Clinicopathological Conference

A Case of Diarrhoea and Goitre

DEMONSTRATED AT THE ROYAL POSTGRADUATE MEDICAL SCHOOL

Clinical History

Dr. C. L. COPE: The patient (Case No. 242467; P.M. No. 11630) to be considered today was a retired Greek-Cypriot government servant, born in 1898. His mother was still alive at the age of 89 but had an enlarged thyroid and a tendency to diarrhoea. His wife and three brothers were alive and well, but his father had died at the age of 61 with congestive heart failure.

The patient was first seen at Hammersmith Hospital in August 1960 when he was admitted for bilateral herniorrhaphy. He was in hospital for 14 days. His cervical spine was reported to be scoliotic but no mention was made of a goitre.

In November 1960 he was seen at Hammersmith Hospital as an outpatient because of a 10-year history of diarrhoea. He was noted to have a large nodule in the thyroid gland, which displaced the trachea to the left. It was considered clinically to be non-toxic. Barium follow-through and barium enema were normal except for a few diverticula in the colon. There was a long-standing story of mild dysuria, but his return to Cyprus prevented further investigations.

In March 1962 amoebiasis was diagnosed in Cyprus and he was treated with emetine and stovarsol. His stools were reported to contain pus and red cells and the cysts of *Entamoeba histolytica*. In spite of this treatment he continued to have three to eight motions each day.

In March 1963 he returned to England and in June of that year he was readmitted to Hammersmith Hospital.

His complaint was that he had lost 7 kg. weight in the past two years, that he was easily tired, and that his stools were watery and pale, though without blood and not bulky. There was no dysphagia and no symptoms of thyrotoxicosis. The goitre, he thought, had been present for about four years, but had shown no evident growth in the last two years. There had been no episodes of symptoms of cardiovascular abnormalities and no paraesthesiae, headaches, or attacks of pallor. There was no history of flushing.

On examination his weight was 53 kg. He had a dorsal kyphoscoliosis. There was no skin abnormality, and no fibromata or café-au-lait spots. His pulse was 100 and blood pressure 130/80 mm Hg. The sleeping pulse was at first 100, but this fell to 80 in a few days. There was a large, very firm, and grossly nodular goitre which displaced the trachea and tilted the thyroid cartilage. It was slightly tender in places and moved on swallowing. There was no stridor and no bruit, and no clinical suggestion of retrosternal extension. He showed a trace of fine finger tremor, but no eye signs. There were a few small shotty glands in both posterior triangles but none elsewhere in the neck. His heart was of normal size, but there was a systolic ejection murmur at the apex. Nothing abnormal was found in the abdomen.

Investigations

On investigation for causes of the diarrhoea the stools showed only occasional traces of occult blood. Culture for salmonella and shigella was negative, and no cysts of *E. histolytica* were seen on eight tests. Sigmoidoscopy was normal to 15 cm. Barium enema showed extensive spasm in the sigmoid colon, with many diverticula in the sigmoid and transverse colon. These may have been the cause of the traces of occult blood. Barium meal and follow-through showed diverticula in the second and third parts of the duodenum. There was rapid transit and the rectum was reached in just over three hours. An *x*-ray film of the chest showed the heart and lungs to be normal. *X*-rays of spine showed ankylosing spondylitis with dorsal scoliosis. The intravenous pyelogram showed the kidneys and renal excretion to be normal. There were two diverticula in a trabeculated bladder. The urine contained no pus cells, but grew *Escherichia coli* on culture.

The chronic diarrhoea had caused relatively little metabolic change. The E.S.R. was 16 mm./hour. The haemoglobin was 13.6 g./100 ml., the M.C.H.C. 31.5, and the W.B.C. 7,000/cu. mm. with a normal differential count. The serum level of vitamin B_{12} was 520 mμg./ml. The urea was 23 mg./100 ml., and the sodium 137, potassium 3.6, chloride 96, and bicarbonate 29 mEq/l.

The total proteins were 7.1 g./100 ml., with albumin 3.8 and globulin 3.3. The α_2 and β fractions were elevated. The calcium was 4.9 and phosphate 1.8 mEq/l. The alkaline phosphatase was 12 King–Armstrong units. The xylose absorption was 4.1 g. after a 25 g. dose (normal 5–8).

Thyroid function tests showed the B.M.R. to be −5%. The 48-hour radioactive iodine output in urine was 63% (normal 35–70), with T index of 3.1 (normal 2.8–13); the 48-hour neck uptake was 19% (normal >20%); 48-hour plasma protein bound ^{131}I was 0.17% (normal up to 0.3). These tests suggested a mild degree of hypothyroidism.

Treatment

Treatment included a therapeutic trial of emetine for one week followed by diodoquine 650 mg. t.d.s., with emetine bismuth iodide 200 mg. daily. This produced no evident improvement. Symptomatic treatment with probanthine and codeine phosphate controlled the diarrhoea. He was discharged on 2 August 1963 with only mild improvement and an uncertain diagnosis.

