing the (sometimes blurred) line between the normal and abnormal.

Part I concerns the thyroid at birth - an age at which the histological pattern often differs greatly from the familiar one of adult life. The origin of the work was the chance finding of a neonatal thyroid whose microscopic structure was so disorganised as to cast doubt on the identity of the organ. An examination of over 200 infants' thyroids was undertaken in order to assess the incidence of such changes and to determine whether they are wholly or partly due to post-mortem degeneration. In the

course of the investigation, I had the opportunity of studying the thyroids of 3 infants born of mothers suffering from thyroid disease. To elucidate some of the problems raised by the study of normal and abnormal thyroids at birth, there follows an account of the neonatal guinea pig thyroid and the effect on it of various experimental procedures.

The histological changes supposedly peculiar to the neonatal thyroid were looked for - and found - in the thyroid at all other ages. The study of a large number of adult thyroids led in turn to observations on squamous epithelium and anisotropic crystals in the thyroid. These findings make up Part II.

In Part III, the same material is used for an assessment of lymphocytic infiltration in the "normal" thyroid. The question is found to be inseparable from the problem of lymphocytic infiltration in the abnormal thyroid, and leads to a consideration of the pathogenesis of chronic thyroiditis and myxoedema.

The "relative weight" of the thyroid is the index used by Schamaun (1954), i.e. the thyroid weight in grams divided by the body weight in kilograms. For two reasons, however, little emphasis has been placed on the weights of the glands. Firstly, the variable and often intense congestion of the gland at birth must give rise to misleading results. Secondly, the objectives of the investigation required the careful assessment of post-mortem changes, and the additional handling and dissection involved in weighing the gland was usually avoided.

In the anatomy and pathology of the thyroid, no less than in other organs, chaotic terminology is the source as well as the result of much confusion. Until a fuller understanding of the subject allows a more rational terminology, each writer must explain his terms and strive for consistency in their use.

The terms follicle, acinus and vesicle are all freely used to denote the same glandular structure. The first appears to me to be the most suitable term, expressing the idea of a functional unit, but as lymphoid follicles occupy such a prominent place in

thyroid pathology, there is a danger of confusion between the two types of follicle. The word "vesicle" has a distinctly pathological connotation. I have therefore used the term "acinus" throughout.

Interacinar cells are referred to in the full knowledge that they are often regarded as merely acini cut tangentially. The controversy over interacinar cells need not be touched on here, but the evidence in favour of their existence (Zechel, 1933; Nonidez, 1933; Baillif, 1937; Sandritter et al., 1956) seems to me to be overwhelming.

"Endothelioid cell" has other connotations, but is in use to denote the flattened type of cell which lines the least active acini in the thyroid.

Hürthle cells are also known as Askanazy cells, and were in any case first described by Baber. There seems to be an incontestable case for dropping the eponyms and substituting the accurate and descriptive term "oxyphilic cells".

The unfamiliar and ugly terms "lymphocrine" and "diskomplexation" are used here to the minimum, and their inclusion is only justified on the grounds that they have already been introduced in the continental

literature, and that no satisfactory English alternative is available.

Multinucleate cells within the acinar lumina often appear to be derived from macrophages, but there are some doughty opponents of this view, such as Goetsch and Kamner (1955) and Weber and Bettini (1956), who insist on their epithelial origin. Believing that either view can be correct in different instances, I have found the non-committal term "pseudogiant cell" to be useful, and it also distinguishes the intra-acinar multinucleate cells from the giant cells which are sometimes seen in the thyroid stroma.

Chronic thyroiditis is perhaps the most confused field of all, because of the generally loose usage of the terms Hashimoto's disease, Riedel's disease, and their synonyms. The former wide use of the term Riedel's struma, which relegated Hashimoto's disease to the position of a sub-division or early stage, has been superseded by the modern tendency to reserve the term Riedel's disease for a few distinctive cases and designate all the remainder Hashimoto's disease. Both usages ignore the fact that many cases of

chronic thyroiditis do not conform to the criteria of either Riedel or Hashimoto. In this thesis, the simple term "chronic thyroiditis" is preferred. The eponyms are retained only when intended in their strict sense, or in reference to published work in which they are employed.

Finally, with regard to the organ itself, I have no scruples about omitting the word "gland". Thyroid, like adrenal and pituitary, is an adjective which has now achieved the status of a noun.

Abbreviations used are the well-known ones: H & E for haematoxylin and eosin, P.A.S. for periodic acid-Schiff, and TSH for thyrotropic hormone.

For ease of reference, illustrations, tables and appendices have been grouped together in a separate volume.

Parts of Sections 1, 2 and 8 have already been published (references 203, 220 and 221). Considerable additions have been made here to the published material.

It should be noted that in Section 1, where the

results differ slightly from those published, this is due to the addition of 12 further cases, and the restriction of the series to infants surviving for up to 7 days.

The work has been carried out in the Departments of Pathology of Stobhill Hospital, Glasgow, Withington Hospital, Manchester, and the University of Manchester, under the direction of Dr. J.C. Dick, Dr. L. Stent, and Professor A.C.P. Campbell.

It is a pleasure to record my gratitude to Dr. Dick and Professor Campbell for their constant encouragement and for their valuable criticism and advice.

The entire technical work for the study of the human neonatal thyroid, from the preparation of the tissues to the cutting and staining of the sections and the taking of the photographs, was carried out by myself. For the preparation of all the remaining tissues, I am indebted to Mr. K. Hollins, of Withington Hospital, and to Mr. N. Mowat and the technical staff of the University of Manchester Department of Pathology. Mr. Mowat has been

responsible also for all the remaining photographs, with the exception of Figs. 17, 35, 47 and 61 (Professor Campbell), Figs. 29, 30, 72 and 83 (Mr. E. Smith), and Fig. 26 (Mr. I. Mackie).

The numbers of cases concerned are in general insufficient for statistical analysis, but I am grateful to Dr. M.G. Bulmer, Lecturer in Medical Statistics at Manchester University, for advice in the interpretation of the results.

Carbimazole in powder form was kindly made available by British Schering Ltd.

Manchester,
February, 1959.

PART I

THE THYROID IN THE NEWBORN

1. THE NORMAL HUMAN THYROID AT BIRTH

Of the seven ages of man, the first is the only one in which the normal histological structure of the thyroid is not well established. The familiar arrangement of the epithelial cells to form colloid-containing acini is not constantly present in the newborn, and sometimes disorganisation of the structure is so advanced that little resemblance is seen to the thyroid of the adult.

The variations are usually thought to be peculiar to the neonatal period, and do not stem from any variations in earlier life.

It is known that the developing thyroid consists initially of a solid mass of cells, and begins to assume an acinar structure at the twelfth to fourteenth week of foetal life. The appearance of acini coincides with the onset of physiological function, as shown by the simultaneous development of the ability to accumulate radioactive iodine (Chapman et al., 1948; Hodges et al., 1955). Acini appear first at the periphery of the gland, and differentiation gradually extends towards the centre, until

the entire gland consists of tiny colloid-containing acini, resembling the adult thyroid in miniature. At the seventeenth week differentiation into acini is complete (Fig. 1).

The partial or total loss of acinar structure and of colloid at birth therefore comes as something of a surprise. It is usual to regard such changes as being due to post-mortem degeneration (Potter and Adair, 1949), and in the recently published Atlas of Fetal and Neonatal Histology (Valdés-Dapena, 1957), they are illustrated only in the last of 13 photomicrographs, with the caption "This picture was added to show what one most often sees in the ordinary infant autopsy. The thyroid at this age undergoes autolysis very quickly; when it does, the lining epithelial cells seem to fall together, and the colloid disappears from view. As a matter of fact, it is rather difficult to collect a set of autopsy specimens because of this marked tendency . . . ".

The thyroid at other ages is not unduly susceptible to post-mortem degeneration, and there is no known reason why it should degenerate so rapidly after death in the newborn. The object of this

study is to investigate the relationship, if any, of the histological changes to delay in fixation, to establish the "normal" structure of the gland at birth, and to provide a standard by which possible abnormalities may be judged.

MATERIALS AND METHODS

Thyroids were obtained at autopsy from over 200 infants who were stillborn or who survived for up to 7 days. The data recorded in each case were the history of pregnancy and labour, subsequent clinical course, age, sex, maturity, interval between death and fixation of the tissues, and post-mortem findings.

The glands were dissected free with the minimum of trauma, fixed first in 10 per cent formol-saline and subsequently in formol-corrosive, dehydrated in the usual way and embedded in paraffin. Three staining techniques were used in every case: haematoxylin and eosin, Masson's trichrome, and periodic acid-Schiff (Pearse's "tripas" method). Other staining methods used in certain instances were

Heidenhain's iron haematoxylin and van Gieson, Mallory's aniline blue-orange G, haematoxylin and 0.5 per cent Congo red, brazilin-wasserblau (Bensley, 1916), phosphomolybdic acid-metanil yellow (Okkels, 1932), and Gordon and Sweets' method for reticulin.

In the analysis of results, all cases have been eliminated in which an accurate history of pregnancy or labour could not be obtained (as was often the case with infants delivered elsewhere and subsequently admitted to hospital), or in which there was obvious autolysis of the organs microscopically (the liver and kidney especially being used as a guide), or in which the death-fixation interval exceeded 48 hours. Stillbirths were included only when death was known to have occurred during delivery, or when there was a reliable record of the interval between cessation of the foetal heart and delivery. Three cases in which the mother's thyroid function was known to be abnormal are considered separately in the next Section.

There remain 106 cases for consideration. Of these, 22 were stillborn and 84 liveborn. Taking the dividing line as 5 lb. (2265 g.) birth-weight,

52 infants were judged to be premature, and in 19 of these the birth-weight was under 3 lb. (1360 g.). The interval between death and fixation of the thyroid ranged from 3 to 45½ hours. Details of the 106 cases are given in Appendix 1.

RESULTS

The histological appearances varied so widely that no single description is applicable to all the thyroids, and indeed in any individual gland there was commonly a considerable difference between the central and peripheral zones of each lobe. The types of thyroid acini observed, however, fall into three broad categories, which will be designated A, B and C.

Type A: In this category are included all ordinary colloid-containing acini, with numerous interacinar cells, as seen in the normal adult thyroid (Fig. 2). The size of the acinus was roughly proportional to the total size of the gland, so that it never reached the dimensions of the average adult acinus, and was smaller in the

premature than in the mature infant. The shape was sometimes spherical, but more often irregular or even elongated. The lining epithelium was either columnar or cuboidal; it was very rarely flattened. The colloid usually stained poorly with cosin and the P.A.S. method, especially in acini lined by columnar epithelium. Deeper staining, when it occurred, was seldom of the degree seen in foetal or in adult thyroids. Corresponding staining reactions with other methods are listed in Table 1. The rather different staining reactions found in foetal thyroids and designated "Type Ia" by Hewer (1927) were not observed.

Two types of vacuole occurred in the colloid, especially in acini lined by columnar epithelium: a large solitary central vacuole, or a series of small peripheral vacuoles. In many instances colloid was apparently absent, although sometimes P.A.S. staining gave a faint reaction which was not detectable by the other methods.

Type B: The second type of acinus was characterised by columnar epithelium, basal vacuolation of the cytoplasm, partial or complete absorption of the

colloid, and absence of interacinar cells (Fig. 3). The vacuolation of the cytoplasm was sometimes so pronounced as to suggest at first sight total detachment of the cells from the acinar wall. The contents of these vacuoles failed to stain with all the methods used, including brazilin-wasserblau and phosphomolybdic acid-metanil yellow. The luminal border of the cytoplasm was indistinct, in contrast to that in the first type of acinus described. The bulk of the stainable cytoplasm was supranuclear, and in many instances it was P.A.S.-positive. Colloid, if present, was in one of two forms. In the first, it stained deeply and was confined to the centre of the lumen, with thin filaments radiating towards the acinar wall, this being merely an exaggerated form of peripheral vacuolation (Fig. 4). In the second, it stained faintly and uniformly, filling the entire lumen (Fig. 5).

Type C: This includes a wide variety of changes which may be summarised as desquamation, collapse and disorganisation of the acinus. Desquamated cells occurred singly or in small groups, or even occupied the entire lumen (Figs. 6, 7). In

some instances, the lining epithelium remained intact, even though the lumen was filled with cells; in others, lining and desquamated cells were not clearly distinguishable, though the acinar outlines remained evident (Fig. 8). At a more advanced stage, there was partial or complete disintegration of the row of cells lining the acinus, and in the extreme form the tissue consisted of a solid mass of cells in which little or no acinar structure was recognisable (Figs. 9, 10, 11).

The nuclei of the desquamated cells were often pyknotic, and the cytoplasmic boundaries of both lining and desquamated cells were indistinct. The rarely-encountered large amoeboid cells described by Williams (1937) were readily distinguished from desquamated cells (Fig. 12).

In the compact cellular masses, where no distinction could be made between lining and desquamated cells, the nuclei ranged from small and dark-staining to large and vesicular, usually with a definite predominance of one or other type (Figs. 10, 11).

The origin of the compact masses from hollow acini was not evident in H and E sections, but was clearly shown by reticulin staining, which revealed

a pattern in no way different from that in tissue of ordinary acinar structure. In the more congested glands, the distended capillaries outlined the former acini in a similar manner.

Colloid was uncommon in acini showing desquamation, and was absent from all the more advanced stages of disorganisation. With the P.A.S. technique, only the cytoplasm of the desquamated cells gave a reaction, and then not constantly so. Rarely, in compact areas, a strongly positive P.A.S. reaction together with fusion of the cytoplasm of neighbouring cells gave the appearance of nuclei lying free in a meshwork of colloid.

Distribution of the different types of acinus

When a section of an entire lateral lobe was examined, acini of types A and C showed a characteristic distribution (Fig. 13). Type A acini were almost constantly present at the periphery, sometimes in a broad irregular peripheral zone, sometimes only as a few minute clusters just under the capsule or even apparently isolated from the rest of the gland. When present throughout the gland, they became gradually smaller, and their colloid content stained

less intensely, from the periphery to the centre.

Type C tissue showed the reverse distribution. That is, desquamation and disorganisation occurred characteristically in the centre of the lobe; when more extensive, they made increasing inroads into the peripheral zone, perhaps sparing only a few small areas at the periphery. When the changes were extensive, they were more advanced in the central than in the peripheral zone.

Type B acini were sometimes confined to the central zone, but more often they showed no special distribution.

Incidence of the different types of acinus

The different types commonly co-existed in the same gland. Even when the gland was at first sight composed entirely of normal well-preserved acini, a careful search almost always revealed a few central acini showing basal vacuolation of the epithelium or some desquamation of cells into the lumina, and conversely, whatever the degree of desquamation or acinar disorganisation, well-preserved acini, singly or in groups, could usually be found at the extreme periphery.

In classifying the glands, therefore, the incidence has been assessed only according to the predominating type of acinus - A, B or C - or where more than one type of acinus was prominent, as AB, AC, BC, or ABC.

The over-all incidence of the various types (see Table 2) was:-

A	24
B	13
C	33
AB	4
AC	19
BC	11
ABC	2

When this series is sub-divided according to maturity, age in days, etc., the individual groups become too small for accurate comparison; each of the possible influencing factors is therefore considered in relation to the entire series (Tables 3 to 10).

Age (Table 3): The incidence of the various types of acinus did not differ appreciably in the stillborn (22 cases), those dying within 24 hours (47 cases), or those dying at 24 to 72 hours (28 cases). At 4 to 7 days (9 cases), type A became commoner, type C less common, while type B showed

little change. That is to say, the incidence of desquamation and disorganisation diminished after the first three days of life.

Sex (Table 4): The sex of the subject, which is such an important factor in thyroid pathology in the adult, showed no obvious influence on the histological structure in the newborn. (A slight sex difference in the thyroid weight at birth was reported by Potter (1938). Too few glands in this series were weighed to allow of any conclusions).

Maturity (Table 5): A simple division into mature and premature does not reveal any striking difference between the two groups: both showed the same wide variation in types of acini, and, when compact areas were present they showed the same proportion of nuclear types. If the 19 cases in which the birth-weight was under 3 lb. (1360 g.) are considered separately, there appears to be some increase in the number of glands which were wholly or almost wholly composed of normal well-preserved (type A) acini.

History of pregnancy and labour (Tables 6, 7, 8) did not have any obvious relation to the histological picture. In particular, a note was made of pre-eclamptic toxaemia (12 cases), difficult or prolonged labour with foetal distress (31 cases), and Caesarian section (12 cases), all of which appeared to be without influence. There was nothing to suggest that foetal distress is conducive to histological changes in the thyroid, or that avoidance of the normal birth process by Caesarian section protects against them.

Cause of death: This is notoriously difficult to assess in the newborn, but so far as could be judged there was little relation between the histology of the thyroid and the post-mortem findings in other organs.

In the 74 cases showing evidence of asphyxia (Table 9), there was the same wide range of structure as in the remainder. There was a slight increase in the incidence of type A acini in the asphyxial group, and, perhaps more significant, a rather greater increase in type B.

None of the infants were considered to have died as a result of bacterial infection. Other causes of

death (birth trauma, congenital abnormalities, haemolytic disease and haemorrhagic disease of the newborn, etc.) did not reach sufficient numbers for their influence to be assessed, but there was nothing to suggest that they had any relevance.

Death-fixation interval (Table 10): With increasing delay in fixation there was a tendency for the incidence of type A acini to diminish, yet there was certainly no direct correlation between early fixation and preservation of acinar structure. Figs. 14 and 15 illustrate a case in which the acini were perfectly preserved in spite of a long death-fixation interval, and another in which there was widespread disorganisation after a comparatively short interval. Many other cases, excluded from this series because of a death-fixation interval of more than 48 hours, have been seen which further illustrate this lack of correlation. In the more advanced stages of autolysis (Fig. 16), the picture is often unlike any of those described, and does not permit of classification according to this scheme.

Generally speaking, desquamation occurred in the majority of glands irrespective of death-fixation

interval, but when fixation occurred within 12 hours of death it was more often confined to the central zone and showed less tendency to encroach on the periphery.

In addition to the variations in acinar structure, and the distinction between the central and peripheral zones, other noteworthy features of the neonatal thyroid were distension of the lymphatics, engorgement of the blood vessels, intra-acinar haemorrhages and rarely, the presence of squamous or atypical epithelium. The last-mentioned is discussed later (Section 5), and will not be further referred to here.

Distension of the lymphatics

The lymphatic vessels of the thyroid take the form of a connected system of wide sinuses which enclose groups of acini. They are inconspicuous except when abnormally distended.

In this series of cases, the lymphatics, both within and outside the thyroid, were often distended by a homogeneous eosinophilic substance resembling colloid. The entire system, from the small inter-acinar channels to the larger perivascular trunks in the interlobular septa, was thus outlined (Figs. 17,

18). The staining reactions of the contained substance were identical with those of colloid (Table 1); the P.A.S. technique was by far the most satisfactory for demonstrating it. The intensity of the staining varied as much as that of the colloid; it often appeared, however, to be inversely related to the staining intensity of the colloid in the adjoining acini.

Within the gland, colloid-like substance in the lymphatics was seen in relation to type B acini, and to all stages of "desquamation" included under type C with the exception of tissue of true compact structure in which the acinar outlines were lost. Its presence in relation to these types of acini was not invariable. It seldom, if ever, occurred in relation to type A acini. Distended lymphatics, like disintegrating acini, were often confined to the central zone of the gland.

Distension of the lymphatics outside the capsule (Fig. 19) occurred in association with the same epithelial changes, but was seldom so prominent, and the staining reactions of the colloid-like substance were usually weaker.

The two manifestations of the phenomenon did not necessarily occur together; of the 58 cases in which colloid-like substance was observed in the lymphatics, the intraglandular channels alone were involved in 26 cases, those outside the capsule alone in 17 cases, and both were involved in 15 cases.

Lymphatic distension was not related to delay in fixation (Table 11).

Vascular engorgement

Congestion of the blood vessels was common, especially in the stillborn and those dying within the first three days. Congestion of the inter-acinar capillaries was conspicuous in about half of the cases, and was sometimes of such a degree that congestion alone appeared to have contributed to collapse of the acini (Fig. 20).

It was unrelated to the type of acini composing the gland, and reflected fairly accurately the degree of congestion in other organs.

Intra-acinar haemorrhages

Isolated intra-acinar haemorrhages, of recent occurrence, were noted in 6 cases, and were

associated with epithelial desquamation (Fig. 21). In two other cases, haemorrhages were numerous, occurring in normal well-preserved acini; they were attributable to haemorrhagic disease of the newborn.

DISCUSSION

The significance will be discussed first, of the various types of acinus, then of the other phenomena, and finally of the histological appearances as a whole.

Significance of the three types of acinus

Type A: This, the familiar well-formed acinus of the normal thyroid, requires little comment. As the height of the acinar epithelium is an accurate measure of the degree of physiological activity (Rawson and Starr, 1938; Abel, 1940), the prevalence in the newborn of columnar and cuboidal epithelium and the rarity of flattened epithelium are evidence of a high level of activity. In the normal adult thyroid, flattened or "endothelioid" cells predominate (Goddard and Sommers, 1954). Goormaghtigh and Thomas (1934) designated the columnar cell as the

"excretory" cell, and observed that it is present in late foetal life, and especially at birth. Other features indicating active resorption of colloid are the generally weak staining reactions of the colloid, the presence of solitary central vacuoles in the colloid (Popoff, 1943), and indentations of the acinar walls (Williams, 1937). The two types of staining reaction in the colloid probably have no significance other than indicating differing concentrations of colloid (De Robertis, 1941).

Type B: Basal vacuolation of the acinar cells, with apical displacement of the nuclei, was first described by Bensley (1916) in the hyperplastic thyroid of the opossum. His method for staining the content of the vacuoles has not been successfully used by subsequent investigators, but acini of similar appearance have been observed in the guinea pig thyroid as a result of compensatory hypertrophy (Loeb, 1929), and in the human thyroid in exophthalmic goitre (Okkels, 1932). Loeb gave a good account of how the colloid comes to assume the form of a central mass with fine threads radiating to the epithelial lining. Severinghaus (1933) noted basal vacuolation

in the duck thyroid within 24 hours after injection of thyrotropic principle.

Ponse and Altschuler (1940) thought that basal vacuolation might be due to artefact, as apical displacement of nuclei in the guinea pig thyroid two to four days after injection of anterior pituitary extract was not accompanied by vacuolation. My own observations on the guinea pig thyroid (p. 92) confirm this, and show that basal vacuolation may be due to autolysis alone; the point is further discussed in Section 3. However, De Robertis (1941) showed that basal vacuolation can occur even in frozen-dried material, and that basal vacuoles are much more evident in activated than in normal glands.

Acini of this type did not form part of the secretory cycle described by Williams (1937) in living thyroid tissue, and it is clear that they represent the response to a more powerful stimulus than occurs under normal circumstances.

Type C: Controversy has from the first centred on the significance of epithelial desquamation and disorganisation of the acini. Ignoring the more bizarre explanations offered by many earlier writers,

of which a full account is given by Allara (1951a), two possibilities are deserving of serious consideration: the changes are the result of unduly rapid autolysis, or they indicate a state of increased physiological activity.

The close similarity between the changes of post-mortem autolysis and those of hyperactivity has given rise to endless confusion. Both processes consist essentially of absorption of the colloid and collapse of the acini. Even pyknosis and cytoplasmic degeneration, usually reliable indications of autolysis, occur in the gland activated by thyrotropic hormone (Severinghaus, 1933). Desquamation of the epithelium is so strongly suggestive of autolysis that it is often accepted without question as such, yet here again there is reason to believe that a similar process may occur during life. De Quervain (1904) noted that "both toxic effects and disturbances of the circulation of a high degree cause histological changes in the thyroid, and these are in the main symptomised by proliferation, desquamation and degeneration of the epithelial cells . . . The reaction of the epithelial cells to any irritation

whatever is in the form of desquamation". Rice (1938) went so far as to state that "epithelial desquamation is not found in the normal thyroid, whereas it is one of the characteristic features of exophthalmic goiter".

It might be thought that in animal experiments, where no difficulty attends immediate fixation, there would be no question of confusing the two processes. But Jackson (1916), reporting the effects of inanition in rats, found difficulty in distinguishing between them, and drew an interesting analogy with degenerative changes in the kidney: "So-called degenerative conditions (desquamation and degeneration of epithelium) appear to a limited extent in the thyroids of normal animals (including man), although these changes probably have no physiological significance. Under various abnormal conditions, these retrogressive changes appear to be increased in extent and intensity . . . Changes in the renal epithelium following ligation of vessels, infarcts, intoxications, infections, post-mortem changes, etc., form a familiar example, in which the phenomena are in many respects strikingly similar to the

degenerative changes above described for the thyroid gland".

Desquamated cells were seen in frozen-dried normal rat thyroid by De Robertis (1941); the nuclei were pyknotic, and the cytoplasm was loaded with colloid droplets. Desquamation following stimulation has been noted in the rat thyroid by Baillif (1937) and Řeřábek and Řeřábek (1947), and in electron microscopic observations on the guinea pig thyroid by Braunsteiner et al. (1953); desquamated cells in the colloid have also been seen in experimental thyroiditis (Terplan et al., 1958).

The belief that epithelial desquamation and colloid depletion are purely post-mortem phenomena received its greatest support from the work of Gloor (1926) and Murray (1927). By fixing fragments of a single gland at varying intervals after death, these authors were able to demonstrate a succession of changes closely imitating those under consideration. Murray, however, made no comment on the fact that the changes which occurred, on an average, within $2\frac{1}{2}$ days of death in the newborn child, took 7 days to occur in the adult dog thyroid. Gloor, while

admitting the probability that some degree of desquamation might occur during life, concluded that the thyroid at the time of birth is more susceptible to post-mortem change than in the mid-foetal period or after the first two weeks of life. This left unanswered the question as to why, during a particular spell of two weeks, the thyroid should undergo autolysis more rapidly than at any other time of life.

On the other hand, Allara (1951a), in a careful study of 16 neonatal thyroids, found no correlation between delay in fixation and histological structure. He observed that the thyroid in late foetal life was composed of compact cellular masses, and that acini began to form at the periphery of the gland in the early hours of extra-uterine life. In the foetus of 7 to 8 months, the cellular masses were characterised by small dark-staining nuclei, while at term large vesicular nuclei predominated. He brought forward a wealth of evidence to show that the former were an expression of increased physiological activity while the latter represented the stage of exhaustion. In a later paper (Allara, 1953), he noted the coincident intense degranulation of the basophils in the

anterior pituitary. Whether by chance, or for some other reason which is not obvious, none of the thyroids he examined showed epithelial desquamation; the structure was either acinar or compact.

The present series of 106 cases, though dominated by the phenomenon of epithelial desquamation, resembles Allara's series in the lack of correlation between delay in fixation and histological structure. It may be conceded that desquamation tends to be more extensive when fixation is delayed beyond 12 hours, but this tendency does not offset the many instances in which desquamation occurred with only a short delay in fixation, or good preservation was seen after a long delay. The failure to demonstrate any clear relationship leads inescapably to the conclusion that autolysis is not the principal cause of desquamation, but is at most a contributory factor.

In rejecting autolysis and accepting the alternative explanation of "physiological crisis", the following evidence has also been taken into account:

1. Preservation of the peripheral zone has often been taken as an indication that the changes in the remainder of the gland are due to autolysis. Yet this preservation is itself strong evidence to the

contrary. It is unreasonable to suppose that the short time taken for the fixative to penetrate a few millimetres from the surface to the deeper zones of the gland would result in gross differences in the histological picture; such an occurrence would be without parallel in any of the organs which are known to degenerate rapidly after death. It is, in any event, often not a uniform band of preservation round the margin of the gland, but is of focal distribution, as is the distribution of less active acini in a well-preserved gland. Moreover, preservation occurs to an equal degree in the medial and lateral margins, even when the thyroid and trachea have been left attached to one another, allowing the fixative to reach the central zone of the gland before the medial margin. A simple experiment puts the matter beyond doubt: when one lobe is fixed whole and the other is first bisected, the degree of peripheral preservation remains the same.

2. As described later in Section 4, the changes, when they occur in the adult thyroid, are often focal and are totally unrelated to the time of penetration of the fixative. Preservation of acinar structure and of colloid occurs not at the periphery

but in the larger acini and in pre-existing nodules of colloid storage. In the adult, as in the newborn, the less active acini do not respond to the stimulus which affects the remainder of the gland.

3. From the contributions of Roger and Garnier (1898a,b,c) onwards, similar changes have been reported many times in the human thyroid in bacterial infections, when the demand for thyroid hormone is presumably greater. It is also true, of course, that autolysis tends to be more rapid after death from infection, but the experiments of Womack and Cole (1931), mentioned below, confirm the occurrence of the changes during life. Frantz (1955) states that the change is most striking in infants after terminal illness, particularly a febrile illness, and interprets it as "exhaustion hyperplasia".

4. A study of the effects of autolysis on the neonatal guinea pig thyroid, described in Section 3, shows that ante-mortem and post-mortem "desquamation" are distinguishable from one another. Autolysis in the normal gland was characterised by progressive detachment of the row of epithelial cells from the acinar wall, the ring of cells remaining intact even at the stage of disappearance of the nuclei. At no

stage in the process did the lumen become filled with cells as it does in the ante-mortem state, nor was collapse of the acinus accompanied by an apparent increase in the total number of cells. Autolytic changes in the hyperplastic gland were similar. Although there was some evidence that the detached ring of cells is more likely to disintegrate in the activated than in the normal gland, the early form of desquamation following thyrotropic hormone injections did not progress after death, and the lumen did not become filled with cells.

5. Loss of colloid and of acinar structure have been demonstrated in animals at birth and at other times of physiological crisis. Smith and Starkey (1940) described a "relatively undifferentiated appearance" in the newborn mouse thyroid, indicating a "very high plane of activity", while a similar, though less pronounced, alteration was again seen at the onset of sexual maturity; in some acini, total loss of colloid was accompanied by a breakdown of the epithelium. Glebina (1936) noted similar but transient changes in the newborn fox thyroid and again during one phase of the seasonal

cycle (September to March) in the adult fox; her term "diskomplexation" is hardly capable of translation into English, but expresses quite well the loss of organised structure which occurs at the time of birth. She found that "diskomplexation" in the newborn was followed by rapid regeneration. The same phenomena are associated with metamorphosis in the salamander (Uhlenhuth, 1923) and the development of feathers in chicks (Benazzi, 1929, 1932). Glebina's Fig. 11, reproduced here (Fig. 22), makes it clear that "diskomplexation" is not merely loss of colloid and of acinar structure, but includes the apparently degenerative changes in nuclei and cytoplasm usually attributable to autolysis.

6. Comparable changes have been described in experimental animals by Cramer (1926) and in a series of papers by Cole and Womack between 1927 and 1931 (references 36 to 39; 274, 275). Cramer produced them in the rat by exposure to cold, and by injections of β-tetrahydronaphthylamin; among his illustrations of desquamation was one (Fig. 5) showing typical "activated" acini, indicating that "activation" and "desquamation" are different stages of the same process. In the experiments of Womack and Cole (1931),

similar changes were produced in the dog thyroid by production of infections, injection of drugs, chiefly methylated purines, and implantation of contaminated foreign bodies in the neck muscles. Most important, they showed by means of serial biopsies not only that such changes could occur during life, but that the changes were readily reversible when the stimulus had ceased to operate. Intestinal obstruction also brought about these changes, as did histamine injections without production of fever (Womack et al., 1928), and it was noted by Cole et al. (1929) that following infections and toxaemias of a severe nature, the same changes take place in the human thyroid as in the thyroid of animals, though to a lesser extent.

More significantly, the typical picture of desquamation (see Fig. 23) has been produced in the rat by long-continued injections of thyrotropic hormone (Weber and Bettini, 1956).

For all these reasons, the changes characteristic of the neonatal thyroid are regarded as being of antemortem origin.

Is autolysis therefore to be dismissed as of no importance? Not entirely. With the similarity of the two processes in mind, it must be acknowledged

that the changes, when already present, may be accentuated by autolysis. Indeed, the increased rate of proteolytic activity known to be present in hyperactive thyroid tissue (De Robertis and Nowinski, 1946) may be particularly favourable to the development of autolytic changes. If so, then the artefact, if such it is, is a significant one, and of the same significance as the true ante-mortem changes.

While there may be, therefore, some basis for Gloor's belief in an increased susceptibility to autolysis at the time of birth, I would postulate that the changes are in the main due to an increased susceptibility to functional exhaustion.

Such evidence as is available indicates that the thyroid at the time of birth is in a high state of activity. Even in those glands which are entirely free from desquamation or disintegration, the histological appearances are those of greatly increased activity. The high level of protein-bound iodine in the serum of newborn infants (Danowski et al., 1951), and the high uptake of radioactive iodine - lying within the range found in hyperthyroid adults (Van Middlesworth, 1954) - provide ample corroboration; it is noteworthy, too, that the results in both

these reports showed a wide range in keeping with the widely varying histological structure reported here.

It is at this time of life, therefore - a time of prolonged hyperactivity in order to meet the needs of the rapidly-growing child - that the thyroid is most likely to be precipitated into a state of "exhaustion hyperplasia" by an additional stimulus.

There is nothing in this series to suggest that the additional stimulus necessarily occurs during the process of birth, or that restoration of the normal picture begins immediately after birth, as suggested by Allara (1951a). All possible combinations of the various types of acini were seen both in the still-born and in the liveborn. The one pair of twins in this series (cases 74 and 75) afforded an opportunity of observing any immediately post-natal changes, but none were found. The thyroids of the first twin (aged 1¼ hours) and the second twin (7¼ hours) were indistinguishable, both showing extensive "desquamation" with small groups of well-preserved acini at the periphery.

Relative inactivity of the peripheral zone

This is a well-known feature of the foetal and neonatal thyroid, but it has never been satisfactorily explained. The distinction between the two zones rapidly diminishes after birth in the human thyroid, but in experimental animals it persists into adult life. The functional difference between the two zones has been demonstrated experimentally. In the rat thyroid, it has been noted that the peripheral zone showed little or no involvement in collapse of the acini following exposure to cold (Baillif, 1937), in hyperplasia due to vitamin A deficiency (Van Dyke, 1955), and in desquamation and disorganisation due to an auto-immune reaction (Lilien, 1954). In 6 out of 12 dogs which had been given large doses of radioactive iodine to destroy the thyroid, viable tissue remained at the poles and periphery of the gland (Goldberg and Chaikoff, 1952), and similarly in the mouse thyroid, maximal injury by radioactive iodine occurs in the central zone (Speert et al., 1951). Feeding of anti-thyroid drugs, too, causes hyperplasia especially in the central zone of the guinea pig thyroid (Fig. 41).

These findings provide further support for the view that the changes characteristic of the central zone of the human thyroid at birth are not due to autolysis but to a higher degree of physiological activity and a readier response to stimuli.

Distension of the lymphatics

The frequent presence of a colloid-like substance in the lymphatics raises the question as to whether the thyroid hormone might be secreted into the lymphatics as well as into the blood vessels.

Following the observation of King (1836) that gentle compression of the thyroid expelled "the contents" into delicate lymphatics, which united on the surface to form larger trunks, there was nearly a century of inconclusive controversy until Rienhoff (1931) made a detailed study of the lymphatics in the thyroid of dog and man. The interacinar lymphatic network was shown to lie external to the blood capillary plexus around the acinus. "Differing thus from the blood capillary system, the lymphatic capillary system is not individually devoted to separate and distinct follicles but rather to the spaces between groups of follicles . . . The

specific secretion would therefore have to go out of its way to avoid the more delicate blood capillary plexus to gain access to the lymphatic capillary plexus. This would seem unlikely from the structure alone, but, of course, is possible". From a study of the lymphatics in the human neonatal thyroid, Kulenkampff (1950) reached a similar conclusion. His findings leave no doubt that the spaces in question are indeed lymphatic channels (Fig. 24). He pointed out that the lymphatics were separated from the epithelium by blood capillaries; he had noted a homogeneous coagulum in the lymphatics, and suggested that collapse of the acini in the phase of colloid release allows filling of the intervening lymphatic spaces by lymph from outwith the thyroid.

On the other hand, Allara (1951a,b) suggested that the presence of colloid-like substance in the lymphatics might represent an emergency "lymphocrine" mechanism whereby the thyroid hormone was secreted directly into the lymphatics in states of hyperactivity. In his cases, unlike those reported here, lymphatic distension occurred constantly and exclusively in relation to tissue of compact structure. In this series, its presence during the intermediate

stages of epithelial desquamation and colloid depletion, and its absence from the final stage of functional exhaustion, provide stronger evidence in favour of a "lymphocrine" mechanism.

A major difficulty all along has been the lack of a satisfactory histochemical method for detecting iodine (Gersh and Stieglitz, 1933). All the staining methods showing the similarity between colloid and the substance in the lymphatics can equally well be used to demonstrate other protein accumulations, such as renal casts, and are by no means specific for thyroid colloid (Mayer, 1949). A P.A.S. reaction of comparable intensity may occasionally be seen in distended lymphatics in other organs, and in any event the P.A.S. reaction of thyroid colloid is not attributable to its thyroxin content (Fisher, 1953).

The introduction of radioactive iodine has gone some way towards resolving this question. Dobyns (1956) stated that the lymphatics leading from the thyroid are important pathways of exit for the thyroid hormone; administration of TSH into the thyroid artery results in a rapid rise in the amount of radioactivity in the thyroid lymphatics. And again Dobyns and Hirsh (1956) showed that there is an

enormous increase in output of radioactivity in the lymphatic pathways from the thyroid after intravenous administration of TSH, and that the increase in the cervical lymphatics is greater than the increase in the thyroid veins. The increase appears to be in the form of a protein molecule, possibly thyroglobulin, rather than as thyroxin per se.

Whatever the anatomical objections, it is evident that the "lymphocrine" mechanism cannot be altogether dismissed, and that further studies with radioactive iodine will be necessary. In the meantime lymphatic distension can be accepted as part of the complex changes which occur in the thyroid at about the time of birth, and can be used as an index of such changes when they occur under other circumstances.

Vascular engorgement

Much has been written on this subject, and congestion has repeatedly been cited as a characteristic feature of the neonatal thyroid, but the question deserves only a brief mention. As pointed out by Koch (1938), the parathyroids show a similar condition, and indeed in the present series so also did the abdominal viscera. The generalised congestion associated with an asphyxial death is so common, and

often so pronounced, in the organs of the newborn, that there can be no justification for interpreting congestion of the thyroid capillaries as physiological hyperaemia. Any greater degree of congestion in the thyroid might well be only a measure of that organ's very rich blood supply.

Intra-acinar haemorrhages

When not associated with generalised haemorrhages (as in haemorrhagic disease of the newborn), haemorrhage into the acinar lumen may be regarded as yet another manifestation of the response to a powerful stimulus. This is suggested by the constant association with "epithelial desquamation". Such haemorrhages occurred, too, in Cramer's experiments, already cited, and in the response to injections of TSH (Loeb, 1929; Braunsteiner et al., 1953).

Causation of hyperactivity in the newborn

The appearance of the newborn babe in no way suggests that its thyroid is hyperactive. As Hiilesmaa (1948) put it, "In spite of histological changes suggesting hyperfunction, the functional value of the thyroid of the newborn has proved to be slight". One must assume that the excessive activity is a response to increased demand during the later

stages of gestation - a time when growth is proceeding very rapidly indeed.

Although the histological changes are similar to those induced by administration of TSH, the hyperactivity is not necessarily mediated through the pituitary, as suggested by Hiilesmaa. Doniach (1957) considers that it is part of the growth process, unrelated to the influence of the child's pituitary. He points out that the ability of the thyroid to grow and of its cells to divide without TSH can be demonstrated by tissue culture, and that the thyroid grows in the hypophysectomised young animal although it shrinks in the hypophysectomised adult.

It is readily understandable that in late foetal life the thyroid would be precipitated into "exhaustion hyperplasia" by a less powerful stimulus than would be required at any other time. Little information is available as to the nature of any additional stimulus which might operate. It would be natural to suppose, as did Morison (1952) that when difficult labour has resulted in foetal or early neonatal death, the maternal hormones evoked by the stress of labour might have crossed the placental

barrier and stimulated the foetal thyroid. Yet no correlation has been shown here between difficult or prolonged labour and histological structure. Moreover, the presence of the same wide range of changes both in the stillborn and in those surviving for several days, and the persistence of the changes, though with diminishing frequency, into later childhood (see p.136) would exclude the influence of maternal TSH as an important factor.

The stimulus is not necessarily the same in all cases, as the changes have been shown to occur under many different conditions. Perhaps the factors which cause death, even though acting for only a short time, are partly responsible for the changes in the thyroid, and indeed it may well be that the glands of infants who survive do not undergo the grosser degrees of acinar collapse and disorganisation.

It is not necessary to suppose that the additional stimulus is a long-acting one. Womack and Cole, in one of their experiments, observed a marked transformation in as short a period as 18 hours, reaching such a degree that the thyroid was difficult to recognise as such microscopically, and Farrant (1914) illustrated a guinea pig thyroid, devoid of

colloid and showing little trace of acinar structure, 24 hours after inoculation with glanders. Other experiments, though unsupported by histological study, lead to the same conclusion. For example, in rats subjected to intramuscular injections of formalin (Paschkis et al., 1950), the decrease in thyroid weight, 21 to 28 hours after injection, ranged from 17 to 36 per cent. These decreases are too great and too rapid to represent "atrophy and involution", which were stated by Selye (1946) to be the response of the thyroid to stress; they suggest, rather, massive colloid release. And again, Hetzel et al. (1952), studying the effects of stress on the human thyroid, noted marked fluctuations in serum protein-bound iodine - rises as great as 100% from 1 to 3 hours afterwards, or falls of as much as 60%.

Whether or not "stress", in the modern sense, can result in the histological changes in question must be a subject for future study. Meanwhile, it would be idle to speculate further until more is known of the circumstances which provoke a demand for thyroid hormone.

SUMMARY AND CONCLUSIONS

The human thyroid at birth often bears little resemblance to the adult gland. The thyroid in the newborn is characterised by a series of changes, occurring especially in the central zone of each lobe, which involve loss of the colloid, desquamation of the epithelium, and collapse or disorganisation of the acini. Such changes, though closely resembling those of post-mortem autolysis, and probably accentuated by autolysis, are interpreted as evidence of increased physiological activity.

The extent of the changes varies greatly in different cases. They do not appear to be related to the maturity of the child, its sex, the nature of labour, or the cause of death; they occur as frequently in the liveborn as in the stillborn, but are of decreasing prevalence after the third day of life.

The view that the thyroid at birth is unduly susceptible to autolysis is not regarded as an adequate explanation for the histological changes. It is suggested, instead, that the thyroid in late foetal life is normally in a higher state of physiological activity than at any other period in life, and is unduly susceptible to functional exhaustion.

2. THE INFLUENCE OF MATERNAL THYROID DYSFUNCTION ON THE NEONATAL THYROID, AND THE INFLUENCE OF ANTITHYROID DRUGS GIVEN DURING PREGNANCY

In the course of collecting sections of infants' thyroids, three cases were seen in which the mother had suffered from thyroid disease during pregnancy: myxoedema in one case and thyrotoxicosis in the other two. The three case-reports are followed by a discussion on congenital thyrotoxicosis.

Case 1

The mother, aged 34, had had a severe post-partum haemorrhage, following ante-partum haemorrhage and stillbirth, 6 years previously. She had subsequently developed myxoedema, and was considered to have suffered necrosis of the anterior pituitary: since then, she had been treated with desiccated thyroid, 3 gr. daily.

She presented shortly before delivery with signs of hyperthyroidism, due apparently to excessive thyroid medication. The estimated duration of pregnancy was 41 weeks.

Labour: Occipito-posterior presentation, manual

rotation, followed by mid-cavity forceps delivery. The cord was twice round the neck, the second loop quite tightly, and there were signs of foetal distress (meconium staining).

The child, a male weighing 2945 g., lived for only 15 minutes. Autopsy was carried out 41 hours after death. Two congenital abnormalities were present: atresia of the R. lung, and an interventricular septal defect in the heart.

The thyroid was symmetrical, was not enlarged, and was of normal appearance both superficially and on section. Microscopically, the acinar structure was for the most part preserved, but all degrees of epithelial desquamation were present; many of the acini were devoid of colloid and contained only desquamated cells, while others contained both colloid and desquamated cells (Fig. 25). The peripheral acini showed less desquamation; many were well formed, lined by cuboidal epithelium, and filled with colloid.

Comment: The histological picture in the thyroid is within normal limits, and exhibits no feature which would raise any suspicion of thyroid dysfunction in the mother. There has as yet been

no reported case of infant thyroid abnormality due to pituitary myxoedema in the mother, though single cases have been recorded due to primary myxoedema (Moran, 1952) and post-thyroidectomy hypothyroidism (Koerner, 1954), in which of course the hormonal abnormalities in the mother are different.

In Moran's case, the mother was myxoedematous, but could tolerate only low doses of desiccated thyroid. The infant had an interventricular septal defect in the heart, and the thyroid, though considerably enlarged, was microscopically similar to that just described.

It is open to question whether the maternal hypothyroidism, or even the excessive thyroid medication, in the present case played any part in causing the congenital abnormalities of heart and lung. Myant (1958) studied the passage of thyroxine and tri-iodothyronine across the human placenta; his results suggested that thyroid hormone is not concerned with early stages of growth and differentiation of the foetal organs. However, Mayer and Hemmer (1956) were able to collect a series of cases showing an association between maternal hyper- or hypo-thyroidism and malformations of the infant,

including athyrosis, hypothyrosis, congenital heart defects, true cretinism and faulty ossification.

In the present case, there is the additional possibility that the absence of pituitary hormones (other than the thyrotropic hormone) may have been deleterious to foetal development.

Case 2

The microscopic sections of this case were kindly shown to me by Dr. I.D. Riley. The history as given to me was as follows: The mother, a 29-year old primigravida, developed thyrotoxicosis for the first time during pregnancy. She was treated with thiouracil for a period of 10 weeks, the treatment ceasing 3 weeks before delivery. The daily dosage was 1000 mg. for the first 4 weeks, then 600 mg. for one week, then 400 mg. for the remaining 5 weeks. The child, a full-term male, weighed 2764 g. at birth. There was visible enlargement of the R. lobe of the thyroid, and the baby was thought to be hypothyroid in appearance. He developed vomiting and diarrhoea, and died on the 13th day. At autopsy, the body was emaciated, with loss of nearly all subcutaneous and body fat. There was no information as to the size

of the thyroid, or the interval between death and autopsy.

Microscopically, the thyroid acini were poorly preserved in all areas; they showed varying degrees of epithelial desquamation, and in many instances the lumen was totally occupied by desquamated epithelial cells. The nuclei were small and stained deeply; the cytoplasm stained faintly, and had indistinct margins. Colloid was absent throughout.

Comment: Here again the histological picture is within normal limits. There is nothing that points to thiouracil as the cause of the goitre. It can be shown experimentally (p. 96) that thiouracil goitre in the newborn, as at any other age, is characterised by the conventional picture of hyperplasia, and that autolysis would not account for the conversion of such a picture into the one described here.

Persistence of thyroid enlargement with reversion of the histological picture to normal has been noted in the rat 65 days after cessation of prolonged thiourea administration (Goldsmith et al., 1945), and it may be that the interval of 5 weeks between cessation of treatment and death in this case allowed

a similar return to normal. Yet there are on record other cases of congenital goitre with normal histological picture which cannot be explained in this way. In the case reported by Salm (1954), in which comparatively small doses of methylthiouracil had been given during pregnancy, the child was stillborn, and the thyroid, though enlarged, showed only doubtful evidence of hyperplasia histologically and was closely similar to that in the present case. In another stillbirth (one of twins) following propylthiouracil treatment during pregnancy (Saye et al., 1952), the infant's thyroid weighed 32 g., yet was composed of empty acini lined by cuboidal epithelium, a description which does not suggest hyperplasia. In both these cases, antithyroid medication had been continued to term.

Case 2 of Skelton and Gans (1955), in which antithyroid drugs were not implicated, is again similar, and Zampi and Cinti (1957), describing congenital goitre in twins, remarked on the similarity to the normal histological structure. Indeed, many other descriptions of congenital goitre, whether or not following antithyroid medication, leave one in doubt as to the presence of true hyperplasia. It may be

noted here that in 6 cases of congenital (endemic) goitre reported by Hiilesmaa (1948), the histological picture in no way differed from the normal.

Enlargement of the thyroid associated with a normal histological structure is contrary to our general experience of thyroid pathology in the adult. The present case adds nothing to our understanding of this phenomenon, except to show that it can occur even with high doses of antithyroid drugs.

Case 3

The mother, aged 34, developed thyrotoxicosis and exophthalmos during pregnancy, and was treated up to delivery with 100 mg. methylthiouracil and 0.1 mg. laevothyroxine daily. This dosage was insufficient to control the symptoms, but was not increased for fear of affecting the foetal thyroid. The gestation period was 34 weeks. The child, a premature male weighing 1937 g., had visible thyroid enlargement at birth. Signs of thyrotoxicosis were noted on the 8th day (tremor, moist skin, hyperactivity, tachycardia, slight exophthalmos). There was no gain in weight during the second week, although hyperactivity temporarily diminished. The blood cholesterol was

104 mg. % on the 2nd day, and 124 mg. % on the 23rd day. Signs of hyperactivity returned, and treatment with Lugol's iodine was begun on the 36th day, but death occurred one day later, apparently due to aspiration of a feed.

At autopsy, 60 hours after death, the body weight was 1865 g., and emaciation was pronounced. The presence of food in the respiratory tract was confirmed.

The thyroid weighed 10 g., and showed uniform enlargement of both lateral lobes and isthmus (Fig. 26). The external surface was smooth. The gland was firm, and the cut surface was of fleshy appearance, without nodules; the individual lobules were clearly visible.

Microscopically, the acini were rather small, of irregular outline, and lined by cuboidal or occasionally low columnar epithelium (Fig. 27). Desquamated cells were common in the lumina, but there was no disintegration of the acinar walls. Interacinar cells were numerous. The colloid stained poorly in all areas. The interlobular septa were considerably thickened, and in some areas there was intralobular fibrosis. High-power examination showed that

although the epithelium was mainly cuboidal, there was considerable variation in nuclear structure (Fig. 28). The nuclei varied both in size and in staining intensity, ranging from medium-sized and dark-staining to large and vesicular; many were of irregular shape, and a few were exceptionally large. Mitotic figures were not seen. The cytoplasmic boundaries were well defined.

Comment: The general structure and the colloid content of the thyroid (like the body weight) are more in keeping with those of a newborn child than one aged 5 weeks. The obvious abnormalities are in the nuclear variability and the increase in connective tissue. The findings are best explained as a stage in the involution of a hyperplastic thyroid. The contradictory presence of nuclear variability and colloid depletion with cuboidal epithelium and increased connective tissue suggests recurrent hyperplasia and involution, as is indeed apparent from the clinical history. The picture so little resembles that of active hyperplasia that one would scarcely expect it to have been associated with hyperthyroid symptoms. However, the very bulk of the gland would account for an output of thyroid hormone many times greater than

normal. It can be inferred that, had the child survived, he would have made a spontaneous recovery from his condition of hyperthyroidism.

An attempt must be made to determine the respective roles of maternal thyrotoxicosis and of thiouracil treatment in the pathogenesis of congenital thyrotoxicosis in this case. Before thiouracil is held accountable, it is well to recall Case 2, in which a much higher dosage, and a similar interval between cessation of the drug and death, produced no histological change in the infant thyroid, and to note that the great majority of infants born of thiouracil-treated mothers show no thyroid abnormality whatever (literature summarised by Elphinstone, 1953). Moreover, while congenital goitre following thiouracil treatment has in different cases been associated with hyperthyroidism, hypothyroidism, or normal thyroid function, so also has congenital goitre in untreated cases.

CONGENITAL THYROTOXICOSIS: A REVIEW

As I have been able to find in the literature only 12 published cases of congenital thyrotoxicosis, it would seem more rewarding to review them all rather than attempt to unravel the tangled etiology in this

case alone. It seems justifiable to include also the much-quoted but briefly-described case of Keynes (1952), in which the child, like the mother, had exophthalmos without thyrotoxicosis. Case 2 of Bongiovanni et al. (1956) is excluded, since hyperthyroidism was diagnosed only in the laboratory and the infant does not appear to have been clinically thyrotoxic.

Details of the 13 cases are tabulated in chronological order (Table 12) and will be referred to for convenience by the case numbers which they have been given here. The present case is No. 12 in the series.

It will be seen from the Table that all the mothers either were or had previously been thyrotoxic. Five had previously undergone thyroidectomy (Cases 5, 6, 8, 10, 11), one had been treated with radioactive iodine (Case 13), and one had had both thyroidectomy and radioactive iodine (Case 7). Of the five cases in which exophthalmos was the chief symptom, one was only slightly hyperthyroid (Case 13), three were euthyroid (Cases 5, 6, 8), and the fifth hypothyroid (Case 7). Five mothers had been treated during pregnancy with thiouracil or its derivatives (Cases 2, 4, 9, 11, 12), and in at least four of these

control was incomplete.

Thus only Case 1, and perhaps Case 3, can be regarded as examples of straightforward hyperthyroidism in the mother. In the remainder, there had been surgical or medical treatment of the condition, with varying degrees of success, and therefore a disturbance of the pituitary-thyroid relationship ordinarily present in primary hyperthyroidism. In particular, this small series seems to include an undue proportion of cases in which thiouracil derivatives were not wholly effective, and of cases in which exophthalmos occurred or persisted in spite of more or less successful treatment of the thyrotoxic state. When one recalls that the great majority of thyrotoxic mothers give birth to normal infants, in many cases after thiouracil treatment, it is clear that the cases reviewed here are of a distinct type or types showing a special tendency to result in congenital hyperthyroidism.

A study of the infants' histories is also rewarding.

Sex: Of the infants whose sex was stated, 9 were males and 3 females. Such a disparity could well occur by chance, but it is of interest that in two

families described by Davies (1943), congenital goitre (without hyperthyroidism) affected males only.

Maturity: This has not always been stated with accuracy, and where the birth weight alone is given it must be remembered that intra-uterine thyrotoxicosis may have resulted in a birth weight disproportionately low in relation to gestation age. Premature and mature infants are about equally represented; the three which succumbed were all premature.

Clinical picture: Thyrotoxicosis was present in all except Case 5, goitre in all except Cases 2, 3 and 5, exophthalmos in all except Cases 9 and 11. The incidence of exophthalmos is high, as compared with the incidence in adult thyrotoxicosis, and reflects the high incidence of this symptom in the mothers.

Onset of symptoms: In 4 cases, it was noted that symptoms of thyrotoxicosis were not present at birth, but appeared a variable time afterwards. In Case 2, there was a delay of about 6 weeks. In Case 4, thyrotoxic symptoms appeared at 3 days, goitre at 6 days, and exophthalmos at 8 days. In Case 11, there was a delay of 8 days, and in Case 12 goitre was

present at birth but thyrotoxic symptoms did not appear until the 8th day. The one factor common to these four cases of delayed onset was treatment of the mother with thiouracil derivatives during pregnancy. Indeed, in only one thiouracil case (Case 9) was a delay in onset not remarked upon; medication had been discontinued 2 months before delivery.

Reviewing these cases, two clinical pictures emerge. In one, the mother has been treated for thyrotoxicosis either surgically or by radioactive iodine; she has persistent exophthalmos but shows little or no evidence of hyperthyroidism. The child has thyrotoxicosis and exophthalmos, recognisable at birth. In the other, the mother has primary hyperthyroidism, responding incompletely to antithyroid drugs, and the child develops thyrotoxicosis a variable time after birth.

Pathogenesis of congenital hyperthyroidism

This must necessarily be different from that of hyperthyroidism in the adult. It is highly unlikely that the infants developed primary hyperthyroidism analogous to Graves' disease, unrelated except

through hereditary disposition to the mother's condition. There is sufficient evidence against such a concept in the rapid, permanent and often spontaneous recovery which occurred in those infants who survived. It is reasonable to assume that congenital hyperthyroidism is due to transient stimulation of the infant's thyroid by thyrotropic hormone, in contrast to Graves' disease, in which there is strong evidence that the hyperthyroidism is not mediated through the pituitary (Werner, 1955). The question to be answered is: What is the source of the excessive thyrotropic stimulation? Does it lie in the mother's or in the child's pituitary?

To incriminate the maternal thyrotropic hormone requires two assumptions: firstly, that there is excess circulating TSH in the mother's bloodstream, and secondly, that this TSH is capable of crossing the placenta to reach the foetal thyroid.

1. It is usually stated that the serum TSH level in thyrotoxicosis is normal or even lower than normal. Such evidence as there is, however, shows that it is not constantly so. Of 14 cases investigated by Rawson and Starr (1938), 2 had raised TSH levels. Four of the 8 hyperthyroid patients studied

by De Robertis (1948) had very high levels, and these four had special symptoms in addition to those of hyperthyroidism (localised oedema in two, ophthalmopathy in two). A higher level occurred in myxoedema, and the highest (nearly 100 times normal) was in a case of myxoedema and persistent exophthalmos following treatment of thyrotoxicosis by radiotherapy. Purves and Griesbach (1949) found the level to be normal in untreated thyrotoxicosis, but significantly increased on treatment with thiouracil, and high also in malignant exophthalmos. Gilliland and Strudwick (1956) separated their cases into those with and those withoutsevere eye signs. In those with severe eye signs, 7 out of 8 had high levels, while of those without, 2 out of 5 had moderately high levels. Of great interest is the report of Asboe-Hansen et al. (1952). TSH was not detectable in the serum of normal controls, cases of Graves' disease without severe eye signs, nor in myxoedema, but high levels were found in 9 out of 10 cases of progressive exophthalmos. This series included 7 cases of progressive exophthalmos following thyroidectomy for thyrotoxicosis. On the other hand, D'Angelo et al. (1951) found a high level in one of

10 cases of thyrotoxicosis without severe eye signs, and in only 2 out of 8 cases of ophthalmopathy. Bottari (1958) reported an increased level in "most cases" of thyrotoxicosis.

While there are many contradictory results, partly owing to the differing sensitivities of the methods employed, it is fair to conclude that a minority of thyrotoxic cases, especially those with exophthalmos, have raised TSH levels, that the level is possibly increased by thiouracil treatment, and that cases of progressive exophthalmos following thyroidectomy have high levels, perhaps most notably those who have become hypothyroid.

Thus 11 of the 13 cases reviewed here belong to the minority in which one might expect a raised TSH level (6 because of previous surgical or radioiodine thyroidectomy, with persistent exophthalmos, and 5 because of thiouracil treatment).

2. If it is accepted that some or all of these mothers had high serum TSH levels, it is also necessary to assume that maternal TSH is capable of crossing the placenta. Such a possibility has often been discounted because of experimental evidence that it cannot do so (Tobin, 1941; Peterson and Young,

1952; Nikitovitch and Knobil, 1955). However, there are probably differences between species, and the rat and guinea pig experiments provide no grounds for concluding that maternal TSH is unable to influence the human foetus. Perhaps it does so only exceptionally, or perhaps an abnormal form of TSH can cross the placenta, such as that which Adams (1958) considered might be the "exophthalmos-producing factor".

Considering for the moment only those cases in which antithyroid drugs were not concerned, there are strong reasons for believing that excess maternal TSH was responsible. It is clear from the generally benign course of congenital hyperthyroidism and the tendency to spontaneous recovery that this is not a primary disease of the infant, but a transient disturbance due to maternal influence. As the condition is recognisable at or even before birth, it is equally clear that the cause of the hyperthyroidism is operating during intra-uterine life, and does not lie in release of the foetus from maternal influence at the time of birth.

The only maternal factor other than TSH which need be considered is excess thyroid hormone, and this

is readily dismissed because it would not cause goitre or exophthalmos, and would not account for the prolongation of thyrotoxic symptoms beyond a few days. From the case histories, and from the TSH assay studies already quoted, it can be seen that most of the mothers have belonged to the small group of thyrotoxic cases in whom one might expect high serum TSH levels.

It might be objected that the duration of symptoms in all cases was greater than could be accounted for simply by maternal thyrotropic stimulation of the foetal thyroid; if this were the whole explanation, the symptoms would disappear shortly after birth, as soon as the excess TSH is eliminated. But if prolonged stimulation of the foetal thyroid has resulted in a gland several times the normal size, then even after the excessive stimulus has been removed the increased volume of functioning tissue would account for an abnormally high output of thyroid hormone.

Into this complex picture must be fitted the influence of antithyroid drugs given to the mother during pregnancy. We do know that the incidence of congenital hyperthyroidism is very low, irrespective of antithyroid drugs, but it is not known whether

these drugs influence the likelihood of congenital hyperthyroidism developing. It is arguable that the 5 cases in which thiouracil derivatives had been given may have been cases in which congenital thyrotoxicosis would have occurred in any event. The demonstrably higher serum levels of TSH during thiouracil treatment, and the occurrence of exophthalmos in 3 of the 5 infants in this group, might suggest that the same mechanism is operating. However, there are good reasons for believing that the role of antithyroid drugs is not confined to increasing the maternal output of TSH.

Experimentally, transplacental transmission of thiouracil and related drugs has been demonstrated in the guinea pig (Hughes, 1944; Webster and Young, 1948; Webster, 1949; Logothetopoulos and Scott, 1956), in the rat (Goldsmith et al., 1945; Freiesleben and Kjerulf-Jensen, 1947), in the rabbit (Freiesleben and Kjerulf-Jensen, 1947; Krementz et al., 1957), in the mouse (Kauffman et al., 1948), and again in the guinea pig by myself, in the next Section of this work. It has further been shown that development of a hyperplastic goitre in the foetal guinea pig can be counteracted by the simultaneous

administration of thyroxine (Peterson and Young, 1952). There is no reason to suppose that in the human the small molecule of thiouracil behaves differently. There is indeed one case on record (Aaron et al., 1955) in which propylthiouracil administration throughout pregnancy to a woman who had no thyroid disease resulted in a congenital goitre, apparently with normal thyroid function, in the child.

A study of the mothers' and infants' histories in the 5 thiouracil cases suggests that these form a separate group, significantly different from the other ("untreated") group of 8 cases. All the thiouracil-treated mothers had a moderate to severe degree of thyrotoxicosis during pregnancy, while in 6 of the untreated cases thyrotoxicosis was absent or only slight. Only one of the treated mothers had had a previous thyroidectomy or radioiodine treatment, compared with 6 in the untreated group, and in none was exophthalmos the predominant symptom, compared with 5 or perhaps 6 in the untreated group. In the treated group, 4 out of 5 infants showed a delay of from 3 days to 6 weeks in the onset of symptoms, while in none of the untreated group was

any such delay noted.

It is postulated here that antithyroid drugs initiate a wholly different mechanism of stimulation of the infant thyroid. It cannot be accepted that they only delay the onset of the mechanism which operated in the untreated group, as transplacental transmission of maternal TSH could hardly be responsible for thyrotoxicosis developing as late as the 6th week of life, or even the 8th day. In at least 4 of the treated cases, therefore, it would seem that the infant's thyroid was responding to excess secretion of TSH by the infant's pituitary. This could be explained by the fact that during intra-uterine life synthesis of thyroid hormone had been blocked by thiouracil, resulting in a long-standing hyperactivity of the thyrotropic cells of the foetal pituitary; the thyrotropic hypersecretion could not result in thyrotoxic symptoms until the thiouracil had ceased to be effective. Thyrotoxicosis would not therefore be expected to occur until some days after birth, although the goitre might be clinically evident at the time of birth (as in Case 12). A rebound high uptake of radioactive iodine was demonstrated in the foetal guinea pig by

Logothetopoulos and Scott (1956) 3 days after withdrawal of propylthiouracil from the mother. Persistence of the thyrotoxic symptoms for some weeks or months, with gradual spontaneous recovery, is not difficult of explanation. Just as in the untreated group the hyperplastic thyroid oversecretes after the stimulus to hyperplasia has been removed, if only because of the increased bulk of the tissue now released from the abnormal stimulation, so in the treated group the hypertrophic pituitary continues to secrete excess TSH until, some weeks or months after the influence of thiouracil is removed, it slowly adjusts itself to the normal pituitary-thyroid equilibrium.

If antithyroid drugs set the stage for thyrotoxicosis developing shortly after birth, why have so few cases been reported? It may be that many milder cases have gone unrecognised, as the symptoms would more readily escape notice in the newborn child than in the adult; such cases could only be diagnosed by modern laboratory methods, as in Case 2 of Bongiovanni et al. (1956). In many cases the child has been described as goitrous but euthyroid (Eaton, 1945; Herrera, 1948; Vérel, 1949; Lund, 1950;

one of the twins reported by Saye et al., 1952; Thamdrup, 1952; Branch and Tuthill, 1957); in all except the cases of Herrera and Thamdrup, anti-thyroid medication had been continued until delivery. A more serious objection to the above hypothesis is that hypo- as well as hyper-thyroidism has been reported in the offspring of thiouracil-treated mothers (Morris, 1953; Elphinstone, 1953; Scarizza, 1954; Krementz et al., 1957; and Case 2 reported here). In at least the last-mentioned case, as already stated, the histological evidence does not confirm that thiouracil was responsible for the goitre.

It has often been suggested that thiouracil treatment in pregnancy is dangerous to the foetus only if the dosage is excessive (Caren, 1949; Crooks, 1957, and many others). Only Elphinstone's case of congenital hypothyroidism is a possible example of overdosage, the mother having been rendered mildly hypothyroid with methylthiouracil. In congenital thyrotoxicosis, overdosage does not seem to be a factor, as at least 4 of the 5 cases were inadequately controlled with thiouracil derivatives. The <u>duration</u> of treatment is probably of greater

significance. Continuation of treatment up to the time of delivery in 4 of the 5 cases was probably unwise, as it subjected the foetal thyroid to the effects of thiouracil at a time when it is normally in a state of great activity.

The histological findings in congenital thyrotoxicosis unfortunately contribute little to our understanding of the problem. Only 3 cases have come to necropsy. In Case 1, White described a hyperplastic goitre, but did not illustrate the microscopic appearances; the description is rather vague, and appears to refer to the changes characteristic of the normal neonatal thyroid as well as those of hyperplasia. In Case 8, Skelton and Gans illustrate a truly astonishing picture in which the acinar structure is totally lost and the thyroid is composed of small nodular aggregates of cells; there is little resemblance to the picture of either a normal or a hyperplastic thyroid. The only thiouracil-treated case is the one described here, in which the picture suggests involution in a hyperplastic gland.

SUMMARY AND CONCLUSIONS

Three cases are described in which thyroid dysfunction in pregnancy was followed by early death of the infant.

In the first case, the mother had pituitary myxoedema. The infant survived only 15 minutes, and its thyroid was macroscopically and histologically normal; there were congenital abnormalities of heart and lung.

The second mother had thyrotoxicosis, treated by thiouracil. The infant survived 13 days, and was considered to be hypothyroid. Its thyroid was enlarged, but, despite the high dosage of thiouracil to which it had been subjected, the histological picture was of a type which commonly occurs in the normal newborn.

The third mother had exophthalmic goitre, treated by methylthiouracil. The infant was goitrous, thyrotoxic and exophthalmic, and died on the 37th day. The histological appearance of the thyroid suggested involution of a hyperplastic state.

From a review of all the reported cases of congenital thyrotoxicosis, it is concluded that there

are two different mechanisms of pathogenesis. In the first, maternal thyrotropic hormone crosses the placenta and stimulates the foetal thyroid; this is the probable explanation in cases where the mother has persistent exophthalmos, though not necessarily persistent thyrotoxicosis following thyroidectomy, and the infant is recognisably thyrotoxic at birth. In the second mechanism, antithyroid drugs administered to the mother during pregnancy block the foetal synthesis of thyroid hormone and thus indirectly stimulate the foetal pituitary; in these cases, the onset of thyrotoxicosis is delayed, and is attributable to the action of the infant's own thyrotropic hormone.

3. EXPERIMENTAL OBSERVATIONS

The studies of the neonatal thyroid in the two preceding Sections raised almost as many questions as they answered. The greatest handicap in studying the human gland and its varying histological appearances was the inability to exercise any control over the many factors which might be implicated.

Over 50 litters of newborn guinea pigs have therefore been examined, in order to gain more precise information on some of the questions raised.

The objects were (1) to clarify the significance of the epithelial desquamation and colloid depletion noted in the human gland, (2) to note the occurrence of the associated features of congestion, lymphatic distension and inactivity of the peripheral zone, (3) to determine whether the histological picture is the same in animals dying spontaneously as in their sacrificed littermates, and (4) to study the effects on the neonatal thyroid of antithyroid drugs administered to the mother during pregnancy and lactation. As hyperactivity and post-mortem degeneration are the two factors most often held responsible for the

peculiar histological appearances of the human neonatal thyroid, particular attention was given to the effects of thyrotropic stimulation and to the degenerative changes observed in the thyroid at measured intervals after death. An attempt was made to determine whether these factors, singly or in combination, could be employed to produce a histological picture resembling that found in the human neonatal thyroid.

In some instances, the possible factors were as inextricably intermingled as in the human cases. For example, if an animal died during the hours when the animal house was unattended, the result was an inexact death-fixation interval combined with (usually) an unknown cause of death; in the case of stillbirths there was the additional unknown factor of the interval between intra-uterine death and delivery. Under such circumstances, there was difficulty in gauging the effect of any experimental procedure.

Uncertainty as to the precise hour of livebirth proved to be less important, as there was no detectable variation in the histological structure during the first few days of life.

Except when otherwise stated, the histological

descriptions refer to cases in which only one factor was known to be implicated.

The guinea pig was chosen as the most suitable experimental animal for several reasons other than its ready availability. The newborn guinea pig is of a sufficient size to allow easy identification of its thyroid; the newborn rat proved to be far too small. The effect of pituitary extract on the thyroid is more intense in the guinea pig than in other experimental animals (Thurston, 1933). The guinea pig is one of the animals which does not normally show colloid depletion and collapse of the acini in the neonatal thyroid (Benazzi, 1929); it was therefore considered to be a suitable animal in which to attempt to produce these changes experimentally, unhampered by the possibility that they might occur as part of a normal physiological process. The onset of physiological function in the foetal guinea pig thyroid at the 28th day of foetal life (Logothetopoulos and Scott, 1956), with a total gestation period of 66 to 72 days (Hughes, 1947), allows a period of 5 to 6 weeks in which antithyroid drugs administered to the mother might affect the foetal thyroid. The corresponding periods of 4 days in the

mouse (Speert et al., 1951) and 3 days in the rat (Gorbman and Evans, 1943) between the onset of thyroid function and delivery, are too short. The rabbit is a poor animal for antithyroid drug studies (Krementz et al., 1957), as only a limited response is obtained even with high dosage.

The obvious disadvantage of the guinea pig is the relatively small number of animals in each litter.

METHODS

Animals were killed by chloroform. The neck structures were removed in toto and fixed immediately in formalin. On the following day, the portion of trachea bearing the thyroid was separated, and after further fixation the tissue was dehydrated and embedded in the usual way. In some instances, the thyroid was dissected free and weighed; to minimise any fallacy due to fixation, weighing was always carried out after exactly 24 hours of fixation. Diagrams were drawn representing the size of the thyroid after fixation; some of these diagrams are reproduced in Fig. 30.

Sections were cut at six levels from each block, and at each level H and E, Masson's trichrome and

P.A.S. stains were used.

Blocks were taken simultaneously from heart, lung, liver, kidney, adrenal and sternum.

The experimental procedures are summarised below (details of individual litters are given in Appendix 2).

1. Untreated newborn guinea pigs were killed at varying intervals after birth; when the precise time of birth was not known, the probable limits of the age in hours are given.

2. All animals stillborn during the period of the investigation were examined as soon as possible after delivery. Six guinea pigs died late in pregnancy, and the foetuses were extracted from the uterus.

3. Newborn guinea pigs were injected intramuscularly with a preparation of thyrotropin supplied by Armour & Co., Chicago, and were killed at varying intervals up to 96 hours after injection. Each injection of thyrotropin was equivalent to 15 mg. Armour standard.

4. Antithyroid drugs were administered to pregnant guinea pigs by substituting solutions or suspensions of the drugs for drinking water, and administration was continued during lactation. The three substances used were thiouracil, in concentrations of

0.1%, 0.05% and 0.005%, potassium perchlorate, in concentrations of 0.1% and 0.005%, and carbimazole ("Neomercazole"), in concentrations of 0.005% and 0.0005%. Despite the very low solubility of thiouracil, this method proved to be satisfactory.

The lower concentration of each drug represented a dosage per kilo equivalent to, or just a little higher than, the usual human therapeutic dosage.

Most of the offspring were killed within 24 hours of birth. Others were sacrificed at intervals up to the time of weaning, and some neonates were suckled by untreated sows.

5. Autopsy was carried out on some animals at measured intervals up to 5 days after death. One of a litter was examined and the tissues fixed immediately, while the others were allowed to remain at normal animal-house temperature (about 20°C) between death and autopsy. This method was used to assess the effect of autolysis in normal neonates, in the stillborn, after TSH injection, and after administration of anti-thyroid drugs during gestation.

RESULTS

1. The normal guinea pig thyroid

The weights and relative weights (thyroid weight in mg. divided by body weight in g.) are listed in Table 13A. In the mature neonate, the relative weight ranged from 0.38 to 0.43, while higher values were found in the immature. The average for six neonates, mature and immature, was 0.44 - that is, 0.00044 or 1/2300 of the body weight. The relative weight in 3 untreated adult guinea pigs was 0.15, 0.16 and 0.08, and was therefore one-third or less of the relative weight in the newborn.

The thyroid isthmus was usually absent in the newborn, and was always absent in the adult.

Histological structure at birth: The gland was composed of rounded or polygonal acini, with few interacinar cells (Fig. 31). The acini were filled with deep-staining colloid which, with the fixation method used here, was retracted from the margins but was seldom vacuolated. The epithelium lining the acini was cuboidal or low cuboidal. The nuclei were vesicular, rounded in the cuboidal cells but tending to be elongated when the epithelium was lower. The

cytoplasm was not vacuolated, and cytoplasmic granules were not seen with any of the staining methods used; the cell boundaries were well defined. The row of cells lining the acinus was always intact, and desquamation of the epithelium was not seen in any instance. Rarely, cells with deep-staining nuclei and abundant cytoplasm, apparently macrophages, were seen within the colloid.

In several glands, there were isolated dilated acini, usually empty, lined by flattened or rarely stratified epithelium; occasionally two or three such acini appeared to be in communication with one another. Within the substance of the thyroid, also, there were sometimes islets of parathyroid tissue, and, less often, of thymus.

There was constantly an easily-recognised distinction between the centre and the periphery of the gland, and usually a narrow intermediate zone could also be distinguished. The central zone occupied by far the largest area; the acini were large, sometimes of rather irregular outline, and were well filled with colloid. The lining epithelium was perceptibly taller in this zone than elsewhere, though the height rarely exceeded the breadth of the cells.

In the intermediate zone, the acini were smaller and more often rounded, and the colloid staining was relatively weak.

The peripheral zone usually consisted of a single row of acini which were oval or pear-shaped, with their long axes directed towards the centre of the lobe. The epithelium was lower than in the other two zones, especially at the peripheral margin of each acinus, where it could be justifiably described as "endothelioid". In H and E sections, the staining intensity of the colloid differed little from that in the central zone, but in trichrome and P.A.S. sections it was seen to be considerably greater.

The larger blood vessels were congested, but blood corpuscles were not seen in the interacinar capillaries.

Colloid-like substance was seen in the lymphatics in only two of 14 cases, once within the gland and once just outside the capsule. In each instance, a single narrow lymphatic channel was seen. Neither gland showed any evidence of increased activity.

Colloid-like substance was more often seen in the veins.

Groups of lymphocytes were present in the

connective-tissue septa in most glands.

In one case, there were scanty small haemorrhages into the colloid, unaccompanied by epithelial desquamation or other abnormality.

Neither the birth-weight nor the age in hours had any demonstrable effect on the histological picture, whether judged by a comparison of unrelated neonates or by a comparison of littermates of differing birth-weight or age. At the age of 16 days, the histological picture remained the same.

In the adult guinea pig thyroid, the basic structure was the same, though part of the gland was replaced by fat. The distinction between the central and peripheral zones was as clear as in the newborn; the epithelium, however, tended to be lower, and the peripheral zone of acini lined by flattened epithelium was much broader. Clumps of interacinar cells were numerous in the central zone.

Lymphocytes were fewer than in the newborn; neither macrophages nor epithelial cells were seen in the acinar lumina.

Rarely, single acini were lined by stratified epithelium; these were often empty, but sometimes contained discrete strands or particles which were

intensely P.A.S.-positive, or a homogeneous substance of the same staining intensity as colloid.

2. Stillbirths and intra-uterine deaths

Some of the stillborn animals were macerated, and were of little value for studying the histology of the thyroid. The following description refers only to those cases in which post-mortem changes were negligible in the other organs examined.

The histological picture in the stillborn did not show the same uniformity as in the normal neonates, both colloid content and epithelium varying from case to case.

Colloid depletion was usually considerable, and often the surviving colloid showed marked peripheral vacuolation (Fig. 32). Colloid depletion was greatest in the intermediate zone, and least in the peripheral zone.

The lining epithelium was normal in many cases, but in others it was slightly taller, often varying from one acinus to another; large hyperchromatic nuclei were seen in a few instances, and in one there were scanty mitotic figures (Fig. 34). The cytoplasmic margins tended to be indistinct. Occasional

segments of taller epithelium showed displacement of the nucleus to the centre of the cells, and P.A.S.-positive granules were present in the cytoplasm; sometimes similar granules were seen in the inter-acinar cells. Vacuolation of the cytoplasm was uncommon, and was more often diffuse than localised to the base of the cell. (Figs. 34, 35).

Desquamation of the epithelium was seen in only one case, in which it was accompanied by early disintegration of the row of lining cells (Fig. 33). In another, a few nuclei were protruded towards the lumen, but the cells had not completely separated from the lining (Fig. 34).

Congestion was usually much greater in the stillborn than in the sacrificed liveborn, irrespective of the structure of the acini. It affected the inter-acinar capillaries as well as the larger vessels, and in every instance it was paralleled by increased congestion in the neighbouring tissues and in the abdominal viscera.

Distension of the lymphatics by colloid-like substance was seen in most instances, involving the lymphatics both within and outside the gland, and sometimes the degree and extent of the distension

equalled that already described in the human neonatal thyroid. It occurred especially in those glands showing peripheral vacuolation of the colloid, and in those showing vacuolation of the cytoplasm (Figs. 32, 35).

The offspring of two untreated sows dying late in pregnancy are of importance here, although again the death-fixation interval is not known. (In a third litter, autolysis had proceeded too far for useful study). In each case, autopsy was carried out within a few hours of the mother's death, and 3 foetuses were found in utero. The foetal viscera all showed some degree of autolysis, while the maternal tissues did not. The foetal thyroids were devoid of colloid and of colloid-like substance in the lymphatics. The acinar epithelium was detached, here and there the row of cells was disintegrating and epithelial cells were seen in many lumina; degenerative changes in the nuclei were not advanced. The resulting picture, although suggestive of autolysis, was unlike that produced by deliberately delaying fixation in the normal neonatal thyroid.

There were only three spontaneous neonatal deaths among the untreated animals - at a few hours, at 3

days, and at 5 days. The thyroids showed no abnormalities which could not have been due to autolysis alone.

3. The effects of thyrotropic hormone

Eight newborn animals were given single injections of TSH, and killed after intervals of 20 to 96 hours. The tissues were fixed immediately after death. Untreated littermates were examined simultaneously.

At 20 hours after injection, the acini were slightly reduced in size, and had become definitely irregular in outline. The colloid stained poorly, and showed large peripheral vacuoles. The lining epithelium was cuboidal or high cuboidal, with vesicular nuclei; there was no desquamation or cytoplasmic vacuolation. The peripheral zone was unaffected, as regards both epithelium and colloid content.

At 23 to 28 hours, there was further colloid depletion; the acini of the intermediate zone were now empty, and those in the central zone contained only faint-staining strands (Fig. 36). The epithelium was now cuboidal even in many peripheral acini; many of the nuclei were hyperchromatic, and tended to be

displaced towards the apex of the cell, though there was no vacuolation of the basal cytoplasm. Mitotic figures were seen for the first time in the 28-hour specimen. P.A.S.-positive cytoplasmic granules were seen in one case.

At 44 to 46 hours, epithelial hyperplasia and colloid depletion were further advanced. The acini were now enlarged and irregular, with infoldings of their walls. Colloid persisted as faint strands in the central zone, but was absent elsewhere. The epithelium in the central and intermediate zones was columnar. In the peripheral zone, it was high cuboidal in the greater part of each acinus, while at the peripheral margin of the acinus it remained low cuboidal or flat. The nuclei were enlarged, and varied considerably in shape; some showed prominent clumps of chromatin, while others were uniformly dark-staining. The majority of the nuclei were situated at the base of the cell, but some were displaced towards the apex and others - especially if hyperchromatic or undergoing mitosis - protruded beyond the apical margin of the cell into the lumen (Fig.37), in much the same manner as the dividing nuclei of a proliferative endometrium project into the lumen.

Rarely, the cells lay free in the lumen (Fig. 38).

Other cells in the lumen resembled macrophages rather than epithelial cells. Sometimes they were fused to form a giant cell in which the nuclei either formed an irregular clump, or were arranged in a peripheral ring around a central mass of P.A.S.-negative cytoplasm.

At 96 hours, hyperplasia was increased (Fig. 39) but there was no further loss of colloid. Most of the acini now showed papillary projections into the lumen, and the epithelium was columnar even in the peripheral acini. Mitotic figures were most numerous at this stage, but the nuclei had reverted to the central or basal position and there was no suggestion of desquamation. Scanty red cells were seen in the lumina.

At all stages, there was appreciable congestion of the inter-acinar capillaries. Colloid-like substance in the lymphatics provided a very different picture from that seen in the stillborn: it took the form of very narrow interacinar strands, just perceptible in P.A.S. sections, and did not involve the larger lymphatic channels.

Large acini lined by flat epithelium did not share in the hyperplasia, or showed only mild changes (Fig. 36).

4. Effect of antithyroid drugs administered during gestation.

Thiouracil was administered to 8 pregnant guinea pigs, potassium perchlorate to 9, and carbimazole to 7. The offspring were born with congenital goitres. They showed no exophthalmos, no abnormalities of behaviour, and no evidence of respiratory distress. At autopsy no abnormality was detected in any organ other than the thyroid; the bone marrow was of normal cellularity.

The isthmus was well developed in most of the enlarged thyroids, but was sometimes absent even with massive enlargement of the lateral lobes (Fig. 30).

The relative weights of the thyroids were increased up to 5 times the normal value for a mature newborn guinea pig (Table 13C). They did not show the constancy observed in the untreated animals, and there were considerable differences even in littermates. Given in the same concentration, thiouracil produced generally greater increases in weight than did potassium perchlorate. Carbimazole, even when given

in the same concentration (though supposedly 10 or more times as potent) caused no greater enlargement of the thyroid than did potassium perchlorate.

The relative weights of two adult thyroids following thiouracil and potassium perchlorate administration (Table 13D) did not reach the values for the untreated neonate.

Histological picture in the thiouracil- and potassium perchlorate-treated neonates: After administration of the drugs in the lowest concentration (0.005%), the central acini were larger and perhaps more irregular than normally, but without papillary infoldings (Fig. 40). Colloid depletion was considerable only in the intermediate zone. The epithelium was cuboidal or high cuboidal for the most part, and was only a little lower in the peripheral zone than elsewhere. Of the three litters treated with this concentration of each drug, one in each group showed columnar epithelium. The nuclei were basally situated; some were hyperchromatic, but there were no mitotic figures. The cytoplasm was not vacuolated; in one case, a few segments of epithelium showed strongly P.A.S.-positive granules.

With a concentration of 0.05% (thiouracil only),

and similar duration of treatment, hyperplasia and colloid depletion were more advanced. In one case where thiouracil administration was begun only two days before delivery, there was no detectable effect on the neonatal thyroid.

With a concentration of 0.1%, hyperplasia was intense and colloid was absent (Figs. 41, 45). The epithelium was uniformly columnar, and some hyperchromatic nuclei were displaced towards the apex of the cell; there was no desquamation of the epithelium. Clusters of fuchsinophil P.A.S.-negative granules were seen in some cells in the central zone.

In spite of the uniformly columnar epithelium, the peripheral zone was still easily recognisable in that the acini retained their normal size and shape.

With all concentrations, there was no increase in intra-acinar macrophages, and no increase in lymphocytes. Colloid-like substance in the lymphatics was as inconspicuous as in the untreated neonates.

Variations in the degree of hyperplasia occurred even with identical concentrations of each drug. These were not due to differences in the ages of the animals, as only those examined within 24 hours of

birth are considered here, nor were they due to differences in the duration of treatment, as hyperplasia was no less intense after 17 days than after 35 days or more. Varying daily intake of the drug may have been a factor.

Hyperplasia was in general more marked in the thiouracil-treated than in the perchlorate-treated animals. Another difference between the two drugs was in the degree of congestion produced in the thyroid. With the lower concentrations, congestion was evident only after perchlorate treatment. With the higher concentrations, congestion was notable in all cases, and was definitely greater in those treated with perchlorate. In one remarkable case, in which there had been only 17 days of 0.1% potassium perchlorate administration ante-natally, the right lobe of the thyroid was enormously enlarged macroscopically, (Fig. 30) and was greenish-black. Microscopically, almost the entire lobe was destroyed by old and recent haemorrhage (Fig. 42).

Neither drug produced any hyperplasia in the flattened or stratified lining of abnormally large acini (Fig. 40).

The effect of carbimazole was relatively mild. The concentrations used were 0.0005% and 0.005%, in the expectation that carbimazole would produce similar effects in one-tenth of the concentrations used for thiouracil. Hyperplasia and colloid depletion were not striking (Fig. 43), in spite of weight increases comparable to those produced by potassium perchlorate. The case with the longest duration of treatment - 34 days - showed the most pronounced hyperplasia (Fig. 44), but was yet less hyperplastic than the goitres produced by the same concentrations of thiouracil or potassium perchlorate.

Hyperplasia equal to that produced by the other drugs was seen only in one litter. The concentration of carbimazole administered to the mother had been increased after 22 days from 0.0005% to 0.05%, and continued at this high level until death of the animal - presumably from the effects of the drug - 12 days later. In the foetal thyroids, irregularity of the acini and heightening of the epithelium were no less than were obtained with the 0.05% thiouracil.

To judge the effect of antithyroid drug secretion

in the mother's milk, administration was continued after parturition, and some of the offspring were sacrificed at intervals up to 16 days. For comparison, three other neonates were suckled by untreated mothers, and two normal offspring of untreated mothers were suckled by animals receiving antithyroid drugs.

When administration was continued during lactation, some regression of the hyperplasia occurred in the thyroids of the offspring. Re-filling of the acini with colloid, beginning at the periphery of the gland, occurred before there was any detectable fall in the height of the epithelium. With 0.05% thiouracil, re-filling was already evident at 2 days, and some fall in the height of the epithelium was seen at 7 days. At 16 days, both colloid content and epithelium had reverted to normal, and the hyperplasia left its mark only in the persistent enlargement of the acini in the central zone.

With 0.1% potassium perchlorate, as would be expected, involution was slower. Colloid was still absent at 5 and 9 days; there was considerable re-filling at 12 and 14 days, but the epithelium remained high cuboidal. Only one case with similar

dosage of thiouracil is available for comparison: at 3 days, there was considerable re-filling with colloid and a slight fall in the height of the epithelium.

Regression was more rapid in the two 0.1%-perchlorate-treated neonates suckled by untreated sows. At 12 and 14 days, colloid re-filling was almost complete and the epithelium had reverted to cuboidal or low cuboidal; enlargement of the acini persisted (Fig. 46).

Intra-acinar macrophages, which were rare in the normal gland and in the drug-induced goitres at birth, became more numerous during regression (Fig. 47). The increase was already evident 2 days after birth, and was still present at 16 days; it occurred both in those receiving transmammary antithyroid drugs and in those suckled by untreated sows.

The lesser effectiveness of transmammary as compared with transplacental passage of antithyroid drugs was demonstrated again in the three normal neonates suckled by treated sows. Fourteen days of transmammary 0.1% potassium perchlorate resulted in only a mild hyperplasia, confined to the central zone; 14 days of 0.05% thiouracil, and 12 days of 0.005% carbimazole, had no detectable effect. The duration

of treatment in this way was of course limited by the occurrence of weaning at about 2 weeks, but the transplacental experiments had already shown that hyperplasia had reached its maximum at 17 days.

The effect of antithyroid drugs on the maternal thyroid was comparatively slight. The fat deposits disappeared, and were replaced by glandular tissue. The central zone of cuboidal epithelium was more extensive than in untreated animals, leaving only a single row of acini at the periphery unaffected. Colloid depletion was negligible.

With the highest concentration of thiouracil, the epithelium was columnar. Colloid persisted in many of the acini. Macrophages and multinucleate cells appeared within the lumina (Fig. 48) and lymphocytes were more numerous in the stroma.

Administration of the drugs was discontinued after lactation, and the animals were re-mated. They showed no loss of fertility, and in one litter born 12 weeks after cessation of treatment the neonatal thyroids were normal in weight and in histological appearance.

5. The effect of autolysis under different conditions

Autolysis did not proceed at the same rate in all glands, even when they were subjected to identical conditions and (judging by the appearances in littermates) were histologically similar. Unexplained variations in the rate of post-mortem change were well shown in the liver and kidney as well as in the thyroid. However, it is possible to form a composite picture of the stages of autolysis by studying all the glands in which fixation was delayed for a measured interval after death.

In the untreated neonate, the earliest change was colloid depletion. This was shown by a gradual reduction in the intensity of staining (Fig. 49), the reaction becoming fainter until it was no longer detectable; only rarely did loss of colloid develop at the periphery of the lumen, leaving a central mass of colloid unaffected (Fig. 50).

The next stage, which usually began before absorption of colloid was complete, was detachment of the epithelium from the acinar wall. An early and inconstant form was the appearance of vacuoles in the basal cytoplasm, with preservation of the intercellular boundaries and displacement of the nuclei towards the

lumen. The epithelium then became totally separated from the acinar wall and persisted as an intact ring of apparently normal cells (Figs. 49, 50). Later, the nuclei underwent pyknosis, and some disappeared. When the nuclear substance no longer gave any staining reaction with haematoxylin, the ring of cytoplasm still remained intact (Fig. 51). Desquamation of cells into the lumen did not occur at any stage.

When colloid-like substance was present in the lymphatics, it disappeared during post-mortem degeneration in the same way as did the intra-acinar colloid.

In the peripheral zone, the process of autolysis was considerably slower than elsewhere. Loss of colloid, detachment of the epithelium, and pyknosis and disappearance of the nuclei all lagged behind the corresponding changes in the central zone, so that at an intermediate stage the peripheral acini retained their normal appearance while the central acini showed loss of colloid and detachment of epithelium (Fig. 49), or nuclei survived at the periphery when they were absent elsewhere (Fig. 51). Disappearance of the nuclei generally occurred in the central zone at 3 to 4 days, and in the peripheral zone a day or two later. When the process was complete, the two zones could no

longer be distinguished from one another.

Of the other organs examined, only the adrenal showed a similar preservation of the peripheral zone during autolysis.

Autolysis in the stillborn could not be studied so satisfactorily; even when there was more than one stillbirth in a litter, one could not know whether the interval between intra-uterine death and delivery had been the same in each. One litter of four stillbirths in which all were free from obvious maceration was studied by fixing the tissues as soon as possible in two, and after delays of 49 and 73 hours in the other two; the process of autolysis did not differ from that already described.

Autolysis in TSH-injected animals: Fixation was delayed for varying periods up to 5 days after sacrifice in TSH-injected neonates, using as controls similarly injected littermates with immediate fixation and non-injected littermates with similar delays in fixation.

The stages of autolysis were broadly the same as in the non-injected animals (Fig. 52). Protrusion of the nuclei into the lumen, occurring at the 23 to 46 hour stages of activation, was not accentuated by

autolysis. In 3 of the 7 animals in which fixation was delayed for a measured period, however, there was some disintegration of the acinar lining, especially in the central zone (Fig. 53). The result was a picture not unlike that described in the neonatal thyroid, differing in that disintegration did not occur until the nuclear substance had almost ceased to stain. The greatest degree of disintegration occurred in the animal sacrificed 46 hours after injection.

An attempt to determine whether autolysis proceeded at a different rate in the thyroids of injected and non-injected animals gave curiously inconstant results (Table 14). In 5 instances, injected animals and littermate controls were subjected to identical delays in fixation. As judged by the degree of epithelial detachment, and of pyknosis and disappearance of nuclei, 1 case showed considerably more rapid autolysis in the injected animal, 3 showed slightly more rapid autolysis in the controls, and in one case the rates were about equal.

In two instances, segments of P.A.S.-positive cytoplasm were seen in the autolytic glands while they were absent from the immediately-fixed TSH-injected controls.

Autolysis in thiouracil and potassium perchlorate goitres: In addition to the animals which died naturally and were not autopsied immediately, there were 4 litters in which the animals were subjected to measured delays in fixation, ranging from 29½ to 97 hours. Two had been treated with thiouracil and two with potassium perchlorate.

In all cases, post-mortem degreneration began with loss of any remaining colloid, followed by basal vacuolation and then detachment of the epithelium, pyknosis, and finally disappearance of the nuclei with persistence of a shrunken but intact ring of cytoplasm (Figs. 54, 55, 56). Desquamation or disintegration of the epithelium did not occur at any stage. The autolytic process was notably retarded in the peripheral zone.

Autolysis thus took the same form as in the untreated thyroid. Whether or not it proceeded at the same rate is uncertain, as with this method there can of course be no untreated littermate controls. Comparison with the untreated neonates which were subjected to measured delays in fixation did not provide conclusive evidence of any difference in the rate of autolysis.

DISCUSSION

Before considering the significance of the results in relation to the human neonatal thyroid, it would be well to note the differences between the normal thyroid in the two species. The guinea pig thyroid, unlike the human thyroid, is relatively much heavier in the newborn than in the adult. The thyroid in the newborn guinea pig is composed of well-filled acini, with few interacinar cells; the epithelium is cuboidal or low cuboidal, but never columnar, and at the periphery of the gland it is flattened. Desquamation of the epithelium does not occur, and colloid-like substance in the lymphatics is inconspicuous. Lymphocytes and intra-acinar macrophages are normally present, as was noted by Gray and Loeb in 1928.

The invariable acinar structure, and the lack of columnar epithelium, are in contrast with the picture seen in the human neonate and in many other species. The newborn guinea pig is an active animal, and a comparative study by Benazzi (1929, 1932) demonstrated that the typically acinar structure, with abundant colloid, occurs in the thyroids of active neonates, while in inactive neonates, such as the mouse, the

gland is composed of solid cords and of acini containing little colloid and lined by tall epithelium.

The implications of the findings will be considered first in relation to the histological structure of the normal human thyroid at birth, and then in regard to the problem of congenital goitre. In the normal human thyroid, the main point at issue was the significance of the acini designated types B and C.

The type B acinus

Basal vacuolation of the epithelial cytoplasm, associated with colloid depletion, was seen as an early stage of post-mortem degeneration both in normal and in activated guinea pig thyroids. Activation alone did not result in basal vacuolation, as was noted also by Ponse and Altschuler (1940) and Ponse (1951), though it has been reported as doing so in other species (p. 28).

Normal acini undergoing autolysis sometimes closely imitated the type B acini described in the human thyroid; the resemblances between Fig. 50 (autolysis in the guinea pig thyroid) and Fig. 3 (human neonatal thyroid) are considerable. One cannot but accept that, at least in some instances, the

type B acinus in the human thyroid is a post-mortem artefact.

The persistence of well-stained colloid, deeply indented by peripheral vacuolation, however, was common in the type B acini in the human thyroid; this was rarely seen in the guinea pig thyroid undergoing autolysis. The peripheral vacuoles are probably a fixation artefact (De Robertis, 1941), but indicate that active colloid resorption was occurring during life. Such acini, and those associated with colloid-like substance in the lymphatics (which is not a post-mortem phenomenon) can be accepted as examples of hyper-activity. Moreover, basal vacuolation in experimental autolysis has not been seen to occur with such a short death-fixation interval as in many of the human cases, and it occurred only as a transient stage before complete separation of the epithelium from the acinar wall. In the human cases, the incidence of type B acini varied little whatever the death-fixation interval.

The observations indicate that the type B acinus in the human neonatal thyroid may often be a consequence of post-mortem degeneration, but do not affect the likelihood that other instances are a

manifestation of hyperactivity.

The type C acinus

It may be said straight away that none of the experimental procedures used were successful in bringing about the epithelial desquamation and disorganisation of acini designated Type C in the description of the human neonatal thyroid.

Autolysis, whether in the normal gland or in the goitre produced by antithyroid drugs, resulted in colloid depletion, separation of the epithelium from the acinar wall, and eventually collapse of the acinus, but the row of epithelial cells remained intact and epithelial cells did not appear in the lumen. Even when autolysis had proceeded so far as to cause complete disappearance of the nuclei, the remaining cytoplasm still formed an intact ring.

Both thyrotropic hormone injection and the administration of antithyroid drugs (which results in prolonged thyrotropic stimulation) produced for the most part the conventional picture of epithelial hyperplasia, without loss of the normal acinar structure. The much higher doses of thyrotropic hormone used by Weber and Bettini (1956) in experiments on the rat

gave different results. Injections on alternate days for several weeks produced first an intense hyperplasia, followed by the picture of "functional exhaustion" (Fig. 23) in which the nuclei were pyknotic and the cells were desquamated into the lumina.

In the present experiments, little desquamation followed single injections of thyrotropic hormone. Between 44 and 48 hours after injection, the picture suggested incipient desquamation, though few cells separated completely from the lining; thereafter, the more advanced stages of desquamation did not develop, and the displaced nuclei seemed to revert to their normal position.

The picture closest to that seen in the human neonatal thyroid was produced by combining the effects of activation and autolysis (Fig. 53). It is perhaps significant that autolysis produced this effect only at one stage of activation; it did not do so at earlier or later stages, nor in the gland subjected to long-standing thyrotropic stimulation by administration of antithyroid drugs. The stage at which this change occurred was the one at which the colloid depletion, though not the hyperplasia, had reached its maximum, and is therefore the stage at which there would be

the greatest content of proteolytic enzyme in the thyroid. Only at this stage, too, did autolysis occur more rapidly in the activated than in the untreated thyroid.

On the other hand, in a proportion of untreated animals dying spontaneously before or during birth, the thyroid showed changes similar to those occurring in the human gland, though of lesser degree. These glands had inevitably undergone some degree of autolysis, which was not susceptible to the same precise control as in the animals which were sacrificed. The epithelial desquamation and disorganisation of acini contrast sharply with the appearances observed during autolysis in the normal thyroid, so that whatever part autolysis played in the stillborn, it is unlikely to have been solely responsible. It must be admitted that the different environmental conditions in utero might result in some modification of the autolytic process, but some of the signs of increased activity in the stillborn are undoubtedly of ante-mortem origin.

Of especial interest is the stillbirth illustrated in Fig. 34. This thyroid showed what appeared to be an early form of desquamation. While most of the

nuclei remained in the basal position, a few had moved towards the apex or even protruded beyond the apical margin of the cell into the lumen - a picture very similar to that seen in the TSH-activated thyroid (Fig. 37). The presence of hyperchromatic nuclei and of scanty mitotic figures added to the resemblance, leading to the conclusion that this thyroid had been subjected to endogenous thyrotropic stimulation a short time before death.

It has already been shown (Fig. 53) that autolysis alone, in the activated gland, may result in some disintegration of the epithelial lining but does not produce the typical picture of desquamation; clumps of cells do not appear in the lumina, and disintegration occurs only when the nuclei have already disappeared. The examples of established desquamation in the stillborn, such as that illustrated in Fig. 33, must be attributed to further thyrotropic stimulation, with autolysis playing at the most an accessory role.

These findings strengthen the suspicion that in the human neonatal thyroid, similar changes are to some extent a result of the factors which cause death; they are perhaps less likely to occur in surviving infants, in whom of course there can never be an opportunity to

study the thyroid histologically.

The lower frequency of these changes in the guinea pig thyroid is only to be expected, this animal having been deliberately chosen as the one least likely to show the changes spontaneously.

The less active peripheral zone

This was as evident in the guinea pig thyroid as in the human thyroid at birth, and as evident in the adult as in the newborn guinea pig. The anatomical separation of two zones of differing functional activity is a fortunate arrangement for the study of their response to abnormal conditions. The peripheral zone was not only less active in the normal animals examined, as judged by its flat epithelium and deeper-staining colloid, but showed a slower response to thyrotropic stimulation; in the later stages of the response, the hyperplasia in the peripheral zone began to approach that in the rest of the gland. In the response to antithyroid drugs, too, and in the return to normal after withdrawal of the drugs, the lesser activity of the peripheral zone was evident.

The presence of the two distinct zones is of greatest value in the study of the autolytic process.

It was suggested in the discussion on the human neonatal thyroid that the rate of autolysis might be related to the degree of physiological activity in the acinus. Comparisons of autolytic changes in the normal and activated guinea pig thyroid gave equivocal results, partly perhaps because of the difficulty in controlling all the factors affecting the rate of autolysis. More constant results were obtained by comparing the rates of autolysis in the central and peripheral zones of individual glands, thus excluding the unknown factors which might influence the rate even in littermates subjected to identical delays in fixation.

Examination of many normal glands at differing intervals after death left no doubt that the rate of autolysis is indeed related to the degree of activity of the acini. Detachment of the epithelium from the acinar wall, and degenerative changes in the nuclei, occurred first in the central zone; but by the time similar changes were occurring in the peripheral zone, the nuclei in the central zone had begun to disappear. After 4 to 5 days, all nuclei had disappeared, and only a slight difference in the diameters of the surviving cytoplasmic rings remained to distinguish

one zone from the other.

With such a narrow peripheral zone, and with equal preservation of the exposed margin and the margin attached to the trachea, there can be no question of more rapid fixation of the peripheral zone leading to its better preservation. Presumably the peripheral preservation noted in the autolytic adrenal is similarly related to differences in functional activity of the "adult" and "foetal" cortex.

Colloid-like substance in the lymphatics

This phenomenon occurred in very minor degree both in normal glands and in those modified by TSH or antithyroid drugs. Accumulation of sufficient substance in the lymphatics to cause distension was seen, as in the human gland, in association with loss of colloid from the acini and desquamation of the epithelium, and so was confined to a few stillborn cases.

Examination of the guines pig thyroid has not solved the problem of the colloid-like substance. It has shown, however, that the phenomenon is not produced by subjecting either the normal or the hyperplastic gland to post-mortem degeneration, and has

confirmed its association with colloid depletion and disorganisation of the acini. Its occurrence during life, under these circumstances, lends some support to the view that the substance is indeed colloid, or a constituent of colloid.

Whether or not this is the true significance of the colloid-like substance, it seems that its presence will be of value in studying the human thyroid, where there is so often difficulty in distinguishing ante-mortem "neonatal changes" from the effects of post-mortem degeneration. In doubtful cases, its presence will be a strong indication in favour of true ante-mortem change.

Congestion

The experimental observations provide an opportunity of testing the proposition that the congestion so commonly seen in the neonatal thyroid is a measure of its hyperactivity.

In the guinea pig, undoubted congestion of the thyroid followed administration of thyrotropic hormone, and of antithyroid drugs. The degree of congestion, however, did not approach that occurring in the stillborn, where the thyroid shared in the generalised

congestion of all the viscera, whatever the degree of activity of the gland.

The hyperaemia associated with increased activity must therefore be of little consequence in comparison with the intense congestion associated with an asphyxial death. Only in the animal killed instantaneously could the state of the blood vessels be accepted as reflecting the degree of activity of the thyroid.

Evidently the degree of congestion is of no value as a measure of the functional state of the human thyroid at birth.

The abnormally large acini

The presence of a few abnormally large acini, lined by flat or stratified epithelium and often empty, suggests that such acini represent non-thyroidal tissue incorporated within the gland; so also does their poor response to thyrotropic stimulation. Such "acini", though closely similar to functioning thyroid tissue (Kingsbury, 1935b) are probably of ultimo-branchial origin (de Winiwarter, 1933). The presence of developmental inclusions within the thyroid is discussed in Section 5.

The effect of antithyroid drugs administered to the mother during pregnancy and lactation

Reference has already been made (p. 71) to experimental work demonstrating the transmission of antithyroid drugs across the placenta in the guinea pig, rat, rabbit and mouse.

Goldsmith et al. (1945) postulated three mechanisms by which feeding of thiourea to pregnant rats might cause thyroid enlargement in the offspring:
(1) Passage of the drug through the placenta.
(2) Lowered thyroxin production by the mother, so that the foetus receives less thyroxin than normally and responds by increasing its own output. (3) Passage of maternal thyrotropic hormone through the placenta. The experiments of Peterson and Young (1952), who administered propylthiouracil, thyrotropin and thyroxin to pregnant guinea pigs, demonstrated that in this animal at least passage of the drug through the placenta is the most probable mechanism. The antithyroid drug blocks the synthesis of thyroid hormone by the foetal thyroid, leading to hypersecretion of TSH by the foetal pituitary.

Thiouracil, potassium perchlorate and carbimazole (2-carbethoxythio-1-methyl-glyoxaline, "Neomercazole")

have been selected as representative of the various antithyroid drugs in therapeutic use. Potassium perchlorate has an antithyroid action qualitatively similar to that of thiocyanate (Stanbury and Wyngaarden, 1952) but about ten times more effective (Wyngaarden et al. 1952), while carbimazole probably acts in similar fashion to thiouracil, at a later stage of hormone synthesis (Burrell et al., 1956).

Carbimazole was synthesised by Lawson et al. (1951), in a search for less toxic alternatives to methimazole. Macgregor and Miller (1953) found by radioactive iodine studies that methimazole and carbimazole had a potency possibly 50 times greater than that of methylthiouracil, but they noted that considerably higher doses of the new drugs were required in clinical practice than were originally assumed to be necessary. Clinical experience indicates that carbimazole is about ten times as active as methylthiouracil or propylthiouracil (McGavack et al., 1956).

Thiouracil and its derivatives have repeatedly been implicated in the causation of human congenital goitre (references in Section 2). So far there have been no reports of congenital goitre following

potassium perchlorate therapy, though potassium chlorate, administered to euthyroid pregnant women, has caused congenital goitre in the offspring (Anderson, 1958). Chlorate was one of the anions found by Wyngaarden et al. (1952) to have a weak antithyroid activity. I am not aware of any cases of congenital goitre due to methimazole or carbimazole therapy.

The present experiments with three antithyroid drugs show that all affect the foetal thyroid in similar fashion, though in differing degree. The hyperplasia was rather more intense with thiouracil than with potassium perchlorate, and was considerably milder with carbimazole. Potassium perchlorate is particularly liable to cause hyperaemia of the gland.

Feeding the drugs directly to rats, Wyngaarden et al. (1952) found that thyroid hyperplasia due to potassium perchlorate was at least equal to, or rather greater than, that due to propylthiouracil. They noted a great increase in the vascularity of the thyroid following perchlorate administration, and Godley and Stanbury (1954) recorded the same observation in the human thyroid. Because of this, potassium perchlorate is probably unsuitable for

pre-operative therapy (Crooks, 1957).

The relatively slight effect of the antithyroid drugs on the maternal thyroid is attributable to the lower level of activity of the adult guinea pig thyroid. Both from the relative weight of the normal gland, and from its histological structure, it can be seen that the thyroid in the adult guinea pig is a comparatively inactive organ, with a much greater reserve capacity than in the newborn. The persistence of colloid and the presence of intra-acinar macrophages (Fig. 48) indicate that even a high dosage of thiouracil does not completely block the synthesis of thyroid hormones.

The range of changes in the maternal thyroid was not sufficiently great to be of much value in assessing the effectiveness of the antithyroid drug. Some doubt therefore remains as to why carbimazole failed to cause the same degree of foetal thyroid hyperplasia as did the other drugs. It may have been due to diminished passage through the placenta, but the possibility remains that for some undetected reason the drug was not reaching the mother in sufficient concentration.

The effects of transmammary passage of antithyroid drugs are of importance in view of the usual prohibition against breast feeding during antithyroid drug therapy. Regression of hyperplasia was seen in congenital goitres in spite of continued administration of the drug to the mother during lactation, indicating that the drug passes into the milk in lower concentration than it passes through the placenta. The tendency of the newborn guinea pig - a very lively animal within a few hours of birth - to forage for itself at an early age is probably not sufficiently great to affect the validity of these results; refilling with colloid was already evident 2 days after birth.

It seems therefore that the danger involved in transmammary passage of antithyroid drugs is not great, and is less than the danger associated with antithyroid medication during pregnancy. However, if antithyroid drug medication has of necessity been continued up to delivery, a more rapid regression of the infant thyroid hyperplasia can be obtained by

artificial rather than breast feeding. If an infant's goitre is of such a size that it might embarrass respiration, the importance of obtaining the speediest possible regression of thyroid hyperplasia is obvious.

On the other hand, when respiratory obstruction is not the chief cause of concern, one must weigh also the danger of precipitating an upsurge of thyroid hormone secretion by sudden withdrawal of the drug. Such an event could well endanger the life of a premature infant, even though not producing clinically recognisable hyperthyroidism. There must be occasions when a more gradual withdrawal of the drug is desirable.

The increase in intra-acinar macrophages and multinucleate cells during regression is of great interest. These cells, and their presence as a response to thyrotropic stimulation, were observed experimentally by Thurston (1933), Williams (1939, 1944), and others, as well as in the present experiments; the relation of "colloidophagy" to epithelial hyperplasia in the human thyroid has been

studied by Hellwig in 1951 and in subsequent papers (see p.202).

Intra-acinar macrophages characteristically occur during the process of activation, not of involution. Their paradoxical presence here, in the early stage of regression, indicates that resumption of hormone synthesis, when it occurs on withdrawal of the drug, does so in the presence of excess TSH secretion; this confirms that the hyperplasia is due to hypersecretion by the foetal pituitary and not to transplacental passage of excess maternal TSH. The continued presence of macrophages at 16 days, when the colloid content and the height of the epithelium had both reverted to normal, indicates that the level of TSH secretion remains high after the stimulus to hypersecretion has ceased. Immediately after resumption of thyroid hormone synthesis, the output is necessarily lower than normal, but soon it must reach and then exceed the normal level, both because of the increased bulk of the thyroid and because of the continuing excessive thyrotropic stimulation.

The appearance of intra-acinar macrophages is the histological counterpart of the experimental

finding that a "rebound" high uptake of radioactive iodine by the foetal thyroid occurs three days after the withdrawal of antithyroid drugs from the mother (Logothetopoulos and Scott, 1956), and of the clinical finding that the onset of transient hyperthyroidism is delayed for a short period after birth in infants with congenital thiouracil goitres (Frisk and Joseffson, 1947; Fischer, 1951; Riley and Sclare, 1957). Significantly, in the only case where such a delay has not been noted (Bongiovanni et al., 1956), antithyroid medication had been discontinued 2 months before delivery. On the other hand, thyrotoxic symptoms have been recognisable at birth in all cases of congenital hyperthyroidism not attributable to antithyroid drugs (see Table 12).

As congenital hyperthyroidism, whether or not due to antithyroid drugs, is the result of abnormal conditions prevailing only during foetal life, it is understandable that the condition usually resolves spontaneously. Thyrotoxic symptoms, however, must of necessity persist for some weeks or months after birth, while the excessive amount of functioning thyroid tissue is gradually returning to normal.

SUMMARY AND CONCLUSIONS

The normal guinea pig thyroid, unlike that in many other species, does not go through a phase of colloid depletion and loss of acinar structure about the time of birth. While attempts to produce experimentally the epithelial desquamation and acinar disintegration seen in the human thyroid were only partially successful, such changes were found to occur spontaneously in a few animals which died in utero.

Examination of the thyroid at intervals following single injections of thyrotropic hormone showed that apical displacement of the nuclei, with early desquamation, occurred after 1 to 2 days, but thereafter most of the displaced nuclei reverted to the basal position and the picture of massive desquamation so often seen in the human gland did not develop. Intra-acinar macrophages, which are rare in the normal gland, increased during activation.

Normal glands allowed to undergo post-mortem degeneration likewise failed to show the changes seen in the human thyroid at birth. The epithelium became detached from the acinar wall, but even in an advanced stage of autolysis the ring of cells remained intact and none of the cells entered the lumen.

Post-mortem changes in the TSH-activated gland, and in the gland subjected to long-standing thyrotropic stimulation by administration of antithyroid drugs, followed a similar course; the incipient desquamation of the activated gland was not converted into massive desquamation by autolysis. Disintegration of the acini did occur during post-mortem degeneration in some of the activated glands, but only at a stage when the nuclei were disappearing; loss of acinar arrangement with preservation of the cellular structure, so familiar in the human neonatal thyroid, was not seen.

The thyroids of some untreated stillborn animals, however, showed such a picture, while others closely simulated the activated gland. It would seem that the thyroids of animals dying spontaneously in utero occasionally undergo changes which do not occur in the survivors. These changes may resemble those of activation, or those found in the human neonatal thyroid, and cannot be reproduced by allowing the normal gland to undergo post-mortem degeneration. Weber and Bettini (1956) have shown that they can be reproduced by more prolonged exogenous TSH stimulation than was used here.

While freely admitting the possible role of autolysis in accentuating the changes, it is suggested that they represent the response to excessive thyrotropic stimulation, and that they may in some way be associated with the abnormal conditions obtaining before spontaneous intra-uterine death. It may well be true of the human gland also, that the epithelial desquamation so often found in the neonatal thyroid is less common, or less pronounced, in surviving infants.

The type of acinus which falls under the heaviest suspicion of post-mortem artefact is that in which colloid depletion is accompanied by basal vacuolation of the cytoplasm (the type B acinus). Yet even here there is good reason to believe that post-mortem degeneration, if it produces such a picture, does so only in a hyperactive acinus.

The peripheral zone of the guinea pig thyroid was seen to be the least active zone in the normal gland. It was slower in its response to thyrotropic stimulation, and the first to return to normal when the stimulation ceased. That it was also less susceptible to post-mortem degeneration is attributed not to its earlier fixation but to its lower level of

functional activity.

As in the human gland, distension of the lymphatics by colloid-like substance accompanied the colloid depletion and epithelial changes which are attributed to excessive thyrotropic stimulation. The presence of the colloid-like substance is not a post-mortem artefact. These findings lend support to the concept of a "lymphocrine" mechanism in states of intense hyperactivity.

The thyroid is notably hyperaemic following stimulation by exogenous or endogenous TSH. A much greater degree of vascular engorgement, however, may occur in the normal gland as the result of asphyxial death. The degree of congestion is therefore not a reliable measure of functional activity in the human thyroid at birth.

Administration of antithyroid drugs to pregnant guinea pigs resulted in enlargement of the foetal thyroids. This is considered to be due to passage of the drugs through the placenta, blocking hormone synthesis in the foetal thyroid in the same way as when the drugs are administered directly to animals or human beings.

Thiouracil was slightly more effective than

potassium perchlorate in causing hyperplasia of the foetal thyroid. Carbimazole, although 10 or more times as potent, had to be given in the same concentration as these drugs in order to produce an equal degree of hyperplasia. The goitres produced by potassium perchlorate were notably more vascular than those produced by thiouracil or carbimazole.

Hyperplasia in drug-induced neonatal goitres regressed after birth, even though the mother was still receiving the drug during lactation, indicating that transmammary is less effective than transplacental passage of the drug. Regression was much more rapid in animals not subjected to further antithyroid medication after birth. An increase in intra-acinar macrophages, characteristic of the activated gland, occurred as early as 2 days after birth and was still evident at 16 days; this indicates that hypersecretion of TSH by the pituitary was continuing after the stimulus had been withdrawn.

The findings are in accordance with the clinical observations that congenital hyperthyroidism may follow the administration of antithyroid drugs to the mother during pregnancy, that the onset of thyrotoxicosis

is delayed for a short time after birth, and that congenital hyperthyroidism usually resolves spontaneously within the first few weeks or months of life.

PART II

OBSERVATIONS ON THE THYROID AT OTHER AGES

The foregoing refers only to the thyroid in the newborn. In the following pages are recorded observations on the thyroids of 28 older children and 191 adults, obtained at routine autopsy, as well as 38 surgical specimens. The observations concern, firstly, the occurrence at later ages of the histological changes supposedly peculiar to the newborn, which, for want of a better term, will be called "neonatal changes"; secondly, the presence in the thyroid of squamous or other atypical forms of epithelium; and thirdly, the occurrence of anisotropic crystals in the thyroid.

As the autopsy specimens were not collected with a specific view to studying these features, a further series of 63 specimens was collected with this object. In this second series, the number and site of the pieces of tissue selected for examination were constant, and routine P.A.S. staining was used in addition to haematoxylin and eosin.

It has been thought worth-while to keep these groups separate, in order to discover how far the two methods of approach differ in revealing the features under consideration.

4. THE INCIDENCE AND SIGNIFICANCE OF "NEONATAL CHANGES" IN OTHER AGE GROUPS

The cases discussed in Section 1 were arbitrarily limited to infants surviving for up to 7 days. But in the course of collecting the material it soon became obvious that the histological changes which so commonly occur in the newborn are by no means confined to the first 7 days of life. A wider study, made with a view to determining at what age these changes cease to occur, has led to the conclusion that some of them, at least, may affect the thyroid not only in later infancy, but also in childhood, in adult life, and even in old age.

MATERIAL AND METHODS

Sections of thyroid have been reviewed from a total of 282 autopsies:

23 infants between the ages of 9 days and 6 months,
5 children of from 2 to 10 years,
191 adults between the ages of 21 and 90, and
63 adults between the ages of 20 and 90.

In the first series of adults, one or two blocks of tissue were taken from each gland; all sections

were stained with haematoxylin and eosin, and a few also by the P.A.S. technique. In the second series of adults, three blocks of tissue were taken in each case and both H and E and P.A.S. methods were used with every block. A note was made in every case of the time elapsing between death and fixation of the tissue.

RESULTS

The histological findings in the 23 infants and 5 children are summarised in Appendix 3.

Infants of 9 days to 6 months

Between the ages of 9 and 12 days (7 cases), the histological appearances did not differ greatly from those already described. The most notable change was a diminution in the incidence of "activated" acini. Desquamation of the epithelium and disorganisation of the acini were scarcely less prominent than in the first week of life, and there was the same lack of correlation between death-fixation interval and histological structure. The well-preserved acini were still of irregular outline; their lining epithelium was cuboidal or low columnar; they were

generally well filled with colloid. The distinction between the central and peripheral zones was still evident in most cases, though less conspicuous than before.

Distension of the lymphatics was negligible. Congestion of the blood vessels was prominent in only one case, in which death had been due to aspiration of a feed and there was generalised congestion of all the organs.

At 2½ to 8 weeks (10 cases), there was a considerable change in the picture. The well-preserved acinus was now predominant, making up the whole of the gland in 4 cases and almost all in another. "Activated" acini were rarely seen. Desquamation and disorganisation were extensive in the two cases which had the longest death-fixation intervals.

With the predominance of well-preserved acini, there was a further increase in the colloid content of the glands. Where well-preserved acini only were present, the distinction between the central and peripheral zones, so prominent in the newborn, could still be detected in the larger diameter of the peripheral acini and the deeper staining of their colloid.

Lymphatic distension and congestion of the blood vessels were again inconspicuous in this group.

In the age-group 4 to 6 months (6 cases), there was a further advance towards the adult histological picture. Only one gland showed widespread disorganisation of acini, and one other showed detachment of the epithelium; these were the two cases with the longest death-fixation intervals. The remaining glands were composed of well-preserved acini, lined mostly by cuboidal epithelium and well filled with colloid. The picture still differed from that in the adult in the irregular outline of the acini and the absence of flattened epithelium. The lesser activity in the peripheral zone, too, was still detectable.

Lymphatic distension was seen in two cases, and in one of these it was unaccompanied by changes in the epithelium. Congestion of the blood vessels was prominent in only one case, again a case of death by aspiration of food.

Considering together the 23 cases aged 9 days to 6 months, it can be seen that there is a gradual diminution in the incidence of the histological changes which characterise the neonatal thyroid. In contrast to the neonatal series, there appears to be some relation between the presence of these changes and delay in fixation of the thyroid. There is possibly also an inconstant relation between the changes and the presence of pyogenic infections, but the number of cases is insufficient to justify reaching any conclusion on this point. The changes, when they occur, tend to be less severe than in the newborn, and no case beyond the age of 4 weeks was seen in which the acinar structure was totally lost.

Children of 2 to 10 years

Only 5 cases were seen in this age-group. In two cases, aged 5 and 10 years, the acini were lined by uniformly cuboidal epithelium, they were well filled with colloid, interacinar cells were scanty, and there was little or no distinction between the central and peripheral zones, so that the appearances closely resembled those of the normal adult thyroid. The only abnormal feature was the presence in the younger case

of occasional desquamated cells in the colloid.

In the other three cases, aged 2¼, 7 and 8 years, the appearances resembled those of the neonatal thyroid. (Figs. 57, 64). There was extensive collapse and disorganisation of the acini, desquamation of the epithelium, colloid depletion, and prominent lymphatic distension. The epithelium of the well-preserved acini varied from cuboidal to columnar. The case showing the most advanced changes (aged 8 years) had the shortest death-fixation interval; preservation of the peripheral zone was as distinct as in the neonatal thyroid (Fig. 57).

There is no scope in this small group for assessing the incidence or significance of the changes. It is sufficient to note that they occur also in this age group, that delay in fixation (see Appendix 3) can have played little part in these cases, and that if the changes are sufficiently advanced the distinction between the central and peripheral zones can be appreciable even at the age of 8 years.

Of the three cases showing "neonatal changes", two died of acute infection, and one during anaesthesia and hypothermia. In the case showing only occasional groups of desquamated cells, death also occurred during

anaesthesia and hypothermia. In the case showing perfect preservation of the acinar structure, death was due to multiple injuries, including severance of the spinal cord, and was considered to have been instantaneous.

Adults

The findings in the newborn and in the succeeding weeks of infancy led to the expectation that the incidence of "neonatal changes" in the adult thyroid would be negligible. This proved to be so only in the sense that the grosser degrees of acinar collapse and disorganisation were rarely seen. A less striking change was relatively common, namely, basal vacuolation of the epithelium or early detachment of the lining cells from the acinar walls, together with pyknosis, indistinct or absent staining of the cytoplasm, and often colloid depletion. Although these changes seldom affected the entire gland, they showed no trace of the central distribution characteristic of the neonatal thyroid. They were usually confined to the smaller acini (Fig. 58) so that their extent and distribution were governed by the extent and distribution of small acini. A common pattern was one of

large well-preserved acini scattered at random throughout a field of small acini showing colloid depletion, with pyknosis and loss of cytoplasm in the epithelium. Alternatively, groups of small acini showing the changes were scattered throughout a field of larger well-preserved acini. The susceptibility of smaller acini to the changes was often seen more strikingly in nodular glands, in which there was often a considerable difference in size between the acini composing the nodules and those in the remainder of the gland, (Fig. 59). The changes might affect microfollicular areas or nodules in a gland composed of normal-sized well-preserved acini, or might spare involutional nodules in a gland which was otherwise extensively affected. Fig. 60 shows preservation of the larger, less active acini in an autopsy thyroid specimen from an elderly thyrotoxic subject.

Of the other changes described in the neonatal thyroid, the only one found to be conspicuous in the adult series was distension of the lymphatics (Fig. 61). This was no less common than in the newborn, and was often just as prominent; the lymphatics outside the capsule, however, were only rarely

involved. The staining reactions of the colloid-like substance, and the tendency for the staining intensity to vary inversely with that of the intra-acinar colloid, were the same as in the newborn. In the first series of 191 adult cases, in which usually only H and E sections were studied, lymphatic distension was seen in 62, or 32%. In the second series of 63 adult cases, in which P.A.S. sections were also available, lymphatic distension was seen in 38, or 60%. This is a measure of the value of the P.A.S. technique in demonstrating the colloid-like substance.

Lymphatic distension was usually associated with the epithelial changes just described (Fig. 78A), less often with the more usual signs of hyperplasia. Rarely, it occurred in areas of only mild hyperplasia, but it was never seen in areas of relative inactivity or of frank involution. The degree of lymphatic distension, however, was not clearly related to the severity of the epithelial changes.

In addition to broad lymphatic sinuses, there were occasionally narrow channels forming a network between small hyperplastic acini; the narrowest channels were not easily distinguished from basement membranes, which are also P.A.S.-positive. Rarely, in P.A.S.

sections, there was apparent continuity between the colloid in the acini and the colloid-like substance in the lymphatics (Fig. 62), an appearance not seen in any of the neonatal series.

In the adult, as in the newborn, the characteristic epithelial changes were not invariably accompanied by lymphatic distension. Thirty-one cases in the first series of adults and 5 cases in the second series showed the epithelial changes in appreciable degree without distension of the lymphatics. Although an assessment of these cases alone (Table 15) does not demonstrate a clear relationship to delay in fixation, the presence of epithelial changes without lymphatic distension does not provide a satisfactory basis for the estimation of "neonatal changes".

Not only are the epithelial changes as seen in the adult too similar to those of autolysis (Fig. 78A), but the milder degrees merge imperceptibly with the normal, so that classification of the cases on this basis would be entirely arbitrary. The same is true of colloid depletion. On the other hand, the presence of colloid-like substance in the lymphatics, although rather capricious in its occurrence, has the advantages that it is readily recognised, cannot be confused with

other abnormalities, and is unlikely to be a post-mortem artefact. It will therefore be used here as the principal index of "neonatal changes" in the adult thyroid.

Considering together all cases in which colloid-like substance was seen in the lymphatics, the incidence varies remarkably little with age (Table 16). A different result is obtained, however, by ignoring the lesser degrees and selecting the cases in which lymphatic distension was both prominent and extensive, equalling or exceeding the picture seen in any of the neonatal cases. Lymphatic distension of this degree occurred especially in the aged (Table 17). Of the 12 outstanding cases, the youngest was aged 44, and there was only one case in each of the fifth and sixth decades. Seven of the 12 cases occurred in the age-group 76 to 82. Exceptional degrees of lymphatic distension were accompanied by a notable increase in the severity of the epithelial changes, sometimes approaching the picture seen in the neonatal thyroid.

There was no definite sex incidence (Table 18).

Whether or not there was any relationship to the cause of death was more difficult to determine, because of the multiplicity of causes and because of

the possibility that the actual mode of dying might be more important than the primary cause of death. To circumvent the difficulties involved in classifying so many heterogeneous conditions, and in classifying cases in which more than one disease of importance was present, the conditions incriminated by previous investigators - tuberculosis, pyogenic infections, and intestinal obstruction - were first selected, and the incidence in these cases compared with the total incidence. From a study of the remainder, it became clear that a distinction could be made between conditions which were rapidly fatal and chronic diseases of long duration. The causes of death were therefore grouped into four categories:

(1) Cases of relatively sudden death, such as those due to myocardial infarction, pulmonary embolism, accidental injuries, or aspiration of foreign material into the respiratory tract. When any of these conditions had been rapidly fatal, cases were included in this category regardless of any pre-existing disease. In no case could death be said to have been instantaneous; the shortest interval between the onset of the fatal condition and death was 15 minutes, but in most instances the interval ranged from several

hours to two or three days. The use of the term "sudden death" therefore does not imply an instantaneous death, in which one would expect the thyroid to be histologically normal.

(2) Acute peritonitis, whatever the cause, and other abdominal catastrophies, such as intestinal obstruction and mesenteric embolism.

(3) Cases in which pyogenic infection (other than intraperitoneal) was considered to be either a major or a contributory cause of death.

(4) All others. This category includes all cases of malignant disease in which there was no evidence that any of the above conditions had been a significant contributory cause of death. Tuberculosis showed no association with thyroid changes (Table 19), and has therefore been included in this category.

In the first series of 191 cases, omitting the 4 in which there was obvious autolysis, lymphatic distension was commonest in the first category, a little less common in the second, and considerably less common in the third and fourth categories (Table 20). In the second series of 63 cases, when H and E sections alone were studied, the results were

similar except for a markedly increased incidence in the third category (Table 21). The additional examination of P.A.S. sections provided a further 11 cases, but left the relative proportions much the same (Table 22).

Combining the figures of Tables 20 and 21 to make a total of 250 cases (Table 23), lymphatic distension was seen in 51% of cases in the first category, in 41% in the second category, in 32% in the third category, and in 23% in the fourth category. Six of the 12 outstanding cases were in the first category.

It will be seen, therefore, that lymphatic distension is related both to the age of the patient and to the cause of death. The more pronounced examples occur especially in the elderly. It tends to be commoner in cases of "sudden death" and in those who have died of pyogenic infection, or of acute peritonitis or other acute abdominal condition.

Surgical specimens

The same changes have been looked for in 38 surgical thyroid specimens, in which fixation was prompt and adequate. P.A.S. staining was used only when the changes were already evident in H and E

sections. There were 9 examples of diffuse epithelial hyperplasia, 28 of nodular goitre (focal hyperplasia, involution and degenerative changes), and 1 of normal thyroid tissue removed during a search for a parathyroid adenoma.

Five cases of diffuse epithelial hyperplasia showed "neonatal changes". In two, there were foci of epithelial desquamation, accompanied in one by lymphatic distension. In the other three cases, lymphatic distension was associated with advanced hyperplasia but not with epithelial desquamation or disorganisation of acini.

Of the remaining 29 specimens, only two showed the changes. One thyroid showed focal hyperplasia, involution and fibrosis, and included a nodule showing both lymphatic distension and the epithelial changes. The periphery of the nodule was composed of small well-preserved hyperplastic acini, while in the centre the picture was akin to "diskomplexation" in the newborn, (Fig. 63A). In both zones, there was a network of narrow lymphatics containing colloid-like substance (Fig. 63B). In the centre of the nodule, too, were masses of free colloid surrounded by multinucleate giant cells.

Another nodular thyroid showed lymphatic distension in association with epithelial hyperplasia (Fig. 81A).

In none of the specimens was lymphatic distension seen in relation to normal or involutional areas.

DISCUSSION

Whatever the controversy surrounding the histological changes in the neonatal thyroid, at least the existence of such changes is well established. Not so with the adult thyroid. Epithelial desquamation and acinar disorganisation in the adult thyroid have received comparatively little attention, and they have never been regarded as part of the normal structure.

The morphological significance of the epithelial changes and lymphatic distension has already been discussed in Section 1. It is sufficient to note here that in the adult, as in the newborn, the smaller acini are the most severely affected, so that the characteristic involvement of the central zone in the newborn is replaced in the adult by a variety of patterns dependent on the distribution of the smaller acini. In either case, it is the smaller, and therefore the more active acini (Nadler et al., 1954), which respond

most readily to the unknown stimulus. Because the changes in the adult thyroid are milder, and of the type most difficult to distinguish from autolytic changes, the presence of colloid-like substance in the lymphatics has been preferred as a measure of "activation". The fact that lymphatic distension may occur also with the more usual picture of hyperplasia, as in the surgical cases of toxic goitre, does not detract from its value; hyperplasia and "desquamation" are considered to be of similar significance, differing only in degree.

Nearly all reports of "desquamation" in the adult thyroid have concerned its association with infections and toxaemias; Sokolow (1895) is credited with having been the first to record this association. Roger and Garnier (1898a) described a sclerosis of the human thyroid in tuberculosis, and commented on the signs of hyperactivity and the presence of acini "en voie de disparition". A more detailed description of desquamation and disorganisation was given in their experimental observations on the effect of typhoid bacilli on the rabbit thyroid (Roger and Garnier, 1898c). In a later paper on the human thyroid in acute infections (Roger and Garnier, 1899), they noted

distension of the lymphatics, colloid depletion, and detachment or desquamation of the epithelium, and commented that the general appearance recalled that of the infantile thyroid. A number of similar observations were cited by Hashimoto (1912).

A high degree of specificity in relation to different causal infections was claimed by Farrant (1914). He stated that the degree of change was dependent on the amount, virulence and duration of the toxaemia, and separated the diseases studied into three groups according to their effect on the thyroid. Chronic tuberculosis was among those producing a "chronic hyperplasia", that is, a slight increase in cells accompanied by abundant masses of colloid, while acute tuberculosis was among those producing an "acute hyperplasia", that is, loss of colloid and of acinar structure. So constant were the changes in the thyroid that they could be used to determine the duration of the disease, and even to differentiate one causal organism from another. McCarrison (1917) included the childhood fevers among the many diseases causing such changes, but stressed above all the influence of intestinal bacteria and their toxins.

The production of similar changes experimentally

by Cramer (1926) and by Cole and Womack has already been referred to (p. 38). Particularly effective in producing the changes was the content of a loop of small intestine of dogs dying of obstruction in the region of the ileo-caecal valve (Cole and Womack, 1929). It was shown by Cole et al. (1929) that infections and toxaemias are associated with similar, though less extensive, changes in the human gland. The most advanced changes were in cases of respiratory infection or peritonitis. Womack et al. (1928) attached considerable importance to the production of the changes by injection of histamine, as in these experiments the metabolic, structural and chemical changes were not accompanied by a rise in temperature, showing that pyrexia alone was not responsible.

The changes reported in young dogs following infection with Trypanosoma cruzi (Goble, 1954) were similar, though the cells in the acinar lumina more closely resembled macrophages than desquamated epithelial cells. The changes occurred in 12 out of 17 females, but in only 1 out of 17 males.

Nolan (1938), in a study of 725 autopsy specimens, did not observe extensive epithelial desquamation; he noted that colloid depletion was associated with

acute infections, but not with death from accidental injuries. On the other hand, Sigurjónsson (1940) considered that signs of colloid resorption were more frequent in tuberculosis than in acute infections; lymphatic distension and epithelial desquamation he dismissed as being post-mortem artefacts.

In the two series of adults reported here, there is an undoubted relation to infection and toxaemia. Acute peritonitis and intestinal obstruction were rather more prone to produce the changes than were pyogenic infections generally, of which the great majority were bronchopneumonia. None of the disease groups considered showed an invariable association with thyroid changes.

The present findings differ from those of previous observers in that the changes occurred most commonly, not in infections and toxaemias, but in a group of non-infective conditions which had in common a relatively short interval between onset and death. This unexpected finding provides the link between the changes in the adult and those in the newborn. The exact cause of death in the newborn is often difficult to determine, but there can be little doubt that in the majority of stillbirths and neonatal deaths the

cause of death is one which operated for a relatively short period. The "sudden death" group in the adult series is therefore the one which corresponds most closely with the newborn.

The rapidity with which the changes have been shown to occur has already been mentioned (p. 49).

The reported association with tuberculosis has not been confirmed here, but tuberculosis nowadays is seldom the acute rapidly-killing disease it was at the time of the earlier reports.

In the discussion on the neonatal series, and again in the guinea pig experiments, a doubt has already been raised as to whether the changes which are presumed to have occurred during life are indeed those of the normal thyroid, or whether they might be attributed in some measure to the factors which caused death. This doubt is considerably strengthened by the clear, though inconstant, association with the cause of death in adults, and especially by the association with "sudden death". The lower incidence and the lesser extent of the changes in the adult are explained by the normally lower level of functional activity in the adult thyroid.

The observations in the different age groups

suggest that the susceptibility to such changes diminishes very gradually after the third day of life, is considerably reduced by the age of 6 months but in middle childhood has not yet fallen to the adult level. Cooper (1925), describing the histological structure of the normal thyroid from intrauterine life to old age, first mentioned "piling" and detachment of the epithelium in her account of the thyroid at 3 to 4 months.

In old age, though one would not suggest that the thyroid enters its second childhood, there appears to be again some increase in susceptibility. It is indeed possible that in the aged, thyroid function might diminish more rapidly than hormone requirements, resulting in a state of diminished reserve or potential insufficiency analogous to the state of the gland in late foetal life.

SUMMARY

The changes described in the thyroid at birth have been looked for in thyroids at other ages up to 90 years.

The epithelial changes and accompanying colloid depletion occur with gradually diminishing frequency during the first six months of life, but may occur also in later childhood. In adult life, the severer changes, involving disorganisation of the acini, are rare; milder changes are common, but cannot be distinguished with certainty from those of autolysis.

Distension of the lymphatics by colloid-like substance is no less common in the adult than in the neonatal thyroid, and tends to be more prominent in old age. It is most commonly seen when death has been due to some rapidly-fatal condition such as myocardial infarction, pulmonary embolism, or accidental injury, and shows also an association with pyogenic infections, acute peritonitis and intestinal obstruction.

It is suggested that the diminished susceptibility of the adult thyroid to the epithelial changes so commonly found at birth is due to the normally lower level of physiological activity in the adult thyroid, and a greater reserve capacity. The greater severity of the changes in old age may be due to loss of this reserve capacity.

5. THE PRESENCE OF ATYPICAL AND SQUAMOUS EPITHELIUM IN THE THYROID

Only rarely is squamous epithelium seen in the human thyroid. In most reported instances, the gland has been the seat of a chronic inflammatory process, and the condition has been interpreted as one of squamous metaplasia, though some authors have regarded squamous islets as representing ultimobranchial or thyroglossal remnants.

My own observations suggest that while true stratified squamous epithelium is rare in the human thyroid, other forms of atypical epithelium, more or less resembling squamous epithelium, are not uncommon. This study arose out of the observation of atypical epithelium in 5 of the neonatal thyroids described in Section 1. A search for similar epithelium in autopsy specimens from 28 infants and children and 191 adults yielded 26 examples. The blocks of tissue from these cases had been taken at random, the site and the number of blocks varying from case to case. To gain a clearer idea of the incidence of atypical epithelium in the thyroid at autopsy, a consecutive series of 63 adult thyroids was examined in which the blocks were

taken from 3 standard sites: one from the central zone of each lateral lobe, and the third in the midline. Eighteen examples were found. Twelve surgical and 4 autopsy specimens from other sources bring the total number of cases considered here to 65 (Appendix 4).

Morphology

Many varieties of atypical epithelium were seen, and only a few of these could confidently be labelled "squamous". The ultimate criterion for the identification of stratified squamous epithelium is the presence of intercellular prickles or "bridges", and these were seen in only 3 instances. In many other examples, the general structure was that of stratified squamous epithelium, but intercellular bridges could not be identified with certainty. Keratinisation was not observed.

The atypical epithelium took the form of solid cell nests, nests with lumina, and thyroid acini partly or wholly lined by stratified epithelium (Figs. 64, 65) but these forms were not necessarily present together in any individual case.

The commonest appearance was a solid nest of

cells with large oval or elliptical nuclei and cytoplasm which stained purplish in H and E sections, both nucleus and cytoplasm contrasting sharply with those of the neighbouring thyroid epithelium (Fig. 64A). The nests were sometimes rounded, sometimes elongated, and often showed many apparently branching processes. In a few instances, the nests were solitary; more often, there was a cluster of closely-related nests, which on serial section were usually seen to be continuous with one another.

A small round or elongated lumen was occasionally present in the centre of the epithelial nest, and the long axes of the nuclei tended to form concentric rings about the lumen. When the lumen was larger, there was a close resemblance to the true thyroid acini (Figs. 64B, 65); the contents, however, were sometimes unlike colloid, consisting of discrete strands or particles which took both eosin and the P.A.S. stain much more strongly. Rarely, the lumen was distended, and the lining epithelium was reduced to a single flattened layer (Fig. 69).

Direct continuity was demonstrated in several cases between the atypical epithelium and true thyroid epithelium (Figs. 65A and B). When acini were lined

partly by stratified and partly by normal thyroid epithelium, the contents stained as for normal colloid.

Another variety of atypical epithelium, seen only in adult thyroids, took the form of a single ring of cells resembling those of the basal layer of stratified squamous epithelium, with their nuclei arranged radially (Fig. 67). The ring enclosed a group of cells with darker-staining nuclei in some instances, or a tiny empty lumen in others. Cell nests of this type were nearly always seen in conjunction with those described above, and were associated with lymphocytic infiltration. The few instances in which they were not accompanied by other varieties of atypical epithelium are excluded from consideration, as a clear distinction could not always be made between epithelium of this type and other cells which occur in lymphocytic foci in the thyroid, particularly those of small empty disintegrating acini.

In one neonatal thyroid (Case 4), a nest of stratified epithelium, its wall about six cells thick, surrounded a small lumen without stainable contents. The inner layer of cells appeared to be ciliated.

In further describing the atypical epithelium,

a distinction must be made between normal and abnormal thyroids.

Histologically normal thyroids

Thirty two adult thyroids, and all 7 thyroids from subjects below the age of 10 years, were considered to be histologically normal. Included in this group are Case 12, in which there were scanty lymphocytic foci unrelated to the atypical epithelium, Case 47, in which there was a history of thyroidectomy for Graves' disease 10 years previously but no histological abnormality in the thyroid, and Case 49, in which there was a true adenoma unrelated to the atypical epithelium.

In nearly all cases, the cell nests were either solitary or occurred in a single cluster, the whole of which could be viewed in a single high-power field. Examination of serial sections contradicted the impression sometimes gained of a duct or branching system of ducts; the extent of the atypical epithelium, as judged from further sections of the same block, was no greater than the extent as seen in the original plane of section. When the focus was traced to its termination by means of serial sections, the lumen, if

present, became gradually smaller and finally disappeared, leaving a solid nest; then this nest too became smaller, until it was represented only by an inconspicuous band of flattened cells which might otherwise easily have escaped notice.

When atypical epithelium had been identified, further blocks of tissue were taken from the same gland. In 36 of the 39 cases, no further atypical epithelium was found. In 2 cases, a similar focus was found in the opposite lobe, and in one case the foci proved to be multiple.

The foci occurred with about equal frequency in the right and left lobes, but were less commonly seen in the isthmus.

In 4 cases, the foci were accompanied by trivial lymphocytic infiltration, while lymphocytes were not seen elsewhere in the gland. In the one case already mentioned where scanty small lymphocytic foci were scattered throughout the gland, these were not associated with the atypical epithelium. Lymphocytes were not seen in any of the remaining cases.

Histologically abnormal thyroids

This group comprises all the remaining autopsy specimens, and all the surgical specimens - 26 cases

in all. There were 6 cases of toxic goitre, 2 of non-toxic nodular goitre, 6 of chronic thyroiditis, and 3 of myxoedema, as well as 9 clinically normal thyroids which at autopsy showed focal lymphocytic infiltration.

The foci of atypical epithelium in these cases were associated either with chronic inflammatory cellular infiltration or with focal or diffuse fibrosis (Fig. 89). Multiple foci were the rule in this group, and there was a wider range of types of epithelium than in the histologically normal thyroids. In all cases there were cell nests, with or without lumina, similar to those already described; the three examples in which intercellular bridges were identified all belong to this group. In addition, there could be seen within the lymphocytic foci epithelial nests which showed less resemblance to squamous epithelium, as well as some in which the basal cells only appeared to be represented, and others which in their different forms resembled the structures more usually associated with lymphocytic infiltration - small empty hyperplastic acini, intra-acinar giant cells, and oxyphilic cells. It was occasionally possible to trace in a single section

several transition forms between hyperplastic thyroid epithelium and solid cell nests (Figs. 66, 67, 68). Several other clinically normal thyroids, not listed here, showed such transition forms in relation to lymphocytic foci or to areas of fibrosis, without the solid or hollow cell nests which are suggestive of squamous epithelium.

The most extensive example was in a case of myxoedema (Case 8), in which the parenchyma was reduced to small irregular islets widely separated by dense fibrous tissue (Figs. 69, 70). No normal thyroid epithelium was present, the islets consisting either of atypical or of oxyphilic epithelium. All the forms of atypical epithelium already described were seen, including true stratified squamous epithelium (Fig. 71).

The incidence of atypical epithelium in the thyroid at autopsy

(1) The adult thyroid (Table 24). The total incidence in the 191 adult thyroids initially examined was 12.6%. In the later series of 63 adult thyroids, in which more blocks of tissue were examined and care was taken to include the central zone of each lateral

lobe, the incidence was 28.6%. As even in the second series only a very small proportion of the total thyroid tissue was examined, it is certain that the true incidence is very much higher.

Sex incidence: There was a predominance of males (Table 24), which was accounted for entirely by the higher incidence in the male of atypical epithelium in histologically normal thyroids (Table 25).

Atypical epithelium associated with lymphocytic infiltration or fibrosis was seen in 7 out of 106 females, but in only 3 out of 148 males. The disparity was due to the higher incidence of "focal thyroiditis" in the female. "Focal thyroiditis", when present, appeared to be equally likely to provoke transformation to atypical epithelium in either sex (Table 26).

Age incidence: The incidence of atypical epithelium rose during early and middle adult life, reaching its maximum in the seventh decade, with a subsequent fall (Table 24). Such an age incidence might indicate that the development of atypical epithelium follows in the wake of lymphocytic infiltration, which reaches its maximum in the sixth decade (Table 31). Yet even when thyroids showing

lymphocytic infiltration are excluded from consideration, there is again a similar age distribution (Table 25 and Fig. 72).

(2) The infant thyroid. The finding of atypical epithelium in only 5 out of 106 neonatal thyroids, and in none of the subjects aged 9 days to 6 months, indicates that the incidence is lower in infancy than in adult life. When it is remembered that a section through the infant thyroid displays a much greater proportion of the total tissue than does a section of the adult gland, it is obvious that the discrepancy is considerably greater than would appear from these figures.

DISCUSSION

There can be little doubt that many of the references in the literature to "squamous epithelium" in the thyroid concern also the other varieties of atypical epithelium described here. Most reports have related to the association between squamous epithelium and chronic thyroiditis or fibrous sclerosis of the thyroid. Some of these are summarised below:

Wegelin (1926): Squamous epithelium in three adenomas with extensive inflammatory changes.

Boyden et al. (1935): In some cases of "Riedel's disease".

Jaffé (1937): Four cases associated with sclerosing and inflammatory changes. Also 3 cases of squamous carcinoma.

Marshall et al. (1948): Occasional epidermidisation in "Group I" (i.e. subacute) thyroiditis.

Joll (1939): Squamous epithelium, with keratinisation, in 1 out of 81 cases of Hashimoto's disease.

Harry (1940): Extensive squamous metaplasia in some cases of Riedel's disease.

Klinck and Menk (1951): 41 cases, including 4 of chronic non-specific thyroiditis, 5 of Hashimoto's disease and 2 of Riedel's disease.

Saxén (1951): In a case of subacute thyroiditis.

Bullock (1952): 4 cases - 3 of chronic thyroiditis and 1 of thyroid adenoma.

Lindsay et al. (1952): In fibrotic forms of lymphadenoid goitre.

Harland and Frantz (1956): In one type of struma lymphomatosa.

Douglass and Jacobson (1957): In all of 9 cases of myxoedema.

The association with inflammatory changes led most of these authors to decide in favour of a metaplastic rather than a developmental origin for the squamous epithelium, on an analogy with the conditions under which squamous metaplasia occurs elsewhere in the body. As Saxén (1951) remarked, the presence of squamous epithelium is "obviously a result of altered conditions due to inflammation". Of particular interest is one of Jaffé's cases, in which squamous epithelium was confined to the region of a metastatic streptococcal abscess.

Squamous epithelium in papillary carcinoma of the thyroid, which reaches an incidence of 15% (Klinck and Menk, 1951) or even higher (Meissner and Adler, 1958), has also been attributed to metaplasia.

That thyroid epithelium is capable of undergoing squamous metaplasia is beyond all doubt. Experimentally, squamous metaplasia has been reported after injections of o-amido-azotoluol (Yoshida, 1932), following large doses of radioactive iodine (Goldberg et al., 1950), and in vitamin A deficiency (McCullough and Dalldorf, 1937; Hume et al. 1939; Gitlin, 1957).

Van Dyke (1955) also described squamous metaplasia in the rat thyroid as a result of vitamin A deficiency, but noted small squamous cysts in 25% of his control animals.

The opposing view, that squamous epithelium in the thyroid is of developmental origin, has been favoured by a small minority of writers who have observed epithelial nests in histologically normal thyroids. Duct-like structures were described in three foetal thyroids by Hermann and Verdun (1899), and interpreted as post-branchial remnants, while Kloeppel (1910) noted squamous nests in one neonatal and three adult thyroids. Getzowa (1907, 1911) described 7 cases, including 3 adult cretins and one idiot. Though nearly all subsequent reports concern squamous epithelium associated with, and apparently attributable to, chronic inflammation, Goldberg and Harvey (1956) described two squamous cysts in adult thyroids, which they considered to be of developmental origin.

Squamous epithelium in histologically normal thyroids has been more often reported in experimental animals, and has usually been attributed to persistence and inclusion of the ultimobranchial body, for example in the cat (Mason, 1931), dog (Godwin, 1937), sheep

(Van Dyke, 1945; Marks et al. 1957) and rat (Van Dyke, 1955). In the guinea pig thyroid, the ultimobranchial body never disappears (de Winiwarter, 1933), and is often, but not always, present within the thyroid.

A study of the literature thus suggests that many examples are clearly metaplastic, while others, and especially those occurring in the foetus and newborn, cannot be interpreted as other than the persistence of embryonic remnants.

The present series is in accord with this concept. The cases fall clearly into two groups: those in which the atypical epithelium is associated with inflammatory cellular infiltration or fibrosis, and those in which the thyroid is histologically normal.

In the former group, the evidence in favour of metaplasia is impressive, and the significance of the associated lymphocytic infiltration or fibrosis, the multiplicity of the lesions, and the presence of transition forms need not be further emphasised. The condition is analogous to the squamous metaplasia occurring in the bronchial mucosa and elsewhere in chronic inflammatory states.

It may be noted in passing that Meeker (1925) suggested the opposite sequence of events, namely, that

the persistence or proliferation of ultimo-branchial remnants within the thyroid conduces to chronic inflammatory changes. On the basis of a single case, designated "Riedel's disease" and histologically similar to the one described by Harry (1940) and to Case 8 in this series, she postulated that a primary pharyngitis or tracheitis might extend by way of the post-branchial system into the thyroid. Such a suggestion does not bear critical examination. The appearances she described are now known to represent a non-infective condition, which may or may not be accompanied by squamous metaplasia. There can be no justification for assuming that the squamous islets represented a system of ducts in communication with the pharynx or trachea.

If metaplasia is readily acceptable as accounting for the cases in which atypical epithelium was associated with lymphocytic infiltration or fibrosis, the same cannot be said of the remaining 39 cases (5 infants, 2 children and 32 adults), in which the thyroids were histologically normal. In many ways, this group contrasts sharply with the preceding one, and the evidence is in favour of a developmental origin.

The thyroids showed no histological abnormality

to which a metaplastic change might be attributed. If an inflammatory process had been present, and had resolved, one would expect it to have left some residual lymphocytic infiltration or fibrosis. The only possible exceptions are Case 12, in which slight lymphocytic infiltration was present but not obviously related to the atypical epithelium, the 4 examples in which a few lymphocytes were seen around the atypical nest but not elsewhere in the gland, and Case 47, in which the thyroid, though histologically normal, consisted of re-grown tissue following thyroidectomy.

The atypical foci in this group were, with three exceptions, solitary, and a search of other blocks revealed no further examples of atypical epithelium. Even in the three cases in which the foci proved to be bilateral or multiple, there was no abnormality which could be interpreted as a transitional state.

While the sex incidence in the "metaplastic" group is linked to that of focal and diffuse "thyroiditis", with a consequent preponderance of females, there is in the histologically-normal group a marked preponderance of males, contrasting with the sex incidence not only of "thyroiditis" but of thyroid disease in general. Adding together the previously-reported cases of

squamous epithelium without inflammatory changes (Hermann and Verdun, Getzowa, Kloeppel, Goldberg and Harvey), there were 9 male and 2 female cases.

The age range, too, differs from the "metaplastic" group in that it includes all age groups from birth to 90 years. In the neonatal thyroid, the only reasonable interpretation of the epithelial nests is a developmental one. The foci closely resemble those described in the thyroids of many animals as ultimo-branchial inclusions, and Kingsbury (1935b) has commented on the difficulty of distinguishing true thyroid acini from colloid-containing vesicles formed by ultimo-branchial tissue. Inclusions of parathyroid and thymus, which are closely related to the ultimo-branchial body in development, were seen in several of the neonatal thyroids reviewed in Section 1.

In the human thyroid, ultimo-branchial inclusions normally disappear at the 25 to 40 mm. embryo stage (Kingsbury, 1935a). If one accepts, however, that they may rarely persist into the neonatal period, one might equally accept their persistence throughout childhood and adult life into old age.

The ciliated epithelium in the duct-like structure in Case 4 is probably indicative of a thyroglossal

rather than an ultimo-branchial remnant (Godwin, 1937).

Before accepting that most, or even some, of the epithelial inclusions are of ultimo-branchial origin, it is worth noting that similarly unexplained islets of atypical epithelium may rarely be seen in the axillary lymph-nodes (Garret and Ada, 1957), as "tumourlets" in the lung (Whitwell, 1955), and in association with fibro-adenoma of breast (Salm, 1957). The importance of the ultimo-branchial body appears to be diminished when the question is considered in this wider context.

The most obvious objection to the developmental theory is the increasing incidence with age. Hunter (1955) noted that squamous nests in the pituitary occurred rarely, if at all, before the age of 20 years, and cited this as evidence in favour of a metaplastic origin. In this series, the inclusions within histologically-normal thyroids were commoner in adult life than in infancy, and commonest of all in the seventh decade. To maintain the developmental view in the face of these facts, it must be supposed that the inclusions exist in a form similar to true thyroid tissue, and that with increasing age they tend increasingly to assume their original structure.

The incidence in adult life, indeed, rises to a peak and subsequently falls, much as does the incidence of clinically-silent lymphocytic infiltration (Fig. 72), as if both abnormalities were responses to influences acting in early and especially in middle adult life.

It may be that the distinction between a developmental and a metaplastic origin is less clear-cut than has been suggested by the protagonists of either view. Van Dyke (1955) stated that in the rat the ultimobranchial tissue becomes indistinguishably transformed into thyroid-like tissue during embryonic development, and the same may be true of human embryonic development (Weller, 1933; Norris, 1937). The presence in the neonatal guinea pig thyroid of acinus-like structures, showing a poor response to thyrotropic stimulation, has already been noted (Figs. 36, 40). Van Dyke's rats, subjected to vitamin A deficiency, developed metaplastic lesions in the precise site occupied by the ultimo-branchial tissue component of the thyroid, that is, in the centre of each lateral lobe and/or near the parathyroid. He stated that the suprabasal cells of the metaplastic epithelium, persisting indefinitely after periods of repair, could multiply and reconstitute

aberrant vesicles resembling thyroid tissue.

The site of the epithelial inclusions in the human thyroids considered here does not show the constancy observed by Van Dyke in the rat thyroid. Solitary nests, though commoner in the centre of the lateral lobes, were seen in other sites, including the isthmus. One might suggest, however, that these nests represent embryonic remnants which had differentiated into thyroid-like tissue and subsequently, in response to some unknown influence, undergone metaplasia.

The two forms in which atypical epithelium occurs would therefore be interpreted in the following way: There is one form in which multiple foci of metaplasia are consequent upon a focal or diffuse chronic inflammatory lesion; this form is naturally commoner in females. There is a second form, commoner in males, in which solitary foci of metaplasia occur in the site occupied by embryonic remnants.

It is possible that many conditions other than chronic inflammation or vitamin A deficiency might induce metaplasia, but in the second group the histological structure of the thyroid affords no clue as to the nature of any other factor which might be responsible. Two other influences which might be incriminated on

experimental grounds are excessive oestrogens (Hume et al., 1939) and epithelial hyperplasia (McCullough and Dalldorf, 1937). The observed preponderance in males suggests that these are unlikely to be concerned.

The true incidence of atypical epithelium in the human thyroid has not been arrived at in this study. The figures of 16.5% for the total of 254 adult autopsy specimens, and 15.1% for the 212 histologically-normal thyroids, are certainly an underestimate.

The highest previously-reported incidence is in the study of Hull (1955), who noted squamous epithelium in 9.5% of 221 autopsy specimens in Colorado - 15 out of 142 nodular thyroids and 6 out of 79 non-nodular thyroids. None of the metaplastic areas were within nodules. Hull concluded, though without justification, that squamous epithelium is twice as common in nodular as in non-nodular thyroids. He gave no further details, beyond commenting on the greater incidence in the advanced age groups, and the much greater incidence in patients dying of primary arteriosclerotic disease than in those dying of cancer. His one illustration, of a squamous nest enclosed by a zone of lymphocytes, leaves one in doubt as to whether his account refers also to solitary nests unrelated to lymphocytic infiltration.

SUMMARY

Squamous epithelium in the human thyroid has usually been reported in association with chronic inflammatory changes, and has therefore been regarded as metaplastic. Rarely, squamous islets have been described in glands which were otherwise histologically normal; these have been interpreted as persistent embryonic remnants.

In this study, the term "atypical" is preferred to "squamous" epithelium, as most of the epithelial inclusions observed could not be definitely identified as stratified squamous epithelium.

The association between atypical epithelium and chronic inflammatory changes has been confirmed, both in abnormal and in clinically normal thyroids.

From a study of 254 adult autopsy specimens and 130 specimens from infants and children, it is concluded that atypical epithelium in the thyroid is much commoner than has hitherto been supposed.

Two types are distinguished. The first is associated with chronic inflammatory changes, and is clearly metaplastic. Its age and sex incidence are linked to those of focal and diffuse "thyroiditis".

The second occurs in histologically-normal thyroids, more commonly in males, and occurs with increasing frequency from birth to old age. The arguments in favour of a developmental derivation are considered, and the suggestion is put forward that the epithelial nests might be the result of metaplasia occurring in thyroid-like tissue of ultimo-branchial origin.

6. THE OCCURRENCE OF ANISOTROPIC CRYSTALS IN THE HUMAN THYROID

Anisotropic crystals are a normal constituent of the human thyroid. The presence of these crystals has been recognised for over 80 years, but they have excited little interest and their significance is not understood.

To assess the incidence of crystals in the normal and abnormal thyroid, I have made use of the same material as in the previous sections, that is, autopsy specimens from 106 newborn infants, 23 infants of 9 days to 6 months, 5 older children, and 254 adults, as well as 38 unselected surgical specimens. In the first series of adult autopsy specimens (191 cases), one or two blocks of thyroid were taken at random in each case; in the second series (63 cases), three blocks were taken in every case - one from the centre of each lateral lobe and one from the isthmus. H and E sections were first scanned with the low-power objective, using crossed polariser and analyser; when anisotropic material was noted, high-power examination was used to observe the morphology and site of the crystals and to assist in differentiating crystals within the thyroid from artefact.

RESULTS

Anisotropic crystals were not seen in any of the infants' or children's thyroids, so that the following account refers only to the adult autopsy and surgical specimens.

The crystals were unstained, and were usually invisible by ordinary examination, though with increasing practice it became possible to identify them in a proportion of cases without the use of polarised light (Fig. 73).

The crystals were always intra-acinar. They occurred in all types of acini, but were commonest in normal acini and were rare in hyperplastic acini of poor colloid content.

Crystals occurred in two sites within the acini. Most commonly, clusters of large crystals were seen within solitary central vacuoles in the colloid (Fig. 74), though usually occupying only a small proportion of the vacuoles in any section. Alternatively, smaller crystals were scattered throughout the colloid (Figs. 73, 75). They were never seen in the peripheral vacuoles of hyperplastic acini.

Within vacuoles, crystals were of varying structure - polyhedral, elongated or irregular - and

occasionally showed a radial arrangement. The shapes of multiple irregular fragments within a vacuole sometimes resembled the separated pieces of a jig-saw, suggesting that a larger crystal had fractured during cutting of the section.

Crystals lying free in the colloid tended to be smaller and more numerous, and, when not too small for their shape to be recognised, they were usually spindle-shaped. They were scattered at random or in small groups through the colloid.

No special significance could be attached to these two sites of occurrence. They were both encountered more commonly in normal or inactive acini than in hyperplastic acini, and the presence of crystals in the colloid was by no means confined to glands in which solitary central vacuoles were absent. Indeed, intra-vacuolar and intra-colloid crystals were often seen in the same gland (Fig. 75) and rarely even in the same acinus.

The numbers of crystals varied greatly in different glands. When most numerous, they might be present in up to 50 per cent of the acini in a field. At the other extreme, a search of three sections revealed only one or two solitary crystals.

In any individual gland, the distribution tended to be uneven, sometimes to the extent that they would be very numerous in one area but very scanty in another area of similar histological appearance. The distribution in nodular glands was equally inconstant (Figs. 76, 77). Crystals were rare in frankly hyperplastic nodules, but were frequently seen in involutional nodules or in the rather common type in which the acini, though lined by columnar epithelium, are larger than normal and well filled with colloid. In some cases, crystals were present in normal tissue but not in the nodules; less often, they showed the reverse distribution, and occasionally they were present both in normal tissue and in nodules.

Their incidence was the same in thyroids showing "neonatal" and post-mortem changes as in normal glands (Fig. 78).

As regards distribution, only three observations can be made with any certainty:

Firstly, a rather common site was the zone of compressed tissue round a nodule (whatever its nature).

Secondly, crystals were rare in hyperplastic glands. Of 10 cases of toxic diffuse goitre (1 autopsy and 9 surgical specimens), 8 showed no crystals.

In another, only three crystals were found in a search of several sections. In the tenth case, a single cluster was seen; it was situated in the centre of an intra-acinar giant cell (Fig. 79) - the only such example in the entire series.

Thirdly, crystals were commoner in normal than in abnormal glands. They were seen in 104 out of 254 adult autopsy specimens, of which the great majority had been clinically normal - an incidence of 41%. In the surgical series, in which generally more sections were available for examination, they were seen in 13 out of 38, or 34%, but the only notable example was in a piece of histologically normal thyroid tissue removed at operation for parathyroid adenoma. The others were all minor examples, and in 7 cases the crystals were confined to normal areas in nodular goitres. The occurrence of numerous crystals in an area of hyperplasia, illustrated in Fig. 80, is exceptional.

Unexpectedly, the more detailed examination of the second autopsy series did not result in a striking increase in incidence. The proportion of thyroids showing crystals rose in females but fell in males. Apparently the examination of a random section gives

a fairly reliable indication as to the presence of crystals, suggesting that when crystals occur they are widely, even if sometimes unevenly, distributed throughout the gland. The two series have therefore been combined, and the age and sex incidence are shown in Table 27 and the accompanying histogram.

The ages ranged from 20 to 90 years, one of the most striking examples occurring in a 20-year-old male. No examples were found under the age of 10 years. As there were no cases in this series in the intervening age-group 10 to 19, it can only be surmised that the lower age-limit for the occurrence of crystals falls within the period of adolescence. The incidence remained fairly constant throughout most of adult life, at between 35 and 40%, but increased sharply in old age, exceeding 70% over the age of 80.

The incidence was slightly higher in females. The disparity was only partly accounted for by the greater proportion of elderly subjects among the females; excluding all cases aged 70 years and over, crystals were still commoner in the female (41% as against 35%).

In eleven cases, the crystals were exceptionally large and numerous. A separate analysis of these

cases (Table 28) emphasises the preponderance in females, and the sharp increase in old age.

DISCUSSION

The principal contributions to the literature on this subject are those of Richter (1940) and Richter and McCarty (1954). The latter reviewed the literature, and attributed the first description to Zeiss (1877). They described the physical properties of the crystals, and by X-ray diffraction identified them as calcium oxalate monohydrate. The crystals were noted to be commoner in normal than in abnormal glands, rare in diffuse hyperplasia and in focal areas of hyperplasia, and of variable occurrence in nodular glands, as has been described here. A gradual increase with age was noted, but sex incidence was not mentioned.

Additional points brought out by this survey are the predilection for solitary central vacuoles

and for the compressed acini around nodules, the increased incidence in the over-80 age-group, and the predominance in females.

Richter and McCarty were unable to account for the presence of calcium oxalate crystals in the normal thyroid, but suggested that their occurrence was related to the functional state of the gland. The rarity of crystals in hyperplastic areas does indeed support such a view, but the commoner occurrence in normal than in involutional acini is against any direct relationship to the degree of physiological activity in the acinus. The crystals must be accepted as a normal, but inconstant, participant in the structure of the thyroid acinus in adult life. The wide variation in the numbers of crystals present is puzzling, as there is otherwise no histological difference between glands in which crystals are abundant and those in which they are absent.

The crystalline substances demonstrated in thyroid acini by Popoff (1943) have no relation to those discussed here. They were thought to represent proteolytic enzyme and thyroxine, and

were demonstrated only by special technical methods.

Calcium oxalate, as pointed out by Richter and McCarty, is a toxic substance, and its presence in normal tissue is unique to the thyroid. While there is no suggestion that its presence results from any abnormality of the thyroid, one cannot be sure that it might not rarely be the cause of thyroid disease. Gross (1955) thought that the crystals might bear a relationship to the granulomatous reaction of subacute thyroiditis. Anisotropic crystals, both within and outside the acini, were seen in all of 14 cases of granulomatous thyroiditis; of 29 examples of other forms of thyroiditis, only 4 showed "a few" crystals. He had shown experimentally that calcium oxalate monohydrate crystals are capable of inciting a typical granulomatous reaction in rat's thigh muscles. I have not found anisotropic crystals in any of three cases of granulomatous thyroiditis examined.

The significance of the crystals remains obscure. There is some experimental evidence relating blood oxalic acid levels to adrenal cortical function

(Zygulska-Machowa, 1955), but I know of none concerning the thyroid.

The occurrence of a toxic substance in about two-fifths of normal adult thyroids is clearly deserving of further study, but here the histologist must acknowledge the limitations of his technique, and leave the task to his colleagues in other fields.

SUMMARY

Anisotropic crystals occur in the acini of the normal thyroid throughout adult life, but not in infancy and childhood. They have been seen in about two-fifths of a series of 254 adult autopsy specimens.

The crystals often occupy solitary central vacuoles in the colloid, but may also lie free in the colloid. They are seen less commonly in involutional areas, and comparatively rarely in hyperplastic areas. They are seldom seen in cases of toxic goitre.

Without the use of polarised light, no histological feature has been found which would distinguish normal thyroids containing crystals from those without crystals.

The chemical constitution of the crystals is known, but their significance is not understood.

PART III

LYMPHOCYTIC INFILTRATION IN NORMAL AND ABNORMAL THYROIDS AND THE EVOLUTION OF CHRONIC THYROIDITIS

The autopsy material used in Part II was re-examined with a view to assessing the incidence and significance of lymphocytic infiltration in the clinically normal thyroid. It has not been possible, however, to consider the focal lymphocytic infiltration of the normal thyroid in isolation from the more diffuse infiltration of abnormal thyroids. Histologically, the extent of the infiltration was found to vary widely, and the range of lesions overlapped that occurring in clinically-manifest thyroid disease. Clinically, one may be able to distinguish a "normal" from an "abnormal" thyroid, but histologically it is impossible to draw a sharp dividing line, and no morphological distinction can be made between the lymphocytic infiltration of the normal and of the abnormal thyroid.

From the study of lymphocytic foci in the normal thyroid, therefore, stems a discussion of the relation of such foci to the diffuse infiltration

of chronic thyroiditis and the focal infiltration and diffuse fibrosis of myxoedema, with illustrative examples of these conditions.

The main question at issue is whether hyperthyroidism, chronic thyroiditis and myxoedema are distinct and unrelated clinico-pathological entities, or whether they represent a series of stages, not necessarily all clinically evident, in the evolution of toxic goitre.

In Section 7, the findings in clinically normal thyroids are considered. Section 8 is concerned with the histological findings following partial thyroidectomy, and the question of whether progression or evolution of the disease can be detected by examination of the remaining tissue after surgical operations on the thyroid. In Section 9, the histological picture in myxoedema is reviewed in relation to the foregoing findings.

7. LYMPHOCYTIC INFILTRATION IN THE NORMAL AND ABNORMAL THYROID AT AUTOPSY

An examination of the 254 autopsy thyroid specimens that were reviewed in Part II has revealed lymphocytic infiltration in 42 cases. Glands showing lymphocytic foci were arbitrarily graded as ±, + or ++, according to the extent of the infiltration. As a rough guide, the grading ± was used when the lymphocytic foci were not visible on naked-eye examination of H and E sections. When only two or three minute foci were seen in an entire section, the degree was considered insufficient to be worth recording.

The earliest lesion was a small perivascular collection of lymphocytes - a "lymphorrhage", to use Levitt's term. Larger aggregations were of irregular outline, often appearing to extend along connective tissue septa to form elongated or branching masses. The more extensive the infiltration, the greater the tendency to form lymphoid follicles with germinal centres. The lymphoid follicles were of the same structure as those occurring in lymph nodes,

and mitotic figures were frequently seen in the germinal centres. The presence of follicles with germinal centres is the justification for using the term "lymphoid hyperplasia".

When infiltration was more extensive, there was actual replacement of the parenchyma by masses of lymphocytes, but even in such glands the smaller aggregations still retained their perivascular distribution. In the most extensive examples, lymphocytic infiltration replaced up to half of the area of the section.

Of the 254 specimens, 10 were from patients who had suffered from clinically-recognised thyroid disease, and these are excluded from the figures for age and sex incidence. A study of the 244 clinically normal thyroids showed that lymphocytic infiltration was present in 35, or 14.3%. The incidence was notably higher in females (Table 29), especially when only the severer degrees of infiltration were considered (Table 30). In early adult life, lymphocytic infiltration was negligible; the incidence reached its maximum in the sixth decade, in both sexes, and fell thereafter.

No less important than the age and sex incidence were the histological accompaniments of lymphocytic infiltration (Table 31). Firstly, plasma cells were often intermingled with the lymphocytes, occurring especially with the more advanced degrees of lymphocytic infiltration and rarely in those glands showing lymphorrhages only. In none of the clinically normal thyroids did the number of plasma cells exceed or even equal the number of lymphocytes. The conventional term "lymphocytic infiltration" is retained here, but with the provision that it often refers to the presence of plasma cells as well as lymphocytes.

Secondly, lymphocytic infiltration was generally accompanied by epithelial hyperplasia. In some instances, there was focal or diffuse hyperplasia of the degree that occurs in exophthalmic goitre. More often, the gland was not frankly hyperplastic, but there were signs of increased functional activity - partial colloid depletion, and cuboidal or high cuboidal epithelium, with occasional columnar segments. Whatever the degree of epithelial hyperplasia, there could be found, immediately adjacent to all but the smallest lymphocytic foci, acini of a distinct type

unlike those in the rest of the gland. These acini were small, collapsed or disintegrating, lined by columnar epithelium, and devoid of colloid (Fig. 66). The lumen was empty, or less often was occupied by macrophages which were occasionally fused to form pseudogiant cells. Sometimes, as already noted in Section 5, total collapse of the acini, with a change in the character of the nuclei, gave an appearance more suggestive of squamous than of thyroid epithelium.

"Increased functional activity" is of course an imprecise term; the minimum histological evidence that was accepted is illustrated in Fig. 81. Apart from 3 very minor examples of lymphocytic infiltration, there were only 2 cases in which the gland was of generally inactive appearance. One, however, included several islets of frank hyperplasia, as well as showing a general increase in connective tissue. The other (Case 39 in Table 31) more closely suggested lymphoid hyperplasia without epithelial hyperplasia. The lymphoid areas, though very extensive, were sharply circumscribed, and the intervening parenchyma was composed of regular well-filled acini lined by flattened epithelium, without

interacinar cells (Fig. 82). Closer examination showed that within the lymphoid areas were columnar epithelial cells, forming collapsed or disintegrating acini devoid of colloid. Epithelial hyperplasia was indeed present, but this case differed from the others in that hyperplasia could be found only within the lymphoid areas, and not in the adjacent acini or in the parenchyma generally.

A less constant epithelial change than hyperplasia was oxyphilia. Large oxyphilic (or"Hürthle" or "Askanazy") cells were present in about half of the cases, and were always in close relation to lymphocytic foci. Oxyphilic change was seldom extensive, and in many instances was confined to a few inconspicuous groups of cells.

Finally, more than half of the cases showed some degree of fibrosis. In the mildest examples, this amounted to no more than a thickening of the connective tissue septa, but more often there were bands of fibrous tissue either enclosing nodules or subdividing the gland into parenchymatous islets of varying size. The degree of fibrosis was not directly related to the degree of lymphocytic infiltration.

Clinically abnormal thyroids

There were 10 cases in this group (Table 32): 3 of non-toxic nodular goitre, 2 of myxoedema, 1 of toxic diffuse goitre, and 4 in which there had been a previous thyroidectomy. Only in the toxic goitre case was it considered likely that thyroid disease had been a cause of death.

Seven of these cases - all females - showed lymphocytic infiltration, and are included in Table 31. The remaining 3 cases - all males - showed no significant degree of lymphocytic infiltration.

The histological findings were the same as in the clinically normal thyroids, except that the two myxoedema cases showed no epithelial hyperplasia. There was no histological feature which would distinguish the lymphocytic infiltration in these cases from that seen in the clinically normal thyroid.

DISCUSSION

Lymphocytic foci are mentioned in at least one standard textbook of histology (Ham, 1957) as being normal constituents of the thyroid; their incidence in the normal thyroid has been estimated as 16.2% (Chesky et al., 1951).

Difficulty arises in defining the "normal" thyroid. If one considers the autopsy cases in which, retrospectively, no evidence is found of clinical thyroid abnormality, the present findings indicate that lymphocytic infiltration occurs in about 1 in 4 adult female thyroids, and in about 1 in 12 adult males. But from the histological point of view, lymphoid foci have not been seen to occur in normal thyroid tissue, and are characteristically associated with epithelial hyperplasia, small empty collapsed or disintegrating acini, pseudogiant cells, oxyphilia and fibrosis.

These histological accompaniments, indeed, are those which in diffuse form make up the characteristic pictures of toxic goitre, chronic thyroiditis and myxoedema. The diffuse epithelial hyperplasia of exophthalmic goitre is frequently associated with lymphoid foci, the estimated incidence ranging from 23.3% (Hellwig, 1938) to 75% (Simmonds, 1913). In chronic thyroiditis, epithelial hyperplasia is inconstant, but oxyphilia, collapsed and disintegrating acini, pseudogiant cells and fibrosis may all be prominent. In myxoedema, all the same features may again be present (Section 9), but here fibrosis,

oxyphilia and metaplasia are predominant.

It is therefore difficult for the histologist to accept lymphocytic infiltration as an occasional "normal" finding, unrelated to the lymphocytic infiltration of toxic goitre, chronic thyroiditis and myxoedema. From the histological appearances, as well as from the similarity of age and sex incidence, it would seem that the significance of lymphocytic infiltration is the same whether it occurs in the clinically normal thyroid or in any of several clinically recognisable thyroid disorders. Fig. 83 shows how the age incidence of lymphocytic infiltration in the clinically normal thyroid corresponds to Levitt's representation of lymphoid hyperplasia in the evolution of toxic goitre.

Two explanations are currently in favour to account for the occurrence of lymphocytic infiltration in the thyroid.

According to one view, inflammatory cells are attracted by chemotaxis following the escape of colloid, or thyroglobulin, from the acini into the stroma. An inflammatory reaction occurring in this way would be analogous with similar processes in the

breast and prostate. In both these organs, as in the thyroid, epithelial hyperplasia tends to be accompanied by lymphocytic infiltration, and rarely there may be a widespread inflammatory reaction (plasma-cell mastitis or granulomatous prostatitis) thought to be due to escape of retained secretion into the stroma.

The mechanism of "colloidophagy" by which colloid reaches the interacinar stroma has been studied principally by Hellwig and his associates (references 34 and 103 to 107), though Hellwig (1954) acknowledged the priority of similar observations by Tanabe and Wakabayashi (1940). Using supravital and paraffin preparations from 169 cases of chronic thyroiditis, Chesky, Hellwig and Dreese (1951) reconstructed three stages of colloidophagy: First, macrophages enter the acinar lumen and ingest the colloid. Secondly, the acinus collapses, and the macrophages fuse to form a syncytium. Thirdly, the macrophages leave the lumen, become stranded in the stroma, and degenerate; the liberated colloid then attracts lymphocytes by chemotaxis. Degeneration of the acinar epithelium would thus be due to accumulation of lymphocytes

around and between the acini, and would not be the primary lesion in chronic thyroiditis, as is more generally supposed.

Chesky et al. considered excess of thyrotropic hormone to be the most important factor in causing the initial colloid changes which result in the attraction of macrophages. The findings applied also to foci of chronic inflammation in goitres other than chronic thyroiditis, and in normal-sized thyroids obtained at autopsy. Hellwig and Wilkinson (1956a,b) were able to produce the "characteristic triad" of macrophages, resorption of colloid, and accumulation of lymphocytes by the action of radioactive iodine on the rat and guinea pig thyroid. It would seem that the inflammatory response in these experiments is not a direct result of damage to the epithelium, but an indirect result of chemical changes induced in the colloid. Administration of TSH alone has been reported as causing focal lymphocytic infiltration in the pigeon's thyroid (Thurston, 1933), and excessive TSH secretion, induced by prolonged administration of thiouracil, has led to a picture resembling struma lymphomatosa in the rat thyroid (Clausen, 1953).

It has been suggested by Sommers and Meissner (1954) that the primary lesion leading to colloidophagy and lymphocytic infiltration is degeneration of the basement membranes. Diffuse abnormalities of basement membrane staining were seen in all cases of chronic thyroiditis, and similar localised changes were seen in cases of primary hyperplasia accompanied by considerable lymphocytic infiltration. The latter observation has recently been confirmed and extended by Stuart and Allan (1958).

The alternative, but not necessarily contradictory, explanation for the accumulation of inflammatory cells in the thyroid is the occurrence of an antigen-antibody reaction. It has been postulated that escape of thyroglobulin from the acini leads to the formation of auto-antibodies, and that interaction of thyroglobulin and the auto-antibody within the thyroid is responsible for the inflammatory reaction. The thyroids of rats injected with anti-rat-thyroid serum have shown a severe disorganisation of the acinar epithelium (Lilien, 1954). It has been shown by Witebsky and Rose (1956) that rabbits injected with extracts of their own thyroids develop

precipitating antibodies, and that injection of antiserum prepared in this way into rabbits provokes a diffuse chronic thyroiditis (Rose and Witebsky, 1956). The presence of similar antibody in the serum of patients with Hashimoto's disease is now well established (Roitt et al., 1956; Goudie et al., 1957), and is already being used in the confirmation of this diagnosis. Later work indicates that there are two distinct antibodies (Roitt and Doniach, 1958), which do not necessarily have the same significance.

The immunological studies have cast some doubt on the wisdom of including plasma-cell infiltration under the general term "lymphocytic infiltration". To do so is perhaps generally justifiable, as there is no clinical distinction, as regards age group, sex incidence, clinical findings, pre-operative diagnosis or post-operative course between the various forms of chronic thyroiditis with or without the presence of plasma cells (Peterson and Shidler, 1957, and the discussion which follows their paper). But immunologically, the lymphocyte and the plasma cell may not have the same significance. "Plasma cells", according to Weiser (1957), "may mean different

things to different persons. To me, the presence of plasma cells means that antibody formation is taking place and, moreover, that it is taking place locally . . ." The different types of chronic inflammatory infiltration, though indistinguishable clinically, are distinguishable immunologically. Paine et al. (1957) defined Hashimoto's disease to exclude cases showing polymorphs, plasma cells or giant cells (a stricter definition than that of Hashimoto himself, who noted considerable numbers of plasma cells among the lymphocytes); defined in this way, Hashimoto's disease was the only thyroid disorder studied in which antibodies were not detected.

Auto-immunisation, like colloidophagy, is a mechanism which could account for the cellular infiltration not only in chronic thyroiditis but also in other thyroid disorders and in the clinically normal thyroid. It is now known that antibodies are present in the serum, though less commonly, in diffuse and nodular toxic goitre, subacute thyroiditis, carcinoma of the thyroid, and especially in myxoedema (Paine et al., 1957; Goudie et al., 1957; Owen and Smart, 1958; Roitt and Doniach, 1958), and

similar results are obtained by the use of skin tests (Buchanan et al., 1958). White (1957) detected antigen in and among the lymphocytes in toxic diffuse goitre.

The studies of Buchanan et al., Owen and Smart, and Roitt and Doniach all revealed a small percentage of positive results in normal controls, and Anderson et al. (1957) found that, at autopsy on such unexplained positive cases, the thyroid showed changes similar to those of chronic thyroiditis.

Leakage of thyroglobulin out of the thyroid acini was accepted by the Lancet (1957) as the initial event in the auto-immunisation process in Hashimoto's thyroiditis, and a substance resembling thyroglobulin has in fact been detected in the serum in Hashimoto's disease (Owen and McConahey, 1956). "It leaves only one thing unanswered", added the Lancet. "What sets the process going?".

It is perhaps too early to combine the two hypotheses and suggest that Hellwig's mechanism of "colloidophagy" accounts for the escape of thyroglobulin and so initiates the process of auto-immunisation. But whether one accepts colloidophagy,

or auto-immunisation, or a combination of the two, as the mechanism responsible for lymphocytic infiltration in the thyroid, there is now both histological and immunological evidence indicating that the process is the same in the clinically normal thyroid and in hyperthyroidism, chronic thyroiditis and myxoedema.

This conclusion has an important bearing on the pathogenesis of these thyroid diseases. Both chronic thyroiditis and myxoedema are generally considered to be clinico-pathological entities, unrelated to each other and to toxic goitre. All three might now fall into place as successive stages in a single pathological process, each being merely a more severe and clinically manifest form of a similar stage in the clinically normal thyroid.

There is evidence in favour of such a concept in the works of Vaux (1938), Bastenie (1944), Goetsch and Kamner (1955), and especially of Levitt (references 143 to 146), all of which are referred to later.

Beattie and Dickson (1948) classified lymphadenoid goitre under secondary changes in toxic goitres, and went so far as to say that "lymphadenoid

goitre is best regarded as a regression rather than as a special type of goitre. Some examples of Riedel's struma may represent a final stage of this regression". Other standard works on pathology did not follow suit, and the concept of a continuous sequence from toxic goitre through chronic thyroiditis to myxoedema did not gain general acceptance. The advent of immunological evidence, however, has won many new adherents to the "unitarian" view, and the new approach was well summarised by the Lancet (1958): "Perhaps we should think in terms of a reaction, expressed histologically by lymphocytic and plasma cell infiltration, and serologically by antibodies against human thyroid extract, rather than in terms of 'diseases' defined by the pathologist and the clinician. On this view it would be possible to picture the same auto-immune reaction occurring in a wide variety of thyroid disorders (including some not detected by the clinician). Only when the same process has involved much of the gland would its effects become clinically evident".

The histological findings described here might alone have been sufficient to suggest such a

conclusion. Since the lymphocytic foci in the clinically normal thyroid, accompanied in varying degree by epithelial hyperplasia and fibrosis, can readily be accepted as different stages in a single process, might not the diseases which they appear to represent in sub-clinical form be similarly interpreted?

Does hyperthyroidism in fact lead to chronic thyroiditis? Do either of these diseases lead to myxoedema? The next two Sections are devoted to a consideration of these questions.

SUMMARY

Lymphocytic infiltration has been studied in 254 adult thyroids obtained at autopsy.

Lymphocytic infiltration was present in 35 of the 244 clinically normal thyroids, and in 7 of the 10 clinically abnormal specimens. It was much commoner, and tended to be more extensive, in females. In both sexes, the incidence reached its maximum in the sixth decade.

Most of the glands showing lymphocytic infiltration were hyperplastic, or showed evidence of increased functional activity.

The lymphocytic foci were accompanied by small collapsed acini, devoid of colloid but sometimes containing macrophages, and in varying degree by oxyphilic epithelium, metaplastic epithelium, plasma-cell infiltration and fibrosis.

Lymphocytic infiltration in the clinically normal thyroid is seen to be similar, histologically and in age and sex incidence, to the infiltration which occurs in the clinically abnormal thyroid. Present-day opinions on the pathogenesis and significance of lymphocytic infiltration in the thyroid are reviewed,

and the implications of the findings in clinically normal thyroids are considered with regard to the pathogenesis of chronic thyroiditis and myxoedema.

8. THE RELATION OF EPITHELIAL HYPERPLASIA TO CHRONIC THYROIDITIS: A study of thyroid histology following partial thyroidectomy

Chronic thyroiditis - using the term here to include both Hashimoto's disease and the more ill-defined "chronic non-specific thyroiditis" - is a condition of obscure etiology, considered at present to be due to auto-immunisation (Roitt et al., 1956) or to primary thyroid failure (Skillern et al., 1956a). Most writers accept that it arises in a previously normal thyroid, and while there is a vast literature on the question of whether the Hashimoto variety progresses to Riedel's struma, less attention has been given to the possibility that chronic thyroiditis is itself due to progression of an earlier thyroid disorder. In the four cases reported by Hashimoto in 1912, there had been no clinical evidence of preceding thyroid disease, and Joll's study of 81 cases led him to the statement that "It is striking how little evidence there is of any pre-existing ill-health, either immediate or remote". Beare (1958), while noting a high incidence of preceding disease in other organs, suggesting a

pathological sensitivity on the part of the body tissues to various stimuli, considered that the presence of any pre-existing thyroid disease was unrelated to the development of lymphadenoid goitre. No association with thyrotoxicosis was found by Heptinstall and Eastcott (1954) or Hendrick (1957).

However, Graham and McCullagh (1931), while agreeing that hyperthyroidism could not be recognised either in their own or in Hashimoto's original cases, surmised from the histological appearances that "were it permissible to assume an antecedent hyperthyroidism, an explanation of pathogenesis would not be difficult".

Some authors have indeed satisfied themselves that a history of hyperthyroidism could be elicited in chronic thyroiditis. Vaux (1938) found clinical as well as histological evidence of preceding thyrotoxicosis and involution, though she confused the issue by using the term "Riedel's disease" for typical cases of Hashimoto's disease. Joll (1939) objected that she had included as an early stage cases which should have been classified with the advanced forms of lymphoid infiltration in Graves' disease, but

this disagreement only serves to emphasise the existence of transitional histological states between toxic goitre and chronic thyroiditis.

Goldberg and Davson (1948), too, could find no sharp dividing line on histological grounds between toxic goitre and lymphadenoid goitre. Their own clinical experience, as well as many observations cited from the literature, suggested to them that "a toxic phase is sufficiently frequent to count as an important factor in pathogenesis". A high incidence of emotional unrest prior to the onset of Hashimoto's disease was noted by Davison and Letton (1949), who were inclined to agree that in the early stages there is a slight hyperthyroidism, followed by euthyroidism and then hypothyroidism. A careful study of 49 cases of chronic non-specific thyroiditis by Goetsch and Kamner (1955) led them to the belief that the early phase is one of epithelial hyperplasia, and the terminal phase one of diffuse fibrosis, resembling Riedel's struma; they considered that chronic thyroiditis is "an inflammatory response to etiological irritative factors residing in the hyperfunctioning epithelium of primary toxic diffuse goitre". A history of hyperthyroidism was elicited in several of

their cases in the terminal phase.

The basal metabolic rate in 41 unquestionable cases of struma lymphomatosa collected by McSwain and Moore (1943) ranged from plus 63% to minus 23%, with an average of plus 5%.

There have even been cases in which the clinical picture was one of exophalmic goitre while the histological picture was that of chronic thyroiditis (Eden and Trotter, 1942; Gürkan, 1945), and in one case of exophthalmic goitre (Case 10 of Pemberton, 1930) the thyroid showed epithelial hyperplasia with "an area of woody thyroiditis involving the left lobe".

The principal protagonist of the "progression" theory has been Levitt (1951, 1952, 1954, 1957), who based his views on a clinico-pathological study of over 2000 thyroidectomies. Levitt described a steady graduated change through six phases, beginning with epithelial hyperplasia and ending with fibro-lymphoid hyperplasia (Hashimoto's disease) and the fibrosis of Riedel. (The second and third cases described by Riedel, in sharp contradistinction to his first, were considered to be examples of chronic thyroiditis unrelated to the six progressive phases).

It appeared to Levitt that progression of the lymphoid phases was the rule, but that progress could be halted at any of the six phases, and the process was still reversible in the earlier phases.

In spite of the prevailing opinion that chronic thyroiditis arises in a previously normal gland, it will be seen that there is a considerable body of evidence for a preceding phase of hyperthyroidism, or at least of epithelial hyperplasia. However, arranging a number of thyroid specimens in the order of a supposed sequence is obviously less satisfactory than demonstrating progression in successive thyroid specimens from the same patient. As Levitt (1954) pointed out, positive proof of progression should be based on the demonstration of changes as they occur in one individual.

MATERIAL

I have had the opportunity of examining 6 thyroidectomy specimens from patients who had undergone previous thyroidectomy (Table 33A), and 4 autopsy cases in which there was a history of thyroidectomy (Table 33B) - a total of 10 cases in which the

possible progression of thyroid disease can be studied.

I have been handicapped by the difficulty of tracing information about the previous thyroidectomies, and of obtaining samples of the excised tissue. In 4 of the 6 surgical cases, tissue from the earlier thyroidectomy was still available for study, but in one case the earlier specimen had not been examined microscopically, and in another thyroidectomy had been performed overseas and the specimen could not be traced. The autopsy cases presented a greater problem, as the 4 patients all died of conditions unrelated to the thyroid, and insufficient details had been obtained during life. In none of these cases was it possible to trace the thyroidectomy specimen.

In spite of these deficiencies, the material is of value in studying the question of progression.

RESULTS

Surgical cases

Of the 6 surgical cases (Table 33A), 4 were recurrences of non-toxic nodular goitre, and 2 were recurrences of goitre many years after thyroidectomy

for Graves' disease. The 4 non-toxic goitres will not be considered in detail, as in three of them there was no significant degree of lymphocytic infiltration in either the first or subsequent specimen. In one (Case 1), in which the first specimen was not available, the recurrence was accompanied by doubtful clinical signs of toxicity; the second specimen showed focal hyperplasia and involution, with foci of lymphocytic and plasma cell infiltration, fibrosis, and nests of squamous epithelium in the fibrous capsule of an involutional nodule.

The other two surgical cases were both examples of progression from diffuse epithelial hyperplasia to diffuse chronic thyroiditis, and are of sufficient importance to justify detailed case-reports:

Case 2.

A married woman, born in 1907, underwent a partial thyroidectomy in 1941 for diffuse toxic goitre. Symptoms of hyperthyroidism had been present for about a year; there was slight exophthalmos, and the basal metabolic rate was plus 65%. The excised tissue was reported as showing "typical hyperplasia of thyro-toxicosis".

She remained well for about 9 years, but thereafter symptoms of thyrotoxicosis steadily returned, and thiouracil treatment was begun in 1952 and continued for 18 months. The goitre increased markedly during the summer of 1956. On examination in September 1956, the thyroid enlargement was much more pronounced in the right lobe. Tremor and tachycardia were of slight degree, and there was no exophthalmos. There had been slight loss of weight. X-ray showed some compression and deviation of the trachea to the left. Hoarseness and irritating cough were the chief symptoms.

Thyroidectomy was delayed by the finding, at direct laryngoscopy, of a mass in the left vallecula, which on biopsy resembled tonsillar tissue and showed no evidence of malignancy.

Right hemithyroidectomy was performed in November 1956. There was gross fibrosis of the infrahyoid musculature, and the thyroid was very adherent to the trachea. The right lobe of the thyroid was excised with considerable difficulty, leaving behind a thick posterior layer which did not appear to contain thyroid tissue.

Post-operatively, the patient was well, and she gained weight. In September 1957, she developed signs of mild hypothyroidism, which responded to 1 gr. thyroid extract daily. When seen again in February 1958, she looked and felt well, there were no signs of hypothyroidism, and the thyroid was not palpable.

Pathology: The sections of the first (1941) specimen showed the typical picture of exophthalmic goitre. There was diffuse epithelial hyperplasia, colloid depletion and "focal thyroiditis" (Figs. 84, 85). The sparse inflammatory foci were composed of lymphocytes, with occasional lymphoid follicles, and a few plasma cells. These foci were associated with collapse of the acini, oxyphilic epithelium, and intra-acinar giant cells. Fibrosis was of slight degree.

The second (1956) specimen measured 7.5 x 5 x 4 cms., and weighed 98 g. It was firm, smooth, greyish-white, and like a lymph-node in consistency. The cut surface was uniformly greyish-white, with a few small cysts but no nodules. Muscle fibres were attached along one margin.

Microscopically, the picture was one of diffuse

chronic thyroiditis, with degenerative changes in the acini and an intense plasma-cell infiltration (Fig. 86). Plasma cells infiltrated all parts of the lobe, though varying in numbers from one area to another. The comparatively few lymphocytes showed a follicular arrangement, often with germinal centres. Polymorphs were not present, nor were there any extra-follicular giant cells.

The acini were small or medium-sized; many were totally collapsed, and in some areas groups of epithelial cells were so intermingled with plasma cells that the acinar structure was not recognisable. Large oxyphilic cells were numerous, forming distinct acini in some areas, solid clumps in others. Normal neutrophilic epithelium was also present, and was predominantly cuboidal or low columnar. There were a few ill-defined nodules showing pronounced epithelial hyperplasia and comparatively sparse inflammatory cell infiltration (Fig. 87).

Only a minority of the acini contained colloid. Many were empty, while others, whether lined by oxyphilic or neutrophilic epithelium, were occupied by multinucleate giant cells (Fig. 88).

The small cysts were empty; they were lined by a single layer of flattened epithelium, and old and recent haemorrhage was seen in their walls. Fibrosis was again slight, not exceeding the degree seen in the previous specimen. The muscle fibres attached to the thyroid were sparsely infiltrated by lymphocytes and plasma cells.

Case 4

A married woman, born in 1917, had been aware of a swelling in the neck since the age of ten. At the age of 19, she had developed symptoms of hyperthyroidism, with a large symmetrical swelling of the thyroid, exophthalmos, and a basal metabolic rate of plus 66%. Subtotal thyroidectomy in 1937 had been followed by a period of good health, apart from transient loss of voice. The excised gland was not examined microscopically. On re-examination in 1947, she appeared myxoedematous; the basal metabolic rate was minus 25%, and the serum cholesterol 222 mg. %; she was treated with thyroid extract. One year later a diagnosis of recurrent thyrotoxicosis was made, and she was treated with thiouracil for one month, but subsequently thyroid medication was

resumed. Enlargement of the thyroid recurred in 1950, and pressure symptoms appeared in 1956. On examination in February 1957, she was pale and overweight, but not definitely myxoedematous. There appeared to be a cyst in the thyroid isthmus. The B.M.R. was minus 33%, and the serum cholesterol 205 mg.%. X-ray showed compression and some deviation of the trachea to the left. At operation in July 1957, there was considerable fibrosis around the thyroid; the enlargement was principally in the right lobe and the isthmus, most of which were resected.

Pathology: The specimen comprised two irregular lobulated pieces of tissue, measuring 5 and 3.5 cms. in their greatest diameters, as well as four smaller fragments, weighing in all 22 g. The cut surface was pale grey throughout, with no obvious cysts or nodules but showing a rather ill-defined lobulation.

Microscopically, the gland was divided into irregular areas of varying size by bands of dense fibrous tissue (Fig. 89). There was diffuse plasma-cell infiltration (Figs. 90, 91), most intense at the periphery of the gland and at the periphery of the parenchymatous islets. Elsewhere, infiltration

varied greatly, but was present everywhere except in a small nodule composed of large pale epithelial cells arranged in trabecular fashion. Lymphocytes occurred in substantially lesser numbers, forming lymphoid follicles with germinal centres (Fig. 89).

The acini were small, lined by cuboidal or low columnar epithelium, and they contained little colloid. In some areas, there was epithelial hyperplasia of the degree that occurs in exophthalmic goitre (Fig. 92). In other areas, the acini were disorganised and the lumina scarcely identifiable (Fig. 90). Some of the acini were lined by oxyphilic cells. Intra-acinar giant cells were numerous. Atypical epithelium was seen in several fields, and there was one focus of squamous epithelium (Fig. 89).

Autopsy cases

The 4 cases are described briefly in Table 33B. All had previously had thyroid operations, and had been euthyroid for many years. At autopsy, the thyroid was enlarged in one case, of normal size in one case, and reduced in size in the other two. Microscopically, the enlarged gland was of normal structure, except for a small involutional nodule.

The other three showed varying degrees of lymphocytic and plasma-cell infiltration, with extensive fibrosis in two and oxyphilic epithelium in two.

With so little information available concerning the surgical operations, no definite conclusions can be drawn from these cases. The one case in which the diagnosis was known to have been Graves' disease showed no progression to a lymphoid phase, and can indeed be regarded as an example of regression from epithelial hyperplasia to a normal structure. The other three showed rather more fibrosis, lymphocytic infiltration or oxyphilic change than would be expected in either toxic or non-toxic goitre, and are possibly examples of progression (Fig. 93).

DISCUSSION

To establish that hyperthyroidism may progress to chronic thyroiditis, it is not necessary to demonstrate that progression occurs in all cases. Everyday experience of the course of toxic goitre is alone sufficient to dispel any such idea. Even if the existence of progression is accepted, it is clear that, at least in the early epithelial and lymphoid

phases, the course may not only be arrested but may be reversible (Levitt, 1954). The earlier immunological studies appeared to conflict with this view, suggesting that the mechanism which brings about lymphocytic infiltration, once established, is self-perpetuating (White, 1957), but later observations indicate that a chain-reaction is far from inevitable (Roitt and Doniach, 1958).

Of the 6 surgical and 4 autopsy thyroid specimens described here, from patients who had previously undergone thyroidectomy, one (Case 10) shows regression to a normal structure 10 years after operation for Graves' disease; in 7 others, including cases of recurrent non-toxic nodular goitre, the evidence is inconclusive.

Interest centres chiefly on Cases 2 and 4, in which there is clear evidence of progression from diffuse epithelial hyperplasia to chronic thyroiditis. In Case 2, the evidence is both clinical and pathological; in Case 4, the earlier thyroidectomy specimen had not been examined microscopically, but the clinical picture had been that of exophthalmic goitre.

The availability of both specimens in Case 2 allows one to trace the development of the lesion from diffuse epithelial hyperplasia with focal chronic thyroiditis to diffuse chronic thyroiditis with focal epithelial hyperplasia. The elements comprising the histological picture are the same in both instances. Epithelial hyperplasia is pronounced and diffuse in the first specimen; it is no less pronounced, but of limited extent, in the second. Lymphocytic and plasma-cell infiltration is confined to small scattered foci in the first specimen, and is diffuse and intense in the second. Oxyphilic epithelium is likewise more extensive in the second specimen. Fibrosis is slight in both. Indeed, perithyroiditis is the only histological feature of the second specimen whose origins cannot be traced in the first.

In accepting these cases as examples of progression from hyperthyroidism to chronic thyroiditis, three observations must be made:

Firstly, account must be taken of the possibility that the two conditions were unrelated, occurring by chance in the same patient with an interval of many

years between them.

Secondly, neither of these cases are acceptable as examples of Hashimoto's disease; they would be more correctly diagnosed as chronic non-specific thyroiditis.

Thirdly, in view of the many published observations on the failure to detect progression, these two cases must be regarded as exceptional.

The possibility of occurrence by chance

This possibility must always be admitted when two conditions affect the same organ with intervals of 15 to 20 years between them. However, chance occurrence becomes much less likely when, as here, the intervals between operations are occupied by recurrent thyrotoxicosis or alternation between thyrotoxicosis and hypothyroidism. Case 2 was probably still suffering from mild hyperthyroidism at the time of the second operation; Case 4 was mildly hypothyroid. Both the clinical histories and the histological findings favour progression from one condition to the other, rather than cure of one condition by operation followed many years later by the onset of a totally different condition.

Diagnosis

Both clinically and pathologically, there is difficulty in defining the exact nature of the thyroid disorder in these cases. The histories differ sharply from those described in struma lymphomatosa by Hashimoto (1912), Graham and McCullagh (1931) and Joll (1939), and this diagnosis could be made only if one accepts the broad view, as for example of Luxton and Cooke (1956) that struma lymphomatosa "should always be considered if a middle-aged woman presents with symptoms of hypothyroidism, however mild, and with a firm goitre, however small" and that the patient may be euthyroid or even hyperthyroid. Histologically, the paucity of lymphoid follicles, the intensity of the plasma-cell infiltration, the presence of foci of epithelial hyperplasia, and the limited extent of the oxyphilic change distinguish the picture from that described by Hashimoto.

Some classifications of thyroiditis fit all cases into the categories of subacute granulomatous thyroiditis, struma lymphomatosa and struma fibrosa (Lindsay et al., 1952; Brown, 1956; Harland and Frantz, 1956), but others allow for a group of

non-specific (Marshall et al., 1948) or unclassified (Hazard, 1955) cases. It seems preferable to assign these two cases to the category of non-specific chronic thyroiditis, or to use the simple descriptive term plasma-cell thyroiditis. Brewer and Orr (1953) mentioned two cases in which the majority of the infiltrating cells were plasma cells, and Druez et al. (1958) report a case of plasma-cell thyroiditis in which lymphocytes could not be identified at all. The case of "plasmocytoma of the thyroid" reported by Shaw and Smith (1940) may have been of similar nature.

Published observations on multiple-operation cases and on thyroid remnants following thyroidectomy

The great majority of published observations give no support to the progression theory.

A Committee of the Clinical Society of London (1888) collected reports on cachexia strumipriva, and concluded that there were no pathological changes in the residual thyroid tissue. Examination of 7 autopsy thyroid specimens (Werner, 1955) and of 7 biopsy and autopsy specimens (Curran et al., 1958) following partial thyroidectomy for thyrotoxicosis showed no progression to a lymphoid phase; in most instances,

indeed, the epithelial hyperplasia had regressed and the microscopic picture differed little from the normal. In a similar study of autopsy remnants, Pemberton (1930) noted not only regression of epithelial hyperplasia but a decrease in lymphocytic infiltration in 6 out of 7 cases; in the remaining case, mild hyperplasia persisted, and was thought to have been due to ulcerative colitis.

Second operations for recurrent hyperthyroidism were carried out in 98 cases by Fahrni (1935); "all these recurrences were and originally had been hyperplastic goiters". Harland and Frantz (1956) studied lymphocytic infiltration in cases of recurrent toxic goitre, non-toxic goitre, and carcinoma, in the hope of tracing a change from focal to diffuse involvement, but in no case was any such transformation found.

Multiple operations in struma lymphomatosa have similarly failed to show progression from supposed early to late stages, or progression to struma fibrosa. Many reports of single cases (listed by Hazard, 1955) are open to the criticism that the interval between operations was too short (as in

Case 1 of Schilling, 1945) or that only small biopsy specimens were available (Statland et al., 1951). Repeat biopsies are unreliable (Lindsay et al., 1952) as the disease is so variable in its distribution within the gland, but cases such as that of Hellwig (1938), in which there was a 9-year interval between thyroidectomies, are acceptable. Hendrick (1957) has reported the case of a girl of 8 years whose thyroid showed early changes of Hashimoto's disease; a second specimen two years later showed no progression, but a papillary adenocarcinoma had developed.

Harry (1940) similarly found no progression from Hashimoto's to Riedel's struma, and Perman and Wahlgren (1927) found no progression in a case of Riedel's disease.

Reports claiming progression in successive examinations of the thyroid are scanty, and are not beyond criticism. Case 5 of Boyden et al. (1935) was diagnosed as Graves' disease at the time of the first operation, and as "Riedel's struma" at the second operation 7 years later; the histology of the first specimen was not described, while in the second the principal features were epithelial hyperplasia,

fibroblastic proliferation, diffuse plasma-cell infiltration and abundant lymphoid follicles - a picture closer to those described here than to Riedel's struma. A report by Scarcello and Goodale (1941) is often quoted as demonstrating progression from diffuse toxic goitre to struma lymphomatosa 13 years later. The second specimen, however, examined at autopsy, was a remnant of less than 1 cm. in diameter, composed chiefly of disorganised masses of oxyphilic cells with lymphocytic infiltration about them, a picture unlike that of Hashimoto's disease. The clinical picture was also inconsistent with this diagnosis, and the statement that the histological findings in the second specimen were "practically identical" with those in the first casts grave doubt on whether this was a true example of progression.

In an article on cellular involution in the thyroid, Friedman (1949) mentioned having seen a number of cases in which the residual tissue after subtotal thyroidectomy for hyperthyroidism showed an over-all pattern indistinguishable from that of Hashimoto's disease. He gave no details of

individual cases, but illustrated one example of progression to Hashimoto's disease; there had been two previous thyroidectomies, and also irradiation of the thyroid, which was regarded as a contributory factor.

Rabson and Arata (1949) proposed that the term "lymphadenoid goitre" should be reserved for thyroids showing profound lymphocytic infiltration and atrophy of epithelium, but no fibrosis; they reported the case of a young man who had two operations within 9 months, the specimens showing progression from lymphadenoid goitre to Hashimoto's struma. Employing the more usual terminology, this would be an example of progression from an early to a later stage of Hashimoto's disease, much the same as that recently described by Thomson (1957).

The above were all short case-reports, or were mentioned only incidentally. The more systematic studies of Levitt (1954) and Spjut et al. (1957) provide few examples of progression.

Levitt, whose published work was devoted to championing progression from epithelial to lymphoid hyperplasia, based his conviction more on single-

operation cases than on demonstrable progression in individual patients. Of 22 patients in his "six progressive phases" who underwent recurrent operations, 16 progressed, 4 regressed, and 2 remained stationary. He divided each of the 6 phases into early, intermediate and late stages; of those cases that progressed, only one advanced through as much as two-and-one-third phases, while the remainder advanced through one-and-one-third or less.

The largest series is that of Spjut et al. (1957), who collected 71 cases of recurrent goitre in which two or more thyroidectomy specimens were available, as well as 5 cases in which the residual tissue was examined at autopsy. The initial diagnoses were Graves' disease, toxic (non-exophthalmic) goitre, and non-toxic nodular goitre. They were "unable to demonstrate convincingly progression of thyroidal hyperplasia to struma lymphomatosa, chronic thyroiditis or Riedel's struma", and indeed it is clear from their findings that in the great majority of cases there is no progression at all, as judged from a comparison of the first with subsequent thyroidectomy specimens or autopsy specimens. The only

case in which the second specimen conformed to their criteria for struma lymphomatosa had been diagnosed at the first thyroidectomy as non-toxic goitre. Seven other cases closely simulated struma lymphomatosa but did not completely fulfil their criteria, and were regarded as "near misses", to be interpreted as exhaustion atrophy rather than chronic thyroiditis; 4 of the 7 had originally had toxic goitre. With these exceptions, no specific histological changes that would distinguish the first from the second specimen were noted in the three disease groups.

This survey of the literature leaves little doubt that most cases of thyrotoxicosis - or at any rate those subjected to partial thyroidectomy - do not progress to any form of chronic thyroiditis. While Friedman (1949) considered that surgical operation itself might conduce to progression, the evidence favours rather the view of Pemberton (1930) that resection of the thyroid breaks an important link in the unknown chain of etiological factors in exophthalmic goitre, allowing readjustment to normal thyroid function; the latter view is more in

accordance with the observed clinical facts. One cannot ignore, either, the weight of clinical opinion against any preceding thyroid abnormality in chronic thyroiditis.

The two cases of progression described here are evidently rare exceptions to the general rule.

The failure in the great majority of cases to demonstrate progression either clinically or pathologically from thyrotoxicosis to chronic thyroiditis is no bar, however, to accepting a direct etiological relationship between epithelial hyperplasia and chronic inflammatory cellular infiltration. Epithelial hyperplasia has been considered hitherto only in the form which is manifested clinically by hyperthyroidism. Yet focal and diffuse epithelial hyperplasia, like lymphocytic infiltration, occur also in the clinically normal thyroid. It may be supposed that the "physiological" hyperplasia of the clinically normal thyroid is no less likely to progress to lymphocytic infiltration than is the epithelial hyperplasia of clinical hyperthyroidism. Indeed, it may be much more likely to do so; epithelial hyperplasia in the clinically normal thyroid

is presumably mediated through excess secretion of TSH, whereas that of thyrotoxicosis is unlikely to be so (Werner, 1955; and see the discussion on TSH levels in thyrotoxicosis on p.67). The process of colloidophagy, with the consequent accumulation of inflammatory cells, was considered by Hellwig to be initiated by excess TSH, and not by epithelial hyperplasia as such. Experimentally, accumulation of lymphocytes has followed TSH injections (Thurston, 1933), and the Hashimoto-like picture following prolonged administration of thiouracil (Clausen, 1953) can only be explained in the same way.

If excess TSH is accepted as the initiating factor in lymphocytic infiltration, then one would expect very few cases of primary hyperthyroidism to lead to chronic thyroiditis, as has indeed been observed. On the other hand, epithelial hyperplasia in the clinically normal thyroid due to excess TSH secretion would favour the development of chronic thyroiditis. Parmley and Hellwig (1946), noting that most cases of lymphadenoid goitre occur near or during the menopause, suggested that a decline of ovarian function removes the antagonistic effect on

the activity of the pituitary and increases its hormone secretion. Vitagliano (1956) similarly postulated a "hormonal disequilibrium" as the factor which initiates the mechanism of colloidophagy and chemotaxis. The explanation of Lindsay et al. (1952) for the failure to elicit a history of hyperthyroidism was on the same lines, though less explicitly stated: "It seems likely that in the majority of instances the epithelial exhaustion follows thyroid hyperplasia unassociated with excessive production of thyroid hormone".

The new concept of struma lymphomatosa as a "primary thyroid failure" is perhaps the most pertinent of all. It has been suggested by Skillern et al. (1956a) that thyroxine deficiency due to failure of the thyroid cells leads to increased production of TSH and so to compensatory epithelial hyperplasia in the thyroid; "due to the compensatory hyperplasia of the thyroid cells, the patient may exist in a clinically euthyroid state (compensated thyroid failure) for months to years before a clinically hypothyroid state (decompensated thyroid failure) occurs". Of 36 examples of chronic thyroiditis in

Skillern's series, 30 were of the Hashimoto type, 4 of the hyperplastic type, and 2 were intermediate, thus demonstrating the continuity between epithelial hyperplasia and chronic thyroiditis. The only likely precipitating factor which could be elicited was pregnancy, which is known to be accompanied by increased activity of the thyroid (Stoffer et al., 1957).

There may be many other circumstances in which epithelial hyperplasia is clinically silent, and even the role of the menstrual cycle, or menstrual abnormalities, must be considered. Experimentally, long-term administration of oestrogens has been shown to be without effect on the thyroid (Feldman, 1958), but there is reason to believe that progesterone might be implicated (Welch et al., 1958).

It would seem that epithelial hyperplasia in the clinically normal thyroid, whether "physiological" or "compensatory", is much more often the precursor of chronic thyroiditis than is the epithelial hyperplasia of hyperthyroidism.

SUMMARY

The theory that epithelial hyperplasia progresses to lymphocytic infiltration is best tested by successive examinations of thyroid tissue from the same patient.

Six cases in which two surgical operations were carried out on the thyroid, and 4 cases in which the residual tissue after partial thyroidectomy was studied at autopsy, have been reviewed. In two cases there was clear evidence of progression from exophthalmic goitre to chronic thyroiditis, and in one of these it was possible to trace the origins of the histological abnormalities in the second specimen by a study of the thyroid tissue resected 15 years earlier. In both cases the second specimen showed focal epithelial hyperplasia, and neither conformed to the histological criteria for the diagnosis of struma lymphomatosa.

A review of the literature reveals that such progression is rare. Thyrotoxicosis is rarely followed by diffuse chronic thyroiditis, and equally in chronic thyroiditis it is rare to elicit evidence

of preceding thyrotoxicosis.

It is suggested that chronic thyroiditis is preceded more usually by a form of epithelial hyperplasia which is not associated with hyperthyroidism, but stems from increased secretion of thyrotropic hormone.

9. THE PATHOLOGY AND PATHOGENESIS OF "PRIMARY" MYXOEDEMA

Myxoedema is ordinarily considered to be two types: a primary form, due to spontaneous atrophy of the thyroid, and a secondary form due to pituitary insufficiency.

The pathological characteristics of the primary form are but briefly described not only in most text-books of pathology but also in many standard works devoted exclusively to the thyroid. The usual description is one of shrinkage of the gland, atrophy and degeneration of the epithelium, dense fibrosis, and a variable amount of lymphocytic infiltration.

It is at once apparent that such a picture is incompatible with the concept of a simple atrophy, which would be represented merely by shrinkage of the organ and its constituent cells, with perhaps a minor degree of fibrous replacement. The density of the fibrosis seen in "primary" myxoedema, and the presence, often in abundance, of chronic inflammatory cells, suggest rather the sequel to a destructive

lesion of the thyroid, possibly a post-inflammatory fibrosis.

The possibility that classical myxoedema, as distinct from goitrous hypothyroidism and from hypothyroidism of pituitary origin, might be a consequence of chronic thyroiditis, has been mentioned several times in the foregoing pages. Ten cases of "primary" myxoedema are reviewed here in order, firstly, to study the general histological picture, and secondly, to see whether this casts any light on the pathogenesis of the condition. One case of thyroid atrophy following hypophysectomy is also described.

A summary of the clinical and pathological findings is given in Appendix 5. The sections have been made available to me by the kindness of my colleagues; as I did not see any of these patients during life, and performed the autopsy myself in only two cases, the clinical and macroscopic reports are as obtained from medical records.

Histological findings

Eight out of ten cases of primary myxoedema showed the expected histological features, namely,

fibrosis, round-cell infiltration, scanty small acini and solid clumps of epithelial cells, and marked diminution of colloid content. Fibrous tissue replaced a variable amount of the parenchyma, and in the extreme examples fibrous replacement was almost complete (Fig. 94). Infiltration by inflammatory cells was confined to the surviving parenchymatous tissue, and tended to be most profuse at the periphery of the nodules (Fig. 95). Lymphocytes predominated, but variable numbers of plasma cells were present in every case. Lymphoid follicles were seen in only one case (Case 6); surprisingly, this was the case in which lymphocytic infiltration and fibrosis were the least advanced.

The epithelium showed either oxyphilia or metaplastic changes (Fig. 96). Oxyphilic epithelium was constantly present, but varied greatly in amount from one case to another. The metaplastic changes were of the type described in Section 5 (Figs. 69, 70, 71). Most common were the forms of epithelium which were considered there to be intermediate between normal thyroid epithelium and stratified squamous epithelium. True squamous nests were seen in three cases.

Both oxyphilic and metaplastic epithelium occurred either as small irregular acini or as solid clumps without a lumen. Acini formed by metaplastic epithelium were usually empty; those formed by oxyphilic cells occasionally contained colloid.

There were also occasional epithelial foci showing neither oxyphilia nor metaplasia. These were composed either of very small ragged acini, usually empty, or of larger acini lined by columnar epithelium and showing infoldings of their walls, containing scanty pale-staining colloid (Figs. 97, 98). The hyperplastic acini were morphologically similar to those of exophthalmic goitre, with occasional intra-acinar macrophages and a sparser inter-acinar lymphocytic infiltration than was seen in the other parenchymatous islets.

Cases 1 and 2 differed significantly from the others, and would not, on histological appearances alone, have been diagnosed as primary myxoedema. In one, the gland was very small, but in the other it was stated to have been of normal size. Microscopically, cellular infiltration was much more intense than in the other cases, and fibrous replace-

ment was comparatively slight. Both cellular infiltration and fibrosis, indeed, were of the order that occurs in diffuse chronic thyroiditis (Fig.99). The epithelium was almost entirely oxyphilic, and formed small disintegrating acini which occasionally contained pseudogiant cells. The absence of thyroid enlargement, and of lymphoid follicles, preclude a diagnosis of Hashimoto's disease, and the appearances are those of chronic non-specific thyroiditis.

The one case of thyroid atrophy following hypophysectomy differed radically from the "primary" cases. The gland was considerably diminished in size, but microscopically there was little fibrosis and round-cell infiltration (Figs. 100, 101). There were neither oxyphilic nor metaplastic changes in the epithelium, and the colloid content was not diminished. The histological appearances did not differ greatly from the normal, and were compatible with simple atrophy.

Correlation of the histological picture with the size of the gland

As the notes on the macroscopic appearances were made by different observers, they should not be compared too closely. Generally, it appears that the greater the fibrosis, the smaller the gland, and in four cases which did not show the fully-developed histological picture (Cases 2, 5, 6, 7), there was little or no diminution in size. Case 10, however, was an exception, as the gland was stated to have been of normal size (and judging from the size of the sections available it certainly could not have been much reduced), while the microscopic appearance was one of extensive fibrosis.

Correlation with the clinical picture

A detailed correlation cannot be attempted, because here again I am dependent on records unconfirmed by personal observation. It appears, however, that the histological picture is unrelated to the known duration of the disease. This is best illustrated by the two extreme examples: In Case 2, the picture was one of diffuse chronic thyroiditis, without a great deal of fibrosis; typical myxoedema

was said to have been present for 3 years. In Case 8, there was almost complete fibrous replacement of the gland, yet myxoedema had been first diagnosed only 5 days before death in myxoedema coma; the condition appeared to be of acute onset, following an abdominal operation, and had not been suspected when the patient was admitted to hospital.

The histological picture did not in general correspond closely with the reported severity of the clinical condition. In the 3 patients who died in myxoedema coma, the picture was that of chronic thyroiditis (Case 2), moderate fibrosis (Case 7), and almost complete fibrous replacement (Case 9). In Case 6, however, the mildness of the fibrosis and lymphocytic infiltration was in agreement with the mildness of the clinical symptoms; after 5 years of thyroid medication, the condition had been reviewed and considered to be one of simple obesity, while shortly before death mild myxoedema had again been diagnosed.

DISCUSSION

Although myxoedema is by no means an uncommon disease, descriptions of the histological appearances have been few and brief. The account of the microscopic findings in 13 cases in the Report of the Clinical Society of London's Committee (1888) remains the largest series on record. Ten cases were described by Bastenie (1944), 9 by Means (1948) and 9 by Douglass and Jacobson (1957). Two cases of this last series followed partial thyroidectomy, but were included in a single histological description with 7 primary cases. Most other reports have related to single cases, and have chiefly concerned changes in organs other than the thyroid.

All these accounts have emphasised the extensive fibrous replacement, lymphocytic infiltration, and degenerative and atrophic changes in the epithelium. Fibrous replacement has occasionally been considered complete (two cases in the 1888 Report, one case of Means). The inflammatory cells have usually been designated as lymphocytes, without mention of plasma cells, though Berkheiser (1955) specifically noted

the absence of plasma cells in his case. Oxyphilic epithelium has not always been mentioned by name, but is perhaps usually implied by the term "degenerative changes". Squamous metaplasia was noted in all cases by Douglass and Jacobson, and in the case of Foster and Barr (1944); Bastenie described similar changes though apparently accepting a developmental origin for them.

An important point brought out by the 1888 Report, though not evident from subsequent studies, is that the picture is not invariably one of fibrous replacement. Although the Report noted "striking and uniform" changes in every instance, there were two or three cases in which the affection was more advanced in one lobe than the other, and in Case 9 one area showed the characteristic changes while another area showed very little departure from the normal. Some cases showed the changes in a comparatively early stage. It was concluded that death might ensue before affection of the gland becomes advanced, and also before the entire gland becomes invaded. While it is possible that the clinical descriptions in the Report include cases of Hashimoto's or of

Riedel's struma (4 of 59 thyroids were enlarged, and another was "hard, as though calcareous"), the microscopic account refers exclusively to cases in which the gland was reduced in size.

The findings presented here show a wider range than is suggested even by the Report. The gland was not invariably the shrivelled remnant which is usually described. Indeed, in 3 cases it was stated to have been of normal size, and in 2 others there was little diminution. Similarly, in 4 of Douglass and Jacobson's 9 cases the gland weighed 20 g. or more, and the "small" thyroid in Brewer's (1951) case also weighed 20 g.

Microscopically, 5 of the cases may be said to conform to the standard description. Of the remainder, Cases 1, 2, 5 and 7 appear to represent stages of progression from chronic thyroiditis to diffuse fibrosis, and Case 6 (in which the symptoms had been very mild though of long duration) showed an exceptional lack of both fibrosis and lymphocytic infiltration. There was also a considerable variation from case to case in the extent of oxyphilic and metaplastic epithelium. The constant

presence of plasma cells, and the occasional presence of epithelial hyperplasia, noted here, are not usually considered to be features of the condition.

The histological stages of progression cannot be clearly correlated with corresponding stages in the clinical picture. In three cases there was no record of myxoedema having been diagnosed before the final admission to hospital, and in two of these the condition was thought to be of acute onset, a few days before death. Had these patients died a short time earlier of some other affection, they would have been recorded as examples of myxoedema-like changes occurring in a clinically normal thyroid. Such changes are occasionally seen in the absence of any history of thyroid disorder, and in reviewing the routine autopsy sections of Manchester University Department of Pathology for the past year I have encountered two examples showing a well-developed myxoedema-like picture (Fig. 102). Both were elderly females.

It is probable that the lack of correlation between the clinical and pathological findings

results in some measure from the failure to detect myxoedema clinically. The milder degrees are often regarded as part of the general "slowing-down" in old age, and even a severer degree might escape notice in a patient admitted to hospital for some condition unrelated to the thyroid. The earliest symptoms are too often attributed to age by both patient and physician (Kimble and Stieglitz, 1952).

It may be said in summary that the histological picture of chronic thyroiditis seems to merge with that of myxoedema. Recalling the evidence already presented (Section 8) linking epithelial hyperplasia with chronic thyroiditis, there now seems to be a strong argument in favour of considering all three conditions as stages in a single pathological process.

The derivation of myxoedema from hyperthyroidism or chronic thyroiditis has from the first been more readily accepted than the derivation of chronic thyroiditis from toxic goitre. Even before the recent immunological studies focussed new attention on the question, there was strong clinical and pathological evidence that at least a proportion of

cases of myxoedema were preceded by thyrotoxicosis or chronic thyroiditis.

Clinical evidence

This is too well known to require a detailed account. Before the days of rational therapy for thyrotoxicosis, it was a familiar fact that some cases ultimately "burned themselves out" and ended as typical examples of myxoedema. McCarrison (1917) emphasised the importance of Graves' disease and of chronic inflammation of the thyroid in the etiology of myxoedema. As Eason (1928) remarked: "In the ebb and flow of hyperthyroidism, the natural termination in a large proportion of cases . . . is to recede gradually towards and even below the level maintained by normal thyroid tissue". He believed that the failure to trace the sequence from exophthalmic goitre to myxoedema in individual patients was due to the difficulty of obtaining accurate histories. "There is a ring fence cutting off from our knowledge the later histories of many cases of exophthalmic goitre, and the earlier histories of many cases of myxoedema. . . The proof of the

secondary derivation of a higher proportion of cases of myxoedema and chronic thyroiditis would appear to depend on the care with which clinical histories are worked out". Although Means (1948) wrote that "Why the atrophy takes place is quite unknown", he mentioned having seen 4 cases in which myxoedema seemed to be the end-result of toxic goitre, and also conceded that myxoedema could be the result of chronic thyroiditis.

It is well recognised that even after partial thyroidectomy for Graves' disease, a proportion of patients progress to myxoedema, and that this is especially liable to occur when the excised tissue shows excessive lymphocytic infiltration and fibrosis (Bartels, 1953). These are examples of true progression, for, as pointed out by Whitesell and Black (1949), in view of the known capacity of the thyroid to regenerate when required, the development of post-operative myxoedema cannot be explained by lack of sufficient residual tissue. Those cases of hyperthyroidism which have already progressed towards diffuse chronic thyroiditis are the ones most likely to complete the progression to myxoedema. Lee and

McGrath's (1937) case of struma lymphomatosa was clinically, at the time of operation, undergoing evolution from thyrotoxicosis to myxoedema.

Clinically, there is little to distinguish mild myxoedema from Hashimoto's disease, except for the later age incidence and the absence of a palpable thyroid. Hashimoto's disease is goitrous hypothyroidism occurring predominantly in the fifth and sixth decades of life (the stage of diffuse lymphocytic infiltration), while myxoedema is non-goitrous hypothyroidism occurring predominantly in the sixth and seventh decades (the stage of fibrosis).

Pathological evidence

The clinico-pathological and histological studies of Vaux (1938), Chesky et al. (1951), Levitt (1954), and Goetsch and Kamner (1955) have already been mentioned in the preceding Sections as pointing to a continuous sequence from epithelial hyperplasia through chronic thyroiditis to diffuse fibrosis. In these and other studies proposing a continuous sequence, the final stage has been given sometimes as Riedel's disease, sometimes as myxoedema. These

two conditions are closely similar histologically, and may coexist clinically; the presence or absence of myxoedema in Riedel's struma appears to depend on the extent of involvement of thyroidal parenchyma (Woolner et al., 1957). The histological resemblances between struma lymphomatosa and myxoedema are also close, sufficiently so to indicate that the two conditions are probably clinical variants of the same disease (Skillern et al., 1956a). When Shaw and Smith (1925) noted the histological similarity between myxoedema and "Riedel's disease", they were probably referring to struma lymphomatosa. In the latest edition of Muir's text-book, Cappell (1958) notes the histological similarity of primary myxoedema and Hashimoto's disease, and indeed his Fig. 714b, illustrating myxoedema, would equally well serve as an example of chronic thyroiditis.

Bastenie (1944) published a valuable study relating the histological appearances of myxoedema not only to those of hyperthyroidism and chronic thyroiditis but to similar changes occurring in clinically normal thyroids. In the thyroid sections from over 450 routine autopsies, he found 100 cases

which showed in successive stages all the pictures observed in the thyroid of myxoedema, the only distinction being the persistence of a certain quantity of intact parenchyma in the clinically-normal cases. He proposed the term "thyroïdose involutive" for both the clinical and sub-clinical cases. His Table II, reproduced here (Fig. 103) shows the close similarity in age incidence between the onset of myxoedema and the presence of "involutional thyroidosis" in the clinically-normal thyroid.

The 1888 Report likewise noted that "by far the larger number of cases occur between the ages of 30 and 65", which, even allowing for the lesser expectation of life 70 years ago, again suggests that the incidence falls after the seventh decade of life. This age incidence strongly favours the concept of myxoedema as a sequel to chronic thyroiditis rather than a simple atrophy with increasing age.

Only Case 11 of the present series provided a picture of simple atrophy, and this was an example of thyroid atrophy following hypophysectomy; the mildness of the fibrosis and lymphocytic infiltration, and the absence of oxyphilic and metaplastic changes in the epithelium, were in striking contrast to the

picture of chronic thyroiditis or post-inflammatory fibrosis seen in the "primary" cases.

This case is presented as an example of true atrophy with some reserve, as the interval between hypophysectomy and autopsy was only 5 months and one cannot be certain that a later stage would not have shown the typical features of myxoedema. Two of Means' cases, in which the histological appearances were typical, were considered to be of pituitary origin. On the other hand, the early fibrosis and lymphocytic infiltration were not accompanied in even the mildest degree by the characteristic epithelial changes of myxoedema, and this was so at a stage when the gland was already much further reduced in size than in several of the "classical myxoedema" cases.

Immunological evidence

The recent discovery that thyroid antibodies in the serum, originally thought to be specific for Hashimoto's disease, occur in many other thyroid disorders, including myxoedema (Goudie et al., 1957; Owen and Smart, 1958; Roitt and Doniach, 1958), has provided fresh evidence in favour of the unitarian

concept. Owen and Smart noted that antibodies were present in 80% of their myxoedematous patients - exactly the same proportion as in Hashimoto's disease. Antibody levels were significantly higher in Hashimoto's disease when it was of recent origin, but when treatment by thyroidectomy or oral thyroid extract had been instituted more than a year previously, the values closely approximated to those found in primary myxoedema.

There is now evidence, too, that the serum flocculation reactions introduced as a test for Hashimoto's disease (Skirpan et al., 1955; Luxton and Cooke, 1956) and occurring also in subacute thyroiditis (Stemmerman, 1956; Skillern et al., 1956b), may also be positive in myxoedema (Murray, 1958).

The immunological studies have carried more weight than all the clinical and pathological evidence which had accumulated previously, and there is now considered to be good evidence (British Medical Journal, 1958) that myxoedema is often, if not always, the result of chronic thyroiditis.

Pathogenesis of myxoedema

From the histological findings presented here, and from the above brief survey of published work on the subject, the concept of myxoedema as a primary spontaneous atrophy of the thyroid, unrelated to preceding thyroid disease, is seen to be inadequate.

It would seem no longer necessary to argue that the histological picture of myxoedema is derived from that of chronic thyroiditis; the two indeed overlap. The question remains as to why so few myxoedematous patients can be shown clinically to have passed through the preceding stages, to the extent that the condition is known as "primary myxoedema".

It may be, as Eason suggested, that the difficulty is largely one of history-taking. The physician, examining a myxoedematous patient whose mental processes are slow, speech indistinct and memory defective, may well fail to elicit a previous history of toxic goitre or chronic thyroiditis. The pathologist, confronted by the typical autopsy findings of myxoedema, is even less likely to be successful in his enquiries.

However, if the failure to obtain an accurate history accounts for a proportion of cases, it is probable that a larger number can be explained as arising in clinically normal patients with extensive chronic inflammatory changes in the thyroid. Just as the epithelial hyperplasia which precedes chronic thyroiditis need not manifest itself clinically as thyrotoxicosis (p. 238), so also may the chronic thyroiditis which precedes myxoedema be clinically silent. The histological findings presented here, and by Bastenie (1944), demonstrate clearly that the clinically normal thyroid may undergo changes identical with those of chronic thyroiditis and myxoedema. Evidently, the disorder may manifest itself clinically for the first time at any stage, or may even remain unsuspected throughout life.

One clue to the circumstances in which epithelial hyperplasia without thyrotoxicosis might lead to myxoedema is given in the 1888 Report: "A large number of the female patients were married, and nearly all had borne children. In a significant proportion, the child-bearing had been excessive, and in some there had been rapidly succeeding pregnancies.

Indeed, in a few cases there appears to be little doubt that the early symptoms of the disease date from childbirth . . ."

Information about the thyroid in pregnancy is scanty, but Stoffer et al. (1957) were able to demonstrate an increase in the height of the acinar epithelium and an increase in the serum protein-bound iodine, and concluded that "the lack of thyrotoxic symptoms in spite of a higher activity of the thyroid during pregnancy can be explained by a greater demand for, and a greater toleration of, thyroid hormone".

Rapidly succeeding pregnancies might therefore play a part in providing the excessive TSH secretion which initiates Hellwig's mechanism of colloidophagy, leading to chronic thyroiditis. The resulting loss of functioning thyroid tissue, if sufficiently great, would lead to a continued excess of TSH secretion, thus perpetuating the process and resulting eventually in myxoedema. "Primary failure of the thyroid" (p. 240) occurring at about the time of the menopause might also initiate such a sequence of events, by causing, first, compensatory epithelial

hyperplasia, and then diffuse chronic inflammatory cellular infiltration. Only in this indirect manner would "spontaneous atrophy" of the thyroid lead to myxoedema.

It would seem that the sequence is more often a pathological one of excessive TSH secretion - chronic thyroiditis - diffuse fibrosis, than a clinical one of hyperthyroidism - Hashimoto's disease - myxoedema.

SUMMARY

The microscopic findings are described in 10 cases of "primary" myxoedema and one case of thyroid atrophy following hypophysectomy.

The "primary" cases showed a variable degree of fibrosis, with infiltration by lymphocytes and plasma cells. The acini were generally small, and colloid was scanty. Oxyphilic epithelium was present in all cases, and squamous epithelium in three. Foci of epithelial hyperplasia were seen in three cases.

When fibrous replacement of the parenchyma was the predominant feature, the histological picture was the classical one of myxoedema. When fibrosis was slight and round-cell infiltration more intense, the picture was that of chronic non-specific thyroiditis.

The histological changes of myxoedema are seen to merge with those of chronic thyroiditis, and also with those occurring in a proportion of clinically-normal thyroids, especially of elderly females.

The case of thyroid atrophy was quite different. There was slight fibrosis and lymphocytic

infiltration, but the acini were well filled with colloid and showed none of the epithelial changes associated with myxoedema.

The clinical, pathological and immunological evidence on the pathogenesis of myxoedema is reviewed, and it is concluded that myxoedema is the final stage of a sequence in which epithelial hyperplasia is the early and chronic thyroiditis the intermediate stage. In some cases the sequence, or part of it, is evident clinically. There is good reason to believe that in the remaining cases the thyroid has undergone this sequence without clinical manifestations of hyperthyroidism or chronic thyroiditis.

GENERAL SUMMARY

1. The human thyroid in early and middle foetal life is of similar histological structure to the adult gland. In late foetal life and for a variable period after birth, it often shows a different picture. The colloid content is poor, the epithelium is desquamated, and collapse and disintegration of the acini may lead to the formation of compact cellular masses. Such an appearance is usually attributed to post-mortem degeneration, but is considered by some to represent a state of intense activity or of functional exhaustion. Activation and post-mortem degeneration in the thyroid are difficult to distinguish from one another, as absorption of colloid and collapse of the acini are common to both processes.

2. Examination of 106 thyroids, obtained from stillborn infants and infants dying within the first seven days of life, has shown a great variation in the degree and extent of such changes; the most advanced changes occur in the centre of each lateral lobe, the least advanced at the periphery. Three types of acinus are described: (A) the well-preserved

colloid-containing acinus, as seen at other ages, usually lined by cuboidal or columnar epithelium; (B) nuclei displaced towards the lumen by vacuoles in the basal cytoplasm, colloid faint-staining or deeply indented by peripheral vacuolation; (C) desquamated cells in the lumen, colloid faint or absent; at a later stage, disintegration of the acinar wall, and finally solid cellular masses without obvious acinar arrangement.

3. Epithelial desquamation and acinar disorganisation increase little with increasing delay in fixation. The changes do not appear to be related to the maturity of the infant, its sex, the nature of labour, or the cause of death. They occur as frequently in neonatal deaths as in stillbirths, but become less pronounced after the third day of life.

4. Evidence is presented favouring the view that such changes are an expression of increased physiological activity, while the advanced changes represent a state of functional exhaustion. Of the experimental evidence quoted, the most significant facts are the transient phase of colloid depletion and loss of acinar structure in the thyroid of many species not

only at birth but at other times of physiological crisis, and the ability of prolonged thyrotropic hormone administration to bring about similar changes in the thyroid of the adult rat.

5. A study of the thyroid in the newborn guinea pig - one of the animals whose thyroid does not normally undergo any alteration at the time of birth - has shown that changes of this kind cannot be produced by single injections of thyrotropic hormone, nor by allowing the thyroid to undergo post-mortem degeneration. A combination of activation and autolysis came closer to reproducing the disorganisation of acini seen in the human thyroid. While maintaining that the picture in the human neonatal thyroid represents functional hyperactivity or exhaustion, it must be admitted that post-mortem degeneration plays a part in accentuating the changes.

6. The thyroids of stillborn guinea pigs were often normal, but some glands showed unmistakable signs of increased activity while in others there was desquamation of the epithelium and disorganisation of the acini. This again links the latter changes with the signs of activation, and supports the

interpretation of "functional exhaustion". It also suggests that the changes are related to the factors which cause death, and that the degree of change found in the human neonatal thyroid at autopsy may be greater than occurs in the thyroids of surviving infants.

7. Both in the human and in the guinea pig thyroid at birth, a homogeneous colloid-like substance is often present in the lymphatics, in relation to areas of epithelial desquamation and disorganisation of acini. The evidence is not conclusive, but the association of this phenomenon with states of rapid colloid depletion is in favour of a "lymphocrine" mechanism in the thyroid.

8. The susceptibility of the human thyroid to the changes described does not end with the neonatal period, but continues at a lower level throughout childhood. In the adult, the colloid depletion and epithelial changes are relatively mild, and may be almost indistinguishable from post-mortem changes. When the changes characteristic of the neonatal thyroid are looked for in the adult gland, they are best identified by the presence of colloid-like substance

in the lymphatics, which is not a post-mortem phenomenon.

9. Colloid-like substance in the lymphatics is as common in the adult as in the neonatal thyroid, and tends to be more prominent in old age. It is most often seen when death has been due to some catastrophe such as myocardial infarction, pulmonary embolism or accidental injury, and is least common in subjects dying of chronic wasting disease. It also shows an association with pyogenic infections, intestinal obstruction and acute peritonitis.

10. Three cases are described in which thyroid dysfunction in pregnancy was followed by early death of the infant. One of the mothers had pituitary hypothyroidism, while the other two had thyrotoxicosis and were treated with antithyroid drugs during pregnancy.

The two infants born of thyrotoxic mothers had congenital goitres, associated in one with hypothyroidism and in the other with hyperthyroidism. The latter is the first recorded fatal case of congenital hyperthyroidism attributable to antithyroid drugs.

11. A review of all reported cases of congenital hyperthyroidism suggests two probable mechanisms of pathogenesis:

(i) Persistent exophthalmos following surgical or radioiodine treatment of hyperthyroidism is probably associated with excessive secretion of thyrotropic hormone (TSH). When a woman with this condition becomes pregnant, the TSH may cross the placenta and cause hyperplasia of the foetal thyroid. The foetal thyroid increases its output of thyroid hormone, so that thyrotoxicosis is recognisable at birth. As the stimulus to hyperplasia is withdrawn at birth, the size of the thyroid gradually returns to normal and the toxic symptoms subside spontaneously.

(ii) Antithyroid drugs used in the treatment of hyperthyroidism during pregnancy pass through the placenta and block hormone synthesis in the foetal thyroid. The foetal thyroid undergoes hyperplasia in response to excessive secretion of foetal TSH, but produces little or no hormone; when it is released from the inhibiting effect of the drug at birth, the thyroid gradually resumes hormone synthesis and,

because of its increased bulk and the excessive thyrotropic secretion, soon exceeds the normal output. Thyrotoxic symptoms are therefore not present at birth but appear early in neonatal life. For the same reason as in the first mechanism, the condition subsides spontaneously.

12. Administration of antithyroid drugs to pregnant guinea pigs resulted in thyroid hyperplasia in the offspring. Thiouracil produced a rather greater degree of hyperplasia than did potassium perchlorate, while carbimazole had comparatively little effect. The goitres produced by potassium perchlorate were considerably more vascular than the others.

13. Regression of the hyperplasia occurred after birth in drug-induced neonatal goitres, in spite of continued administration of the drug to the mother during lactation. Evidently transmammary is less effective than transplacental passage of the drug. Much more rapid regression occurred when the neonates were not subjected to further antithyroid medication. In either case, the thyroid remained enlarged when both colloid content and the height of the epithelium had returned to normal.

14. An increase in intra-acinar macrophages, characteristic of activation, occurred during regression, indicating that the thyroid was still subject to excessive thyrotropic stimulation in spite of diminishing hyperplasia. This finding accounts for the delayed phase of hyperthyroidism occurring after birth in infants with drug-induced goitres.

15. Atypical epithelium, which can sometimes be identified as squamous epithelium, is not uncommon in the human thyroid. Two forms are distinguishable:

(i) Nests of atypical epithelium associated with lymphocytic infiltration or fibrosis; the nests are often multiple, and transition forms between thyroid epithelium and squamous epithelium are seen. This form has been seen only in adult thyroids, and reaches its maximum incidence in the 7th decade. It is commoner in females.

(ii) Solitary nests of atypical epithelium in a thyroid which is otherwise histologically normal. This form also has its maximum incidence in the 7th decade, but has been seen at all ages from intra-uterine life to 90 years. It is commoner in males.

16. Atypical epithelium associated with lymphocytic infiltration or fibrosis is the result of metaplasia of the thyroid epithelium, analogous to the squamous metaplasia occurring in other tissues in chronic inflammatory conditions. The age and sex incidence are therefore similar to those of focal chronic thyroiditis.

17. Solitary nests of atypical epithelium in histologically normal thyroids represent developmental inclusions within the gland, possibly derived from the ultimo-branchial body. It is known that such inclusions may closely resemble true thyroid tissue, or may actually form part of the functioning thyroid tissue. It is suggested that the increasing incidence of this form of atypical epithelium with advancing years may be due to metaplasia or reversion of developmental inclusions to their embryonic state.

The solitary abnormally large acini occasionally noted in the neonatal guinea pig thyroid are probably of similar nature. It is noteworthy that they responded poorly to stimulation by exogenous or endogenous thyrotropic hormone.

18. Anisotropic crystals have been seen in about two-fifths of adult thyroids obtained at autopsy, but not in the thyroids of infants and children. The incidence increases sharply in old age. The crystals are always intra-acinar, and are commoner in normal than in abnormal glands. They are known to be composed of calcium oxalate monohydrate, but their significance is not understood.

19. Foci of lymphocytic infiltration are not uncommon in clinically normal thyroids; in a study of 244 autopsy specimens, lymphocytic infiltration was seen in 23.2% of females and 8.3% of males. In both sexes, lymphocytic infiltration reached its maximum incidence in the 6th decade, and fell thereafter. The age and sex incidence of lymphocytic infiltration in the clinically normal thyroid are thus similar to those of clinically-manifest chronic thyroiditis.

20. Lymphocytic infiltration in the clinically normal thyroid is associated in variable degree with all the morphological accompaniments of lymphocytic infiltration in the clinically abnormal thyroid:

lymphoid follicles with germinal centres, plasma cell infiltration, epithelial hyperplasia or signs of increased functional activity, collapsed acini which are empty or contain multinucleate cells, oxyphilic epithelium and fibrosis.

21. Two explanations are currently in favour to account for lymphocytic infiltration in the thyroid: (i) The mechanism of "colloidophagy", probably initiated by excess TSH, which leads to the liberation of colloid in the stroma and provokes an inflammatory reaction. (ii) Interaction of thyroglobulin and a circulating auto-antibody, resulting in an inflammatory reaction in the thyroid.

Whichever of the two mechanisms is accepted (and they are not mutually exclusive), lymphocytic infiltration in the clinically normal thyroid is seen to be of the same nature as the infiltration in toxic goitre, chronic thyroiditis and myxoedema. Morphologically, the evidence for colloidophagy is seen alike in the clinically normal and the clinically abnormal examples of lymphocytic infiltration. Immunologically, auto-antibodies occur not only in chronic thyroiditis, as was at first thought, but in other thyroid disorders

associated with lymphocytic infiltration, and rarely in healthy subjects whose thyroids are subsequently found to be infiltrated by lymphocytes.

Lymphocytic infiltration in the clinically normal thyroid is therefore not an occasional "normal" finding, but a clinically silent form of the infiltration which occurs in hyperthyroidism, chronic thyroiditis and myxoedema.

22. The histological picture of toxic goitre merges with that of chronic thyroiditis, but progression from one condition to the other is seldom observed clinically. Two cases are described in which partial thyroidectomy for exophthalmic goitre was followed many years later by a second operation for chronic thyroiditis. It is clear from a review of the literature that these cases are rare exceptions to the general rule.

23. The strong pathological evidence in favour of progression from epithelial hyperplasia to chronic inflammatory cellular infiltration, and the rarity of clinical progression from toxic goitre to chronic thyroiditis, suggest that chronic thyroiditis is more

usually preceded by a form of epithelial hyperplasia which is not associated with hyperthyroidism but is the result of hormonal imbalance and compensatory excess of TSH.

24. The histological appearances of myxoedema, like those of chronic thyroiditis, are represented in clinically silent form by the changes seen in a proportion of clinically normal thyroids at autopsy, especially in elderly females.

25. The histological appearances of the thyroid are described in 10 cases of "primary" myxoedema, and are considered to be inconsistent with the usual concept of a primary spontaneous atrophy. They ranged from typical chronic thyroiditis to almost complete fibrous replacement of the gland, and all showed the epithelial changes and lymphocytic and plasma-cell infiltration associated with chronic thyroiditis. The histological features in a case of thyroid atrophy following hypophysectomy were totally different, consistent with a process of simple atrophy and not suggesting an early stage of the classical myxoedema picture.

26. Though clinical progression from hyperthyroidism to chronic thyroiditis is rare, clinical progression of either of these conditions to myxoedema is commoner. Where there is no evidence for such antecedent thyroid disease in myxoedema, it is suggested that the phases of epithelial hyperplasia and diffuse chronic inflammatory cellular infiltration occurred without manifesting themselves clinically.

27. The view that chronic thyroiditis and myxoedema arise in a previously normal thyroid has been found wanting. So also has the concept of continuous progression from toxic goitre through chronic thyroiditis to myxoedema. The first conflicts with the histological evidence, the second with the clinical evidence.

A study of clinically normal and abnormal thyroids has led to the following conclusions:

There is a continuous progression from epithelial hyperplasia through chronic thyroiditis to diffuse fibrosis.

The process may be arrested at any stage and may be reversible in the early stage.

Any or all of the stages of the pathological process may occur without causing clinical thyroid disease.

REFERENCES

1. Aaron, H.H., Schneierson, S.J., Siegel, E. (1955). Goiter in newborn infant due to mother's ingestion of propylthiouracil. J. Amer. med. Ass., 159 848.

2. Abel, M.S. (1940). A quantitative study of the height of thyroid acinar cells in normal and abnormal thyroids. Amer. J. med. Sci., N.S. 200 220.

3. Adams, D.D. (1958). The presence of an abnormal thyroid-stimulating hormone in the serum of some thyrotoxic patients. J. clin. Endocr., 18 699.

4. Allara, E. (1951a). Sulla struttura della ghiandola tiroide del neonato. Arch. ital. Anat. Embriol., 56 273.

5. Allara, E. (1951b). Esiste una linfocrinia nella ghiandola tiroide del neonato? Boll. Soc. ital. Biol. sper., 27 1027.

6. Allara, E. (1953). Modificazioni isto-patologiche dell'ipofisi nel neonato. ibid., 29, 347.

7. Anderson, G.S. (1958). Personal communication.

8. Anderson, J.R., Goudie, R.B., Gray, K.G., Timbury, G.C. (1957). Auto-antibodies in Addison's disease. Lancet 1 1123.

9. Asboe-Hansen, G., Iversen, K., Wichmann, R. (1952). Malignant exophthalmos; muscular changes and thyrotrophin content in serum. Acta endocr., 11 376.

10. Baillif, R.N. (1937). Cytological changes in the rat thyroid following exposure to heat and cold, and their relationship to the physiology of secretion. Amer. J. Anat., 61 1.

11. Bartels, E.C. (1953). Post-thyroidectomy myxedema after pre-operative use of anti-thyroid drugs. J. clin. Endocr., 13 95.

12. Bastenie, P.A. (1944). Contribution à l'étiologie du myxoedème spontané de l'adulte. Bull. Acad. roy. Méd. belg., 6th series 9 179.

13. Beare, R.L.B. (1958). Lymphadenoid goitre (Hashimoto's disease); a clinico-pathological study. Brit. med. J., 1 480.

14. Beattie, J.M., Dickson, W.E.C. (1948). A Text-book of Pathology: General and Special, 5th ed. London: Heinemann. p. 962.

15. Benazzi, M. (1929). Contributo alla istofisio-logia della ghiandola tiroide. Arch. ital. Anat. Embriol., 27 296.

16. Benazzi, M. (1932). Appunti sulla istofisio-logia della ghiandola tiroide embrionale. ibid., 30 452.

17. Bensley, R.R. (1916). The normal mode of secretion in the thyroid gland. Amer. J. Anat., 19 37.

18. Berkheiser, S.W. (1955). Adult hypothyroidism: report of an advanced case with autopsy study. J. clin. Endocr., 15 44.

19. Bongiovanni, A.M., Eberlein, W.R., Thomas, P.Z., Anderson, W.B. (1956). Sporadic goiter of the newborn. ibid., 16 146.

20. Bottari, P.M. (1958). The estimation of thyro-trophic hormone in the sera of normal patients and those with thyroid disease. J. Endocr., 17 xix (abstr. Proc. Soc. Endocr.)

21. Boyden, A.M., Coller, F.A., Bugher, J.C. (1935). Riedel's struma. Trans. Amer. Ass. Study of Goiter. p. 35.

22. Branch, L.K., Tuthill, S.W. (1957). Goiters in twins resulting from propylthiouracil given during pregnancy. Ann. intern. Med., 46 145.

23. Braunsteiner, H., Fellinger, K., Pakesch, F. (1953). Electron microscopic observations on the thyroid. Endocrinology, 53 123.

24. Brewer, D.B. (1951). Myxoedema: an autopsy report with histochemical observations on the nature of the mucoid infiltrations. J. Path. Bact., 63 503.

25. Brewer, D.B., Orr, J.W. (1953). Struma reticulosa: a reconsideration of the undifferentiated tumours of the thyroid. ibid., 65 193.

26. British Medical Journal (1958). Goitrous hypothyroidism. 2 1092.

27. Brown, D.E. (1956). Subacute thyroiditis with a discussion of other types of thyroiditis. Ann. Otol. Rhinol. Laryngol., 65 595.

28. Buchanan, W.W., Anderson, J.R., Goudie, R.B., Gray, K.G. (1958). A skin test in thyroid disease. Lancet, 2 928.

29. Bullock, W.K., Hummer, G.J., Kahler, J.E. (1952). Squamous metaplasia of the thyroid gland. Cancer, 5 966.

30. Burrell, C.D., Frazer, R., Doniach, D. (1956). The low toxicity of carbimazole: a survey of 1,046 patients. Brit. med. J., 1 1453.

31. Cappell, D.F. (1958). Muir's Text-book of Pathology, 7th ed. London: Arnold. p. 1134.

32. Caren, R. (1949). The goitrogens in thyrotoxicosis complicating pregnancy. J. clin. Endocr., 9 903.

33. Chapman, E.M., Corner, G.W. Jr., Robinson, D., Evans, R.D. (1948). ibid., 8 717.

34. Chesky, V.E., Dreese, W.C., Hellwig, C.A. (1951). Chronic thyroiditis; supra-vital studies of surgical goiter specimens. Surg. Gynec. Obstet., 93 575.

35. Clausen, H.J. (1953). Experimental production of struma lymphomatosa. Proc. Soc. exp. Biol. (N.Y.). 83 835.

36. Cole, W.H., Womack, N.A. (1927). The thyroid in infections and toxemias. ibid., 25 188.

37. Cole, W.H., Womack, N.A. (1929). Reaction of the thyroid gland to infections in other parts of the body. J. Amer. med. Ass., 92 453.

38. Cole, W.H., Womack, N.A., Ellett, W.H. (1931). The production of hyperplasia of the thyroid gland by chemical means, with special reference to purine bases and their derivatives. Arch. Surg. Chicago, 22 926.

39. Cole, W.H., Womack, N.A., Gray, S.H. (1929). The thyroid in infections and toxemias. Amer. J. Surg., 6 221.

40. Committee of the Clinical Society of London (1888). Report on myxoedema. Suppl. Vol. 21, Trans. clin. Soc., London.

41. Cooper, A. See King (1836).

42. Cooper, E.R.A. (1925). The Histology of the more Important Human Endocrine Organs at Various Ages. Oxford University Press. p. 62.

43. Cramer, W. (1926). Fever, infections and the thyroid-adrenal apparatus. Brit. J. exp. Path., 7 95.

44. Crooks, J. (1957). Antithyroid drugs. Postgrad. med. J., 33 322.

45. Curran, R.C., Eckert, H., Wilson, G.M. (1958). The thyroid gland after treatment of hyperthyroidism by partial thyroidectomy or iodine^{131}. J. Path. Bact., 76 541.

46. D'Angelo, S.A., Paschkis, K.E., Gordon, A.S., Cantarow, A. (1951). Thyroid-thyrotropic hormone balance in the blood of normal and endocrinopathic individuals. J. clin. Endocr., 11 1237.

47. Danowski, T.S., Johnston, S.Y., Price, W.C., McKelvy, M., Stevenson, S.S., McCluskey, E.R. (1951). Protein-bound iodine in infants from birth to one year of age. Pediatrics, 7 240.

48. Davies, J.R. (1943). Sporadic congenital obstructive goiter with recovery following operation in a thirteen-day-old infant. J. Pediat., 22 570.

49. Davison, T.C., Letton, A.H. (1949). Hashimoto's disease. J. clin. Endocr., 9 980.

50. De Robertis, E. (1941). The intracellular colloid of the normal and activated thyroid gland of the rat studied by the freezing drying method. Amer. J. Anat., 68 317.

51. De Robertis, E. (1948). Assay of thyrotropic hormone in human blood. J. clin. Endocr., 8 956.

52. De Robertis, E., Nowinski, W.W. (1946). The proteolytic activity of normal and pathological human thyroid tissue. ibid., 6 235.

53. de Quervain, F. (1904). Mitt. Grenzgeb. Med. Chir., 2, suppl., quoted by Jackson (1916).

54. Dobyns, B.M. (1956). Physiologic concepts in the diagnosis and treatment of Graves' disease. Amer. J. Med., 20 684.

55. Dobyns, B.M., Hirsch, E.Z. (1956). Iodinated compounds in the lymphatic pathways leading from the thyroid.
J. clin. Endocr., 16 153.

56. Doniach, I. (1957). Personal communication.

57. Douglass, R.C., Jacobson, S.D. (1957). Pathologic changes in adult myxedema: survey of 10 necropsies.
J. clin. Endocr., 17 1354.

58. Druez, G., Hainaut, J., Parmentier, R., Musin, L. (1958). A propos d'un cas de thyroïdite à plasmocytes.
Acta clin. belg., 13 280.

59. Eason, J. (1928). The correlations of Graves' disease and thyroiditis.
Trans. Edinb. med.-chir. Soc., 107 169.

60. Eaton, J.C. (1945). Treatment of thyrotoxicosis with thiouracil. Lancet, 1 171.

61. Eden, K.C., Trotter, W.R. (1942). A case of lymphadenoid goitre associated with the full clinical picture of Graves' disease.
Brit. J. Surg., 29 320.

62. Elphinstone, N. (1953). Thiouracil in pregnancy; its effect on the foetus.
Lancet, 1 1281.

63. Fahrni, G.S. (1935). The etiology and management of recurrent hyperthyroidism.
West. J. Surg., 43 542.

64. Farrant, R. (1914). The pathological changes of the thyroid in disease.
Brit. med. J., 1 470.

65. Feldman, J.D. (1958). Effect of estrogen on thyroid morphology and metabolism.
Lab. Invest., 7 183.

66. Fischer, P.M.S. (1951). Hyperthyroidism in the first year of life: report of a case occurring in the neonatal period.
S. Afr. med. J., 25 217.

67. Fisher, E.R. (1953). Observations on thyroid colloid. Arch. Path., 56 275.

68. Foster, M., Barr, D. (1944). Myxedema: record of an autopsied case with special emphasis upon lesions of muscles. J. clin. Endocr., 4 417.

69. Frantz, V.K. In Werner (1955), p. 280.

70. Freiesleben, E., Kjerulf-Jensen, K. (1947). The effect of thiouracil derivatives on fetuses and infants. J. clin. Endocr., 7 47.

71. Friedman, N.B., (1949). Cellular involution in the thyroid gland; significance of Hürthle cells in myxedema, exhaustion atrophy, Hashimoto's disease and the reactions to irradiation, thiouracil therapy and subtotal resection. ibid., 9 874.

72. Frisk, A.R., Josefsson, E. (1947). Thiouracil derivatives and pregnancy. Acta med. scand. Suppl. 196 p.85.

73. Garret, R., Ada, A.E.W. (1957). Epithelial inclusion cysts in an axillary lymph node: report of a case simulating metastatic adenocarcinoma. Cancer, 10 173.

74. Gersh, I., Stieglitz, E.J. (1933). Histochemical methods for determination of iodides in tissues. Anat. Rec., 56 185.

75. Getzowa, S. (1907). Über die Glandula parathyreoidea, intrathyreoideale Zellhaufen derselben und Reste des postbranchialen Körpers. Virch. Arch., 188 181.

76. Getzowa, S. (1911). Zur Kenntnis des postbranchialen Körpers und der branchialen Kanälchen des Menschen. ibid., 205 208.

77. Gilliland, I.C., Strudwick, J.I. (1956). Clinical application of an assay of thyroid-stimulating hormone in relation to exophthalmos. Brit. med. J., 1 378.

78. Gitlin, G. (1957). Failure to detect squamous metaplasia in extra-genital organs of the female rat following prolonged estrogen administration. Endocrinology, 60 571.

79. Glebina, H. (1936). Zyklische Veränderungen der Schilddrüse bei Füchsen. Z. Zellforsch. u. mikr. Anat., 25 99.

80. Gloor, H.U. (1926). Beitrag zur Kenntnis der Schilddrüse des Neugeborenen. Frankf. Z. Path., 34 504.

81. Goble, F.C. (1954). Thyroid changes in acute experimental Chagas' disease in dogs. Amer. J. Path., 30 599.

82. Goddard, J.W., Sommers, S.C. (1954). Method for thyroid cell mapping. Lab. Invest., 3 197.

83. Godley, A.F., Stanbury, J.B. (1954). Preliminary experience in the treatment of hyperthyroidism with potassium perchlorate. J. clin. Endocr., 14 70.

84. Godwin, M.C. (1937). Complex IV in the dog with special emphasis on the relation of the ultimobranchial body to interfollicular cells in the postnatal thyroid gland. Amer. J. Anat., 60 299.

85. Goetsch, E., Kamner, M. (1955). Chronic thyroiditis and Riedel's struma; the role of the hyperfunctioning parenchyma of primary hyperplastic goiter. J. clin. Endocr., 15 1010.

86. Goldberg, H.M., Dayson, J. (1948). Lymphadenoid goitre. Brit. J. Surg., 36 41.

87. Goldberg, H.M., Harvey, P. (1956). Squamous-cell cysts of the thyroid with special reference to the aetiology of squamous epithelium in the human thyroid. ibid., 43 565.

88. Goldberg, R.C., Chaikoff, I.L., Lindsay, S., Feller, D.D. (1950). Histopathological changes induced in the normal thyroid and other tissues of the rat by internal radiation with various doses of radioactive iodine. Endocrinology, 46 72.

89. Goldberg, R.C., Chaikoff, I.L. (1952). Myxedema in the radiothyroidectomized dog. ibid., 50 115.

90. Goldsmith, E.D., Gordon, A.S., Charipper, H.A. (1945). An analysis of the effects of continued thiourea treatment in pregnancy and on the development of the offspring in the rat. Amer. J. Obstet. Gynec., 49 197.

91. Goormaghtigh, N., Thomas, F. (1934). The functional reactions of the human thyroid. Amer. J. Path., 10 713.

92. Gorbman, A., Evans, H.M. (1943). Beginning of function in the thyroid of the fetal rat. Endocrinology, 32 113.

93. Goudie, R.B., Anderson, J.R., Gray, K.G., Clark, D.H., Murray, I.P.C., McNicol, G.P. (1957). Precipitin tests in thyroid disease. Lancet, 2 976.

94. Graham, A., McCullagh, E.P. (1931). Atrophy and fibrosis associated with lymphoid tissue in the thyroid: struma lymphomatosa (Hashimoto). Arch. Surg. Chicago, 22 548.

95. Gray, S.H., Loeb, L. (1928). The effect of the oral administration of potassium iodide and thyroid substance on the mitotic proliferation and structure of acini in the thyroid gland in guinea pigs. Amer. J. Path., 4 257.

96. Gross, S. (1955). Granulomatous thyroiditis with anisotropic crystalline material. Arch. Path., 59 412.

97. Gürkan, K.I. (1945). Chronic thyroiditis and primary thyrotoxicosis (exophthalmic goiter). Arch. Surg. Chicago, 50 125.

98. Ham, A.W. (1957). Histology, 3rd ed. London: Pitman. p. 713.

99. Harland, W.A., Frantz, V.K. (1956). Clinico-pathologic study of 261 surgical cases of so-called "thyroiditis". J. clin. Endocr., 16 1433.

100. Harry, N.M. (1940). Riedel's disease and lymphadenoid goitre. Med. J. Aust., 2 595.

101. Hashimoto, H. (1912). Zur Kenntniss der lymphomatösen Veränderung der Schilddrüse. Arch. klin. Chir., 97 219.

102. Hazard, J.B. (1955). Thyroiditis: a review. Amer. J. clin. Path., 25 289 and 399.

103. Hellwig, C.A. (1938). Lymphadenoid goiter. Arch. Path., 25 838.

104. Hellwig, C.A. (1951). Colloidophagy in the human thyroid gland. Science, 113 725.

105. Hellwig, C.A. (1954). Colloidophagy in the human thyroid. Arch. Path., 58 151.

106. Hellwig, C.A., Wilkinson, P.N. (1956a). Experimental production of thyroiditis. ibid., 62 23.

107. Hellwig, C.A., Wilkinson, P.N. (1956b). Experimental production of lymphocytic foci in the thyroid. Growth, 20 315.

108. Hendrick, J.W. (1957). Diagnosis and management of thyroiditis. J. Amer. med. Ass., 164 127.

109. Heptinstall, R.H., Eastcott, H.H.G. (1954). Hashimoto's disease: struma lymphomatosa. Brit. J. Surg., 41 471.

110. Hermann, G., Verdun, P. (1899). Persistance des corps post-branchiaux chez l'homme. Comp. rend. Soc. Biol., 1 853.

111. Herrera, J.M. (1948). Arch. Hosp. S. Tomás (Panamá)., 3 195.
quoted by Salm (1954).

112. Hetzel, B.S., de la Haba, D.S., Hinkle, L.E. Jr. (1952). Life stress and thyroid function in human subjects.
J. clin. Endocr., 12 941.

113. Hewer, E.E. (1927). The activity of the thyroid gland in relation to the staining reactions of the colloid.
J. Path. Bact., 30 621.

114. Hiilesmaa, V. (1948). Studies of the thyroid gland of parturients and newborn infants in Southern Finland (Helsinki).
Acta obstet. gynec. scand., 28 Suppl. 1.

115. Hodges, R.E., Evans, T.C., Bradbury, J.T., Keettel, W.C. (1955). The accumulation of radioactive iodine by human fetal thyroids. J. clin. Endocr., 15 661.

116. Hubble, D. (1956). Thyroid disorders in childhood. Brit. med. J., 1 875.

117. Hughes, A.M. (1944). Cretinism in rats induced by thiouracil. Endocrinology, 34 69.

118. Hughes, D.L. (1947). In The UFAW Handbook on the Care and Management of Laboratory Animals. London: Baillière, Tindall & Cox.

119. Hull, O.H. (1955). Critical analysis of two hundred twenty-one thyroid glands.
Arch. Path., 59 291.

120. Hume, E.M., Burbank, R., Korenchevsky, V. (1939). Some effects of the administration of oestrogens on the organs of castrated and non-castrated rats partially deprived of vitamin A. J. Path. Bact., 49 291.

121. Hunter, I.J. (1955). Squamous metaplasia of cells of the anterior pituitary gland. J. Path. Bact., 69 141.

122. Jackson, C.M. (1916). Effects of inanition upon the structure of the thyroid and parathyroid glands of the albino rat. Amer. J. Anat., 19 305.

123. Jaffé, R.H. (1937). Epithelial metaplasia of the thyroid gland; with special reference to the histogenesis of squamous cell carcinoma of the thyroid gland. Arch. Path., 23 821.

124. Jirsová, V., Brychnáč, V. (1953). Případ hyperthyreosy u nedonošeného dítěte. Pediat. Listy, 8 107.

125. Joll, C.A. (1939). The pathology, diagnosis, and treatment of Hashimoto's disease (struma lymphomatosa). Brit. J. Surg., 27 351.

126. Jost, A. (1956). In Gestation, ed. by C.A. Villee. New York: Josiah Macy Jr. Foundation. p. 129.

127. Kauffman, G., Hurst, V., Turner, C.W. (1948). Histological effect of thiouracil on the fetal thyroid of the mouse. Endocrinology, 43 187.

128. Keynes, G. (1952). Obstetrics and gynaecology in relation to thyrotoxicosis and myasthenia gravis. J. Obstet. Gynaec. Brit. Emp., 59 173.

129. Kimble, B.T., Stieglitz, E.J. (1952). Hypothyroidism: a geriatric problem. Geriatrics, 7 20.

130. King, T.W. (1836). Observations on the thyroid gland; with notes on the same subject by Sir Astley Cooper, Bart. Guy's Hosp. Rep., 1 429.

131. Kingsbury, B.F. (1935a). On the fate of the ultimobranchial body within the human thyroid gland. Anat. Rec., 61 155.

132. Kingsbury, B.F. (1935b). Ultimobranchial body and thyroid gland in the fetal calf. Amer. J. Anat., 56 445.

133. Klinck, G.H., Menk, K.F. (1951). Squamous cells in the human thyroid. Milit. Surgeon, 109 406.

134. Kloeppel, F.C. (1910). Vergleichende Untersuchungen über Gebirgsland- und Tiefland-Schilddrüsen. Beitr. Z. path. Anat., 49 579.

135. Koch, F. (1938). Studien über die Morphologie der Normalen Schilddrüse. I. Die Schilddrüse der Neugeborenen. Acta path. microbiol. scand., 15 198.

136. Koerner, K.A. (1954). Congenital goiter with exophthalmos and hyperthyroidism. J. Pediat., 45 464.

137. Krementz, E.T., Hooper, R.G., Kempson, R.L. (1957). The effect on the rabbit fetus of the maternal administration of propylthiouracil. Surgery, 41 619.

138. Kulenkampff, H. (1950). Acini und Lymphsinus in der Schilddrüse des Neugeborenen. Z. Anat. Entwicklg., 115 82.

139. Lancet (1957). The immunology of thyroid disease. 1 1075.

140. Lancet (1958). Auto-immunity in thyroid disease. 2 1049.

141. Lawson, A., Rimington, C., Searle, C.E. (1951). Antithyroid activity of 2-carbethoxythiol-methylglyoxaline. Lancet, 2 619.

142. Lee, C.M., McGrath, E.J. (1937). Struma lymphomatosa (Hashimoto): a survey of the literature and report of a case. Surgery, 2 238.

143. Levitt, T. (1951). Evolution of the toxic thyroid gland; a clinical and pathological study based on 2114 thyroidectomies. Lancet, 2 957.

144. Levitt, T. (1952). The status of lymphadenoid goitre, Hashimoto's and Riedel's diseases. Ann. roy. Coll. Surg. Eng., 10 369.

145. Levitt, T. (1954). The Thyroid. Edinburgh: Livingstone.

146. Levitt, T. (1957). Lymphoid goitres. Postgrad. med. J., 33 352.

147. Lewis, I.C., Macgregor, A.G. (1957). Congenital hyperthyroidism. Lancet, 1 14.

148. Lilien, O.M. (1954). Anticorps thyroïdiens spécifiques. Comp. rend. Soc. Biol., 148 1572.

149. Lindsay, S., Dailey, M.E., Friedlander, J., Yee, G., Soley, M.H. (1952). Chronic thyroiditis: a clinical and pathologic study of 354 patients. J. clin. Endocr., 12 1578.

150. Loeb, L. (1929). The structural changes which take place in the thyroid glands of guinea pigs during the process of compensatory hypertrophy under the influence of iodine administration. Endocrinology, 13 49.

151. Logothetopoulos, J., Scott, R.F. (1956). Histology and function of the developing foetal thyroid in normal and goitrous guinea-pigs. J. Endocr., 14 217.

152. Lund, J. (1950). Ugesk. laeger., 112 671. Quoted by von Harnack (1957).

153. Luxton, R.W., Cooke, R.T. (1956). Hashimoto's struma lymphomatosa; diagnostic value and significance of serum-flocculation reactions. Lancet, 2 105.

154. McCarrison, R. (1917). The Thyroid Gland in Health and Disease. London: Baillière, Tindall & Cox.

155. McCullough, K., Dalldorf, G., (1937). Epithelial metaplasia; an experimental study. Arch. Path., 24 486.

156. McGavack, T.H., Chevalley, J., Reckendorf, H.K., Haar, H.O. (1956). Clinical experiences with carbimazole (1-methyl-2-carbethoxy-thio-imidazole) in the treatment of hyperthyroidism. J. clin. Endocr., 16 887.

157. Macgregor, A.G., Miller, H. (1953). Antithyroid activity of 2-carbethoxythio-1-methyl-glyoxaline. Lancet, 1 881.

158. McSwain, B., Moore, S.W. (1943). Struma lymphomatosa: Hashimoto's disease. Surg. Gynec. Obstet., 76 562.

159. Margetts, B.M. (1950). Thyrotoxicosis in a newborn infant. Proc. roy. Soc. Med., 43 615.

160. Marks, S., Dockum, N.L., Bustad, L.K. (1957). Histopathology of the thyroid gland of sheep in prolonged administration of I^{131}. Amer. J. Path., 33 219.

161. Marshall, S.F., Meissner, W.A., Smith, D.C. (1948). Chronic thyroiditis. New England J. Med., 238 758.

162. Mason, V.A. (1931). The fate of the ultimo-branchial body in the cat (Felis domestica), with special reference to cyst formation within the thyroid. Amer. J. Anat., 49 43.

163. Mayer, E. (1949). The unspecific properties of thyroid colloid. Anat. Rec., 103 487.

164. Mayer, J.B., Hemmer, A. (1956). Die Embryo-pathia thyreotica. Arch. Kinderhk., 153 123.

165. Means, J.H. (1948). The Thyroid and its Diseases, 2nd ed. Philadelphia: Lippincott. p. 104.

166. Meeker, L.H. (1925). Riedel's struma associated with remnants of the post-branchial body. Amer. J. Path., 1 57.

167. Meissner, W.A., Adler, A. (1958). Papillary carcinoma of the thyroid. Arch. Path., 66 518.

168. Moran, T.J. (1952). Congenital goiter with death from milk-aspiration pneumonia. Arch. Path., 54 213.

169. Morison, J.E. (1952). Foetal and Neonatal Pathology. London: Butterworth. p. 219.

170. Morris, D. (1953). Transient hypothyroidism in a newborn infant. Lancet, 1 1284.

171. Murray, I. (1927). The thyroid gland in the full-time human foetus and newly-born infant. Brit. med. J., 1 5.

172. Murray, I.C.P. (1958). Auto-immunity and thyroid disease. Lancet, 2 1175.

173. Myant, N.B. (1958). Passage of thyroxine and tri-iodo-thyronine from mother to foetus in pregnant women. Clin. Sci., 17 75.

174. Nadler, N.J., Leblond, C.P., Bogoroch, R. (1954). The rate of iodine metabolism by the thyroid follicle as a function of its size. Endocrinology, 54 154.

175. Nikitovitch, M., Knobil, E. (1955). Placental transfer of thyrotropic hormone in the rat. J. clin. Endocr., 15 837.

176. Nolan, L.E. (1938). Variations in the size, weight and histologic structure of the thyroid gland. Arch. Path., 25 1.

177. Nonidez, J.F. (1933). The "parenchymatous" cells of Baber, "Protoplasmareichen Zellen" of Hürthle, and the "parafollicular" cells of the mammalian thyroid. Anat. Rec., 56 131.

178. Norris, E.H. (1937). The parathyroid glands and the lateral thyroid in man: their morphogenesis, histogenesis, topographic anatomy and prenatal growth. Carnegie Inst. Wash. Pub. No. 479, Contrib. Embryol. No. 159, 26 247.

179. Okkels, H. (1932). Studies on the thyroid gland. I. On the histology and cytology of normal and abnormal thyroids in man. Acta path. microbiol. scand., 9 1.

180. Owen, C.A. Jr., McConahey, W.M. (1956). An unusual iodinated protein of the serum in Hashimoto's thyroiditis. J. clin. Endocr., 16 1570.

181. Owen, S.G., Smart, G.A. (1958). Thyroid antibodies in myxoedema. Lancet, 2 1034.

182. Paine, J.R., Terplan, K., Rose, N.R., Witebsky, E., Egan, R.W. (1957). A clinical study of chronic non-infectious thyroiditis and autoimmunisation. Surgery, 42 799.

183. Parmley, C.C., Hellwig, C.A. (1946). Lymphadenoid goiter; its differentiation from chronic thyroiditis. Arch. Surg., 53 190.

184. Paschkis, K.E., Cantarow, A., Eberhard, T., Boyle, D. (1950). Thyroid function in the alarm reaction. Proc. Soc. exp. Biol. (N.Y.), 73 116.

185. Pearse, A.G.E. (1953). Histochemistry. London: Churchill. p. 431.

186. Pemberton, J. de J. (1930). Recurring exophthalmic goiter; its relation to the amount of tissue preserved in operation on the thyroid gland. J. Amer. med. Ass., 94 1483.

187. Perman, E., Wahlgren, F. (1927). Case of chronic thyroiditis (Riedel). Acta chir. scand., 61 535.

188. Peterson, C.A., Shidler, F.P. (1957). Lymphocytic thyroiditis in 757 thyroid operations. Amer. J. Surg., 94 223.

189. Peterson, R.R., Young, W.C. (1952). The problem of placental permeability for thyrotrophin, propylthiouracil and thyroxine in the guinea pig. Endocrinology, 50 218.

190. Ponse, K. (1951). L'histophysiologie thyroïdienne. Ann. d'Endocr., 12 266.

191. Ponse, K., Altschuler, H. (1940). Histophysiologie de l'activation thyroïdienne. Arch. Anat. Histol. Embryol., 29 1.

192. Popoff, N.W. (1943). Mechanism of release of colloid; and the significance of the specific crystalline substance demonstrated in the thyroid gland histologically. Arch. Path., 36 587.

193. Potter, E.L. (1938). Postmortem examination of stillborn and of newly born infants. ibid., 25 607.

194. Potter, E.L., Adair, F.L. (1949). Fetal and Neonatal Death, 2nd ed. University of Chicago Press.

195. Purves, H.D., Griesbach, W.E. (1949). Thyrotropic hormone in thyrotoxicosis, malignant exophthalmos and myxoedema. Brit. J. exp. Path., 30 23.

196. Rabson, S.M., Arata, J.E. (1949). Hashimoto's and Riedel's strumas and lymphadenoid goiter. Amer. J. clin. Path., 19 750.

197. Rawson, R.W., Starr, P. (1938). Direct measurement of height of thyroid epithelium. A method of assay of thyrotropic substance; clinical application. Arch. intern. Med., 61 726.

198. Řeřábek, J., Řeřábek, E. (1947). Nucleic acids and cytological changes in the thyroid after thiouracil. Acta physiol. scand., 14 276.

199. Rice, C.O. (1938). Histologic structure of the normal thyroid gland. Arch. Surg. Chicago, 36 96.

200. Richter, M.N. (1940). Anisotropic crystalloids in the human thyroid gland. Amer. J. Path., 16 654.

201. Richter, M.N., McCarty, K.S. (1954). Anisotropic crystals in the human thyroid gland. ibid., 30 545.

202. Rienhoff, W.F. Jr. (1931). The lymphatic vessels of the thyroid gland in the dog and in man. Arch. Surg. Chicago, 23 783.

203. Riley, I.D., Sclare, G. (1957). Thyroid disorders in the newborn. Brit. med. J., 1 979.

204. Roger, H., Garnier, M. (1898a). La sclerose du corps thyroïde chez les tuberculeux. Comp. rend. Soc. Biol., 50 873.

205. Roger, H., Garnier, M. (1898b). Infection thyroïdienne expérimentale. ibid., 50 889.

206. Roger, H., Garnier, M. (1898c). Action du bacille typhique sur la glande thyroïde. ibid., 50 891.

207. Roger, H., Garnier, M. (1899). La glande thyroïde dans les maladies infectieuses. Presse méd., 7th year 1 181.

208. Roitt, I.M., Doniach, D. (1958). Human autoimmune thyroiditis; serological studies. Lancet, 2 1027.

209. Roitt, I.M., Doniach, D., Campbell, P.N., Hudson, R.V. (1956). Auto-antibodies in Hashimoto's disease (lymphadenoid goitre). ibid., 2 820.

210. Rose, N.R., Witebsky, E. (1956). Studies on organ specificity; V. Changes in thyroid glands of rabbits following active immunization with rabbit thyroid extracts. J. Immunol., 76 417.

211. Salm, R. (1954). Thiouracil goitre in a newborn. J. Obstet. Gynaec. Brit. Emp., 61 831.

212. Salm, R. (1957). Epidermoid metaplasia in mammary fibro-adenoma with formation of keratin cysts. J. Path. Bact., 74 221.

213. Sandritter, W., Kummer, E., Pillat, G., Röwe, L. (1956). Zur Histochemie und Funktion der parafollikulären Zellen in der Schilddrüse. Klin. Wschr. 34 871.

214. Saxén, E. (1951). Squamous metaplasia in the thyroid gland and histogenesis of epidermoid carcinoma of the thyroid. Acta path. microbiol. scand., 28 55.

215. Saye, E.B., Watt, C.H., Foushee, J.C., Palmer, J.I. (1952). Congenital thyroid hyperplasia in twins. J. Amer. med. Ass., 149 1399.

216. Scarcello, N.S., Goodale, R.H. (1941). Struma lymphomatosa; report of a case complicated by myxedema. New Engl. J. Med., 244 60.

217. Scarizza, P.M. (1954). Gozzo congenito in neonato da antitiroidei somministrati alla madre durante la gravidanza. Minerva Pediat. (Torino), 6 433.

218. Schamaun, H.-M. (1954). Pathogisch-anatomische Untersuchungen über die struma congenita im Kanton Aargau 1940-1951. Helvet. Paediat. Acta, 9 455.

219. Schilling, J.A. (1945). Struma lymphomatosa, struma fibrosa and thyroiditis. Surg. Gynec. Obstet., 81 533.

220. Sclare, G. (1956). The histological structure of the thyroid in the newborn. Scot. med. J., 1 251.

221. Sclare, G. (1959). Chronic thyroiditis following thyrotoxicosis. Brit. J. Surg., in press.

222. Selye, H. (1946). The general adaptation syndrome and the diseases of adaptation. J. clin. Endocr., 6 117.

223. Severinghaus, A.E. (1933). Cytological observations on secretion in normal and activated thyroids. Z. Zellforsch. u. mikr. Anat., 19 653.

224. Shaw, A.F.B., Smith, R.P. (1925). Riedel's chronic thyroiditis; with a report of six cases and a contribution to the pathology. Brit. J. Surg., 13 93.

225. Shaw, R.C., Smith, F.B. (1940). Plasmocytoma of the thyroid gland and a report of a case. Arch. Surg., Chicago, 40 646.

226. Sigurjónsson, J. (1940). Studies on the human thyroid in Iceland. Reykjavik. pp. 47, 71.

227. Simmonds, M. (1913). Über lymphatische Herde in der Schilddrüse. Virch. Arch., 211 73.

228. Skelton, M.O., Gans, B. (1955). Congenital thyrotoxicosis, hepatosplenomegaly and jaundice in two infants of exophthalmic mothers. Arch. Dis. Childh., 30 460.

229. Skillern, P.G., Crile, G. Jr., McCullagh, E.P., Hazard, J.B., Lewis, L.A., Brown, H. (1956a). Struma lymphomatosa: primary thyroid failure with compensatory thyroid enlargement. J. clin. Endocr., 16 35.

230. Skillern, P.G., Nelson, H.E., Crile, G. Jr. (1956b). Some new observations on subacute thyroiditis. ibid., 16 1422.

231. Skirpan, P., Reich, A., Crile, G. Jr. (1955). The serum colloidal gold test - an aid to diagnosis of struma lymphomatosa. Amer. J. clin. Path., 25 1274.

232. Smith, R.D., Starkey, W.F. (1940). Histological and quantitative study of age changes in the thyroid of the mouse. Endocrinology, 27 621.

233. Sokolow, A.N. (1895). Quoted by Cole and Womack (1929).

234. Sommers, S.C., Meissner, W.A. (1954). Basement membrane changes in chronic thyroiditis and other thyroid diseases. Amer. J. clin. Path., 24 434.

235. Speert, H., Quimby, E.H., Werner, S.C. (1951). Radioiodine uptake by the fetal mouse thyroid and resultant effects in later life. Surg. Gynec. Obstet., 93 230.

236. Spjut, H.J., Warren, W.D., Ackerman, L.V. (1957). Clinical-pathologic study of 76 cases of recurrent Graves' disease, toxic (non-exophthalmic) goiter, and non-toxic goiter. Does a relation exist between thyroid hyperplasia and struma lymphomatosa? Amer. J. clin. Path., 27 367.

237. Stanbury, J.B., Wyngaarden, J.B. (1952). Effect of perchlorate on the human thyroid gland. Metabolism, 1 533.

238. Statland, H., Wasserman, M.M., Vickery, A.L. (1951). Struma lymphomatosa (Hashimoto's struma). Arch. intern. Med., 88 659.

239. Stemmermann, G.N. (1956). Serum protein changes in subacute thyroiditis. J. Amer. med. Ass., 162 31.

240. Stoffer, R.P., Koeneke, I.A., Chesky, V.E., Hellwig, C.A. (1957). The thyroid in pregnancy. Amer. J. Obstet. Gynec., 74 300.

241. Stuart, A.E., Allan, W.S.A. (1958). The significance of basement-membrane changes in thyroid disease. Lancet, 2 1204.

242. Tanabe, H., Wakabayashi, M. (1940). Colloidophagy in the human thyroid gland. Trans. Soc. Path. Japan, 30 213. Quoted by Hellwig (1954).

243. Terplan, K.L., Witebsky, E., Rose, N.R. (1958). Experimental thyroiditis in rabbits, guinea pigs and dogs, following immunization with species specific thyroid extract. Amer. J. Path., 34 564.

244. Thamdrup, E. (1952). Congenital thyroid hyperplasia in twins. J. Amer. med. Ass., 150 951.

245. Thomson, A.D. (1957). The pathology of Hashimoto's disease. Proc. roy. Soc. Med., 50 950.

246. Thurston, E.W. (1933). A comparison of hypertrophic changes in thyroid; caused in different species by acid extract of the anterior lobe of the bovine pituitary gland. Arch. Path., 15 67.

247. Tobin, C.E. (1941). Some effects of thyrotropic hormone on the pregnant rat. Proc. Soc. exp. Biol. (N.Y.), 48 592.

248. Uhlenhuth, E. (1923). The elaboration and release of the colloid of the thyroid. ibid., 20 494.

249. Valdés-Dapena, M.A. (1957). An Atlas of Fetal and Neonatal Histology. Philadelphia: Lippincott. p. 160.

250. Van Dyke, J.H. (1945). Behavior of ultimobranchial tissue in the postnatal thyroid gland; epithelial cysts, their relation to thyroid parenchyma and to "new-growths" in the thyroid gland of young sheep. Amer. J. Anat. 76 20.

251. Van Dyke, J.H. (1955). Experimental thyroid metaplasia in the rat. Arch. Path., 59 73.

252. Van Middlesworth, L. (1954). Radioactive iodide uptake of normal newborn infants. Amer. J. Dis. Child., 88 439.

253. Vaux, D.M. (1938). Lymphadenoid goitre; a study of thirty-eight cases. J. Path. Bact., 46 441.

254. Vérel, D. (1949). Thiouracil in thyrotoxicosis. Brit. med. J., 1 892.

255. Vitagliano, G. (1956). Le tiroiditi di Riedel e di Hashimoto. Tumori, 42 212.

256. von Harnack, G.-A. (1957). Angeborene Schilddrüsenstörungen; Genetische und peristatische Entstehungsursachen. Dtsch. med. Wschr., 82 650.

257. Weber, G., Bettini, U. (1956). Il problema delle immagini "colloidofagiche", degli infiltrati parvicellulari e dell'influsso tireotropo ipofisario nelle strume di Riedel e di Hashimoto. Arch. "de Vecchi" Anat. Patol., 24 69.

258. Webster, R.C. (1949). Growth and time of sexual maturation in goitrous guinea pigs. Anat. Rec., 103 517.

259. Webster, R.C., Young, W.C. (1948). Thiouracil treatment of the female guinea pig; effect on gestation and the offspring. ibid., 101 722.

260. Wegelin, C. (1926). In Handbuch der Speziellen Pathologischen Anatomie und Histologie, by F. Henke and O. Lubarsch. Berlin: Springer. 8 227.

261. Weiser, R.S. (1957). Mechanisms of immunologic tissue injury. J. Allergy, 28 475.

262. Welch, J.W., Wilkinson, P.N., Hellwig, C.A. (1958). Histology of the thyroid gland of the white rat following injection of progesterone. Growth, 22 31.

263. Weller, G.L. Jr. (1933). Development of the thyroid, parathyroid and thymus glands in man. Carnegie Inst. Wash. Pub. No. 443, Contrib. Embryol. No. 141, 24 95.

264. Werner, S.C. (1955). The Thyroid. London: Cassell. pp. 445, 625.

265. White, C. (1912). A foetus with congenital hereditary Graves's disease. J. Obstet. Gynaec. Brit. Emp., 21 231.

266. White, R.G. (1957). An immunological investigation of Hashimoto's disease. Proc. roy. Soc. Med., 50 953.

267. Whitesell, F.B. Jr., Black, B.M. (1949). A statistical study of the clinical significance of lymphocytic and fibrocytic replacements in the hyperplastic thyroid gland. J. clin. Endocr., 9 1202.

268. Whitwell, F. (1955). Tumourlets of the lung. J. Path. Bact., 70 529.

269. Williams, R.G. (1937). Microscopic studies of living thyroid follicles implanted in transparent chambers installed in the rabbit's ear. Amer. J. Anat., 62 1.

270. Williams, R.G. (1939). Further observations on the microscopic appearance and behavior of living thyroid follicles in the rabbit. J. Morphol., 65 17.

271. Williams, R.G. (1944). Some properties of living thyroid cells and follicles. Amer. J. Anat., 75 95.

272. Winiwarter, H. de (1933). Recherches sur l'évolution des dérivés branchiaux et l'histogenèse du thymus (Cobaye). Arch. de Biol., 44 741.

273. Witebsky, E., Rose, N.R. (1956). Studies on organ specificity: IV. Production of rabbit thyroid antibodies in the rabbit. J. Immunol., 76 408.

274. Womack, N.A., Cole, W.H. (1931). Normal and pathologic repair in the thyroid gland. Arch. Surg. Chicago, 23 466.

275. Womack, N.A., Cole, W.H., Heideman, A.G. (1928). The thyroid gland in infections; the effect upon the basal metabolic rate. Endocrinology, 12 773.

276. Woolner, L.B., McConahey, W.M., Beahrs, O.H. (1957). Invasive fibrous thyroiditis (Riedel's struma). J. clin. Endocr., 17 201.

277. Wyngaarden, J.B., Wright, B.M., Ways, P. (1952). The effect of certain anions upon the accumulation and retention of iodide by the thyroid gland. Endocrinology, 50 537.

278. Yoshida, T. (1932). Experimental epithelial metaplasia of the thyroid gland. Virch. Arch., 283 29. Abstract in Arch. Path., 15 280. (1933).

279. Zampi, G., Cinti, G. (1957). Struma tiroidea congenita in gemelli. Arch. "de Vecchi" Anat. Patol., 27 443.

280. Zechel, G. (1933). Observations on the follicular cycle and on the presence of the "macrothyrocyte" in the human thyroid. Anat. Rec., 56 119.

281. Zeiss, O. (1877). Quoted by Richter and McCarty (1954).

282. Zygulska-Machowa (1955). Pol. Tyg. lek., 11 1827. Abstract in Excerpta Medica, Sec. III, 11 No. 948 (1957).

BOOK 2

CONTENTS

TABLE 1

Staining reactions of colloid

Eosin	Pale	Deep
P.A.S.	Pale	Deep
Aniline blue-orange G	Blue	Yellow
Masson's trichrome	Green	Red
Iron haematoxylin and van Gieson	Yellow	Grey or black
Congo red	Red	Pale blue
Brazilin-wasserblau	Blue	Red

TABLE 2

Incidence of acinar types in 106 neonates

	Males	Females	Total
A	11	13	24
B	8	5	13
C	20	13	33
AB	2	2	4
AC	16	3	19
BC	6	5	11
ABC	1	1	2

* Predominantly A	24	(22.6%)
* Partly A	25	(23.6%)
Total no. in which A was prominent	49	(46.2%)
* Predominantly B	13	(12.3%)
* Partly B	17	(16.0%)
Total no. in which B was prominent	30	(28.3%)
* Predominantly C	33	(31.1%)
* Partly C	32	(30.2%)
Total no. in which C was prominent	65	(61.3%)

* In this and subsequent tables, "predominantly A (or B or C)" refers to all glands which were classified as A (or B or C), irrespective of small amounts of other types of tissue present. "Partly A" refers to all glands in which type A acini formed a significant component, i.e. those classified as AB, AC, or ABC. Several glands therefore appear more than once in each table.

TABLE 3

106 neonates: classified according to age

	Stillborn	0-24 hrs.	Up to 72 hrs.	Up to 7 days
Total cases	22	47	28	9
Predominantly A	6 (27.3%)	8 (17.0%)	5 (17.9%)	5 (55.5%)
Partly A	6 (27.3%)	9 (19.1%)	7 (25.0%)	3 (33.3%)
Total A	12 (54.5%)	17 (36.2%)	12 (42.9%)	8 (88.8%)
Predominantly B	2 (9.1%)	9 (19.1%)	1 (3.6%)	1 (11.1%)
Partly B	4 (18.2%)	6 (12.8%)	6 (21.4%)	1 (11.1%)
Total B	6 (27.3%)	15 (31.9%)	7 (25.0%)	2 (22.2%)
Predominantly C	5 (22.7%)	18 (38.2%)	10 (35.7%)	0
Partly C	8 (36.4%)	11 (23.4%)	11 (39.3%)	2 (22.2%)
Total C	13 (59.1%)	29 (61.7%)	21 (75.0%)	2 (22.2%)

TABLE 4

106 neonates: classified according to sex

	Males	Females
Total	64	42
Predominantly A	11 (17.2%)	13 (30.9%)
Partly A	19 (29.7%)	6 (14.3%)
Total A	30 (46.9%)	19 (45.2%)
Predominantly B	8 (12.5%)	5 (11.8%)
Partly B	9 (14.1%)	8 (19.0%)
Total B	17 (26.6%)	13 (30.9%)
Predominantly C	20 (31.3%)	13 (30.9%)
Partly C	23 (35.9%)	9 (21.4%)
Total C	43 (67.2%)	22 (52.4%)

TABLE 5

106 neonates: classified according to maturity

	A	B	C	AB	AC	BC	ABC	Total
Mature	13	5	18	2	9	4	0	51
Borderline (wt. 5 lb.)	0	0	1	1	0	0	1	3
Premature (3-5 lb.)	3	8	7	1	8	5	1	33
Very premature (under 3 lb.)	8	0	7	0	2	2	0	19

		Mature	All premature	Premature (3-5 lb.)	Premature (under 3lb.)
Predominantly	A	13 (25.5%)	11 (21.1%)	3 (9.1%)	8 (42.1%)
Partly	A	11 (21.6%)	12 (23.1%)	10 (30.3%)	2 (10.5%)
Total	A	24 (47.1%)	23 (44.2%)	13 (39.4%)	10 (52.5%)
Predominantly	B	5 (9.8%)	8 (15.4%)	8 (24.2%)	0
Partly	B	6 (11.8%)	9 (17.3%)	7 (21.2%)	2 (10.5%)
Total	B	11 (21.6%)	17 (32.7%)	15 (45.5%)	2 (10.5%)
Predominantly	C	18 (35.3%)	14 (26.9%)	7 (21.2%)	7 (36.8%)
Partly	C	13 (25.5%)	18 (34.6%)	14 (42.4%)	4 (21.1%)
Total	C	31 (60.8%)	32 (61.6%)	21 (63.6%)	11 (57.9%)

TABLE 6

106 neonates: cases of pre-eclampic toxaemia

A	3
B	2
C	2
AB	1
AC	3
BC	1

Total: 12

TABLE 7

106 neonates: cases of difficult or prolonged labour

A	10	
B	1	
C	10	
AB	1	Total: 31
AC	6	
BC	3	

Predominantly A	10	(32.3%)
Partly A	7	(22.6%)
Total A	17	(54.8%)
Predominantly B	1	(3.2%)
Partly B	4	(12.9%)
Total B	5	(16.1%)
Predominantly C	10	(32.3%)
Partly C	9	(29.1%)
Total C	19	(61.3%)

TABLE 8

106 neonates: Caesarian section

A	2	
C	9	Total: 12
BC	1	

4 of these cases (all C) are included in the "difficult or prolonged labour" group.

TABLE 9

106 neonates: signs of asphyxia

A	18	
B	11	
C	18	
AB	4	Total: 74
AC	13	
BC	8	
ABC	2	

	Asphyxial group		Non-asphyxial group	
Predominantly A	18	(24.3%)	6	(18.8%)
Partly A	19	(25.7%)	6	(18.8%)
Total A	37	(50.0%)	12	(37.5%)
Predominantly B	11	(14.9%)	2	(6.3%)
Partly B	14	(18.9%)	3	(9.4%)
Total B	25	(33.8%)	5	(15.6%)
Predominantly C	18	(24.3%)	15	(46.9%)
Partly C	23	(31.1%)	9	(28.1%)
Total C	41	(55.4%)	24	(75.0%)

TABLE 10

106 neonates: classified according to death-fixation interval

	up to 12 hrs.	12-24 hrs.	24-48 hrs.
A	8	10	6
B	5	3	5
C	5	17	11
AB	1	2	1
AC	10	5	4
BC	4	4	3
ABC	0	2	0
	33	43	30

	Up to 12 hrs.	12-24 hrs.	24-48 hrs.
Predominantly A	8 (24.2%)	10 (23.3%)	6 (20.0%)
Partly A	11 (33.3%)	9 (20.9%)	5 (16.7%)
Total A	19 (57.6%)	19 (44.2%)	11 (36.7%)
Predominantly B	5 (15.1%)	3 (7.0%)	5 (16.7%)
Partly B	5 (15.1%)	8 (18.6%)	4 (13.3%)
Total B	10 (30.3%)	11 (25.6%)	9 (30.0%)
Predominantly C	5 (15.1%)	17 (39.5%)	11 (36.7%)
Partly C	14 (42.4%)	11 (25.6%)	7 (23.3%)
Total C	19 (57.6%)	28 (65.1%)	18 (60.0%)

TABLE 11

Lymphatic distension in relation to death-fixation interval

Delay in fixation (hours)	Total cases	Those showing lymphatic distension
Up to 12	33	17 (51%)
12 - 24	43	29 (67%)
24 - 36	22	10 (45%)
36 - 48	8	2 (25%)

TABLE 12: CASES OF

THE MOTHER

No.	Author and Date	Previous history and treatment	Thyroid status		Treatment during Pregnancy
			In Pregnancy	At Delivery	
1	White (1912)	Nil	G, T, E from 5th month	increased T.	Nil
2	Frisk & Joseffson (1947)	T. Thiourea and MTU, 14 mths.	T, E	? not fully controlled	MTU to term, with interval of 7 weeks
3	Margetts (1950)	T. 1 year	probably toxic	probably toxic	Nil
4	Fischer (1951)	Nil	T from 6 months	still toxic	PTU to term Lugol's iodine
5	Keynes (1952	T. Tx 1 year before	E only	E only	Nil
6	Jirsova & Brychnac (1953)	T. Tx 2 yrs. before	E only	E only	Nil
7	Koerner (1954)	T. Tx I^{131}	hypothyroid E	hypothyroid E	thyroid extract
8	Skelton & Gans (1955) Case 1	T. Tx 2 yrs. before	E only	E only	Nil
9	Bongiovanni et al.(1956) Case 1	Nil	T from 5 months	not stated	PTU from 5th to 7th month. Lugol's iodine, stilboestrol
10	Lewis & Macgregor (1957)	T. Tx 11mths. before	E ? T	E ? T	Nil
11	Riley & Sclare (1957) Case 1	T. Tx 9 yrs. before	recurrence of T	? not fully controlled	TU to term
12	Riley & Sclare (1957) Case 2	Nil	T, E	T, E	MTU to term thyroxine
13	von Harnack (1957)	T. I^{131} 1 yr. before	very slight T marked E	unchanged	Nil

G: goitre T: thyrotoxicosis E: exophthalmos Tx: thyroidectomy TU: thiouracil MTU: methylthiouracil PTU: propylthiouracil

CONGENITAL THYROTOXICOSIS

THE CHILD

Sex	Maturity (birth-weight or gestation age)	Onset of Symptoms	Course
M	4 lb. 6 oz.	in utero G, T, E present at birth	Died at 38 hours Hyperplastic goitre
F	2430 g. 38 weeks	T, E at about 6 weeks No G	T for 3 months or more E for 8 months
M	5 lb. 13 oz.	T, E probably at birth No G	Normal at 3 months
M	7 lb.	T at 3 days G at 6 days E at 8 days	Improved at 27 days Normal at 17 weeks
Not stated		E only, at birth	Normal after many months
M	2106 g.	G, T, E at birth	Normal at 3 months
F	1550 g. 28 weeks	G, T, E at birth	Normal at 20 weeks
M	3 lb. 15 oz.	T at birth G, E at 11 days	Died at 33 days Thyroid 4.6 g.
F	Full term	G at birth T ? at birth	Improved
M	6 lb.	G, T, E at birth	Treated with carbimazole. Normal at 3 months
M	2296 g. Full term	G, T at 8 days	Normal at 4 weeks
M	1927 g. 34 weeks	G at birth T, E at 8 days	Died at 37 days Thyroid 10 g.
M	7 lb.	G, T, E at birth	Normal at 3 months

TABLE 13

Weights of normal and abnormal guinea pig thyroids

A. The normal thyroid in the newborn (in order of maturity)

No.	Thyroid weight (mg.)	Body weight (g.)	Relative thyroid weight
32A	18	36	0.50
41C	38	74	0.51
43A	41	95	0.43
22B	40	99	0.40
42B	40	100	0.40
24A	40	104	0.38

B. The normal thyroid in the adult

No.	Thyroid weight (mg.)	Body weight (g.)	Relative thyroid weight
13M	110	729	0.15
23M	100	622	0.16
29M	62	792	0.08

TABLE 13 (Continued)

C. The influence of antithyroid drugs on the neonatal thyroid

No.	Drug	Concentration	Duration*	Age	Thyroid weight (mg.)	Body weight (g)	Relative thyroid weight
21A	thiouracil	0.05%	29	nil	230	117	1.97
21B	"	"	"	"	240	117	2.05
20C	"	"	"	2 days	145	80	1.81
20D	"	"	"	7 days	155	120	1.28
25B	"	0.005%	"	2½-3 hrs.	70	65	1.08
27A	"	"	35	nil	42	40	1.05
28A	"	"	36	12 hrs.	80	75	1.07
28B	"	"	36	12 hrs.	67	93	0.72
26A	pot. perchlorate	"	32	12 hrs.	65	99	0.66
30A	"	"	36	27-47 hrs.	62	102	0.61
30B	"	"	36	"	88	116	0.75
31A	"	"	38	4 hrs.	38	66	0.58
33A	carbimazole	0.0005%	26	8-22 hrs.	60	73	0.82
34A	"	0.005%	28	1½ hrs.	82	105	0.78
37A	"	"	34	less than ½ hr.	65	100	0.65
38B	"	"	21	1 hr.	40	66	0.61
40B	"	0.0005%	22	nil	100	88	1.14
		0.05%	12				

D. The influence of antithyroid drugs on the adult thyroid

No.	Drug	Concentration	Total duration (days)	Thyroid weight (mg.)	Body weight (g.)	Relative thyroid weight
27M	thiouracil	0.005%	44	111	468	0.24
31M	pot. perchlorate	0.005%	45	145	400	0.36

* Duration of administration before delivery (in days)

TABLE 14

Autolysis in the TSH-activated thyroid

No.	Interval between TSH-injection and death (hrs.)	Interval between death and fixation (hrs.)	Autolytic changes in thyroid	Degree of autolysis compared with degree in non-injected control
3B	20	52½	Increased peripheral vacuolation of colloid. Early detachment of epithelium; no desquamation or disintegration.	-
5B	25	117	Loss of nuclei and early disintegration of acinar lining in central zone.	Rather less advanced
4B	28	120½	Loss of nuclei and a few examples of early disintegration in central zone.	-
50B	24-36	About 34	Early detachment of epithelium	Less advanced
43D	46	72½	Disintegration of acinar lining and loss of nuclei in central zone.	More advanced
53D	71	48½	Early detachment of epithelium.	Equal or, if anything, rather less advanced.
49C	96	66	Detachment of epithelium; no disintegration of lining, no loss of nuclei.	Less advanced

TABLE 15

Relation of death-fixation interval to "neonatal changes" in 191 adult thyroids.

Death-fixation interval (hours)	Total	Cases showing lymphatic distension	Cases showing epithelial changes only
Up to 12	26	6 (23%)	2 (8%)
12 to 24	62	20 (32%)	11 (18%)
24 to 36	47	16 (34%)	8 (17%)
36 to 48	23	11 (48%)	5 (22%)
48 to 72	23	4 (17%)	5 (22%)
Over 72	10	5 (50%)	(4, all showing obvious autolysis)
	191	62	31, omitting the autolytic cases.

TABLE 16

Relation of age to "neonatal changes"

	FIRST SERIES (191 cases)			SECOND SERIES (63 cases)		
Age	Total	Lymphatic distension	Epithelial changes only	Total	Lymphatic distension	Epithelial changes only
20 to 29	4	1 (25%)	0	2	2	0
30 to 39	5	3 (60%)	0	6	2	0
40 to 49	19	5 (26%)	3 (15%)	5	2	0
50 to 59	33	11 (33%)	5 (15%)	11	8	2
60 to 69	59	19 (32%)	13 (22%)	16	11	1
70 to 79	46	14 (30%)	6 (13%)	20	12	1
80 & over	25	9 (36%)	4 (16%)	3	1	1
	191	62 (32%)	31 (16%)	63	38 (60%)	5 (8%)

TABLE 17

Outstanding cases of lymphatic distension

Age	Total	Number of cases
20 to 39	17	0
40 to 59	68	2 (3%)
60 to 79	141	7 (5%)
80 to 99	28	3 (11%)
	254	12

TABLE 18

Relation of "neonatal changes" to sex

	Total	Thyroids showing Lymphatic distension	Epithelial changes only	All Cases
1st Series (omitting the 4 cases showing obvious autolysis)				
Males	102	36 (35%)	18 (18%)	54 (53%)
Females	85	26 (31%)	13 (15%)	39 (46%)
2nd Series				
Males	43	28	2	30 (70%)
Females	20	10	3	13 (65%)
All 12 outstanding cases of lymphatic distension				
Males	145			6 (4%)
Females	105			6 (6%)

TABLE 19

Cases of tuberculosis

	"Neonatal changes"	Remarks
Children		
1. F, 6 weeks	Nil	Generalised miliary tuberculosis.
2. M, 4 months	Extensive	Generalised tuberculosis, thought to be congenital.
Adults		
1. M, 74	Nil	Rheumatic heart disease. Apical tuberculosis an incidental finding at autopsy.
2. F, 48	Nil	Addison's disease (tuberculosis of adrenals)
3. M, 56	Nil	Haemorrhage from duodenal ulcer. Pulmonary tuberculosis an incidental finding.
4. M, 63	Epithelial changes and lymphatic distension.	Co-existing bronchial carcinoma and pulmonary tuberculosis.
5. F, 80	Nil	Bronchial carcinoma, broncho-pneumonia, lung abscesses. Tuberculosis found on microscopy.
6. F, 81	Nil	Tuberculous bronchopneumonia (the only adult case in which tuberculosis was considered to be the principal cause of death).

TABLE 20

Relation of "neonatal changes" to cause of death in 187 adult thyroids

Causes of death	Total	Lymphatic distension	Epithelial changes only	Both
First category	53	27 (51%)	10 (19%)	37 (70%)
Second "	28	12 (43%)	4 (14%)	16 (57%)
Third "	40	9 (22.5%)	7 (17.5%)	16 (40%)
Fourth "	66	14 (21%)	10 (15%)	24 (36%)

TABLE 21

Relation of lymphatic distension to cause of death in 63 adult thyroids

Causes of death	Total	Cases showing lymphatic distension
First category	22	11 (50%)
Second "	9	3 (33%)
Third "	7	6 (86%)
Fourth "	25	7 (28%)

TABLE 22

Same cases as in Table 21, showing increased detection of lymphatic distension when P.A.S. sections are examined

Causes of death	Total	Cases showing lymphatic distension
First category	22	16 (73%)
Second "	9	4 (44%)
Third "	7	6 (86%)
Fourth "	25	12 (48%)

TABLE 23

Relation of lymphatic distension to cause of death in 250 adult thyroids (combining the figures in Tables 20 and 21)

Causes of death	Total	Cases showing lymphatic distension	Outstanding cases only
First category	75	38 (51%)	6
Second "	37	15 (41%)	2
Third "	47	15 (32%)	2
Fourth "	91	21 (23%)	2

TABLE 24

Incidence of atypical epithelium in 254 adult autopsy specimens

	20-29		30-39		40-49		50-59		60-69		70-79		80 and over		Total		
	Total	Cases	Total	Cases	Total	Cases	Total	Cases	Total	Cases	Total	Cases	Total	Cases	Total	Cases	Percent
First series (191 cases)																	
Males	1	0	1	0	8	1	22	4	38	6	26	1	9	2	105	14	13.3
Females	3	0	4	0	11	1	11	0	21	5	20	3	16	1	86	10	11.6
Total	4	0	5	0	19	2	33	4	59	11	46	4	25	3	191	24	12.6
Second series (63 cases)																	
Males	2	0	3	0	5	1	8	3	14	6	9	2	2	2	43	14	32.6
Females	0	0	3	1	0	0	3	1	2	0	11	2	1	0	20	4	20.0
Total	2	0	6	1	5	1	11	4	16	6	20	4	3	2	63	18	28.6
Total of 254 cases																	
Males	3	0	4	0	13	2	30	7	52	12	35	3	11	4	148	28	18.9
Females	3	0	7	1	11	1	14	1	23	5	31	5	17	1	106	14	13.2
Total	6	0	11	1	24	3	44	8	75	17	66	8	28	5	254	42	16.5
Percentage	0		9.1		12.5		18.2		22.7		12.1		17.9			16.5	

TABLE 25

Incidence of atypical epithelium in 212 histologically normal thyroids

	20-29		30-39		40-49		50-59		60-69		70-79		80 and over		Total		
	Total	Cases	Total	Cases	Total	Cases	Total	Cases	Total	Cases	Total	Cases	Total	Cases	Total	Cases	Percent
First series (162 cases)																	
Males	1	0	1	0	7	1	19	3	35	6	25	1	9	2	97	13	13.4
Females	3	0	3	0	9	1	7	0	14	3	15	2	14	0	65	6	9.2
Total	4	0	4	0	16	2	26	3	49	9	40	3	23	2	162	19	11.7
Second series (50 cases)																	
Males	2	0	3	0	5	1	7	2	12	5	8	2	2	2	39	12	30.8
Females	0	0	2	1	0	0	0	0	2	0	6	0	1	0	11	1	9.1
Total	2	0	5	1	5	1	7	2	14	5	14	2	3	2	50	13	26.0
Total of 212 cases																	
Males	3	0	4	3	12	2	26	5	47	11	33	3	11	4	136	25	18.4
Females	3	0	5	1	9	1	7	0	16	3	21	2	15	0	76	7	9.2
Total	6	0	9	1	21	3	33	5	63	14	54	5	26	4	212	32	15.1
Percentage	0		11.1		14.3		15.1		22.2		9.3		15.4		15.1		

TABLE 26

Incidence of atypical epithelium in 42 histologically abnormal thyroids

	20-39		40-59		60-79		80 and over		Total		
	Total	Cases	Total	Cases	Total	Cases	Total	Cases	Total	Cases	Percent
Males	0	0	5	2	7	1	0	0	12	3	25
Females	2	0	9	1	17	5	2	1	30	7	23
Total	2	0	14	3	24	6	2	1	42	10	24

ANISOTROPIC CRYSTALS IN 254 THYROIDS: AGE AND SEX INCIDENCE

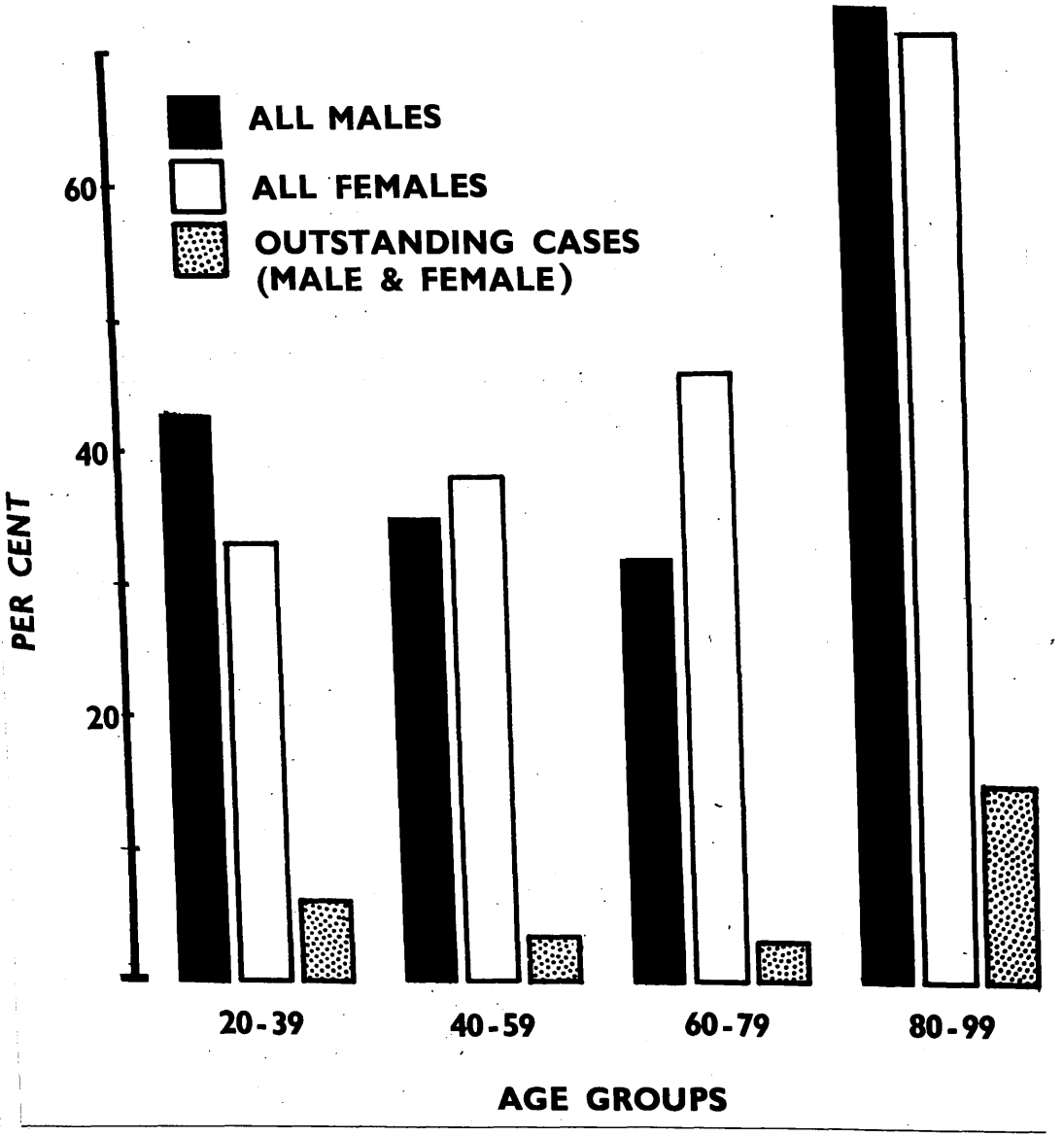


TABLE 27

The incidence of anisotropic crystals in 254 autopsy thyroid specimens

	Males			Females			Total		
	Total	Cases	Percent	Total	Cases	Percent	Total	Cases	Percent
First series (191 cases)									
	105	41	39	86	39	45	191	80	42
Second series (63 cases)									
	43	13	30	20	11	55	63	24	38
The two series combined (254 cases)									
Age Groups									
20 - 39	7	3	43	9	3	33	16	6	37.5
40 - 59	43	15	35	26	10	38	69	25	36
60 - 79	87	28	32	54	25	46	141	53	38
Over 80	11	8	73	17	12	71	28	20	71
Total	148	54	36.5	106	50	47	254	104	41
All cases up to age 69									
	102	36	35	58	24	41	160	60	37.5

TABLE 28

Cases in which anisotropic crystals were exceptionally prominent

	Males			Females			Total		
	Total	Cases	Percent	Total	Cases	Percent	Total	Cases	Percent
Age groups									
20 - 39	7	1		10	0		17	1	6
40 - 59	43	0		25	2		68	2	3
60 - 79	87	2		54	2		141	4	3
Over 80	11	0		17	4		28	4	14
Total	148	3	2	106	8	7.5	254	11	4

TABLE 29

Incidence of lymphocytic infiltration in 244 clinically normal thyroids at autopsy

Age	Males			Females			Total		
	Total	Cases	Percent	Total	Cases	Percent	Total	Cases	Percent
20 - 29	3	0	0	3	0	0	6	0	0
30 - 39	3	0	0	7	2	28.6	10	2	20.0
40 - 49	13	1	7.7	11	2	18.2	24	3	12.5
50 - 59	29	4	13.8	13	6	46.2	42	10	20.8
60 - 69	52	5	9.6	21	5	23.8	73	10	13.7
70 - 79	34	2	5.9	27	6	22.2	61	8	13.1
80 and over	11	0	0	17	2	11.8	28	2	7.1
	145	12	8.3	99	23	23.2	244	35	14.3

TABLE 30

Same cases as in Table 29, excluding the minor degrees of lymphocytic infiltration

Age	Males			Females			Total		
	Total	Cases	Percent	Total	Cases	Percent	Total	Cases	Percent
20 - 29	3	0	0	3	0	0	6	0	0
30 - 39	3	0	0	7	0	0	10	0	0
40 - 49	13	0	0	11	1	9.1	24	1	4.2
50 - 59	29	3	10.3	13	5	38.5	42	8	19.0
60 - 69	52	2	3.8	21	3	14.3	73	4	5.5
70 - 79	34	1	2.9	27	5	18.5	61	6	9.8
80 and over	11	0	0	17	2	11.8	28	2	7.1
	145	6	4.1	99	15	15.2	244	21	8.6

TABLE 31

The histological features of focal thyroiditis in 42 autopsy thyroid specimens

H: epithelial hyperplasia
A: signs of increased activity, without frank hyperplasia
m: no pseudogiant cells, but single intra-acinar macrophages.

			Degree of lymphocytic infiltration	Germinal centres	Plasma cells	Epithelial hyperplasia	Pseudo-giant cells	Oxyphilic epithelium	Fibrosis	Remarks
1	F	64	+±	−	+	A	−	+	+	
2	F	55	±	−	−	A	−	+	+	Nontoxic nodular goitre
3	M	71	±	−	−	A	−	−	−	
4	F	48	+	+	+	A	+	−	−	Addison's disease
5	M	58	+	−	−	Focal H	+	−	−	
6	F	67	+	−	+	A	−	+	+	
7	F	70	+	+	−	A	−	+	−	
8	M	54	+	−	−	A	+	−	−	
9	F	65	+±	−	+	A	−	+	+	
10	F	47	+±	−	−	A	−	+	−	
11	M	68	+	−	+	A	−	+	+	
12	M	63	+±	+	−	A	+	−	+	
13	F	75	+±	−	−	Diffuse H	+	+	−	Diffuse toxic goitre
14	F	76	+±	−	−	−	−	−	−	

TABLE 31 (Continued)

15	M	47	±	–	–	–	–	+	–	
16	F	80	++	+	+	–	+	+	+	Myxoedema? (not confirmed)
17	F	53	+	+	–	A	–	–	+	
18	F	65	+	–	+	Partly A, partly H.	–	+	+	Thyroidectomy
19	F	35	±	–	–	A	+	–	+	
20	F	61	±	–	–	A	+	+	+	
21	F	67	±	–	–	–	–	–	–	
22	F	78	+	+	+	A	+	+	+	
23	F	54	±	+	+	A	–	–	–	
24	F	53	+	+	+	H	+	+	+	
25	F	69	+	–	+	H	–	–	+	Thyroidectomy
26	F	78	++	–	+	–	–	+	+	Myxoedema
27	M	60	±	–	–	A	–	–	–	
28	M	57	+	–	–	Focal H	–	–	+	
29	F	81	+	–	+	Focal H	+	+	+	
30	M	62	+	–	+	Focal H	m	–	–	
31	F	71	++	+	+	A	–	+	+	
32	M	54	+	–	+	A	–	–	+	
33	F	35	±	–	–	Focal H	–	–	+	
34	M	79	+	–	+	A	–	+	+	
35	F	59	+	+	+	Focal H	–	+	+	
36	F	75	++	–	+	–	–	+	+	Myxoedema
37	F	72	++	+	–	A	m	+	+	
38	F	79	+	–	+	Focal A	+	+	+	Thyroidectomy
39	F	70	++	+	+	–	–	–	–	
40	F	50	+	+	+	A	–	–	–	
41	F	59	+	+	+	A	–	+	–	secondary carcinoma
42	M	64	±	–	+	H	–	–	+	

TABLE 32

Lymphocytic infiltration in 10 clinically abnormal thyroids at autopsy

	Sex	Age	Degree of lymphocytic infiltration	Diagnosis
1.	M	74	-	Non-toxic nodular goitre
2.	F	55	±	Non-toxic nodular goitre
3.	F	75	±	Toxic diffuse goitre
4.	F	65	+	Old thyroidectomy
5.	F	69	+	Old thyroidectomy
6.	F	78	++	Myxoedema
7.	F	75	++	Myxoedema
8.	F	79	+	Old thyroidectomy
9.	M	33	-	Acromegaly. Non-toxic nodular goitre
10.	M	55	-	Old thyroidectomy (Graves' disease)

TABLE 33A

Cases in which there was more than one surgical operation on the thyroid

Case No.	Sex	Age at first op.	First operation Date	First operation Diagnosis, histology	Second operation Date	Second operation Diagnosis, histology
1	F	19	1941	Non-toxic nodular goitre Sections not available.	1951	Nodular goitre, ? toxic. Focal hyperplasia, involution, lymphocytic infiltration, fibrosis.
2	F	34	1941	Exophthalmic goitre. Diffuse epithelial hyperplasia. Scanty lymphocytic foci.	1956	Chronic thyroiditis. Diffuse plasma-cell and lymphocytic infiltration, focal epithelial hyperplasia (see text).
3	F	17	1954	Non-toxic nodular goitre. No lymphocytic infiltration.	1957	Recurrence of nodule. No lymphocytic infiltration.
4	F	20	1937	Exophthalmic goitre. Not examined histologically.	1957	Chronic thyroiditis. Diffuse plasma-cell and lymphocytic infiltration, focal epithelial hyperplasia (see text)
5	F	39	1950	Non-toxic nodular goitre. No lymphocytic infiltration.	1958	Non-toxic nodular goitre. No lymphocytic infiltration.
6	F	35	1939	Non-toxic nodular goitre. Not examined histologically.	1942 1958	Non-toxic nodular goitre. Non-toxic nodular goitre. No lymphocytic infiltration in either specimen.

TABLE 33B

Autopsy cases with a previous history of thyroidectomy

Case No.	Sex	Age	Cause of death	Thyroidectomy	Thyroid at autopsy	Histology
7	F	69	Myocardial infarction	18 years previously. Diagnosis not known.	Average size. Cut surface pale; nodules of up to 5 mm. diameter.	"Cirrhosis". Focal epithelial hyperplasia. Many lymphocytic foci, no lymphoid follicles; a few plasma cells. No oxyphilia.
8	F	65	Myocardial infarction. Bronchopneumonia.	No information.	Small focus of thyroid tissue, L. side only.	Small nodules embedded in fibrous tissue: some normal, some hyperplastic, a few oxyphilic. Scattered lymphocytic foci; no lymphoid follicles.
9	F	79	Hypertension. Coronary occlusion.	No information.	Enlarged (68 g.): a single mass on R. side. Composed of small nodules, some calcified.	Involutional and degenerative nodules. Scattered small lymphocytic foci, especially in capsules of nodules. Oxyphilia. No hyperplasia.
10	M	55	Malignant hypertension.	10 years previously. Graves' disease.	2 separate lobes, no isthmus. R. 13 g. L. 3 g.	Normal, apart from a single small colloid nodule.

APPENDIX 1

The thyroid in 106 newborn infants

In Maturity column:
M: Mature (over 5 lb. birth-weight)
P: Premature (between 3 and 5 lb.)
v.P: Very premature (under 3 lb.)

In Remarks column:
P: Pre-eclampsia
L: Difficult or prolonged labour
C: Caesarian section
A: Asphyxia

Case No.	Sex	Age	Maturity	Death fixation interval (hours)	Histological classification	Lymphatic Distension: Outside Capsule	Lymphatic Distension: Within Gland	Congestion	Remarks
1	M	2 days 8hrs.	M	14	C	-	-	+++	A
2	M	1 day	P	27	B	+	-	+	A
3	M	25 hrs.	v.P.	24	C	-	-	+	-
4	F	5 days	P	22½	A	±	-	+	C
5	F	3 hrs.	P	23	C	-	-	-	-
6	F	6½ hrs.	M	44	C	+	-	+	-
7	M	3 days	M	14	C	-	-	++	P L A
8	F	5 days	M	7	AC	+	±	++	A
9	M	15 mins.	M	42	C	±	-	+++	-
10	M	27½ hrs.	P	18	C	+	-	+	L A
11	M	SB	M	18 + ¾*	AC	±	+	++	L A
12	F	1 day	M	24¼	B	-	-	++	-
13	M	5 days	P	27	AC	-	-	++	P
14	M	2½ days	M	12½	A	-	+	++	L A
15	M	1 day	P	19½	B	-	±	++	A
16	F	7 days	M	18	A	-	±	+	-
17	F	25 mins.	M	13	B	+	-	+++	L A
18	F	2 days	v.P	12	BC	±	-	+	A
19	F	SB	M	14+30*	C	-	±	+++	A
20	F	SB	M	14+0 *	A	-	++	++	A
21	M	18½ hrs.	P	3	B	-	+	++	A
22	F	18¾ hrs.	v.P	5	C	-	±	++	A
23	M	3 days	P	6	AC	-	-	+	P A

APPENDIX 1 (Continued)

24	M	1¾ hrs.	P	35	BC	–	–	+	C A
25	F	10¼ hrs.	M	25	A	++	+	++	A
26	F	3¾ hrs.	v.P.	22	AC	±	–	+	–
27	M	SB	M	9 + 0*	A	±	±	++	L A
28	M	11 hrs.	P	26	BC	–	+	++	A
29	F	44 hrs.	M	14	C	+	–	++	L A
30	M	SB	M	14 + 0*	AC	±	–	++	–
31	M	4 days	P	8	AC	–	±	+	P A
32	M	5 days	M	26½	AB	–	–	++	P A
33	F	SB	M	5½ + ½*	A	±	–	++	A
34	F	SB	M	20½ + 0*	AB	±	+	++	L A
35	F	3 hrs.	P	28½	B	–	++	++	A
36	F	SB	M	14½ + 0*	BC	–	++	+	L
37	M	SB	M	14½ + 0*	AC	±	+	++	L A
38	F	2 days	borderline	4½	AB	–	–	+	A
39	F	SB	M	20 + 3½*	B	–	±	++	P A
40	M	SB	M	11 + 0 *	B	–	±	++	A
41	M	39 hrs.	M	3¼	A	–	–	++	L A
42	M	33 hrs.	M	24	BC	–	–	±	A
43	M	20½ hrs.	v.P.	15½	C	–	–	+	C A
44	M	33 hrs.	M	7½	C	–	–	+	–
45	M	SB	M	17 + ¼ *	C	–	++	+++	L C A
46	M	7½ hrs.	M	31	C	±	±	–	C
47	M	4 days	M	23	C	±	–	+	A
48	M	16 hrs.	P	9	B	–	±	++	A
49	M	14 hrs.	M	3½	AC	–	–	++	L A
50	M	11½ hrs.	M	33½	C	–	–	+	L
51	F	SB	M	28 + 0 *	C	±	+	++	A
52	M	11 hrs.	P	3½	B	–	±	++	A
53	M	8½ hrs.	M	20½	C	–	±	+++	L A
54	M	16 hrs.	P	21	ABC	±	+	++	A

APPENDIX 1 (Continued)

55	F	35 mins.	P	18	C	-	-	++	L
56	M	SB	M	13 + 0 *	C	±	-	++	P L C A
57	F	SB	M	28 + 0 *	A	±	±	++	P
58	F	SB	P	17 + ?0 *	BC	-	-	+	L A
59	F	31 hrs.	P	29	BC	-	-	±	P A
60	M	SB	M	8 + 0 *	BC	±	±	++	L
61	M	SB	v.P.	40 + 0 *	A	-	-	+	P A
62	M	17½ hrs.	M	22	A	-	±	++	L A
63	M	1 day	P	45½	AC	-	-	±	L A
64	M	27½ hrs.	P	12	C	-	-	++	A
65	M	SB or 1 min.	M	33 + 0 *	AC	-	+	++	L A
66	M	31½ hrs.	v.P	9	BC	-	-	+	A
67	F	31½ hrs.	P	25½	B	-	+	+	P A
68	M	14 hrs.	P	6½	B	±	++	+	A
69	F	2 days	v.P	25½	C	-	-	+	-
70	M	2 days 8 hrs.	v.P	38½	A	-	-	+	A
71	F	5 days	v.P	23½	A	-	-	+	L A
72	M	13 hrs.	v.P	7½	A	-	-	+	P C A
73	M	22 hrs.	P	8	BC	-	-	+++	A
74	M	Twins 1¼ hrs.	v.P	43½	C	-	-	+	C A
75	F	7¼ hrs.	v.P	37½	C	-	-	+	C A
76	M	3 days	M	19½	C	+	-	+++	A
77	M	9 hrs.	P	19½	C	±	+	+	C
78	M	2 days	P	10	AC	±	-	+	L A
79	F	2 days 8 hrs.	M	13	A	-	±	++	L A
80	M	22 hrs.	P	11½	C	±	-	+	A
81	M	13½ hrs.	M	24	AC	±	+	+++	A
82	F	SB	M	21 + 0 *	A	+	+	++	L A
83	F	a few mins.	P	14½	A	-	-	++	L A
84	M	23½ hrs.	P	12	AC	-	+	+	A
85	M	4 days 6 hrs.	v.P	9	A	-	-	+	-
86	M	2 days 16 hrs.	v.P	10	AC	-	-	+++	-

APPENDIX 1 (Continued)

87	F	3½ days	M	32	A	-	±	+	L A
88	F	1 day	borderline	21	ABC	-	±	+	A
89	M	15 hrs.	v.P	43	A	-	-	+	A
90	F	2½ days	M	9½	A	-	-	+	-
91	F	41½ hrs.	P	6½	AC	-	++	+	A
92	M	6 days	P	23	AB	-	-	+	A
93	M	5½ hrs.	v.P	7	A	-	-	+	-
94	F	SB	M	8¾ + 0 *	C	-	++	++	-
95	F	35 mins.	M	13	C	-	-	++	L C
96	F	18¾ hrs.	M	15½	BC	-	-	-	-
97	M	12 hrs.	borderline	36	C	-	-	+	L C
98	M	7 days	M	28	B	-	-	+	-
99	M	11¼ hrs.	v.P	8	A	-	-	++	L A
100	F	3 mins.	M	36	C	-	-	+	-
101	M	3½ hrs.	M	33	AC	-	-	-	-
102	M	2 days	P	30	C	-	-	+	A
103	M	SB	M	7+2 or 3 *	AC	-	-	+	-
104	F	10 hrs.	P	23	A	-	-	++	A
105	M	2 days 15 hrs.	P	12	AC	-	-	++	A
106	F	2 hrs.	v.P	24	C	±	-	++	-

* In the case of stillbirths, the second figure refers to the estimated interval between intra-uterine death and delivery.

APPENDIX 2

Foetal and Neonatal Guinea Pigs

No.	Age	Sex	Weight (g)	Spontaneous death (S) or killed (K)	Ante-natal treatment	Post-natal treatment	Fixation: Death-fixation interval (or birth-fixation interval if animal was stillborn) in hours.
1A	stillborn	F	110	S	-	-	6
B	6 hrs.	F	107	K	-	-	Immediate
C	6 hrs.	F		K	-	-	70
2A	stillborn	M	100	S	-	-	5 - 18
B	5 - 18 hrs	F	104	K	-	-	Immediate
C	5- 18 hrs	F	108	K	-	-	100½
3A	29 hrs.	M		K	-	TSH 20 hrs. before death	Immediate
B	29 hrs.	F		K	-	TSH 20 hrs. before death	52½
C	29 hrs.	F		K	-	-	Immediate
D	stillborn	M		S	-	-	29
4A	30 hrs.	M		K	-	TSH 28 hrs. before death	Immediate
B	30 hrs.	M	100	K	-	TSH 28 hrs. before death	120½
C	30 hrs.	F		K	-	-	Immediate
5A	36 hrs.	F	86	K	-	TSH 25 hrs. before death	Immediate
B	36 hrs.	F	86	K	-	TSH 25 hrs. before death	117
C	36 hrs.	F	80	K	-	-	Immediate
D	36 hrs.	M	81	K	-	-	117

APPENDIX 2 (Continued)

6A	intra-		30	S		-	Foetal tissues fixed
B	uterine		35	S		-	within 2 hrs. of
C	death		39	S	0.1% thiouracil, 21 days	-	maternal death.
D	(spontaneous		24	S		-	6D, E, F were
E	death of		22	S		-	macerated.
F	mother)		22	S		-	
7A			19	S	-	-	Foetal tissues fixed within 12 hours of maternal death.
B	ditto.		21	S	-	-	
C			20	S	-	-	
D			19	S	-	-	
8A	4 hrs.	M	105	K	0.1% thiouracil, 29 days	-	Immediate
B	4 hrs.	F	80	K		-	Immediate
C	3 days	F	90	K		Thiouracil continued. TSH 72 hrs. before death (8C only)	Immediate
D	3 days	M	85	K			Immediate
9A	a few hrs.	M	111	S	0.1% pot. perchlorate, 19 days	-	A few hours
10A	stillborn	M	87	S	-	-	A few hours
B	stillborn	M	110	S	-	-	120 - 125
C	12 hrs.	F	87	K	-	-	120
D	12 hrs.	M	69	K	-	-	Immediate
E	5 days			S	-	-	About 12
11A	12-28 hrs.	F	102	K	-	-	Immediate
B	12-28 hrs.	M	114	K	-	-	116
12A	4 hrs.	F	91	K	-	-	Immediate
B	4 hrs.	M	91	K	-	-	96
13A	stillborn	M	92	S	-	-	Less than 1 hour
B	$1\frac{1}{2}$ hrs.	F	48	K	-	-	Immediate
C	$1\frac{1}{2}$ hrs.	M	80	K	-	-	Immediate
D	$2\frac{1}{2}$ days	F	90	K	-	-	Immediate

14A	a few hours	F	91	K	0.1% pot. perchlorate, 32 days	-	Immediate
B	a few hours	M	111	K		-	"
C	14 days	F	158	K		Suckled by untreated mother	"
D	14 days			K		Pot. perchlorate continued	"
15A	a few hours	F	73	K	0.05% thiouracil, 2 days	-	"
B	14 days	F	138	K		thiouracil continued.	"
16A	16 days	F	198	K	-	Suckled from 2 days by sow receiving 0.1% pot.perchlorate	"
C	16 days	F	189	K	-	-	"
17A	a few hours	F	92	K	0.1% pot. perchlorate, 34 days	-	"
B	a few hours	F	82	K		-	"
C	12 days	M	182	K		pot.perchlorate continued.	"
D	12 days	F	127	K		Suckled by untreated mother	"
18A	7 days	M	108	K	0.1% pot. perchlorate, 10 days	pot.perchlorate continued	"
B	14 days	M	145	K			"
19A	2 days	M	97	K	0.1% pot. perchlorate, 17 days	pot. perchlorate continued	"
B	5 days	F	136	K			"
C	9 days	F	185	K			"
20A	½ hr.	M	74	K	0.05% thiouracil, 29 days	-	"
B	6 hrs.	M	72	K			"
C	49 hrs.	F	80	K		thiouracil continued	"
D	7 days	M	120	K			"

21A	intra-uterine death	M	117	S	0.05% thiouracil, 29 days	-	No delay in fixation after removal from uterus.
B	(spontaneous		117	S		-	6 hrs. more than 21A
C	death of mother)		105	S		-	25 hrs. more than 21A
22A	½ hr.	M	103	K	-	-	Immediate
B	19 hrs.	M	99	K	-	-	"
24A	stillborn	M	104	S	-	-	Less than 2
B	stillborn	M	102	S	-	-	
C	stillborn	M	113	S	-	-	
25A	stillborn	M	56	S	0.005% thiouracil, 29 days	- thiouracil continued	3
B	2½-3 hrs.	M	65	K			Immediate
C	16 days		110	S			8 - 20
26A	12 hrs.	M	99	K	0.005% pot. perchlorate, 32 days	-	Immediate
B	12 hrs.	M	104	K		-	29½
C	12 hrs.	F	98	K		-	52
27A	stillborn	F	40	S	0.005% thiouracil, 35 days	-	
B	stillborn	F	39	S		-	10 - 17
C	stillborn	M	40	S		-	
D	stillborn	M	40	S		-	Additional delay of 6 hrs.
28A	About 12 hrs.	M	75	K	0.005% thiouracil, 36 days	-	Immediate
B	About 12 hrs.	F	93	K		-	"
C	About 12 hrs.		72	K		-	93
30A	27-47 hrs.	M	102	K	0.005% pot. perchlorate, 36 days	pot.perchlorate continued	Immediate
B	27-47 hrs.	F	116	K			"
31A	4 hrs.	M	66	K	0.005% pot.perchlorate, 38 days	-	"
B	4 hrs.	F	68	K		-	72
C	4 hrs.	F	57	K		-	97
32A	stillborn	F	36	S	-	-	8 - 20
B	stillborn	M	75	S	-	-	
C	stillborn	F	47	S	-	-	Additional delay of 49

32D	stillborn	M	69	S	-	-	Additional delay of 73
33A	8-22 hrs.	M	73	K	0.0005% carbimazole,	-	Immediate
B	8-22 hrs.	F	67	K	26 days	-	"
34A	1½ hrs.		105	K	0.005% carbimazole,	-	"
B	1½ hrs.		100	K	28 days	-	"
35A	stillborn	F	105	S	-	-	
B	28½ hrs.	F	95	K	-	TSH 23½ hrs. before death	"
C	49 hrs.		77	K	-	TSH 44 hrs. before death	"
36A	About 10 hrs.	M	103	K	0.0005% carbimazole,	-	"
B	17 days	M	130	S	29 days	Suckled from 2 days by untreated sow.	24 - 36
37A	Less than ½ hr.	F	100	K	0.005% carbimazole, 34 days	-	Immediate
38A	stillborn	M	86	S	0.005%	-	1
B	1 hr.	M	66	K	carbimazole,	-	Immediate
C	13 days	M	186	K	21 days	Suckled from 1 day by untreated sow.	"
39A	12 days	F	139	K	-	Suckled from birth by sow receiving 0.005% carbimazole	"
B	2 days	F	95	K	-	TSH 45 hrs. before death	"
C	4½ days	M	111	K	-	TSH 96 hrs. before death	"

40A	intra-uterine	M	99	S	Carbimazole: 0.0005% for 22 days, increased to 0.05% for further 12 days	-		
B	death (spontaneous	M	88	S		-		Foetal tissues fixed within 12 hrs. of maternal death
C	maternal	F	83	S		-		
D	death)	M	94	S		-		
41A	8 hrs.	F	93	K	No treatment during pregnancy. 0.1% pot. perchlorate for 5 weeks, ceasing 12 weeks before delivery.	-		Immediate
B	8 hrs.	M	85	K		-		"
C	8 hrs.	M	74	K		-		"
42A	Less than $\frac{1}{2}$ hr.	F	85	S	-	-		
B	less than $\frac{1}{2}$ hr.	M	100	S	-	-		12 - 18
43A	$2\frac{1}{2}$ days	M	95	K	-	-		Immediate
B	$2\frac{1}{2}$ days	M	75	K	-	TSH 46 hrs. before death		"
C	$2\frac{1}{2}$ days	F	94	K	-	-		$72\frac{1}{2}$
D	$2\frac{1}{2}$ days	M	75	K	-	TSH 46 hrs. before death		$72\frac{1}{2}$
45A	stillborn	F	81	S	-	-		About 12
46A	?stillborn		53	S	-	-		6 - 18
47A	stillborn	F	38	S	-	-		1
B	stillborn	M	45	S	-	-		22
C	stillborn	F	42	S	-	-		22
48A	3 days	F	61	S	-	-		6 - 21
49B	$4\frac{1}{2}$ days	M	80	K	-	-		66
C	$4\frac{1}{2}$ days	F	66	K	-	TSH 96 hrs. before death		66

50A	spontaneous	M	65	S	-	-	About 34
B	death at	M	71	S	-	TSH 24-36 hrs. before death	About 34
C	between 32 and 48 hrs.	M	75	S	-	TSH 24-36 hrs. before death	About 10
D		F	64	S	-	-	About 10
51A	intra-uterine	M	97	S	-	-	
B	death (spontaneous	M		S	-	-	Foetal tissues fixed within 6 hrs.
C	death of mother)	M	87	S	-	-	of maternal death.
52A	intra-uterine		35	S	-	-	
B	death (spontaneous		39	S	-	-	Foetal tissues fixed within 1 hr.
C	death of mother)		52	S	-	-	of maternal death.
53C	2-4 days	M	74	S	-	TSH at age of 28 hrs.	less than 48
D	4 days	F	82	K	-	TSH 71 hrs. before death.	48½
E	4 days	F	89	K	-	-	48½

This Appendix omits animals whose identity was in doubt (because of obliteration of distinguishing marks), and those in which insufficient thyroid tissue appeared in the sections of trachea.

APPENDIX 3

The 28 infants and children referred to in Section 4

	Sex, age and diagnosis	Death-fixation interval (hrs.)	Histology of thyroid
1.	F 9 days Very premature.	13	Central zone: desquamation, colloid absent. Peripheral zone: well-preserved well-filled acini, cuboidal or low columnar epithelium.
2.	F 10 days Premature, congenital heart disease, subarachnoid haemorrhage.	21½	Poorly-preserved acini throughout: basal vacuolation, detachment of epithelium, disorganisation of acini. Very little colloid.
3.	M 10 days Congenital heart disease, bronchopneumonia.	26½	Desquamation, disorganisation, no colloid. Thin peripheral zone of well-filled acini; cuboidal or low columnar epithelium.
4.	F 11 days Bronchopneumonia.	17	Small empty acini, disorganisation, and compact tissue. Very thin peripheral zone of normal well-filled acini; cuboidal or low columnar epithelium.
5.	M 11 days Congenital abnormalities, extensive bronchopneumonia.	29	Normal well-filled acini throughout; low columnar epithelium.
6.	M 11 days Gastroenteritis.	25	Normal well-filled acini throughout; cuboidal or columnar epithelium.
7.	F 12 days Aspiration of feed.	8	Desquamation, disorganisation and compact tissue; no colloid. A few normal acini at periphery; columnar epithelium.

APPENDIX 3 (Continued)

8.	M 17 days Bronchopneumonia.	24	Central zone: desquamation, disorganisation, no colloid. Peripheral zone: normal poorly-filled acini; cuboidal or low columnar epithelium.
9.	M 21 days Died 5 days after operation for duodenal atresia.	10	Normal acini throughout, with many interacinar cells; low columnar epithelium. Variable colloid content.
10.	M 25 days Very premature, bronchopneumonia.	12	Normal acini throughout, low columnar epithelium. Colloid present only at periphery.
11.	F 4 weeks Acute enteritis.	30½	Almost all of compact structure, no colloid. Acinar structure recognisable at periphery.
12.	F 4½ weeks Congenital abnormalities, hydrocephalus, purulent meningitis.	36½	Detachment of epithelium or disorganisation of acini, no colloid. A few colloid-containing acini at periphery.
13.	M 5 weeks Premature, gastro-enteritis.	24½	Central zone: desquamation, no colloid. Peripheral zone: normal acini, some containing colloid; cuboidal or low columnar epithelium.
14.	M 5 weeks Acute enteritis, bronchopneumonia.	22	Desquamation, disorganisation, no colloid. A few poorly-filled acini at periphery; low columnar epithelium.
15.	M 6 weeks Miliary tuberculosis, involving thyroid.	4½	Small acini throughout, larger and better-filled at periphery; cuboidal or low columnar epithelium.
16.	F 6 weeks Bronchopneumonia.	27	Normal acini throughout, pale-staining colloid; cuboidal or low columnar epithelium.

APPENDIX 3 (Continued)

17.	M 8 weeks Fibrocystic disease of pancreas, bronchopneumonia.	12½	Normal well-filled acini, cuboidal epithelium, but some desquamation in central zone.
18.	M 4 months Congenital tuberculosis.	39	Detachment of epithelium or disorganisation of acini throughout, no colloid. Columnar epithelium. No tubercles in thyroid.
19.	M 4 months Gastroenteritis.	15	Normal acini throughout, low columnar epithelium. Acini slightly larger at periphery, all well filled.
20.	M 20 weeks Fibrocystic disease of pancreas, bronchiectasis.	6	Well-filled acini, cuboidal epithelium. Deeper staining of colloid in peripheral acini. A few collapsed acini in central zone.
21.	F 5 months Fibrocystic disease of pancreas, bronchiectasis.	6	Well-filled acini, cuboidal epithelium. A small area of desquamation in centre.
22.	M 6 months Fibrocystic disease of pancreas, bronchopneumonia, aspiration.	25	Well-preserved colloid-containing acini only in thin peripheral zone. Basal vacuolation or detachment of epithelium in all remainder.
23.	M 6 months Tetany, bronchopneumonia, enteritis.	19	Well-preserved colloid-containing acini throughout; columnar epithelium, less often cuboidal. Several intra-acinar haemorrhages, without desquamation.

APPENDIX 3 (Continued)

24.	M 2¼ years Bronchopneumonia.	16	Colloid content poor. Acini irregular, epithelium cuboidal or low columnar; basal vacuolation in central zone only; no desquamation; numerous interacinar cells. Prominent lymphatic distension in central zone.
25.	F 5 years Congenital heart disease, post-operative death while still under anaesthesia and hypothermia.	27	Colloid content good. Acini rather irregular, epithelium cuboidal; no interacinar cells. Desquamated cells in colloid, but no abnormality of lining cells.
26.	M 7 years Congenital heart disease, operative death, during anaesthesia and hypothermia.	22½	Colloid content poor. Acini irregular, epithelium cuboidal or columnar; desquamated cells in empty lumina. Prominent lymphatic distension.
27.	F 8 years Acute rheumatism.	9	Colloid content very poor. Acini poorly preserved, except at periphery; extensive desquamation, lining and desquamated cells often indistinguishable. Prominent lymphatic distension.
28.	M 10 years Instantaneous death from multiple injuries.	20	Well-filled well-preserved acini, throughout; cuboidal epithelium. Staining of colloid slightly deeper at periphery. No desquamation. No lymphatic distension.

APPENDIX 4

Cases of atypical or squamous epithelium in the thyroid

HN: thyroid histologically normal.
CN: thyroid clinically normal but histologically abnormal.

Newborn infants

1.	M	7½ hours	
2.	M	25½ hours	
3.	M	14 hours	
4.	F	2½ days	Ciliated epithelium.
5.	F	Stillborn	

Children

6.	M	7 years	Bilateral (in centre of both lateral lobes)
7.	M	10 years	Thymus tissue included in the same lobe.

24 cases from a total of 191 adult autopsy specimens

8.	F	78	Myxoedema.	Numerous squamous nests in all sections.
9.	F	69	CN.	Focal thyroiditis.
10.	F	62	HN	
11.	F	67	CN.	Focal thyroiditis.
12.	M	60	CN.	Scanty small lymphocytic foci.
13.	F	67	HN.	Multiple nests of atypical epithelium.
14.	F	43	HN	
15.	M	58	HN	
16.	M	65	HN	
17.	M	63	HN,	but atypical epithelium accompanied by lymphocytic infiltration.
18.	F	77	HN	
19.	M	55	HN	
20.	F	77	HN	
21.	M	63	HN	
22.	M	82	HN.	Bilateral foci.
23.	M	52	HN	
24.	M	60	HN	
25.	M	57	CN.	Focal thyroiditis.
26.	M	41	HN,	but atypical epithelium accompanied by lymphocytic infiltration.

APPENDIX 4 (Continued)

27.	M	83	HN	
28.	F	81	CN.	Focal thyroiditis.
29.	M	75	HN	
30.	M	60	HN	
31.	F	66	HN	

18 cases from a total of 63 adult autopsy specimens

32.	M	62	CN.	Focal thyroiditis.
33.	M	62	HN	
34.	F	71	CN.	Focal thyroiditis.
35.	M	54	CN.	Focal thyroiditis.
36.	M	90	HN	
37.	M	69	HN,	but atypical epithelium accompanied by lymphocytic infiltration.
38.	F	59	CN.	Focal thyroiditis.
39.	M	78	HN	
40.	F	75	Myxoedema.	
41.	M	75	HN	
42.	M	80	HN	
43.	M	65	HN	
44.	M	62	HN	
45.	M	58	HN	
46.	M	62	HN,	but atypical epithelium accompanied by lymphocytic infiltration.
47.	M	55	HN.	Thyroidectomy 10 years previously.
48.	M	40	HN	
49.	F	38	CN.	Adenoma, unrelated to atypical epithelium.

Additional autopsy cases

50.	M	75	Histologically, chronic thyroiditis. Clinically, myxoedema coma. Squamous islets within fibrotic area.
51.	F	64	Myxoedema.
52.	F	63	Toxic diffuse goitre, with focal thyroiditis.
53.	F	75	CN, but histological picture of myxoedema.

Surgical cases

54.	F	40	Thyrotoxicosis: diffuse epithelial hyperplasia, focal thyroiditis.
55.	F	67	Toxic nodular goitre.

APPENDIX 4 (Continued)

56.	F	40	Chronic thyroiditis. Previous thyroidectomy for Graves' disease.
57.	F	46	"Adenomatous" nodule. Atypical epithelium in fibrotic area.
58.	F	29	Mildly toxic nodular goitre. Previous operation 10 years earlier. Atypical epithelium in fibrotic area.
59.	F	36	Struma lymphomatosa.
60.	F	35	Chronic thyroiditis.
61.	F	59	Struma reticulosa.
62.	F	50	Chronic thyroiditis.
63.	F	37	Mild thyrotoxicosis. Diffuse epithelial hyperplasia; atypical epithelium in an area of lymphocytic infiltration.
64.	F	50	"Toxic nodule" - epithelial hyperplasia, focal thyroiditis.
65.	M	69	Retrosternal goitre - involutional and degenerative nodules. Squamous epithelium in fibrous capsule of a nodule.

APPENDIX 5

Ten cases of primary myxoedema and one case of thyroid atrophy following hypophysectomy

Case 1. Female, 66 years.

Admitted with total loss of memory. Was said by relatives to have been slow in speech, movements and gait for 6 years. Pale; coarse skin, scanty hair. Pulse rate 48/min. (ECG: sinus bradycardia). Serum cholesterol 327 mg. %. Untreated; died 6 days after admission.
Macroscopic: Thyroid small, cut surface fibrous.
Microscopic: "Cirrhotic" gland, divided into islets of varying size by bands of fibrous tissue. Epithelium entirely oxyphilic, mostly forming small colloid-containing acini, but occurring also as small solid clumps. Scanty pseudogiant cells. Diffuse infiltration by lymphocytes and plasma cells in about equal numbers. No lymphoid follicles. General picture: chronic thyroiditis.

Case 2. Male, 75.

Myxoedema well controlled for 3 years by 1 gr. of thyroid extract daily. Found semi-conscious 2 days before admission, died in myxoedema coma.
Macroscopic: Thyroid symmetrical, of normal size. Cut surface fibrous.
Microscopic: "Cirrhotic" gland, divided by fibrous bands into parenchymatous islets ranging from 1 mm. to 2 cms. in diameter. Epithelium nearly all oxyphilic, forming small ragged acini or solid clumps; colloid in only a very few acini. Many foci of atypical and squamous epithelium. Numerous pseudogiant cells. Entire parenchyma heavily and diffusely infiltrated by lymphocytes and plasma cells, the former rather more numerous. No lymphoid follicles. General picture: chronic thyroiditis.

Case 3. Female, 78.

Known myxoedema for at least 7 years before death; daily dose of thyroid extract varied from ½ to 2 gr.

APPENDIX 5 (Continued)

Megaloblastic anaemia, which responded to thyroid therapy alone, Hb rising from 8.5 g.% to 12.3 g.% within 7 months.
Cause of death: cerebral thrombosis.
Macroscopic: Thyroid site occupied by dense fibrous tissue.
Microscopic: Small widely-separated parenchymatous islets scattered throughout dense fibrous tissue. Epithelium partly oxyphilic, partly metaplastic, showing all variations including true squamous epithelium. Both types of epithelium either as solid clumps or as small acini, mostly empty. No pseudogiant cells. Parenchymal islets infiltrated by lymphocytes, as well as a very few plasma cells. No lymphoid follicles.

Case 4. Female, 76.

Known case of myxoedema; said to have been taking thyroid tablets, but dosage appeared to have been insufficient.
Cause of death: Essential hypertension, cerebral haemorrhage.
Macroscopic: Thyroid small, uniformly greyish-white. Weight 9 g. (not greatly diminished, as body weight was only 33 Kg.).
Microscopic: Dense sclerosis, with small widely-separated parenchymatous islets. Epithelium mostly metaplastic, with occasional stratification, but not frankly squamous. Also a few oxyphilic foci, and a few small ragged acini lined by neutrophilic epithelium. Very little colloid. No pseudogiant cells.
Parenchymatous islets infiltrated by lymphocytes and a very few plasma cells. No lymphoid follicles. Little infiltration in the few comparatively normal islets, dense infiltration in the others.

Case 5. Female, 75.

Clinical appearance of myxoedema, though this had not been diagnosed before admission. Serum cholesterol varied from 210 to 350 mg.%. 1 gr. thyroid extract daily for 10 days before death.

APPENDIX 5 (Continued)

Cause of death: Carotico-vertebral stenosis, cerebral infarction.
Macroscopic: Thyroid normal or slightly reduced in size; both lobes firm and fibrous on section, showing many small pale grey foci, coalescing in the central zone of each lobe.
Microscopic: "Cirrhotic" gland, divided by broad fibrous bands. Epithelium mostly oxyphilic, forming small ragged acini; very little colloid. No pseudogiant cells.
Extensive lymphocytic infiltration, with a very few plasma cells. No lymphoid follicles.

Case 6. Female, 56.

Thyroid deficiency diagnosed 9 years before death; treated with 2 gr. thyroid extract daily. Medication discontinued 5 years later as diagnosis was not considered to have been established. Appeared mildly myxoedematous on final admission.
Cause of death: Cardiac failure, following exploratory operation (patent ductus arteriosus).
Macroscopic: Thyroid slightly smaller than normal.
Microscopic: Gland intersected by narrow fibrous bands, with a few areas of more diffuse fibrosis. Parenchyma mostly composed of small or medium-sized acini, lined by cuboidal or occasionally columnar epithelium. Very little colloid. Several small foci of oxyphilic cells, both acinar and solid. Scattered foci of round-cell infiltration (lymphocytes more numerous than plasma cells) but greater part of parenchyma not infiltrated. A few lymphoid follicles, with ill-defined germinal centres.

Case 7. Female, 85.

Admitted in semi-coma, with obvious myxoedema. Treated with tri-iodothyronine. Died 7 days later. No record of myxoedema having been diagnosed previously.
Cause of death: Myxoedema coma.
Macroscopic: Not much reduced in size (14 g.), but of fibrous appearance.
Microscopic: "Cirrhotic" gland; about one-third of parenchyma replaced by fibrous tissue.
Epithelium predominantly oxyphilic, almost all in form of acini, with little colloid; also small

ragged empty acini, and foci of hyperplastic acini lined by tall columnar epithelium and all containing colloid. No pseudogiant cells.
Parenchyma infiltrated by lymphocytes and plasma cells in about equal numbers; infiltration maximal at periphery of nodules, sparse in the hyperplastic foci. No lymphoid follicles.

Case 8. Female, 75.

Myxoedema first diagnosed 3 days after gastro-enterostomy for pyloric stenosis. Treated with tri-iodothyronine till death five days later.
Cause of death: carcinoma of head of pancreas; "acute myxoedema".
Macroscopic: Thyroid small, fibrous (5.5 g.).
Microscopic: Parenchyma almost entirely replaced by dense fibrous tissue, the only remaining foci each occupying less than one high-power field.
Epithelium partly hyperplastic, partly oxyphilic. Scanty colloid, in hyperplastic foci only; intra-acinar macrophages.
Parenchymatous islets infiltrated by lymphocytes and a lesser number of plasma cells; infiltration maximal at periphery of islets. No lymphoid follicles.

Case 9. Female, 77.

Known myxoedema for 8 years. Treated successfully with thyroid extract until 6 months before death, when thyroid medication had been discontinued. Admitted in semi-coma, found to have Paget's disease of bone. Died 2 days later.
Cause of death: myxoedema coma.
Macroscopic: Thyroid site occupied by fibrous tissue.
Microscopic: Dense fibrous tissue, with very scanty parenchymatous islets, the largest 1 mm. in diameter. Most islets composed of oxyphilic cells, without acinar arrangement; largest islet composed of very small acini lined by flattened epithelium and containing deep-staining colloid. Some empty acini lined by stratified epithelium. No pseudogiant cells.
All parenchymatous foci except the largest one infiltrated by lymphocytes and plasma cells, the former predominating. No lymphoid follicles.

APPENDIX 5 (Continued)

Case 10. Female, 64.

Known myxoedema, treated by thyroid extract for 4 - 5 years.
Cause of death: Acute leukaemia, bronchopneumonia.
Macroscopic: Thyroid of normal size, but pale and fibrous.
Microscopic: Extensive fibrosis, with scattered parenchymatous islets of up to 3 mms. in diameter. Epithelium mostly oxyphilic or metaplastic, with foci of stratified epithelium. Some islets composed of small closely-packed acini showing neither oxyphilia nor metaplasia, and containing colloid.
Parenchymatous islets infiltrated by lymphocytes and a lesser number of plasma cells. No lymphoid follicles.

Case 11. Female, 41.

Carcinoma of breast, radical mastectomy. Extensive metastases in bones 2 years later. Hypophysectomy did not lead to improvement. Steady deterioration, diabetes insipidus, extensive metastases. Died 5 months after hypophysectomy. Post-mortem findings: Tumour deposits in skull, vertebrae, pelvis, femur; severe atrophy of ovaries, adrenals.
Macroscopic: Thyroid small (6 g.), but otherwise of normal appearance.
Microscopic: Slight fibrosis, amounting in most areas to little more than thickening of interlobular septa. Also some areas of more diffuse fibrosis, with some replacement of the parenchyma.
Small to medium-sized acini, lined by normal low cuboidal epithelium and containing deep-staining colloid. No oxyphilia, metaplasia or hyperplasia.
Scanty small foci of lymphocytic infiltration, mostly just under the capsule of the gland. No lymphoid follicles, no plasma cells.

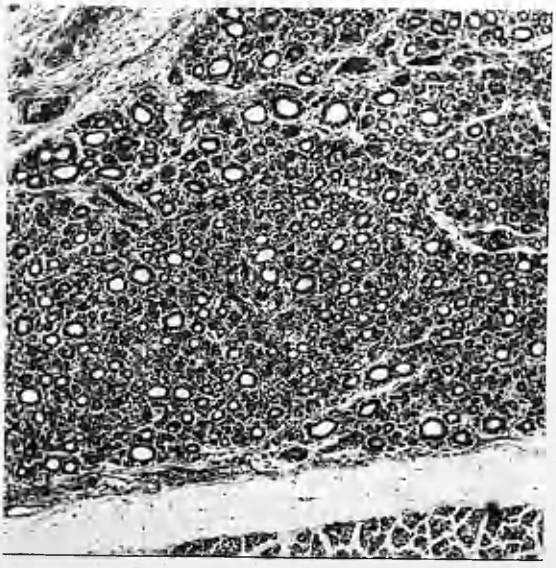


Fig. 1. Thyroid of a 17-week foetus. Differentiation into acini is complete, with the larger acini in the peripheral zone.

H & E, x 100

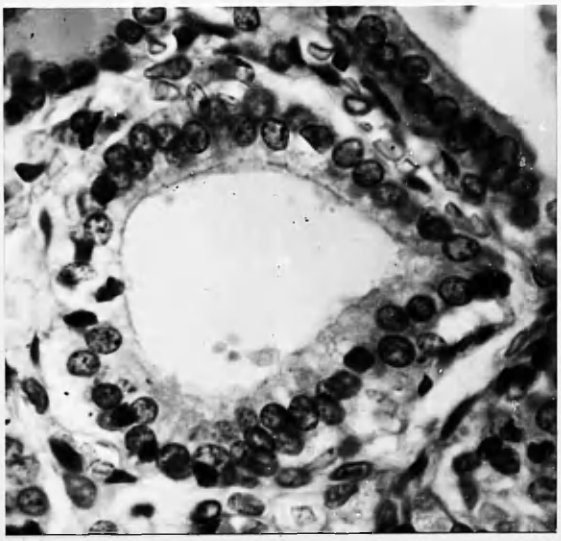


Fig. 2. Case 84. Type A acinus in peripheral zone. Epithelium columnar, luminal margin of cytoplasm well defined.

H & E, x 400

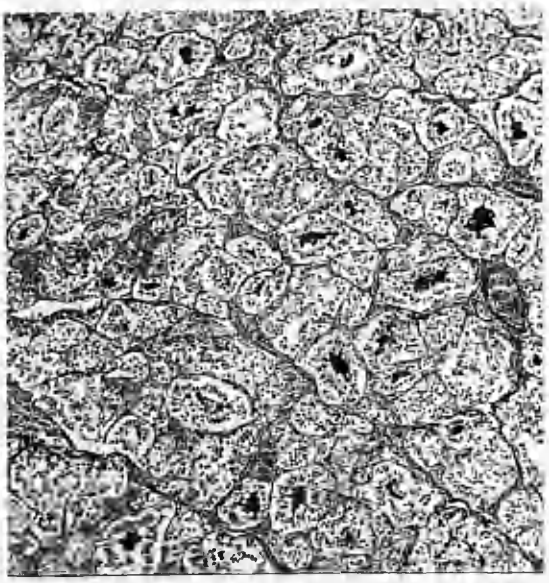


Fig. 3. Case 40. A gland composed entirely of type B acini.
P.A.S., x 80

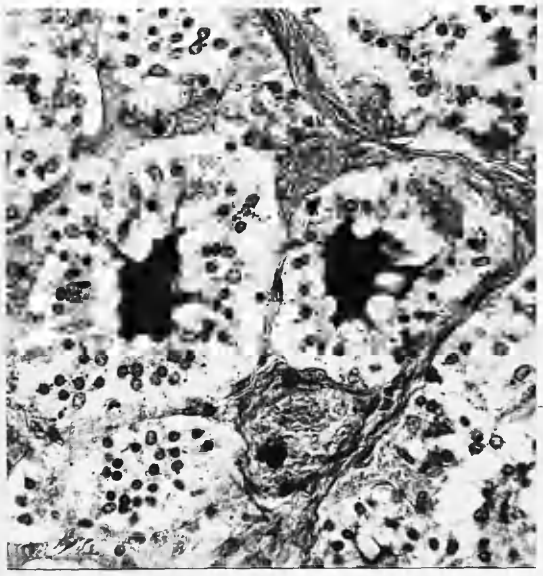


Fig. 4. Higher magnification: persistence of deep-staining colloid, with marked peripheral vacuolation.
P.A.S., x 350

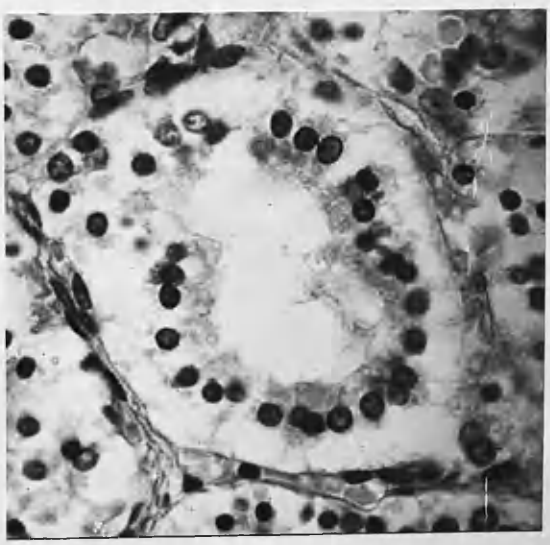


Fig. 5. Case 24. Type B acinus: basal vacuolation of cytoplasm, luminal margin rather indistinct; colloid uniformly pale.
H & E, x 400

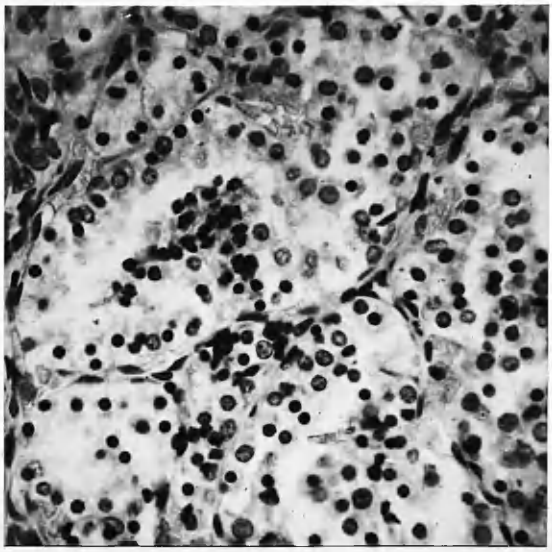
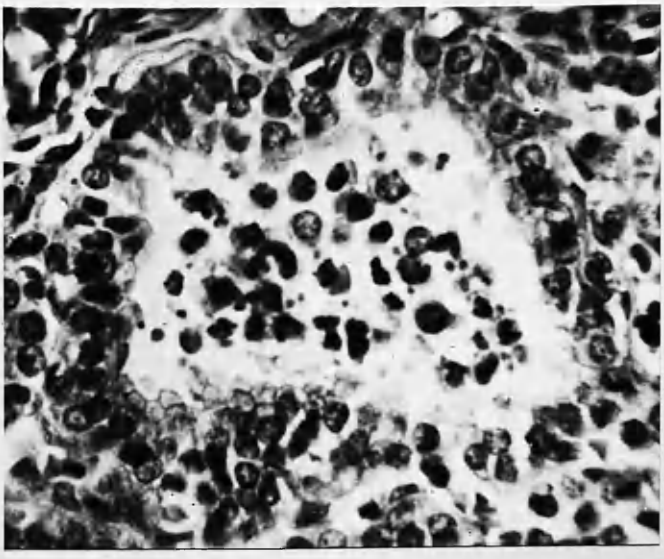


Fig. 6. Case 84. - central zone of same gland as in Fig. 2. Type C: groups of desquamated cells with pyknotic nuclei in lumen. No colloid. Row of lining cells is intact, but luminal margin of cytoplasm is indistinct.

H & E, x 250

Fig. 7. Case 78. Type C: lumen almost filled with desquamated cells; row of lining cells still intact.

Masson, x 400



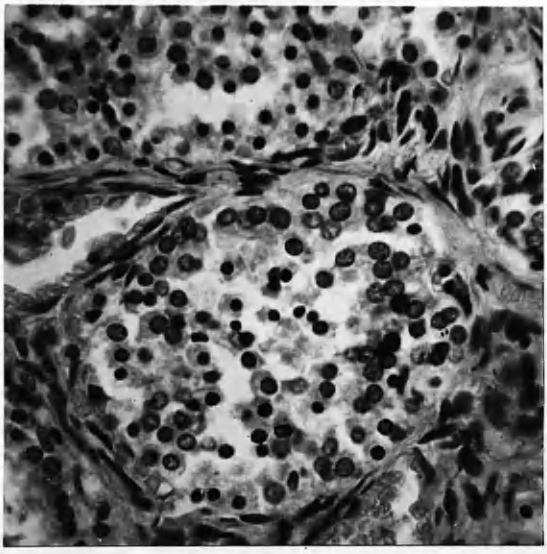
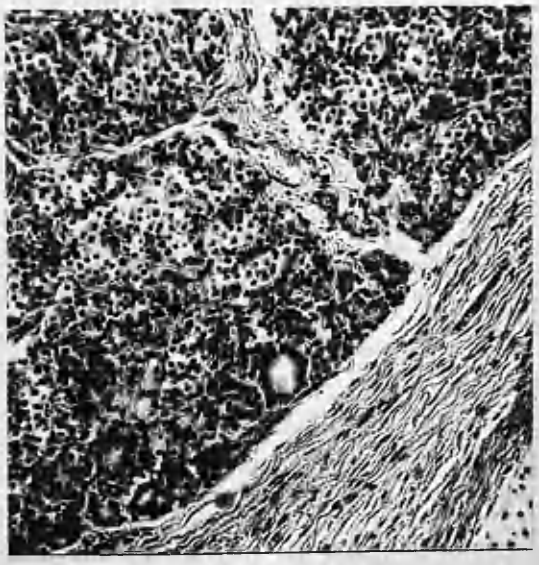


Fig. 8. Case 84. Type C: a more advanced stage of desquamation. The acinar structure is still evident, but the row of lining cells is no longer clearly defined.
H & E, x 250

Fig. 9. Case 3. Type C: further stages in disorganisation of the acini. Acinus in centre of field showing disintegration of the wall and desquamated cells in the lumen, area in which only vague acinar outlines persist (top right), and total loss of acinar structure (top left). Intact acini remain at periphery.
H & E, x 175



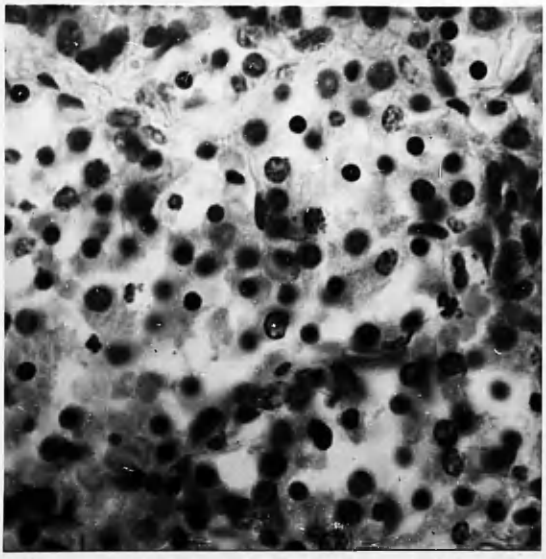
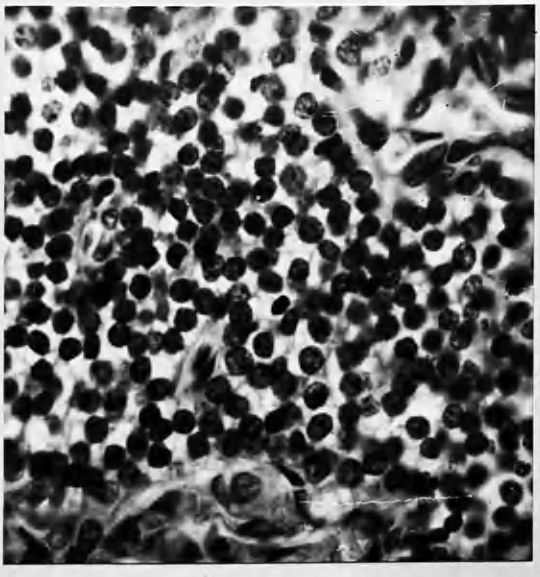


Fig.10. Higher magnification of Fig. 9: compact structure with predominance of small dark-staining nuclei.

H & E, x 400

Fig.11. Case 84. Central zone of same gland as in Figs. 2, 6 and 8: compact structure with predominance of large vesicular nuclei.

H & E, x 400



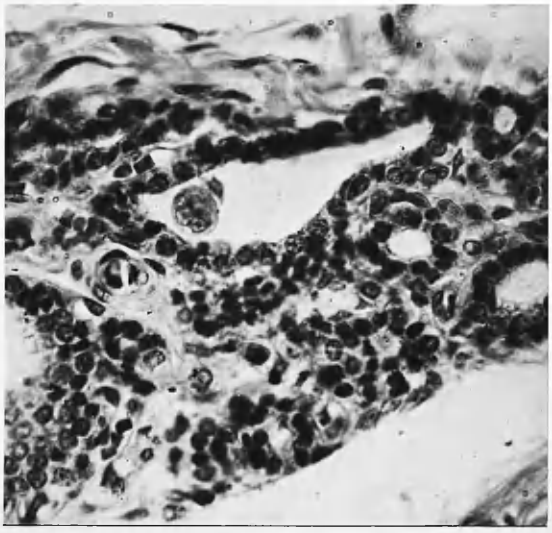
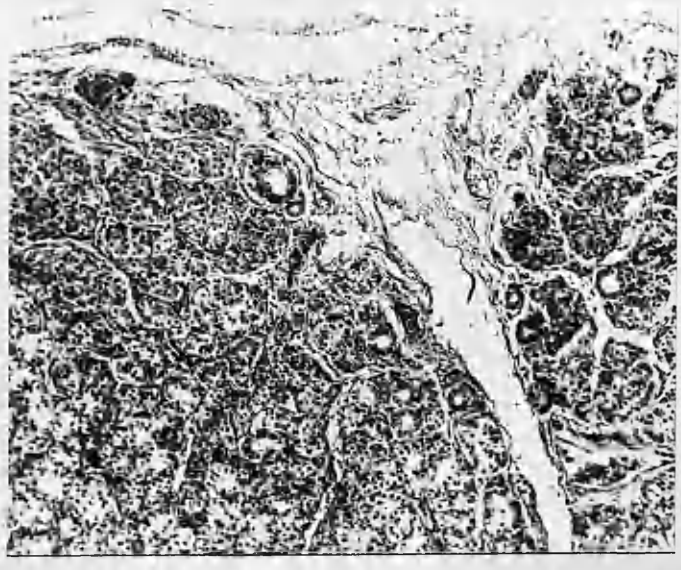


Fig.12. Large amoeboid cells within the colloid are rare; they are quite unlike desquamated epithelial cells.
Masson, x 500

Fig.13. Case 106. Extensive disorganisation of acini, with survival of a few normal acini at peripheral margin.
H & E, x 100



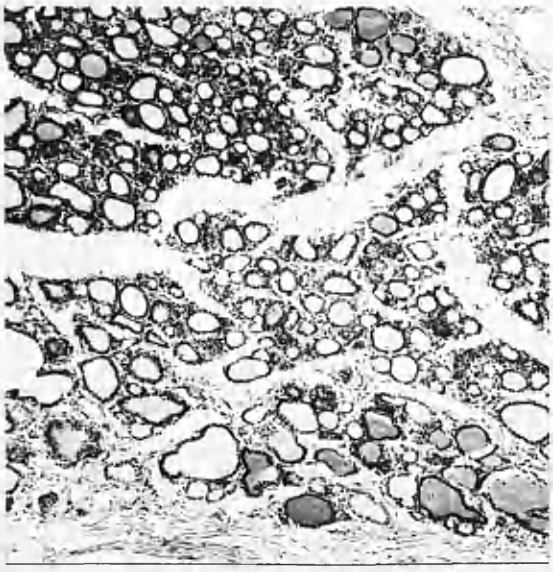
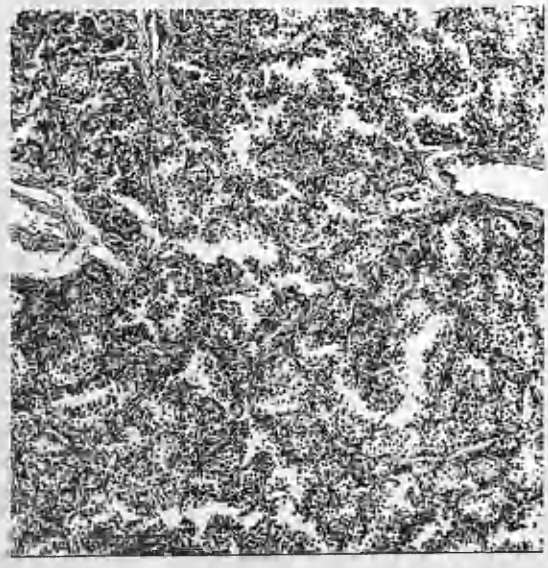


Fig.14. Case 61. Type A, death-fixation interval 40 hours.
H & E, x 80

Fig.15. Case 22. Type C, death-fixation interval 5 hours.
H & E, x 80



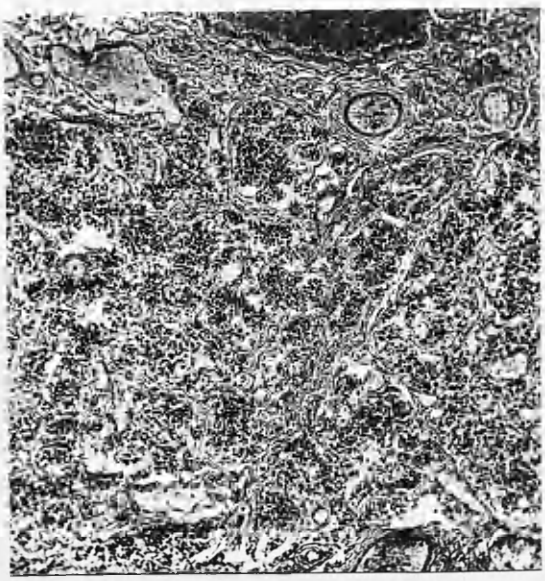


Fig.16. Autolytic thyroid from a stillborn infant - intra-uterine death probably several days before delivery.
H & E, x 80

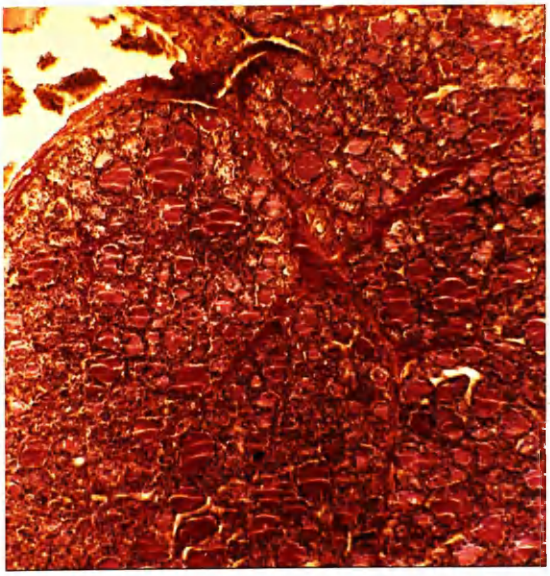


Fig.17. Case 20. Area from central zone, showing distension of lymphatics by colloid-like substance.
P.A.S., x 50

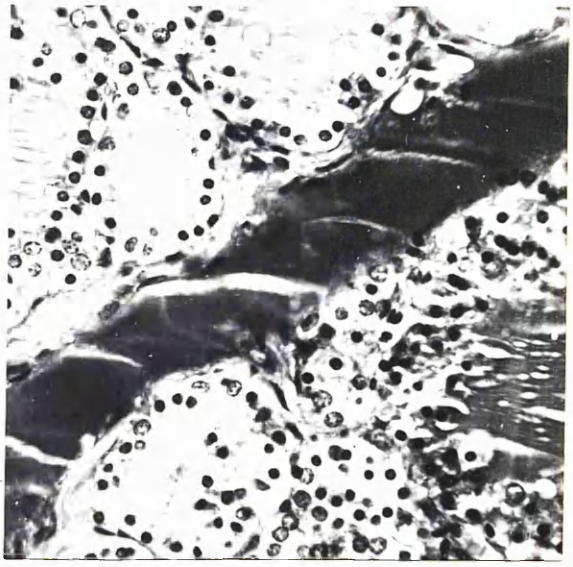


Fig.18. Higher magnification: colloid-like substance stains more intensely than colloid in adjacent acini. Disorganisation of acini. The endothelium lining the lymphatic vessel can be seen.
P.A.S., x 400

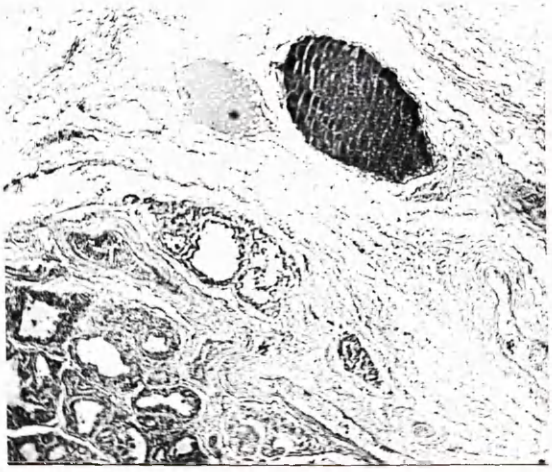


Fig.19. Case 25. Colloid-like substance in the lymphatics outside the thyroid.
P.A.S., x 50

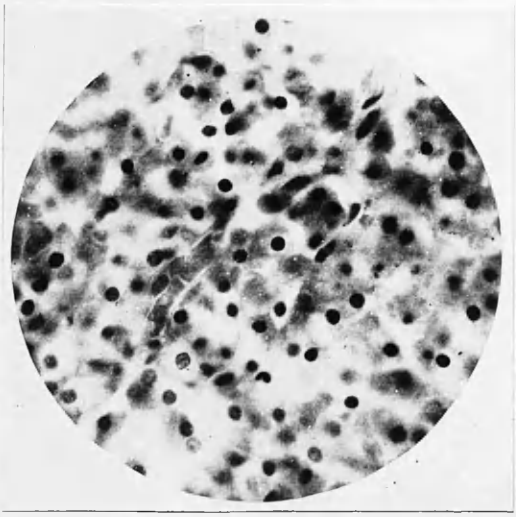
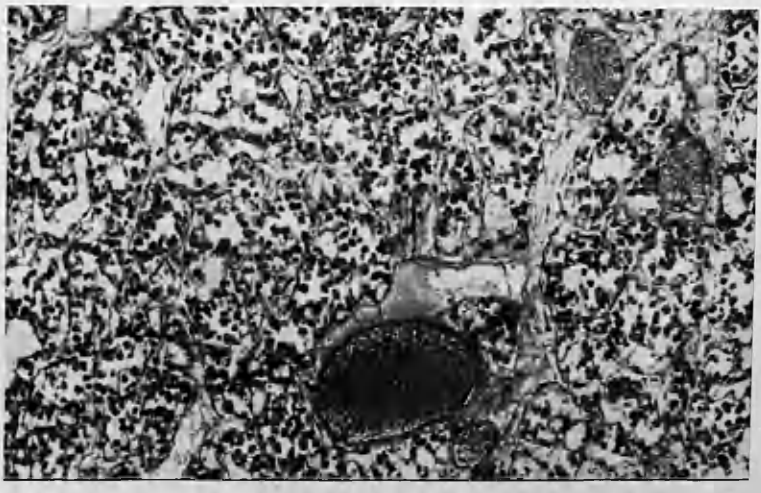


Fig.22. "Diskomplexation" in the fox thyroid (Fig.11 of Glebina, 1936).

Fig.23. Functional exhaustion in the rat thyroid (Fig.26 of Weber & Bettini, 1956). Thyrotropic hormone injections on alternate days for 46 days.

H & E, x 130



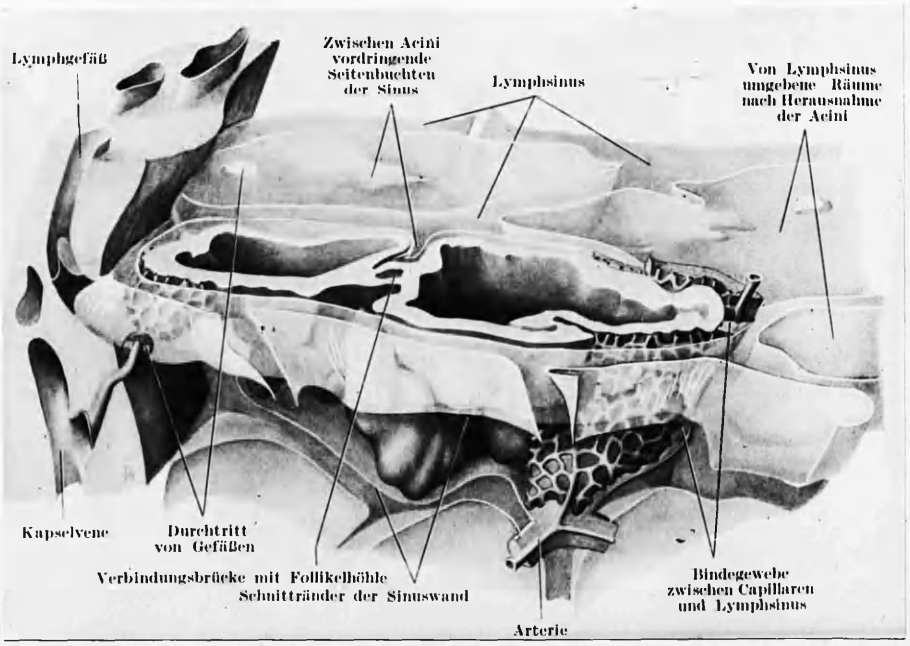


Fig.24. Photograph of Fig. 4 from Kulenkampff (1950): wax model illustrating the lymphatic system in the human neonatal thyroid.

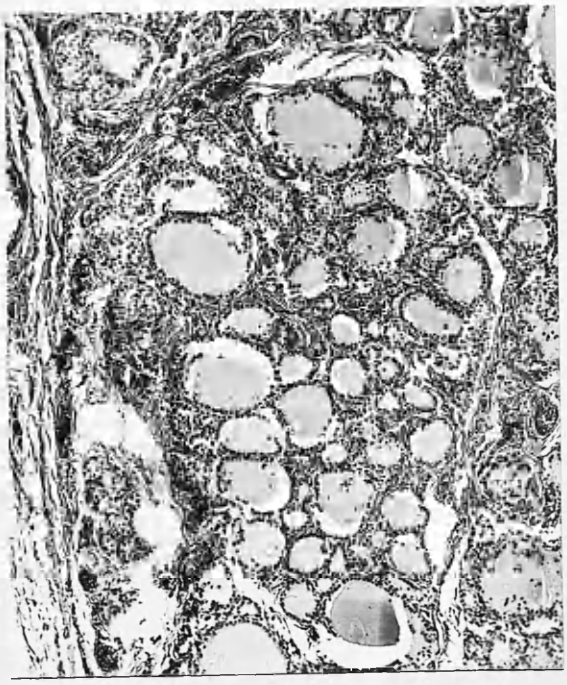


Fig.25. Normal thyroid at birth. Mother suffered from pituitary hypothyroidism. H & E, x 100

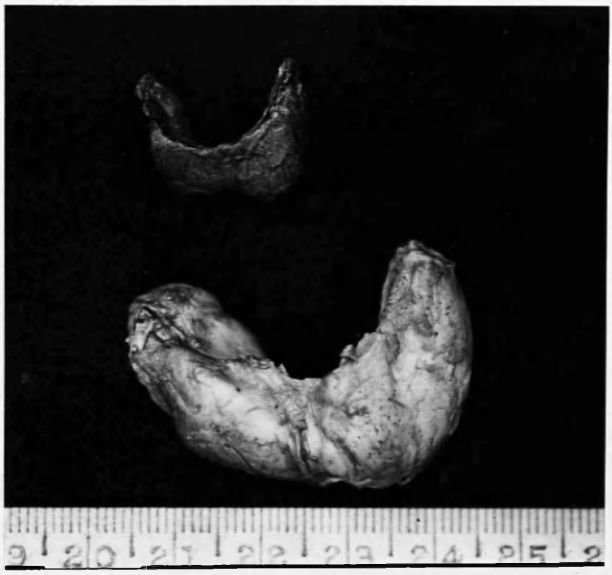


Fig.26. Congenital goitre due to treatment of mother with methylthiouracil.
Above: thyroid of normal newborn child of same body weight, for comparison.

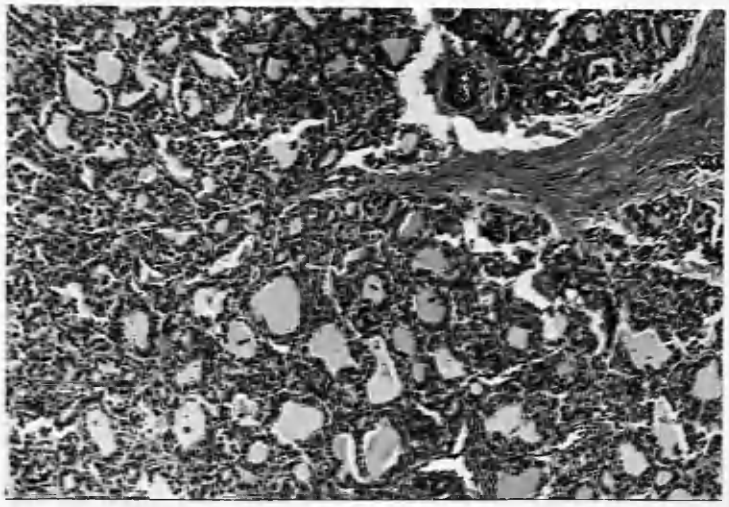
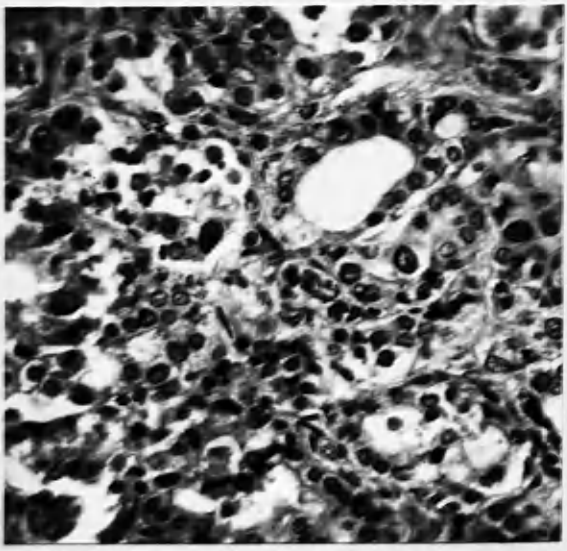


Fig.27. Congenital goitre: irregular acini, cuboidal or low columnar epithelium, broad interlobular septum.
H & E, x 100

Fig.28. Higher magnification: many large mis-shapen nuclei.
H & E, x 400



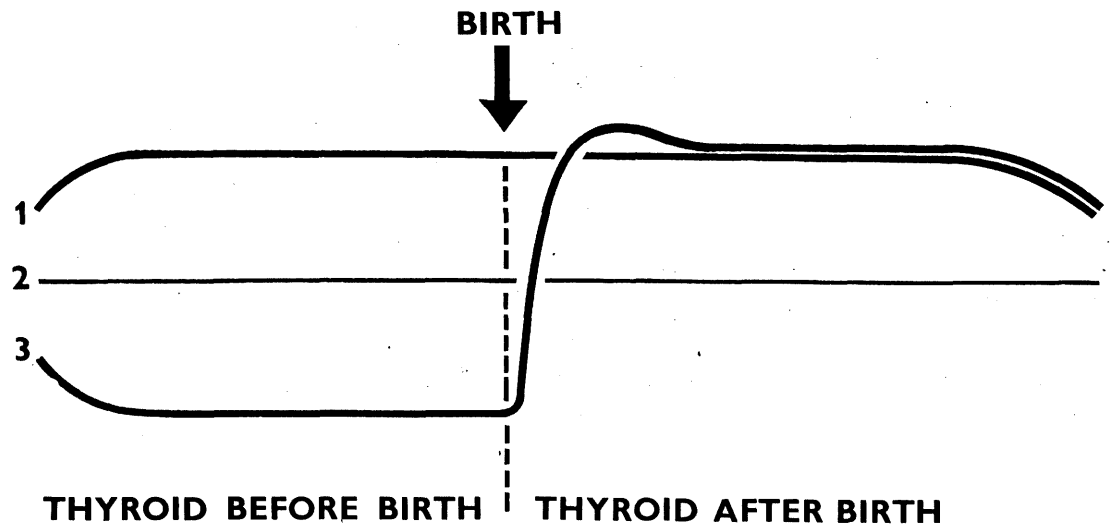


Fig.29. Two mechanisms in the pathogenesis of congenital hyperthyroidism.
1: Increased output in response to maternal TSH.
2: Normal level of secretion by foetal thyroid.
3: Thyroid hormone synthesis blocked by antithyroid drugs.

Fig. 30. Diagrams of the normal and goitrous guinea pig thyroid at birth. (All actual size, after 24 hours' fixation).

13A and 22A: The normal thyroid at birth.
13M: The normal adult thyroid.

8A, 8B: Congenital goitre - 29 days of 0.1% thiouracil.
8C, 8D: Littermates at 3 days (thiouracil continued).
8C injected with TSH.

21A, 21B, 21C: Congenital goitre, intra-uterine death - 29 days 0.05% thiouracil.
25A, 25B: Congenital goitre - 29 days of 0.005% thiouracil.
27A: Congenital goitre - 35 days of 0.005% thiouracil.

14A, 14B: Congenital goitre - 32 days of 0.1% potassium perchlorate.
14C: Littermate at 14 days - no potassium perchlorate post-natally.
14D: Littermate at 14 days (potassium perchlorate continued).
19A: Congenital goitre, with haemorrhage in R. lobe - 0.1% potassium perchlorate for 17 days before and 2 days after delivery.
19B: Littermate at 5 days (potassium perchlorate continued).

26A: Congenital goitre - 32 days of 0.005% potassium perchlorate.
16A: Goitre at 16 days - no treatment during gestation; 14 days of transmammary 0.1% potassium perchlorate.
16C: Untreated littermate at 16 days.

36A: Neonate - 29 days of 0.0005% carbimazole.
38A: Stillborn - 21 days of 0.005% carbimazole.
40B: Congenital goitre, intra-uterine death - 22 days of 0.0005% carbimazole followed by 12 days of 0.05% carbimazole.

13a

13M

22a

8a

8b

8c

8d

21a

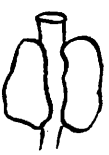
21b

21c

25a

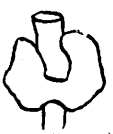
25b

27a

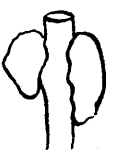


14a

14b



14c



14d

19a

19b

26a

16a

16c

36a

38a

40b

Fig. 30

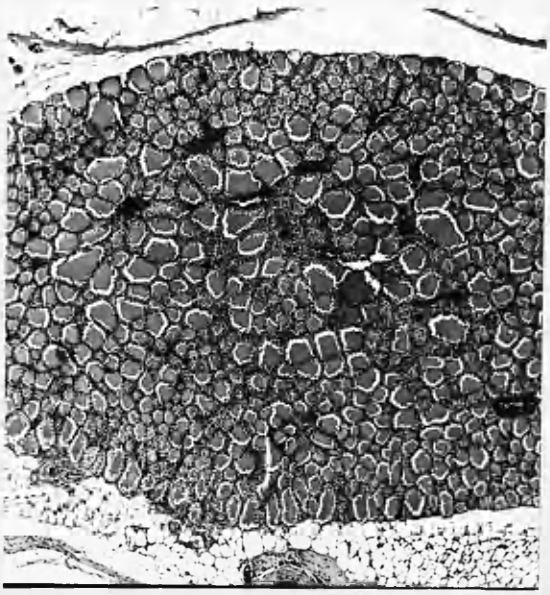


Fig.31. GP1B. Newborn guinea pig: normal thyroid.

H & E, x 50

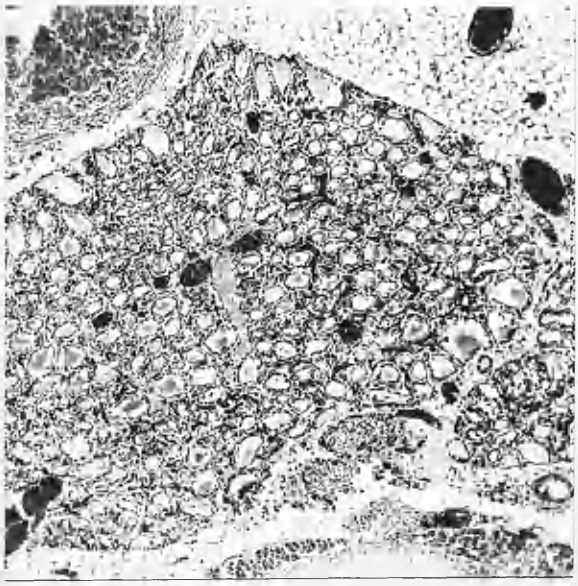
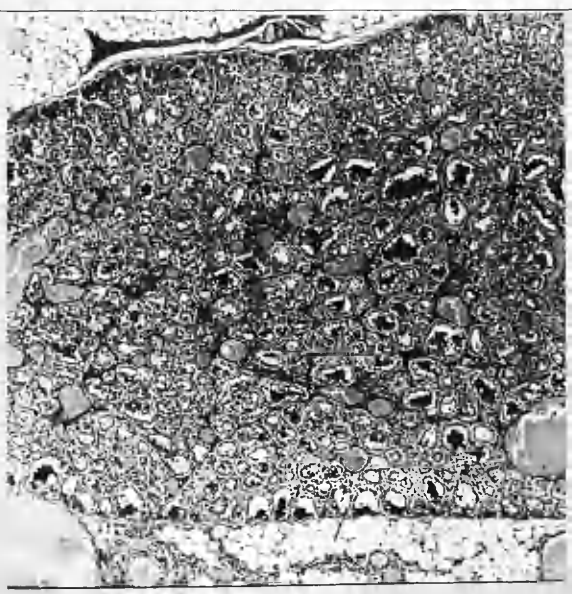


Fig.32A. GP1A, littermate of preceding case. Stillborn, tissue fixed about 6 hours after delivery, negligible post-mortem changes in other organs. Basal vacuolation or early detachment of epithelium, peripheral vacuolation of colloid, distended lymphatic in centre of field.

H & E, x 50

Fig.32B. Same gland stained by "tripas" method. The lymphatic network in the centre of the lobe is outlined by colloid-like substance. One lymphatic outside the thyroid is similarly distended.

P.A.S., x 50



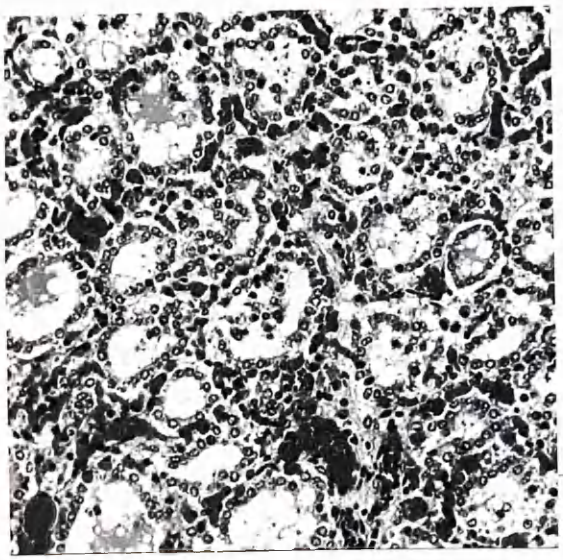


Fig.33. GP1A, stillborn, higher magnification: Early disintegration of acinar lining in centre of field, with desquamated cells in lumen (compare with Fig. 6). Basal vacuoles in some acini. Congestion of inter-acinar capillaries.
H & E, x 200

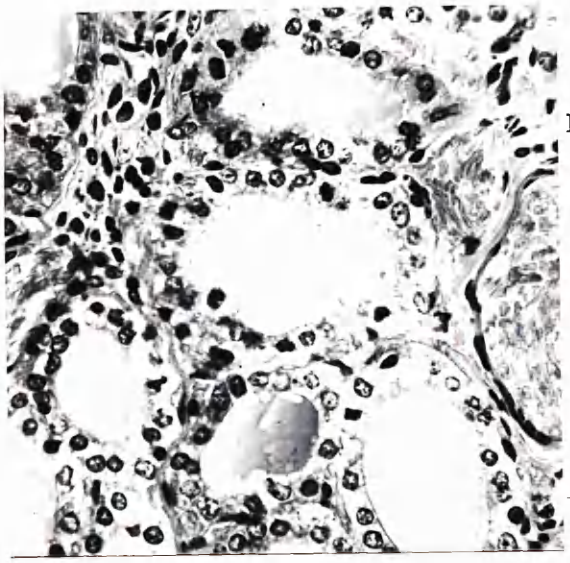


Fig.34. GP45A, stillborn, fixation within a few hours of birth. Epithelium taller than in normal neonate. Some nuclei large, hyperchromatic; one in mitosis, another protruding into the lumen (compare with Fig. 37).
H & E, x 400

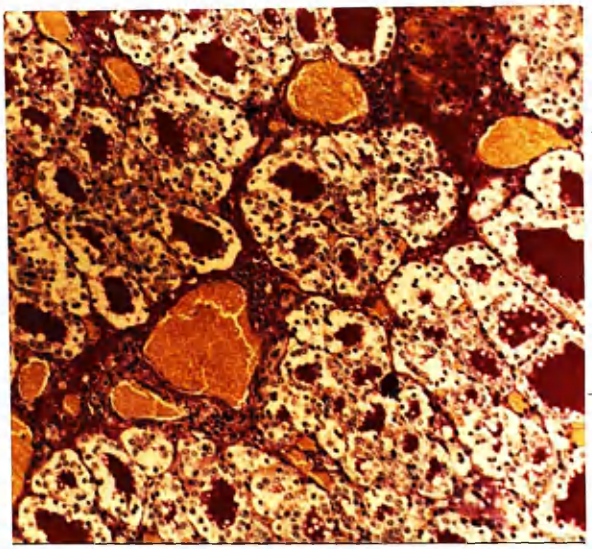


Fig.35. GP3D, stillborn, fixation 29 hours after birth. Vacuolation of cytoplasm, peripheral vacuolation of colloid. Distension of lymphatics by colloid-like substance.
P.A.S., x 135

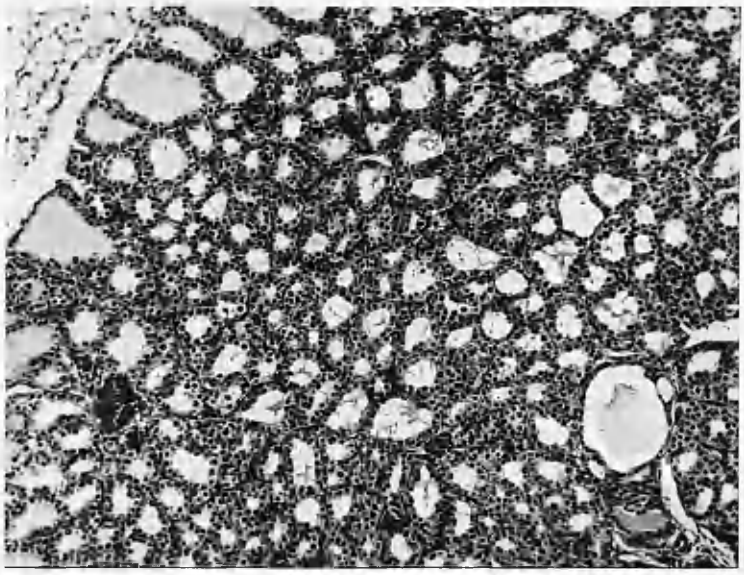
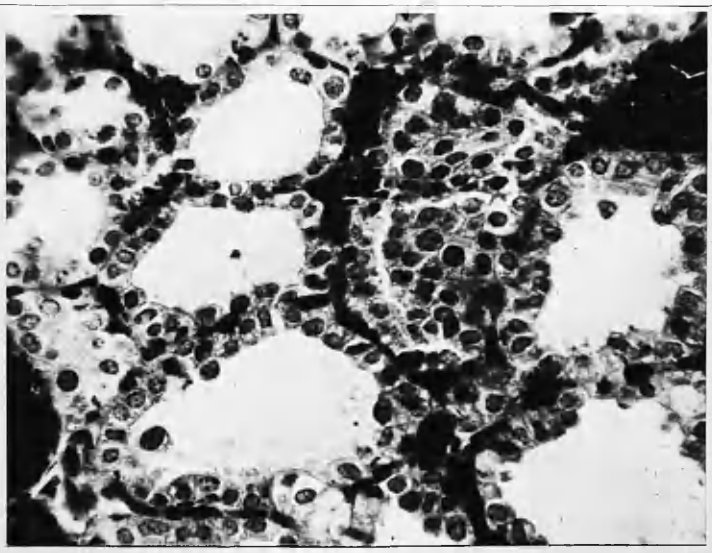


Fig.36. GP4A. Neonatal guinea pig thyroid 28 hours after TSH injection. Colloid scanty in central zone, absent in intermediate zone, persists in peripheral zone. Large hyperchromatic nuclei, some displaced towards lumen. The abnormally large acinus (bottom right) does not share in the hyperplasia.
H & E, x 100

Fig.37. GP43B. Neonatal guinea pig thyroid, 46 hours after TSH injection. More advanced protrusion of cells into the lumen. Congestion of capillaries.
Masson, x 400



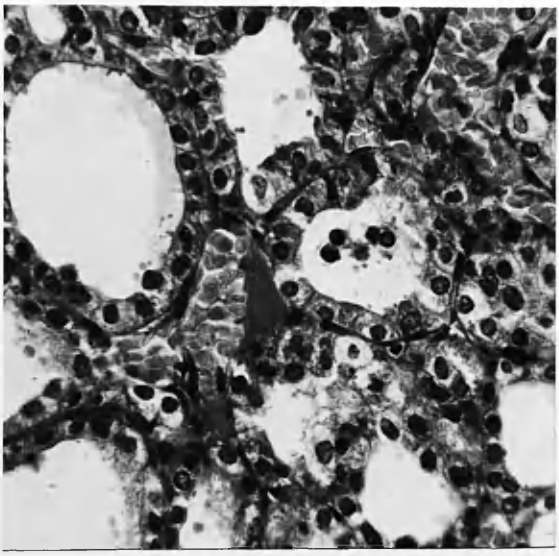
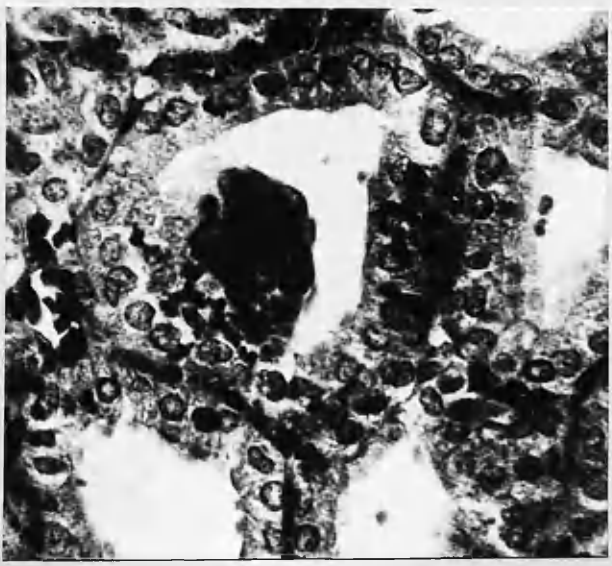


Fig.38. Another field from same gland as in preceding Fig. The cells in the lumen are probably desquamated cells, but these are often difficult to distinguish from macrophages.
H & E, x 400

Fig.39. GP39C. Neonatal guinea pig thyroid, 96 hours after TSH injection. Columnar epithelium, no apical displacement of nuclei. A few red cells were seen in the lumina in this gland. This was the only instance in which the group of extravasated cells was delimited by a ring of cells resembling macrophages.
Masson, x 450



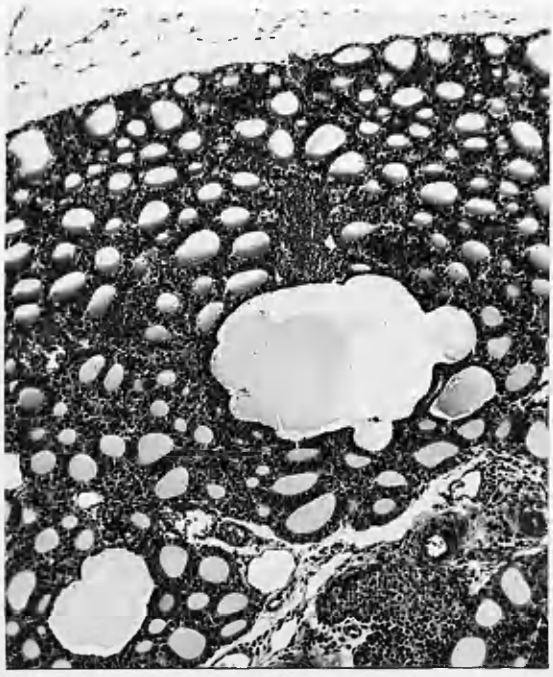


Fig.40. GP30B. Potassium perchlorate (0.005%) for 36 days before delivery. Heightening of epithelium in all zones, but colloid persists in most acini. The field includes parathyroid (bottom right) and two abnormally large acini; the latter do not show hyperplasia, and are probably non-thyroidal tissue of developmental origin.

H & E, x 100

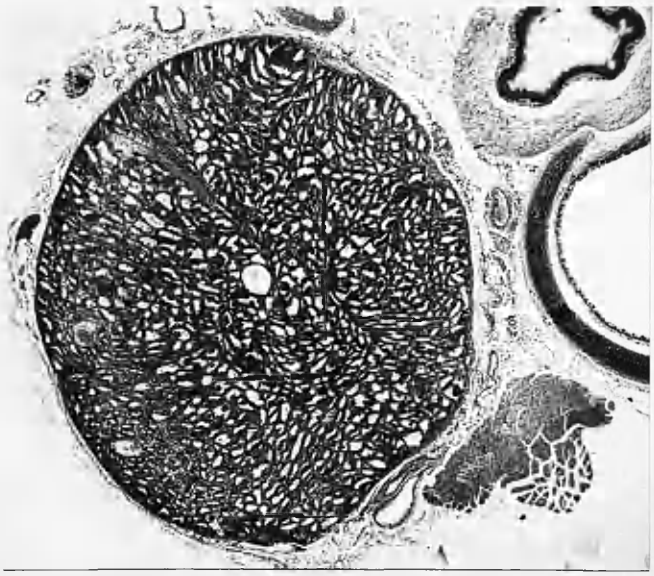
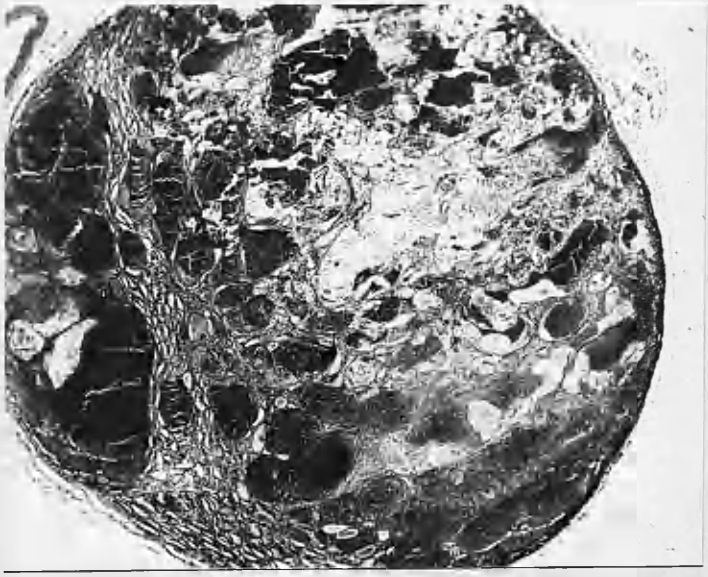


Fig.41. GP19A. Potassium perchlorate (0.1%) for 17 days before delivery. Enlarged hyperplastic L. lobe of thyroid; hyperplasia maximal in the centre.
H & E, x 20

Fig.42. R. lobe of the same gland shows much greater enlargement, and most of it is destroyed by haemorrhage.
H & E, x 20



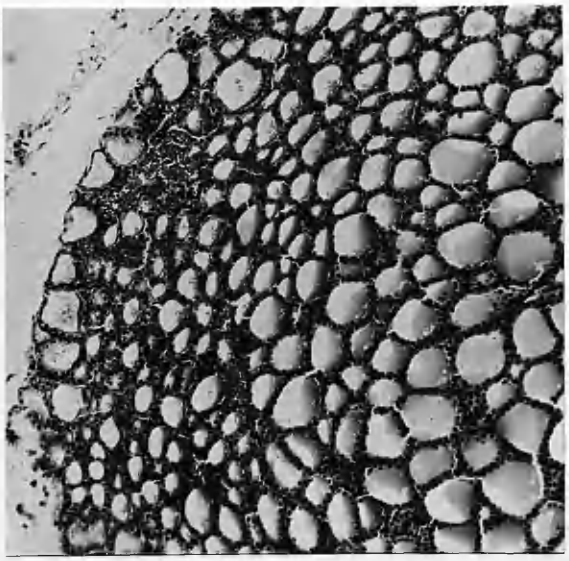
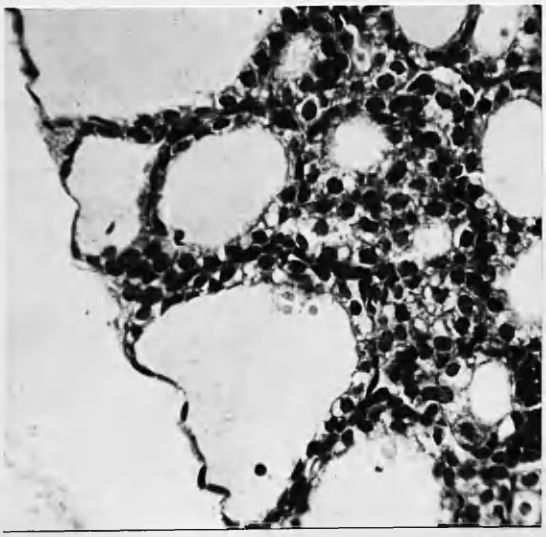


Fig.43. GP34A. Comparatively mild hyperplasia in neonatal guinea pig thyroid following 26 days of carbimazole (0.0005%) administration to mother.
H & E, x 100

Fig.44. GP37A. Carbimazole (0.005%) for 34 days before delivery. Colloid stains poorly. Epithelium is cuboidal or high cuboidal, but remains flat at peripheral margin of peripheral acini.
Masson, x 400



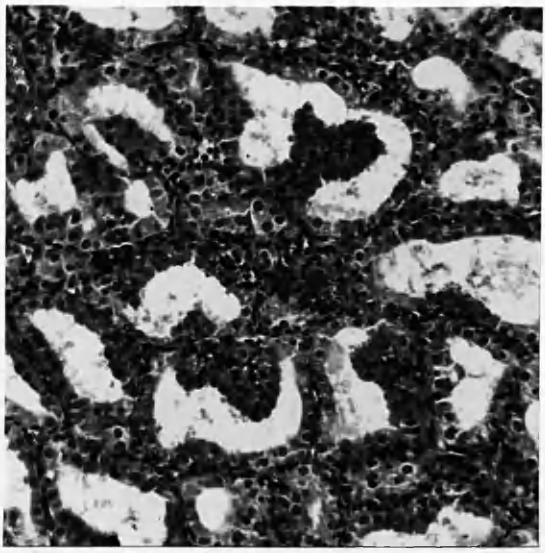
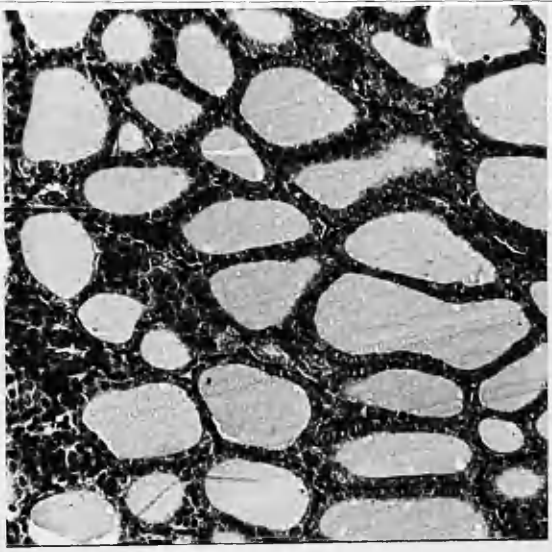


Fig.45. GP14A. Potassium perchlorate for 32 days before delivery. Thyroid at a few hours after birth.
Papillary infoldings of acinar walls, columnar epithelium, little or no colloid. H & E, x 200

Fig.46. GP14C: Littermate at 14 days, suckled by untreated sow from a few hours after birth.
Considerable regression of hyperplasia, with return of colloid. Acini remain enlarged.
H & E, x 200



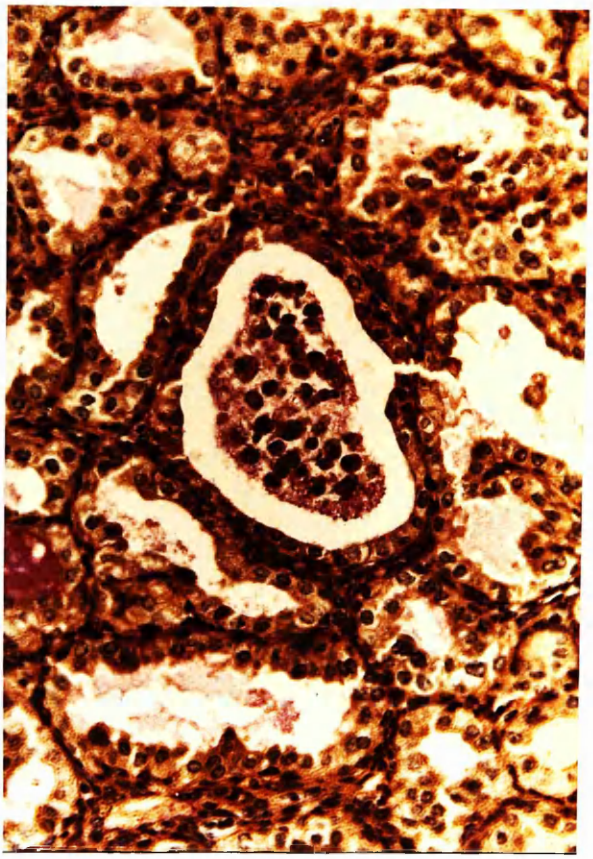


Fig.47. GP17C. Much less regression at 12 days in similarly treated animal suckled by its own (treated) mother. Intra-acinar macrophages containing P.A.S.-positive granules.

P.A.S., x 320

THIOURACIL GOITRE IN THE ADULT GUINEA PIG

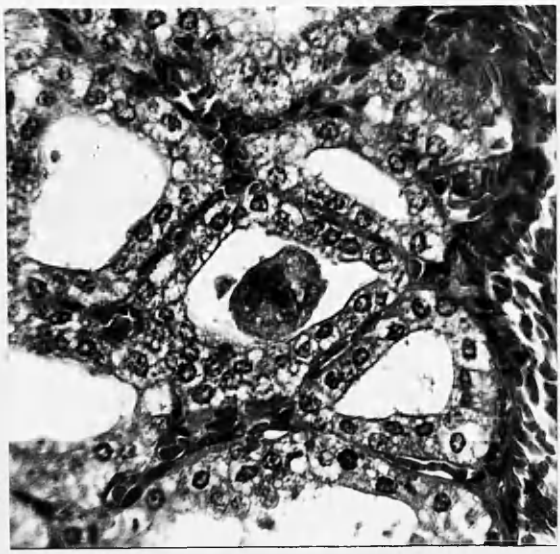


Fig.48. GP6M. Thyroid of pregnant guinea pig, dying after 21 days of thiouracil (0.1%). Columnar epithelium, multinucleate cell in lumen. A moderate amount of colloid remained in this gland.

H & E, x 400

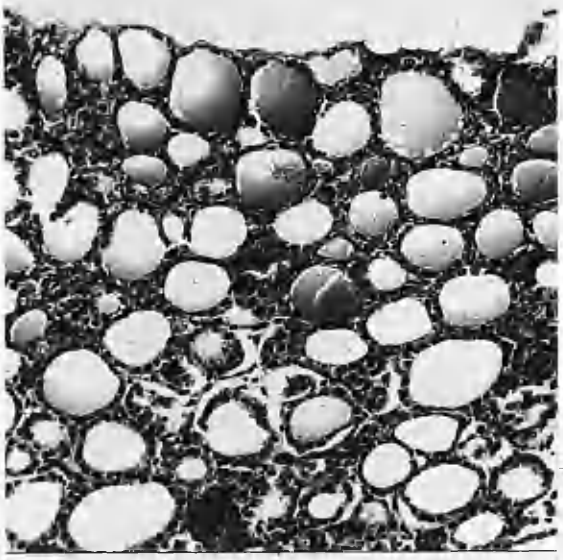


Fig.49. GP50A. Early autolysis in the thyroid of a 2-day-old guinea pig. Death-fixation interval 34 hours. Colloid stains feebly, epithelium is separating from the acinar wall. Peripheral acini unaffected.
H & E, x 200

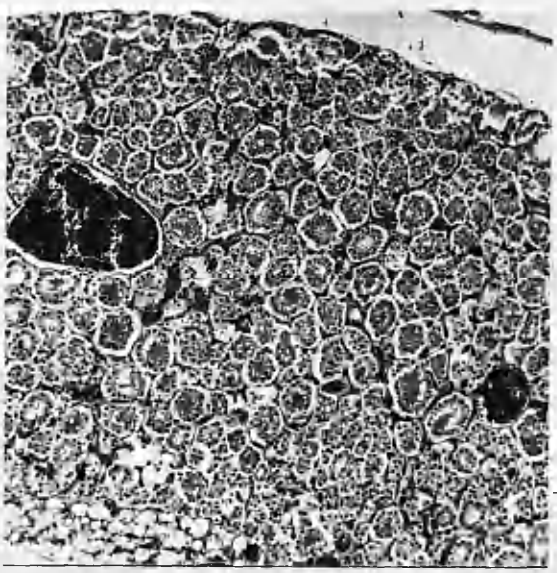


Fig.50. GP1C. A later stage of autolysis: death-fixation interval 70 hours.
Detachment of epithelium in all zones. Peripheral vacuoles have developed in the colloid; this is rare during autolysis in the normal thyroid.
H & E, x 100

Fig.51. GP11B. More advanced autolysis: death-fixation interval 116 hours.
Nuclei still present in peripheral zone. Most nuclei have disappeared in central zone, but ring of cytoplasm remains intact.
Masson, x 100

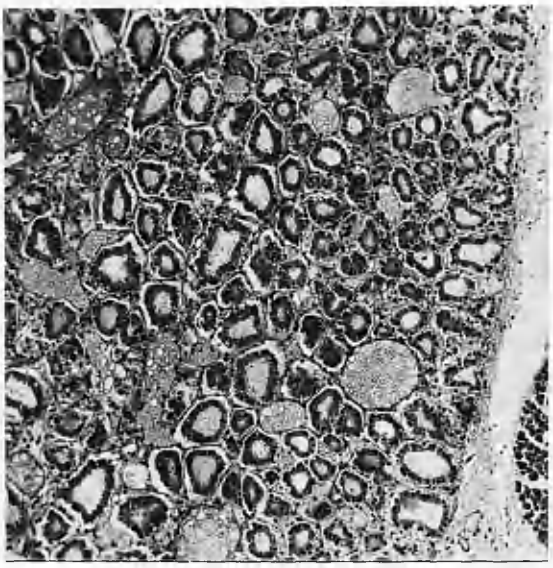
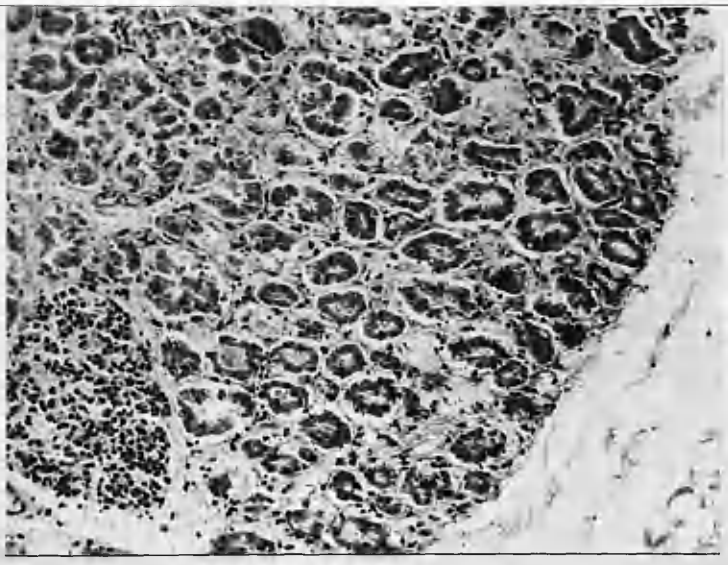


Fig.52. GP49C. TSH injection 96 hours before sacrifice. Death-fixation interval 66 hours.
Detachment of epithelium, but row of cells remains intact.

H & E, x 100

Fig.53. GP43D. TSH injection 46 hours before sacrifice. Death-fixation interval 72½ hours.
Peripheral acini as in Fig. 52. Central acini show disintegration of lining, loss of nuclei. Parathyroid is more resistant to autolysis.

H & E, x 200



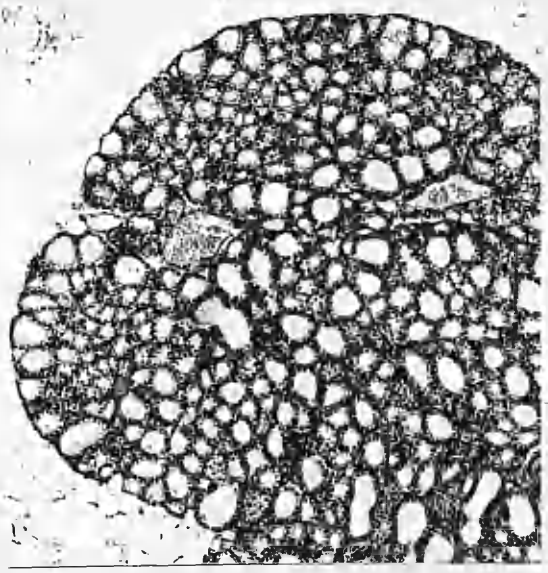


Fig.54. GP31A. Potassium perchlorate (0.005%) for 38 days before delivery. Immediate fixation.
H & E, x 80

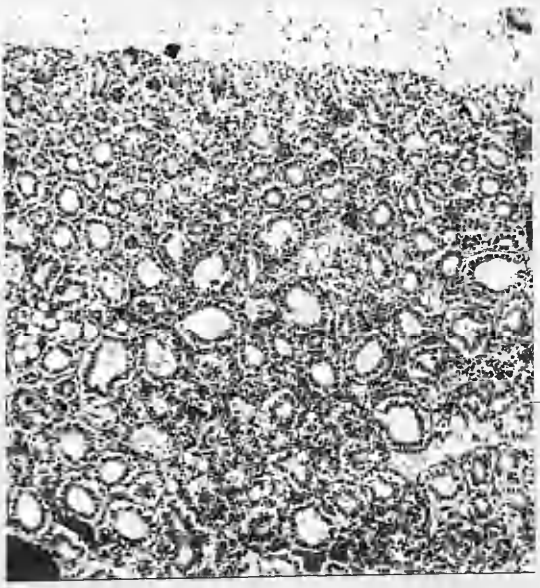


Fig.55. GP31B. Littermate, death-fixation interval 72 hours. Detachment of epithelium.
H & E, x 80

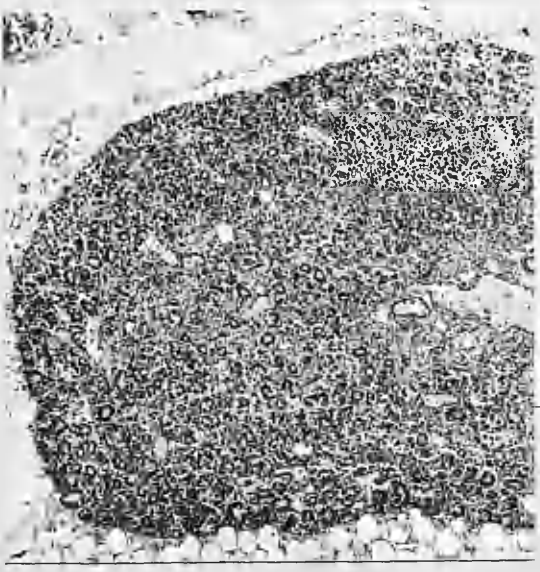


Fig.56. GP31C. Littermate, death-fixation interval 97 hours. More advanced autolysis, with collapse of acini and loss of nuclei in central zone, survival of nuclei in peripheral zone.
H & E, x 80

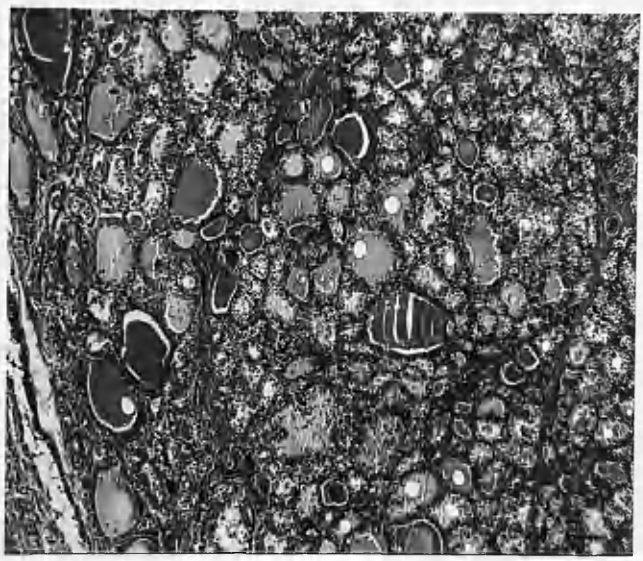
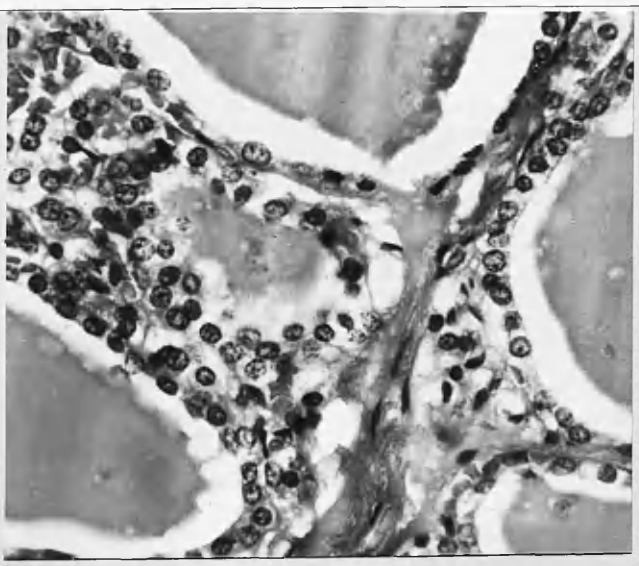


Fig.57. Thyroid of girl aged 8 years, dying of rheumatic fever. Death-fixation interval 9 hours.
Disorganisation of acini, with larger well-preserved acini at periphery, and colloid-like substance in lymphatics.
H & E, x 50

Fig.58. Male, 63 (carcinoma of bronchus, pulmonary tuberculosis). Death-fixation interval 28 hours.
In the small acinus, the cytoplasm is indistinct and vacuolated. The large acini are normal.
H & E, x 450



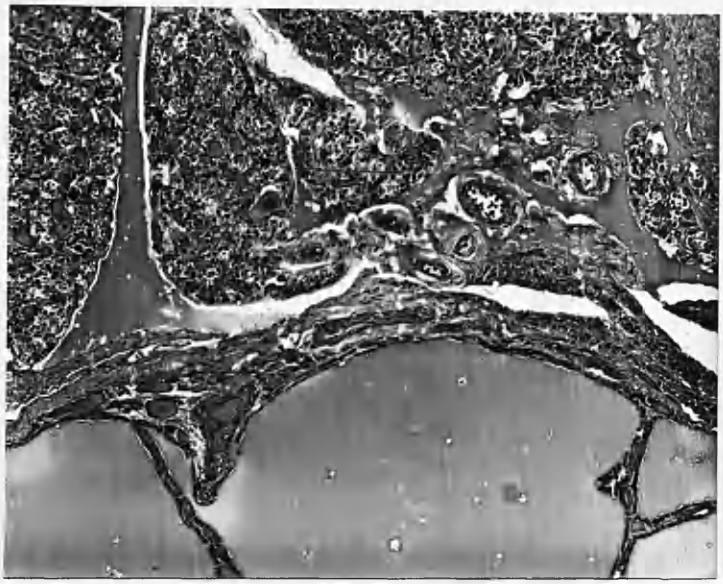
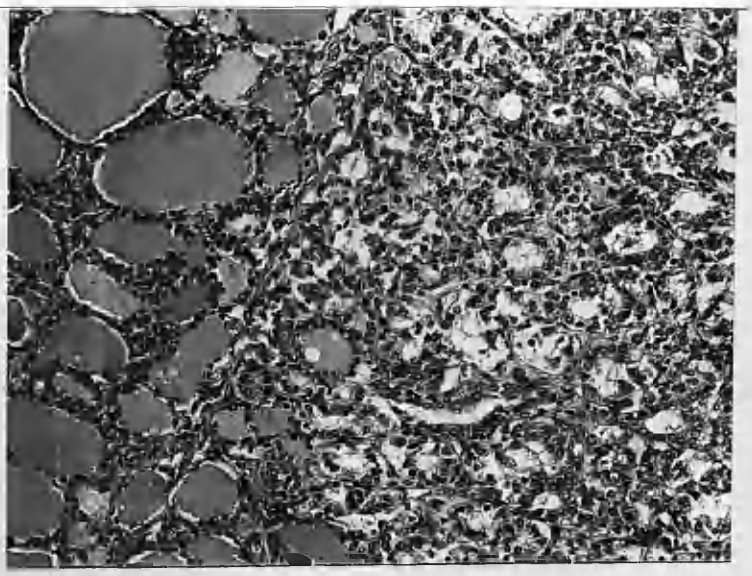


Fig.59. Female, 79 (intestinal obstruction). Death-fixation interval 21 hours. Collapse of the acini and distension of the lymphatics by colloid-like substance. The involutional nodule is unaffected.

H & E, x 100

Fig.60. Female, 75 (thyrotoxicosis). Death-fixation interval 16 hours. Preservation of the larger acini; disorganisation and loss of colloid in the smaller acini.

H & E, x 150.



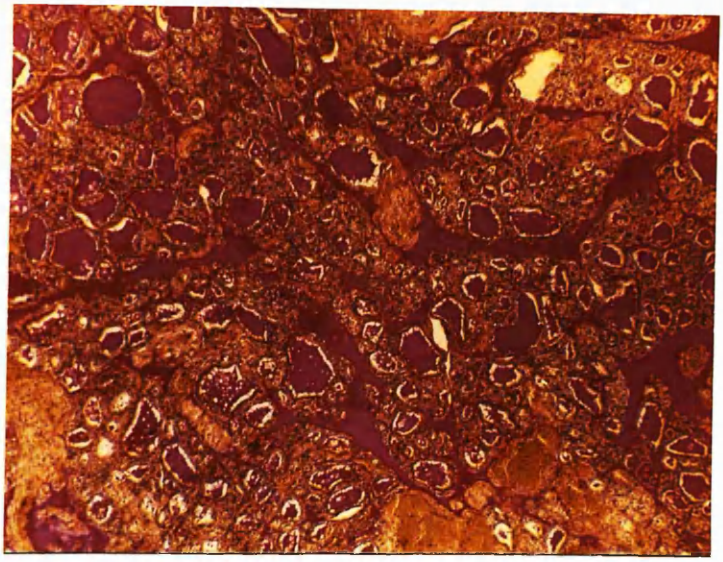
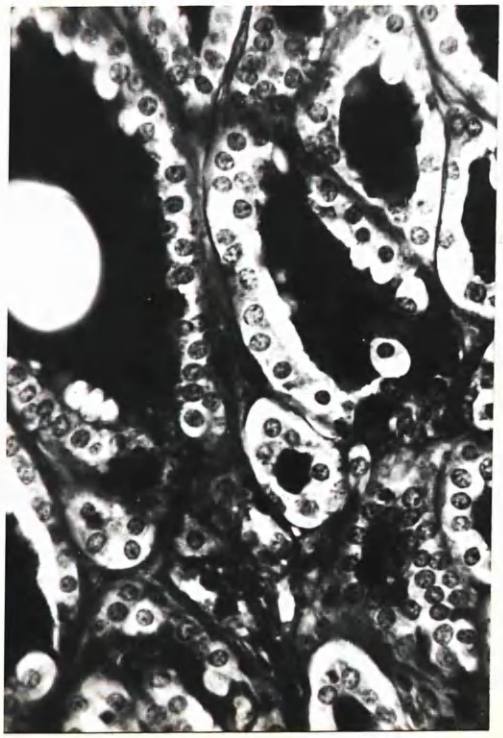


Fig.61. Male, 61 (carcinomatosis, broncho-pneumonia). Death-fixation interval 10 hours.
Lymphatic distension associated with "neonatal changes" in the acini.
P.A.S., x 50

Fig.62. Female, 72 (small intestinal obstruction, acute peritonitis). Death-fixation interval 16 hours.
At several points the intra-acinar colloid appears to be continuous with colloid-like substance in the lymphatics.
P.A.S., x 450



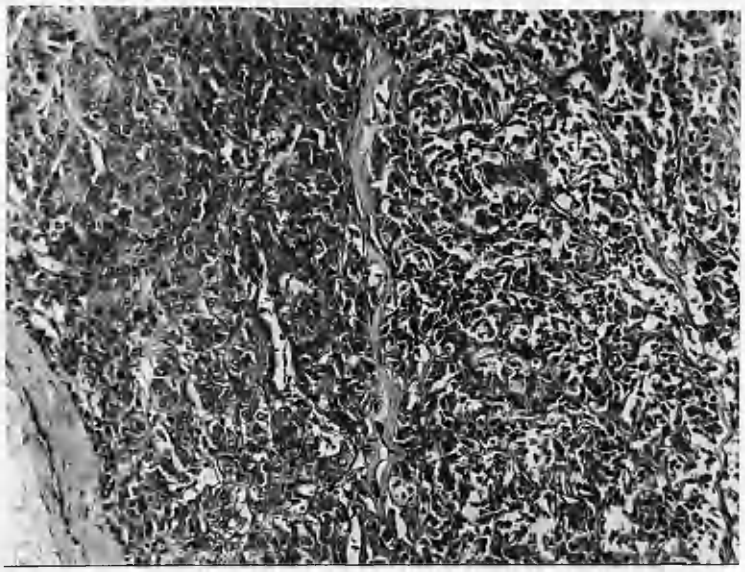
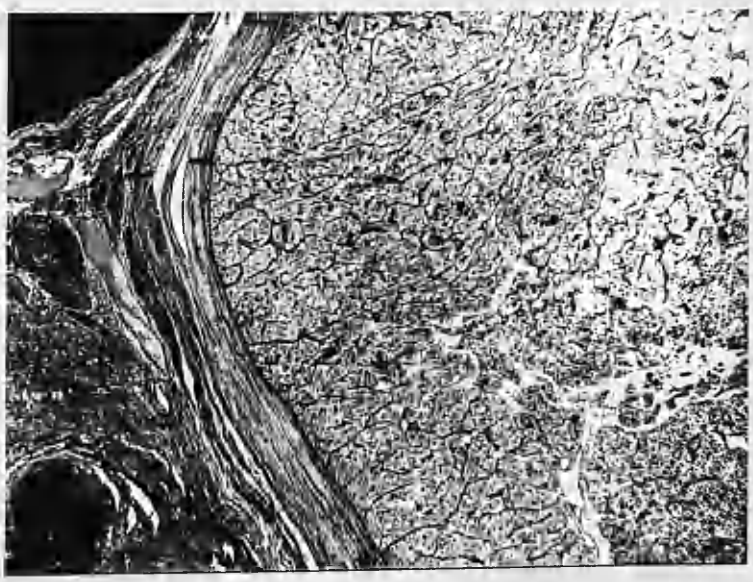


Fig.63. Male, 31. Hyperplastic nodule in non-toxic nodular goitre.
A. The hyperplastic acini at the periphery of the nodule are well preserved, while those in the centre are disorganised. H & E, x 150
B. Interacinar network of P.A.S. - positive material. P.A.S., x 50



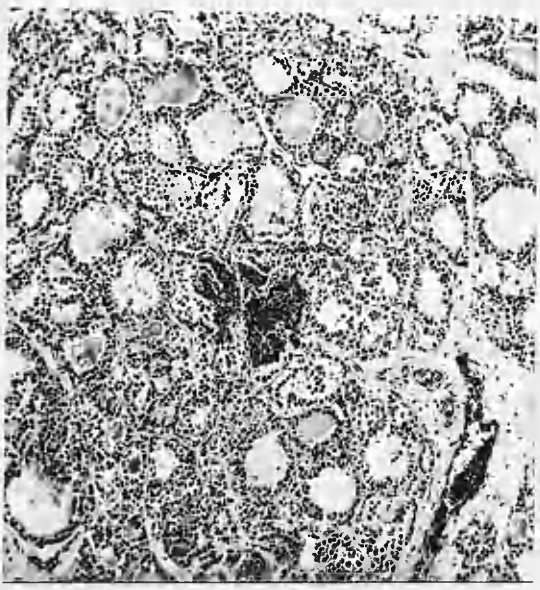
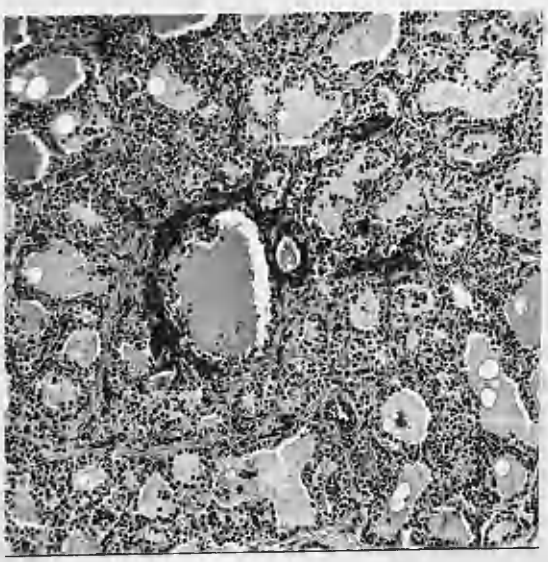


Fig.64. Male, 7 (congenital pulmonary stenosis, death during operation). Death-fixation interval $22\frac{1}{2}$ hours.
Desquamation of epithelium and disorganisation of acini.
A. Solid nest of atypical epithelium.
B. Another section from the same block. At this level, stratified epithelium lines cavities which closely resemble thyroid acini.

H & E, x 100



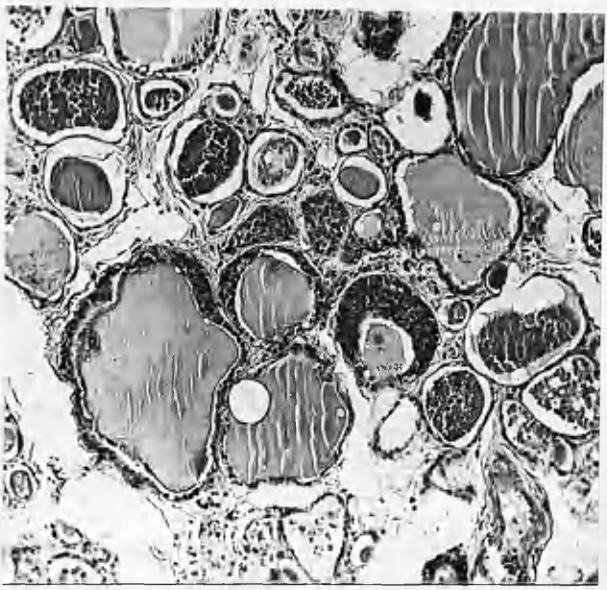
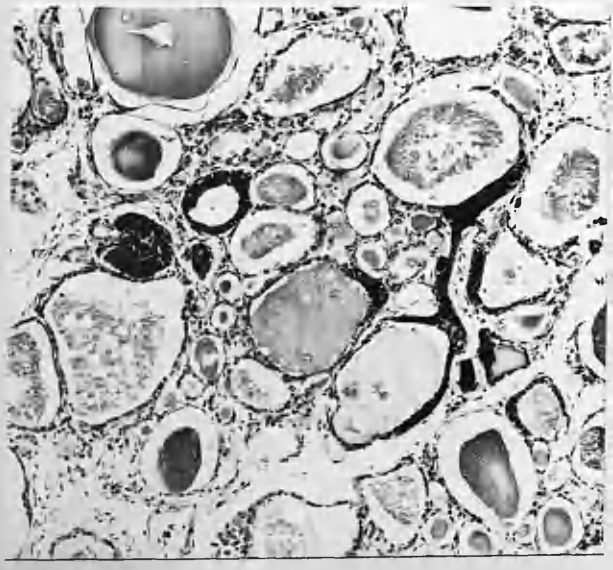


Fig.65A and B (from the same block).
Female, 62: thyroid clinically and histologically normal.
Solid nests, and acini partly lined by stratified epithelium. Direct continuity between atypical and true thyroid epithelium.
Both H & E, x 100.



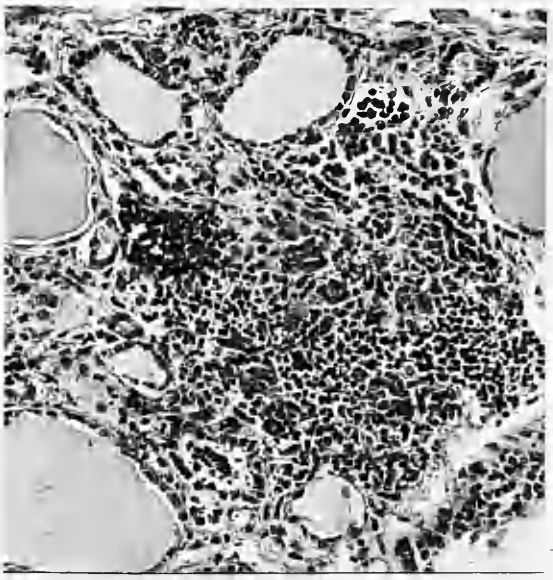


Fig.66. Male, 62: clinically normal thyroid with focal lymphocytic infiltration. A hyperplastic acinus at the margin of the lymphocytic focus is small, devoid of colloid with a clump of macrophages in the lumen. Acini within the lymphocytic focus are collapsed.
H & E, x 200

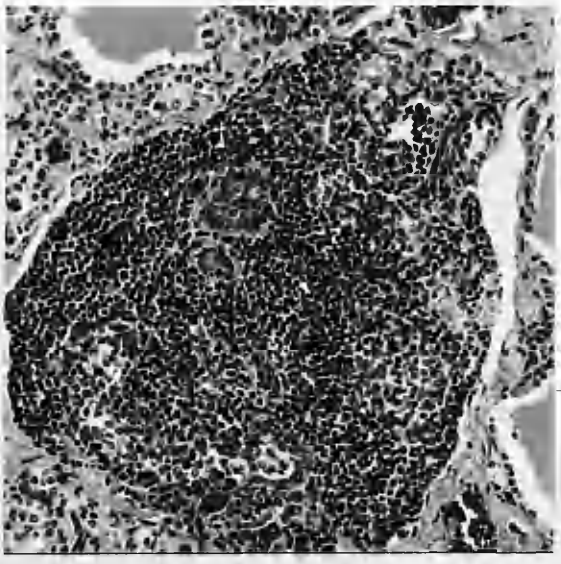


Fig.67. Same case. One cell nest (above centre of field) showing radial arrangement of nuclei.
H & E, x 200

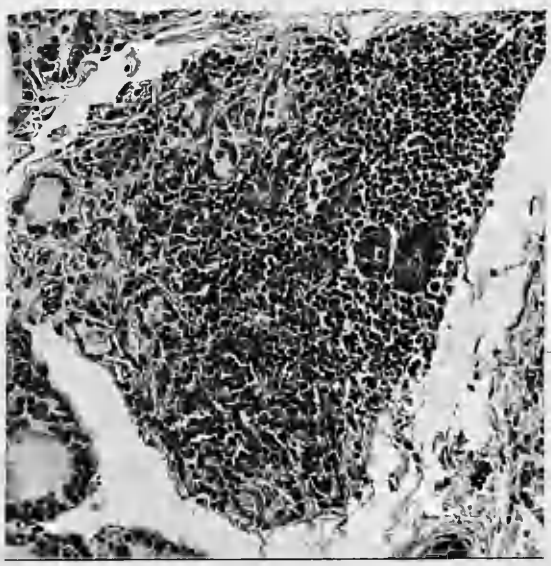
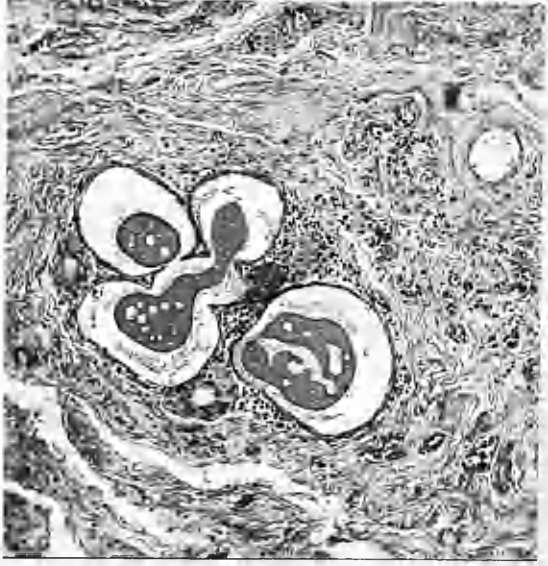


Fig.68. Same case. Two solid cell nests in a lymphocytic focus.
H & E, x 200



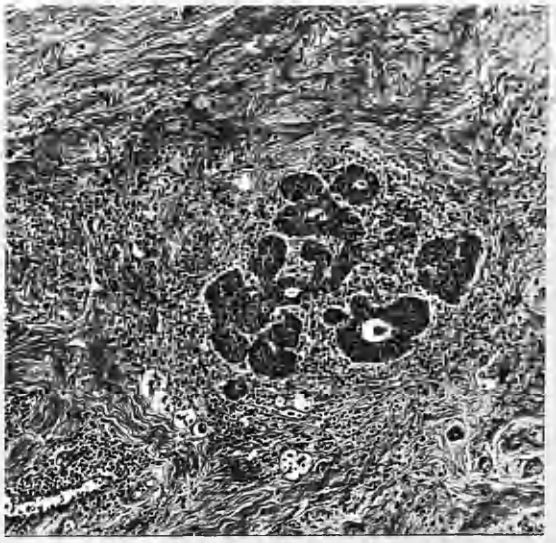


Fig.69 (above), Fig.70 (below). Female, 78 (myxoedema). Foci of atypical epithelium and round-cell infiltration.
Both H & E, x 100

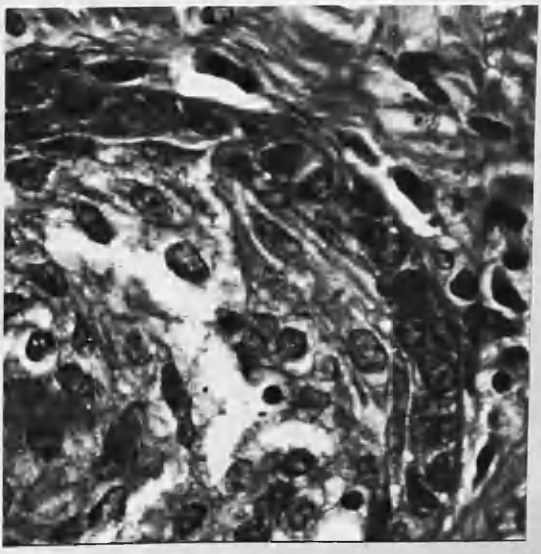


Fig.71. Same case. High magnification, to show true squamous epithelium, with intercellular bridges. Plasma cell infiltration. H & E, x 700

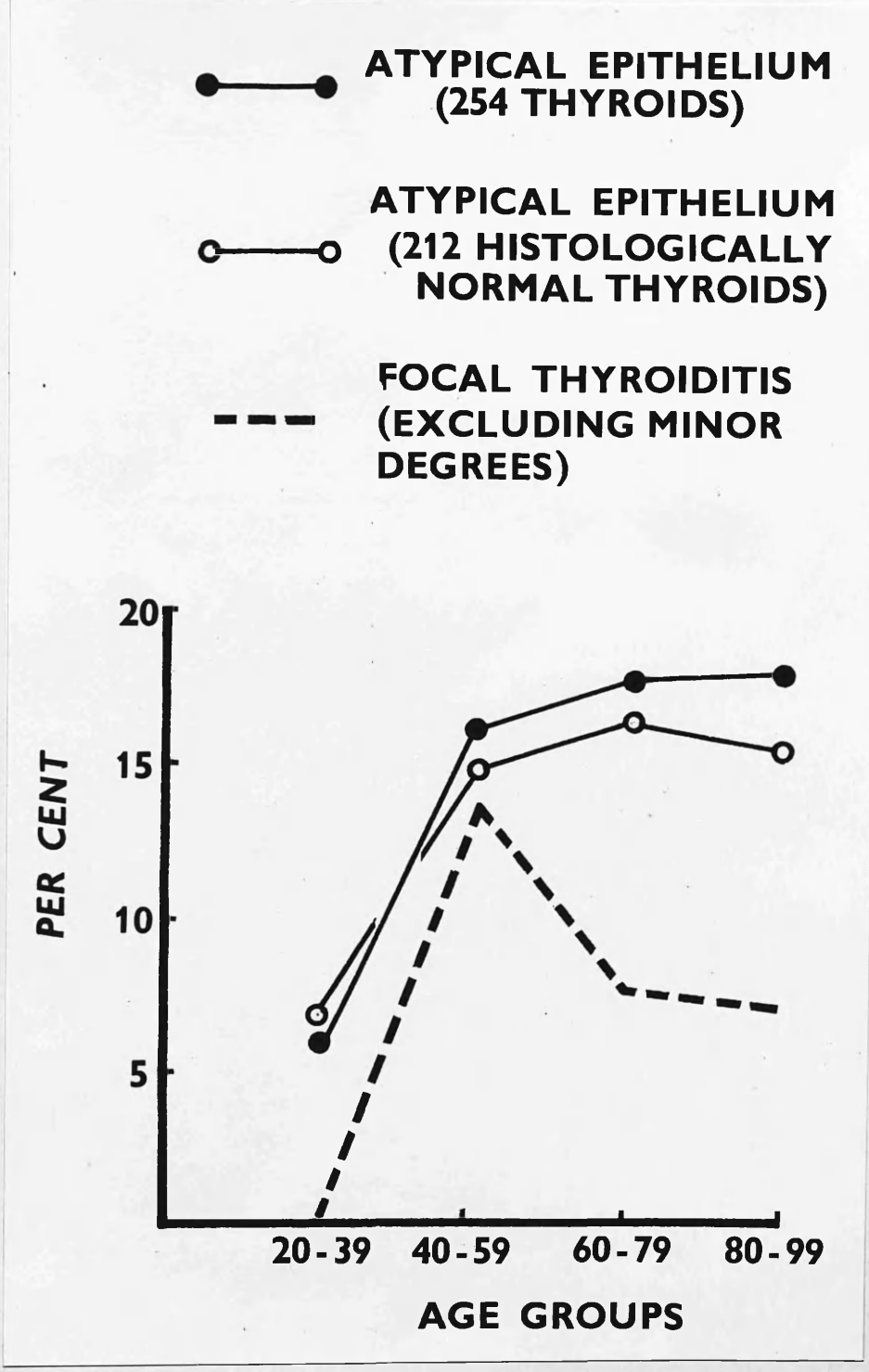


Fig. 72. The incidence of atypical epithelium and of lymphocytic infiltration in the thyroid.

ANISOTROPIC CRYSTALS IN THE THYROID

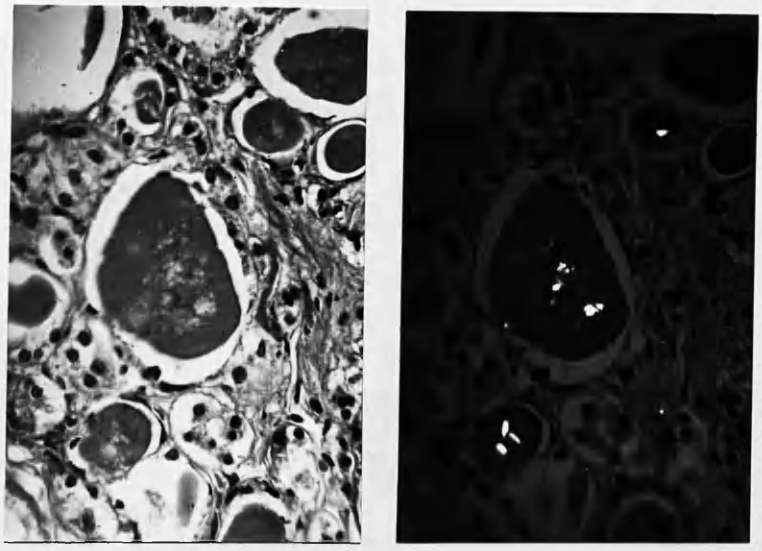


Fig.73. An example of anisotropic crystals whose presence was suspected without the use of polarised light.
H & E, x 300

(Most of the succeeding photographs greatly exaggerate the visibility of the crystals with non-polarised light).

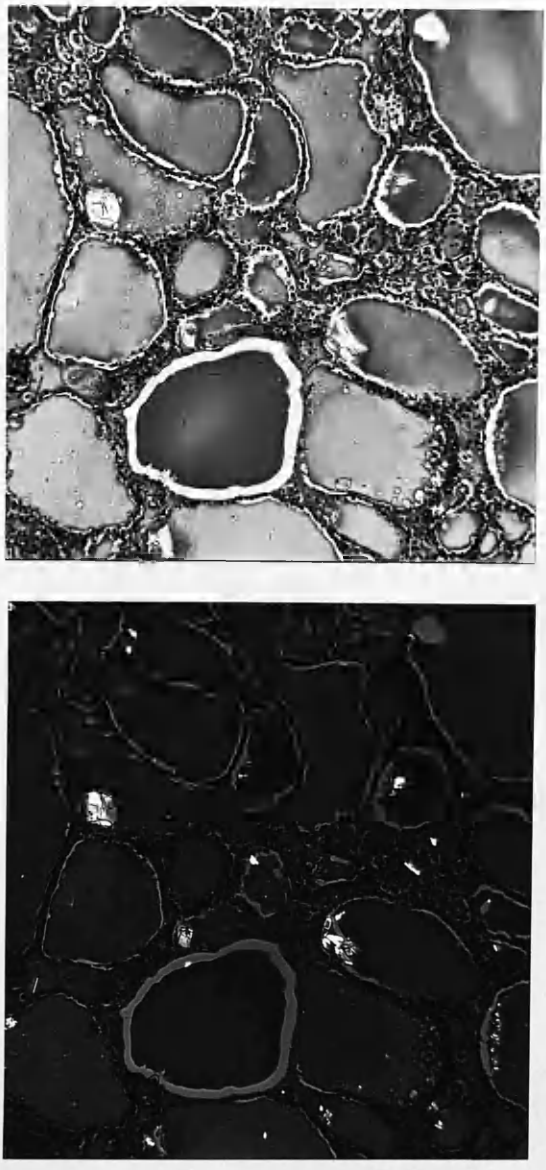


Fig. 74. Female, 58. Normal thyroid: anisotropic crystals in solitary vacuoles. (The abnormal visibility of the crystals with non-polarised light obscures the presence of some of the vacuoles).

H & E, x 80

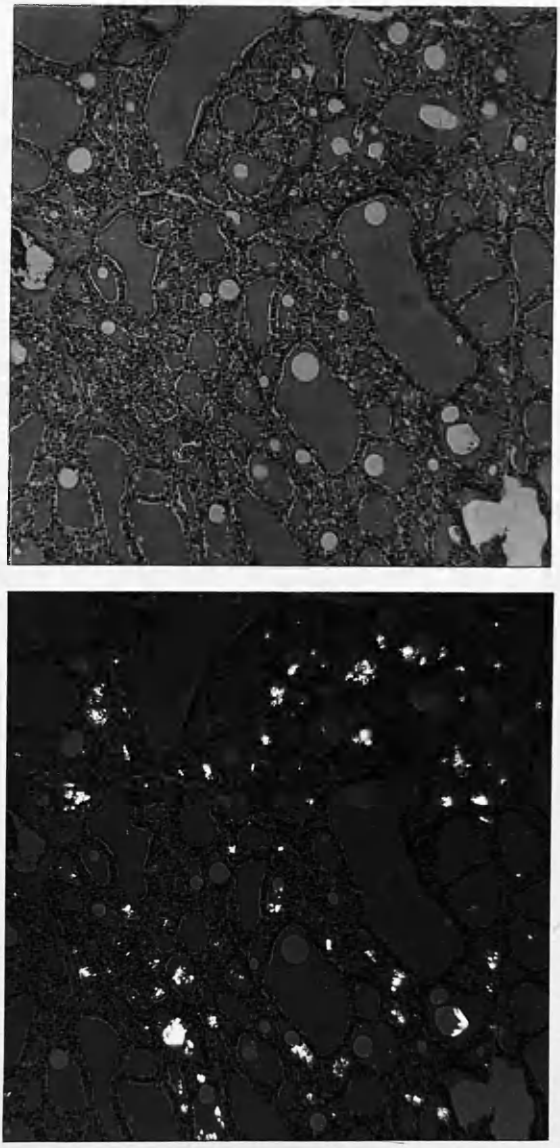


Fig. 75. Female, 82. Normal thyroid: solitary vacuoles are numerous, but most of the crystals lie free in the colloid.
H & E, x 80

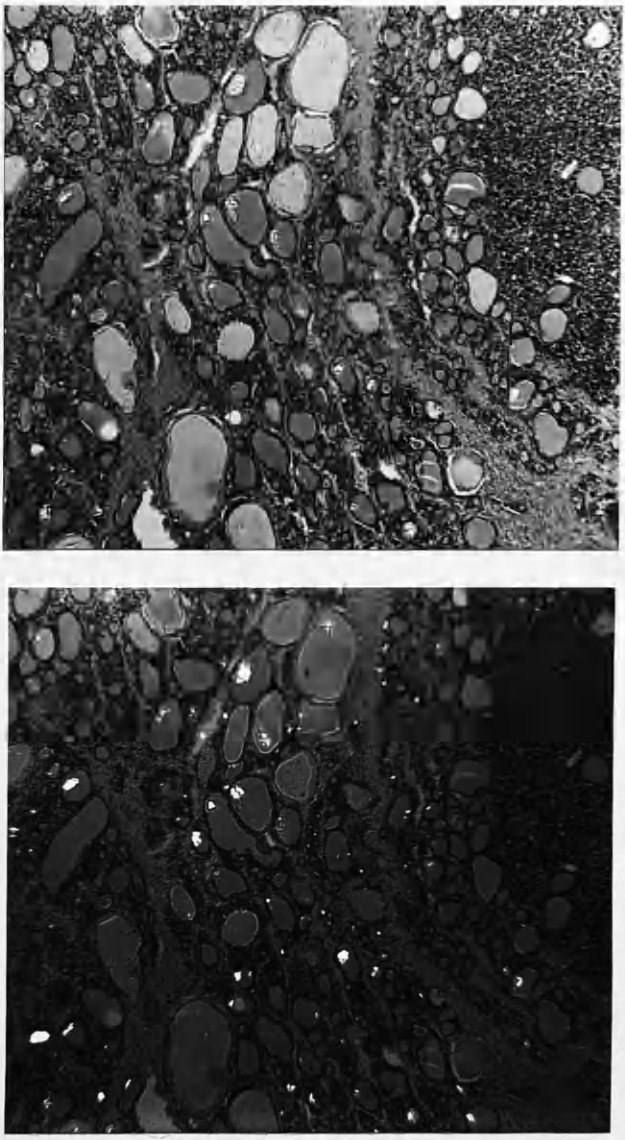


Fig. 76. Female, 52. There are many crystals in the normal thyroid tissue, none in the adenoma.

H & E, x 40

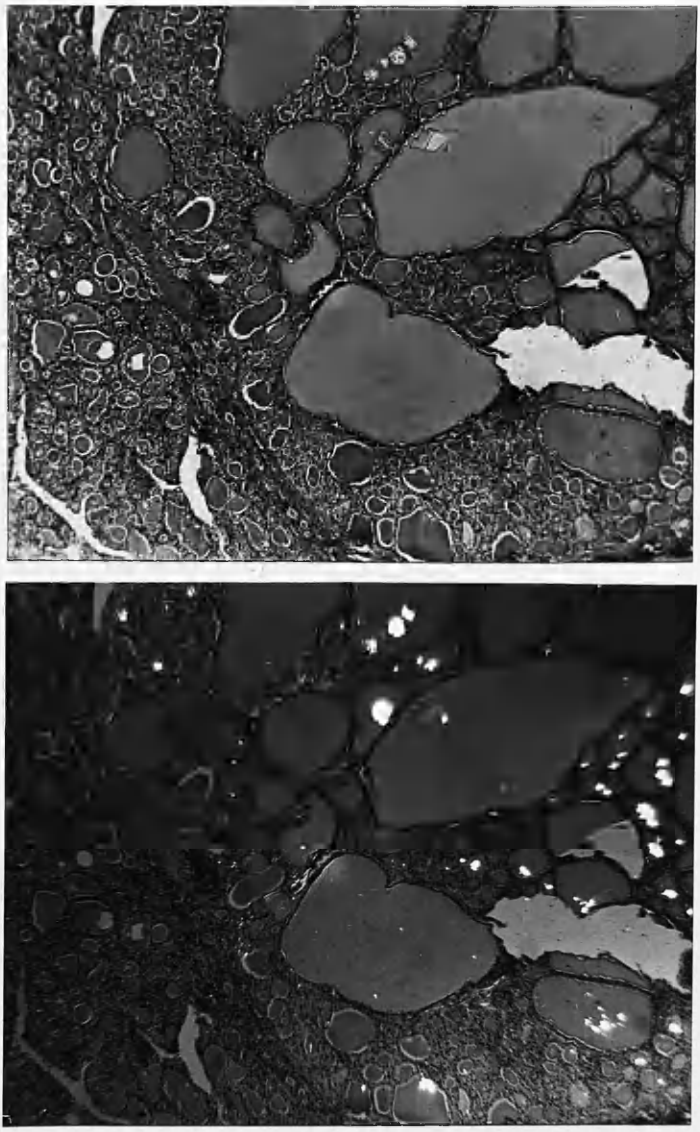
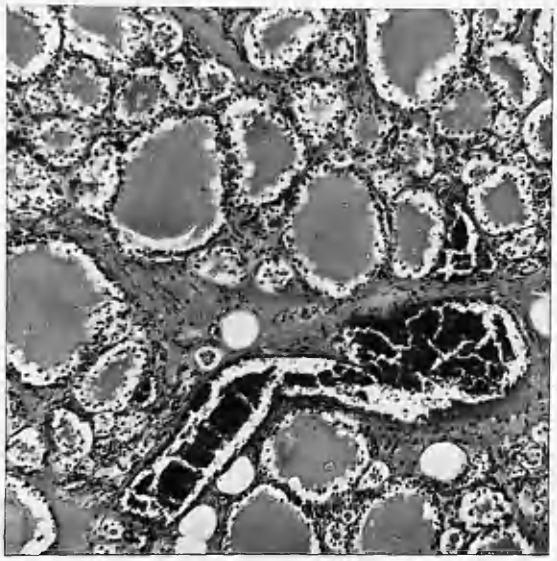


Fig. 77. Female, 81. There are many crystals in the nodule, none in the normal tissue.

H & E, x 40



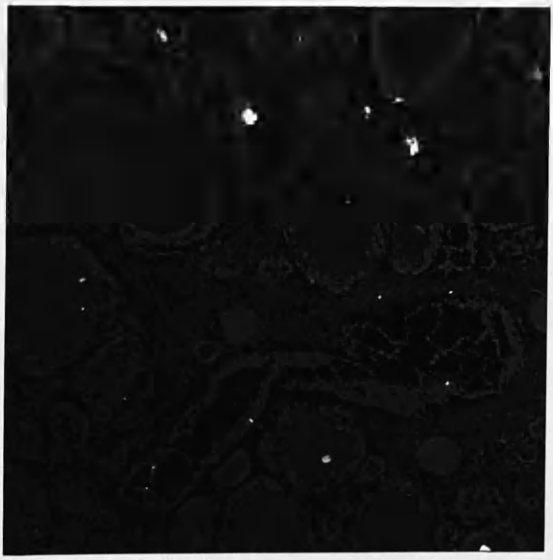


Fig. 78. Male, 82 (death due to laryngeal obstruction, death-fixation interval 21 hours). Pyknosis, loss of cytoplasm. The picture suggests post-mortem degeneration, but the presence of colloid-like substance in the lymphatics is in favour of ante-mortem change.
Anisotropic crystals are no less common in this type of gland.
H & E, x 80

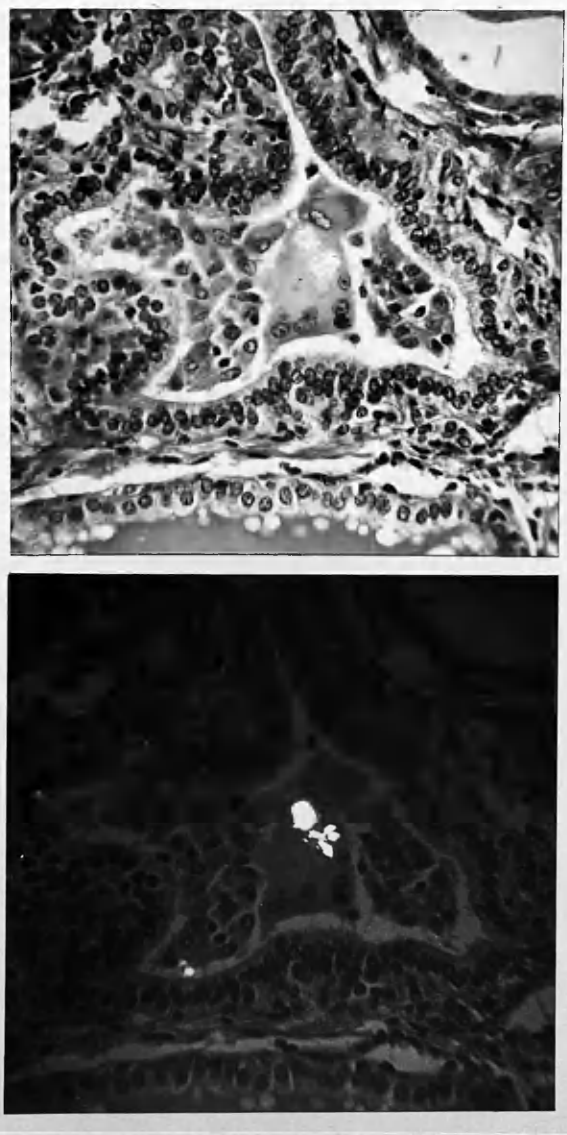


Fig.79. Female, 20 (toxic diffuse goitre). Anisotropic crystals in an intra-acinar giant cell.

H & E, x 300

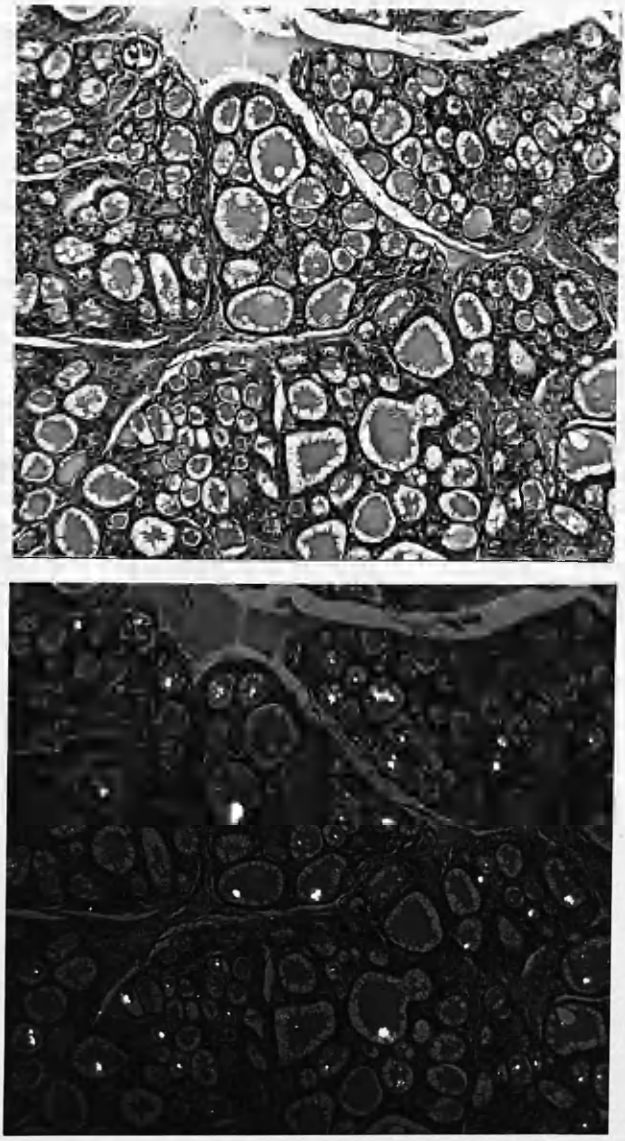


Fig.80. Female, 60: toxic nodular goitre, with colloid-like substance in the lymphatics.
Crystals were numerous in tags of normal tissue, but very scanty in the hyperplastic areas. This field of comparatively mild hyperplasia is exceptional in showing numerous crystals.

H & E, x 80

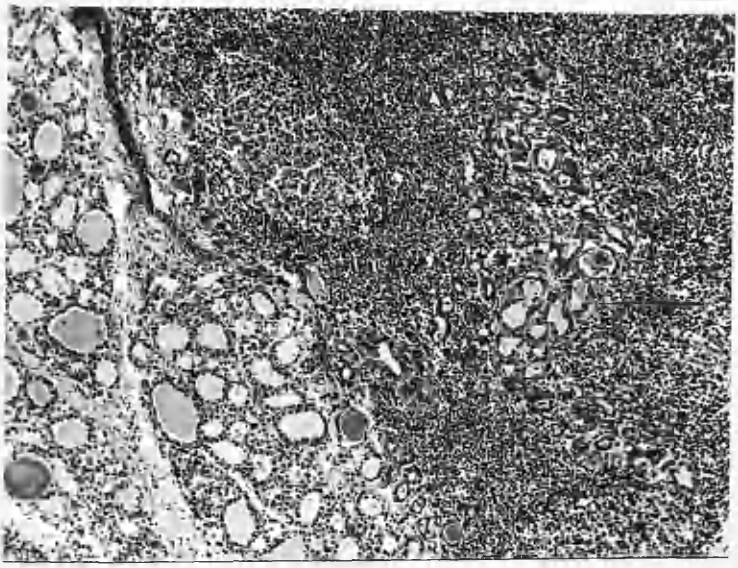
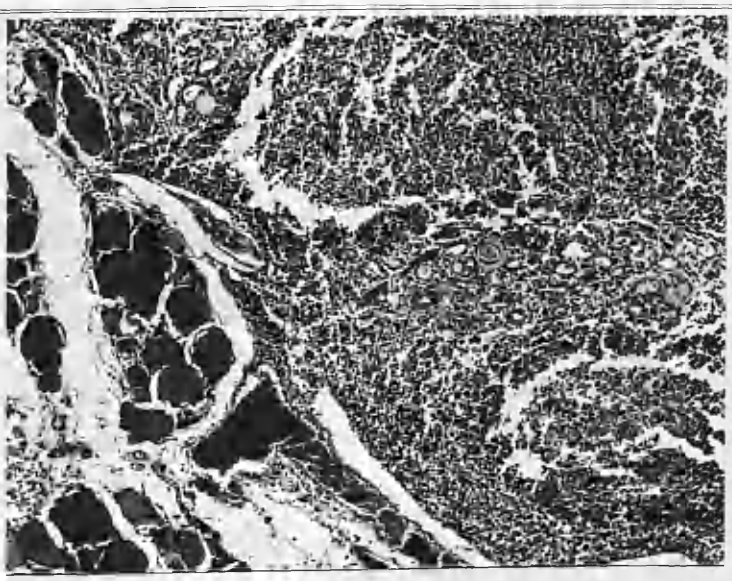
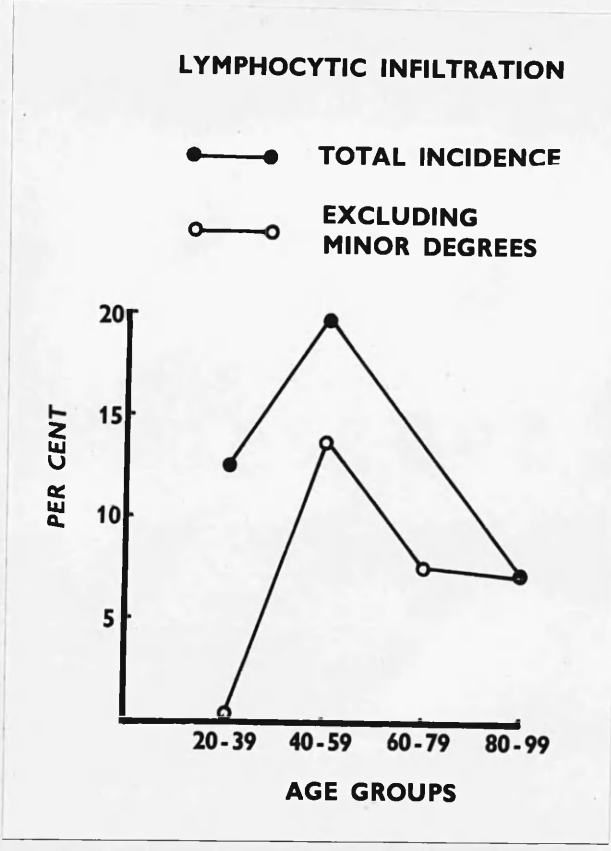


Fig.81. Female, 72. Lymphoid hyperplasia in a clinically normal thyroid; germinal centre, oxyphilic epithelium. Neighbouring thyroid tissue shows minimal signs of increased activity.
H & E, x 80

Fig.82. Female, 70. Lymphoid hyperplasia in a clinically normal thyroid. The gland is of generally inactive appearance, but the acini within the lymphoid areas are collapsed and often empty.
H & E, x 60





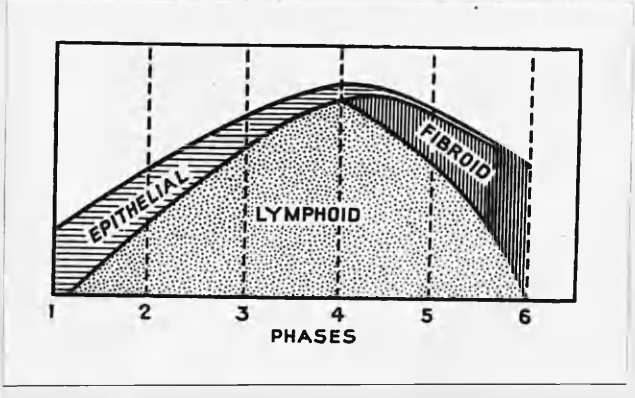


Fig.83. Above: the age incidence of lymphocytic infiltration in the clinically normal thyroid.
Below: Levitt's schematic representation of the life history of the toxic thyroid (from Fig.2 of Levitt, 1957).

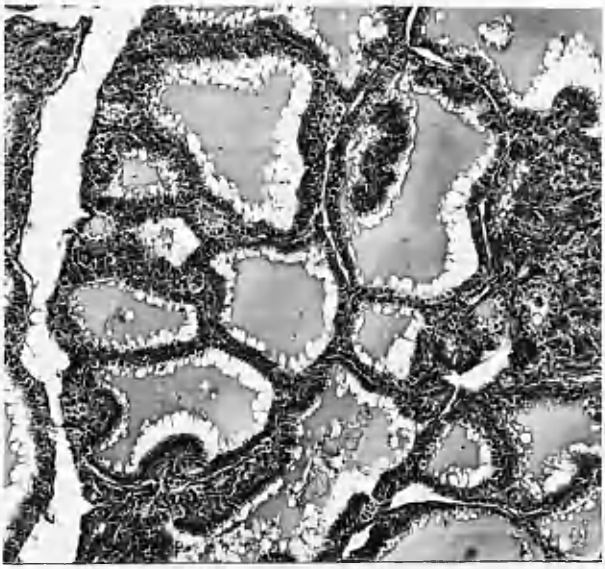
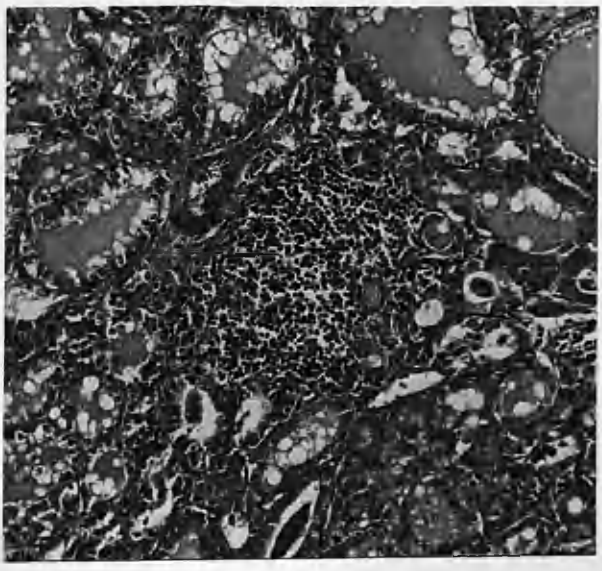


Fig.84. Case 2: toxic goitre in 1941.
H & E, x 120

Fig.85. Another field, showing a focus of round-cell infiltration, pseudogiant cells, a few oxyphilic cells.
H & E, x 150



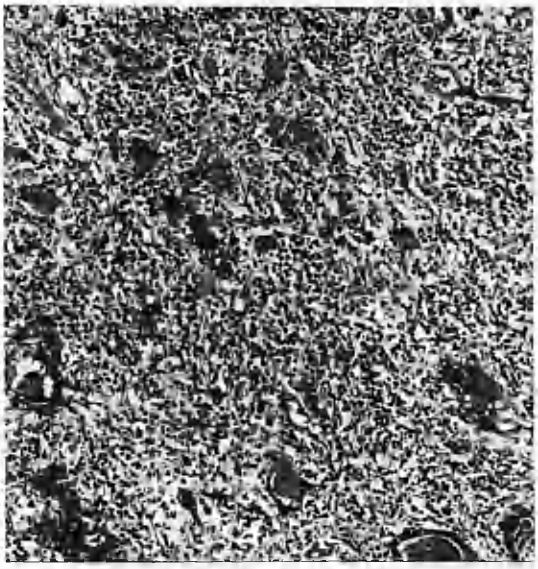


Fig.86. Case 2: chronic thyroiditis in 1956. Diffuse plasma-cell infiltration, degeneration of acini.
H & E, x 120

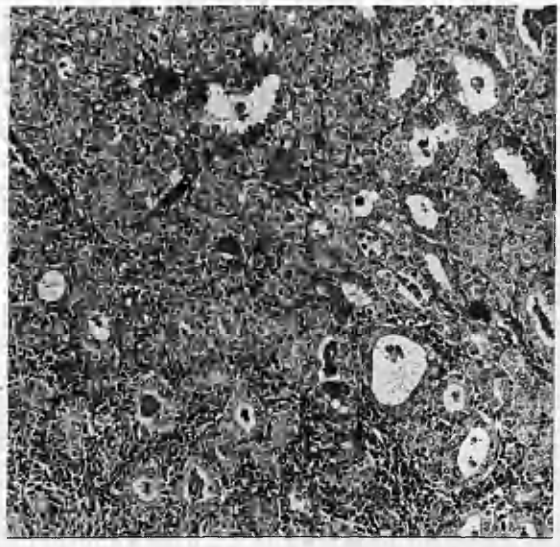


Fig.87. Same case: margin of a hyperplastic focus, showing little cellular infiltration. Abundant plasma cells in neighbouring tissue.
H & E, x 120

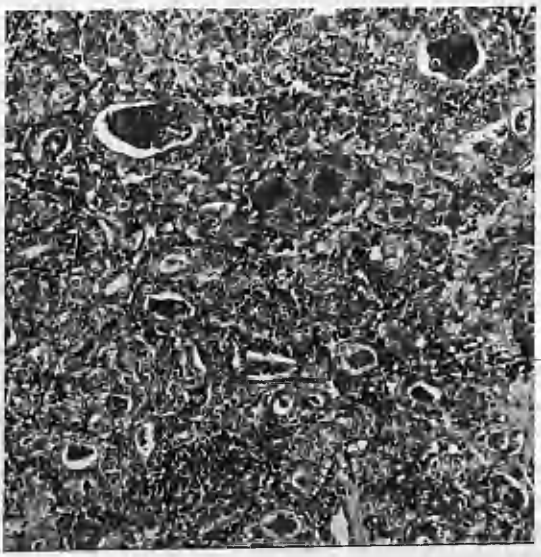


Fig.88. Another field, showing oxyphilic epithelium, large pseudogiant cells.
H & E, x 120

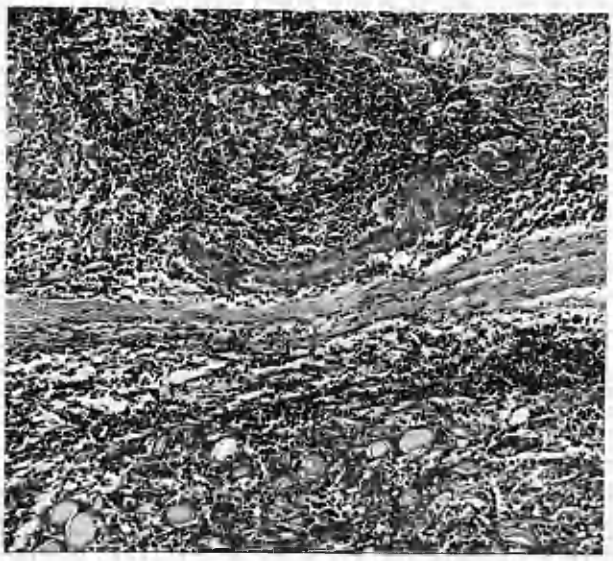
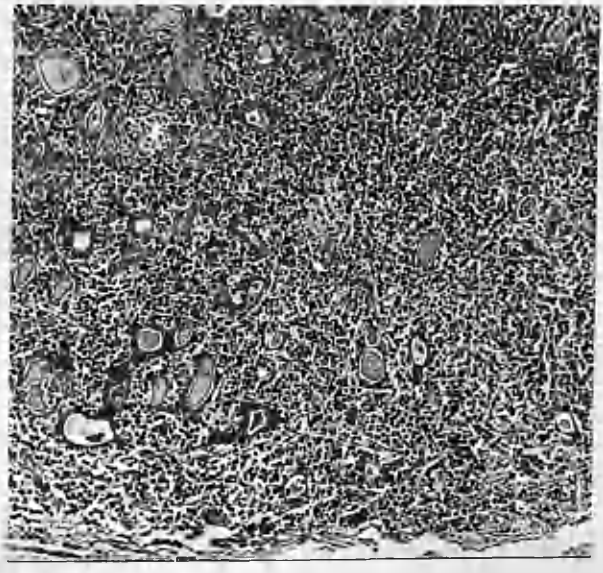


Fig.89. Case 4: chronic thyroiditis 20 years after operation for exophthalmic goitre. Focal and diffuse cellular infiltration, band of fibrous tissue traversing section, nest of squamous epithelium.

H & E, x 120

Fig.90. Same case. Intense plasma-cell infiltration, oxyphilic epithelium. Disorganisation of the acini on the right.

H & E, x 120



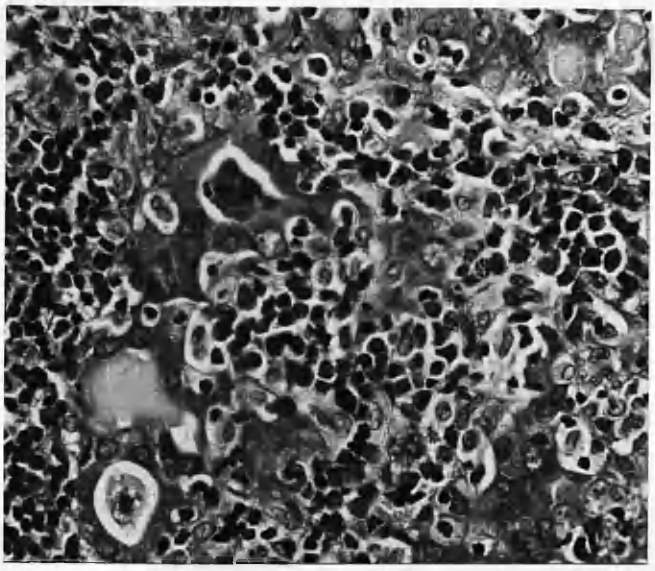
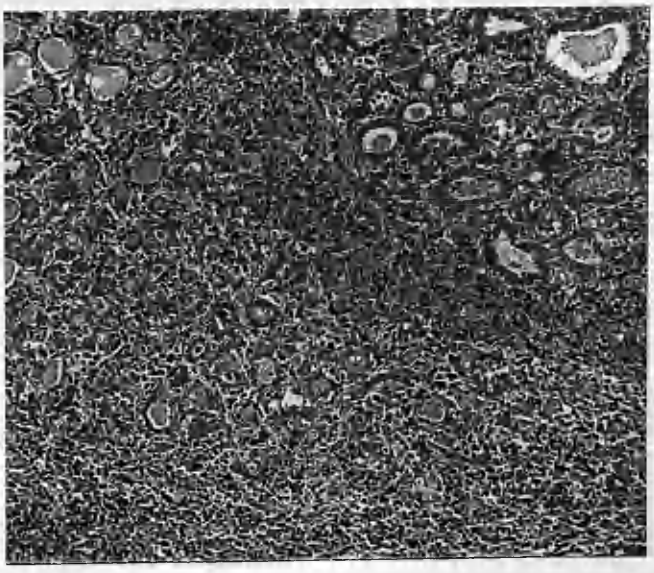


Fig.91. Same case: higher magnification, showing plasma-cell infiltration and oxyphilic epithelium.
H & E, x 400

Fig.92. Same case: margin of a hyperplastic focus. Cellular infiltration is much less intense than in the neighbouring tissue.
H & E, x 100



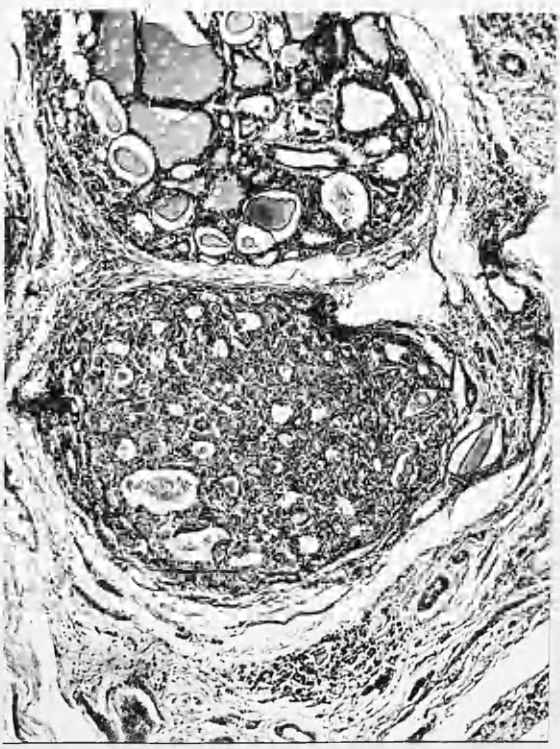


Fig.93. Female, 65. Oxyphilic and hyperplastic nodules in small focus of thyroid tissue remaining after thyroidectomy. Patient was euthyroid; death due to myocardial infarction.

H & E, x 60

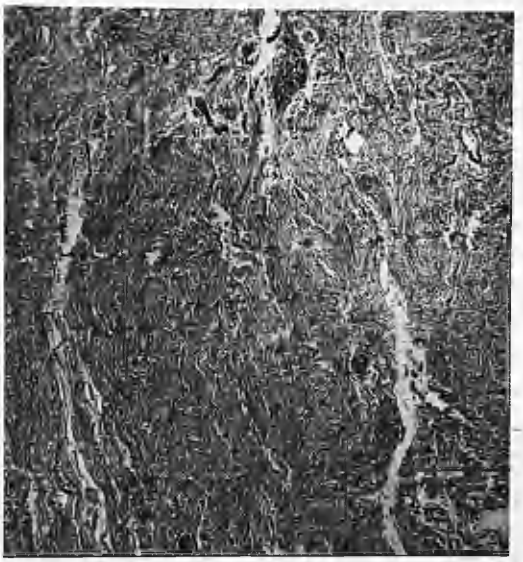


Fig.94. Myxoedema (Case 9): extensive fibrous replacement of the parenchyma, with microscopic foci of surviving epithelium.

H & E, x 60

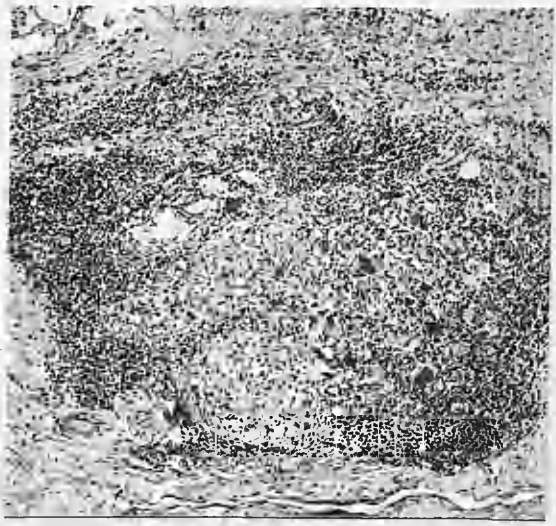


Fig.95. Myxoedema (Case 5); lymphocytic infiltration round a focus of oxyphilic tissue.

H & E, x 60

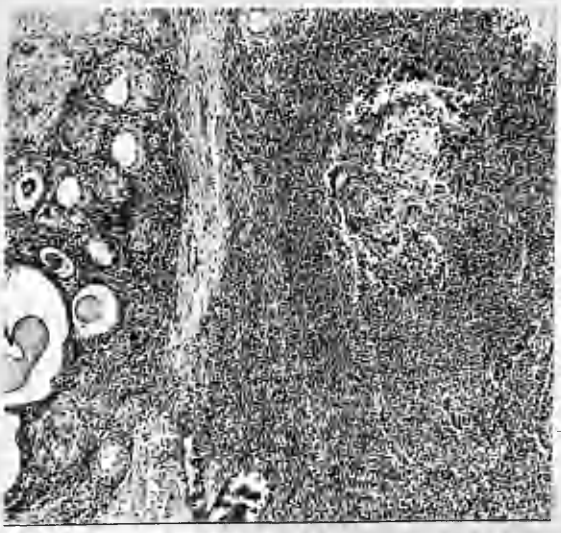


Fig.96. Myxoedema (Case 3): a more cellular area from the gland illustrated in Figs. 69 to 71, showing oxyphilic epithelium, metaplastic epithelium and lymphocytic infiltration.

H & E, x 60

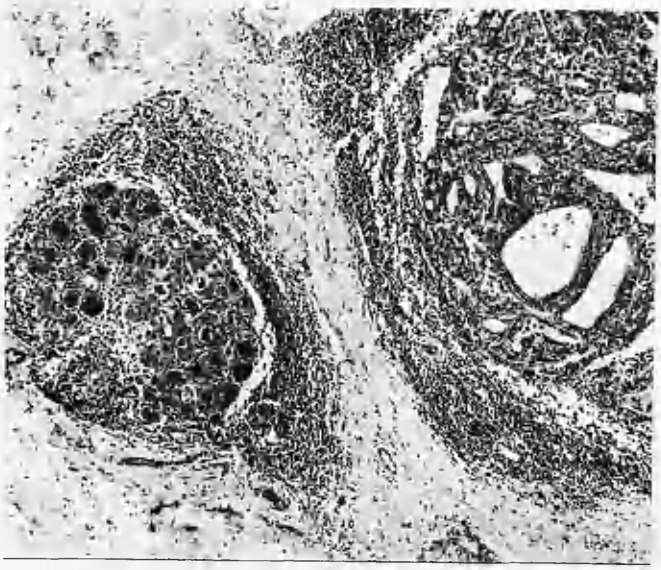
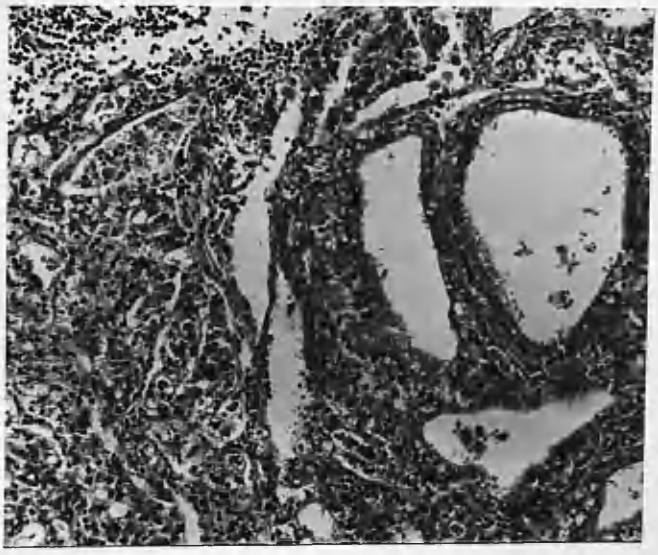


Fig.97. Myxoedema (Case 8): an oxyphilic nodule (left) and a hyperplastic nodule (right), each with a surrounding zone of lymphocytic infiltration.

P.A.S., x 60

Fig.98. Higher magnification of the hyperplastic nodule, to show columnar epithelium, intra-acinar macrophages (top left and bottom right), and comparatively sparse lymphocytic infiltration.

P.A.S., x 150



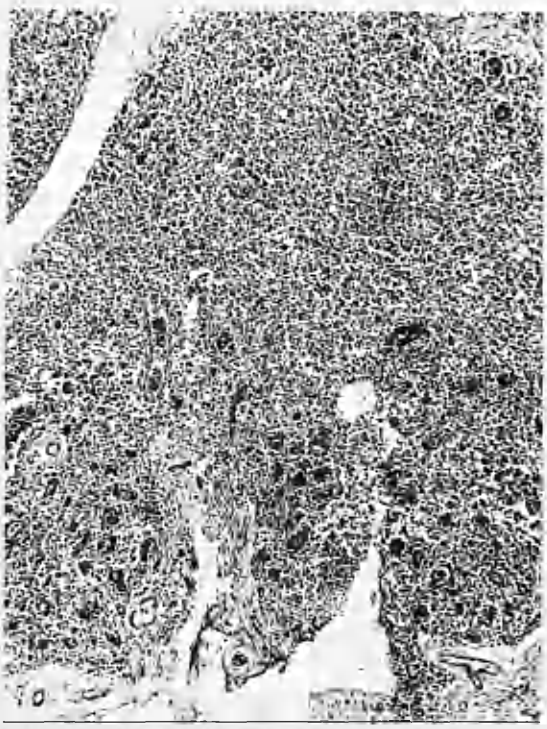


Fig.99. Myxoedema (Case 2): histological picture of diffuse chronic thyroiditis, associated with typical clinical picture of myxoedema and death in myxoedema coma.

H & E, x 60.

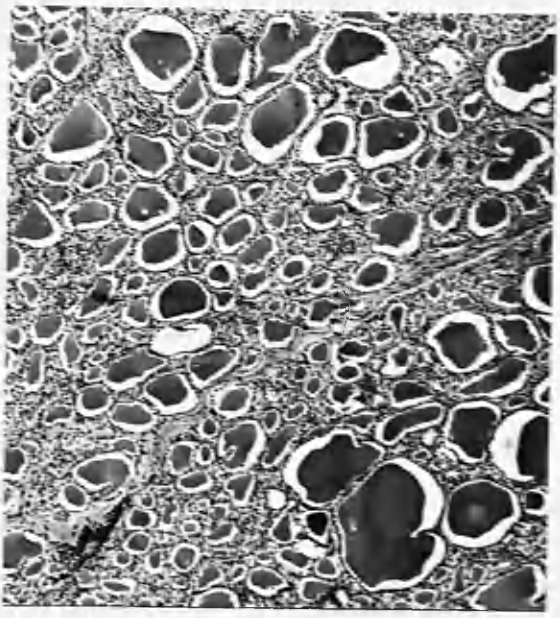
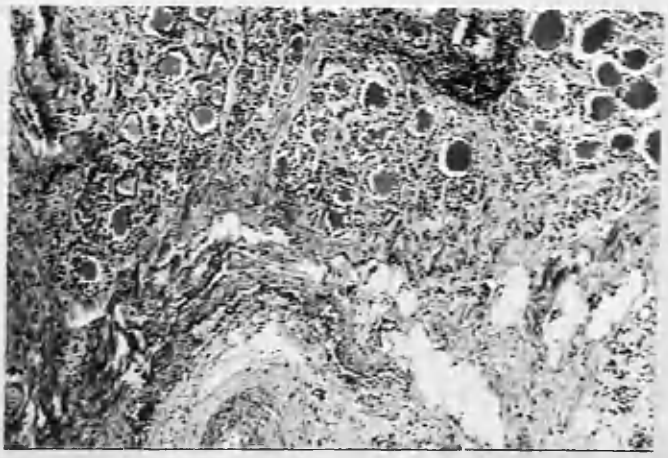


Fig.100. Female, 41: thyroid atrophy following hypophysectomy. No oxyphilia, metaplasia or hyperplasia of the epithelium; normal colloid content.
H & E, x 60

Fig.101. Same case. This was the greatest degree of fibrosis and lymphocytic infiltration in any of the sections examined.
H & E, x 60



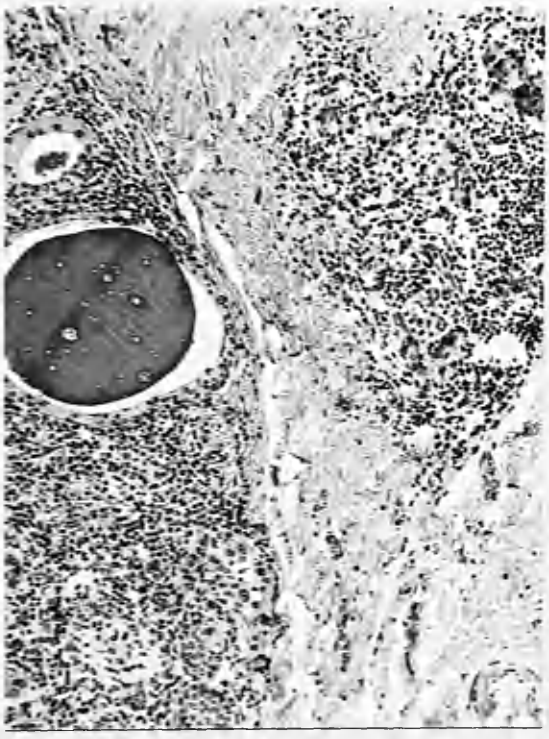


Fig.102. Female, 75. Thyroid clinically normal but histologically typical of myxoedema. Area showing metaplastic epithelium, lymphocytic infiltration and fibrosis.
H & E, x 150

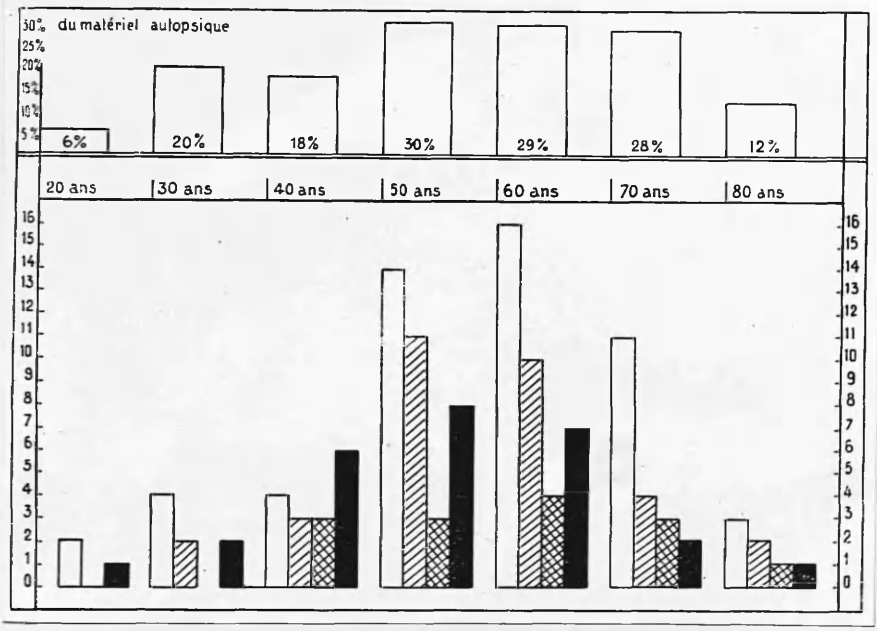


Fig.103. Table II of Bastenie (1944). Above: Relative frequency of "involutional thyroidosis" (myxoedema-like changes) in routine autopsy material. Below: Black columns represent age of onset of clinical signs in 27 cases of myxoedema. The other columns represent the age incidence and degree of "involutional thyroidosis" in 100 clinically normal thyroids.