He was seen again in outpatients in September 1963, when he continued to complain of general weakness and lassitude. There had been no further weight loss, and his bowels were fairly well controlled by codeine phosphate and chlorpromazine. For the first time he was beginning to find swallowing difficult. He returned to Cyprus in the following month.

He again visited Britain in 1965 and was seen in outpatients. His dysphagia was worse and he now tended to cough after swallowing fluids. On examination the goitre did not appear very different from the state two years before, but he now had a large firm supraclavicular gland on the right side. This was a new feature and was suspicious of malignancy. He was therefore readmitted for the third time on 10 August 1965 for biopsy.

Readmission

On examination his weight had dropped to 45 kg. The thyroid was now fixed on swallowing. There was no stridor and no bruit. There were distended veins over the goitre and the veins of his right arm were also distended. The vocal cords

moved normally. The jugular venous pressure was not raised. The pulse was regular at 90–100, and the blood pressure was 120/70 mm. Hg. There were bilateral basal crepitations, and the liver edge could be felt 3 cm. below the costal margin.

The most important investigation was the lymph node biopsy. This showed medullary carcinoma of the thyroid gland with hyaline deposits.

X-ray of the chest showed an enlarging goitre mass extending through the thoracic inlet into the mediastinum. The spine showed severe ankylosing spondylitis, but *x*-ray of hands showed normal bone texture. The E.C.G. showed what were described as minimal non-specific abnormalities.

Culture of the urine produced a heavy growth of *E. coli* resistant to sulphonamide but sensitive to ampicillin.

Thyroid studies showed a neck uptake of 26% at 24 hours. The 48-hour urine excretion of ^{131}I was 59.8% with a T index of 4. A scan showed a particularly poor uptake on the right side of the gland.

The haemoglobin was 13.8 g./100 ml., the M.C.H.C. 31, and the W.B.C. 7,000 with normal differential. The blood urea was 12 mg./100 ml., the sodium 140, potassium 3.5, chloride 97, and bicarbonate 33 mEq/l. The serum bilirubin was 0.5 mg./100 ml., the thymol turbidity 3 units, zinc sulphate 7, and alkaline phosphatase 9 units. The acid phosphatase was 2.3 K.A. units with 0.3 tartrate labile. The lactic dehydrogenase was 135 units with 44% heat stable. The prothrombin time was 13 seconds. The serum calcium was 5.1 and phosphate 2.0 mEq/l.

The excretion of urinary 17-oxosteroids was 5.0 mg. daily and of 17-oxogenic steroids 5.5–9.5 mg. The urinary excretion of 5-hydroxy indole acetic acid was normal, and of vanillyl mandelic acid 4 μg./mg. of creatinine, a figure regarded as the upper limit of the normal range. Calcium excretion in the urine was 320 mg. daily and the output of indoles was 35 mg./24 hours (a normal figure). A glucose tolerance test showed a moderately diabetic curve with a high renal threshold. The stools still contained no pathogenic organisms and faecal fats were 4.4 g./24 hours.

Treatment

Treatment consisted in a course of deep *x*-ray therapy although the tumour was known to be rather insensitive. At first the dysphagia was aggravated, but later it improved. He was discharged on 15 October 1965.

By December 1965 the jugular vein was less obstructed. There was no further loss of weight, but the diarrhoea now needed larger doses of codeine for control. A trial course of neomycin gave no improvement in the diarrhoea. He again paid a visit to Cyprus.

His fourth and final admission to Hammersmith Hospital was on 29 March 1966. The malaise and weakness were more marked and the dysphagia was worse. He aspirated a lot of fluids. His speech was rather rambling, but he complained that something in his abdomen was making him short of breath. He was found to have pneumonia of the right lower and middle lobes. His liver was enlarged 7 cm. and had an irregular edge. The blood pressure was 95/60 mm. Hg. In spite of treatment with antibiotics he deteriorated rapidly and died two days after admission.

Clinical Diagnoses

(1) Medullary carcinoma of the thyroid.
(2) Secondaries in lymph glands and liver.
(3) Terminal right lobar pneumonia.
(4) Ankylosing spondylitis.
(5) Diverticulosis in duodenum, colon, bladder, and pharynx.
(6) Mild diabetes mellitus.

Post-mortem Findings

Dr. E. D. WILLIAMS: The necropsy on this thin elderly male was carried out 12 hours after death. No mucocutaneous tumours were present.

The most interesting findings were in the endocrine system. The right lobe of the *thyroid* (Fig. 1) was uniformly enlarged to form a smooth solid mass, 8×4.5×4.5 cm., with a variegated red-brown cut surface. Microscopy showed that this was a medullary carcinoma (Fig. 2), largely the spindle cell variant, with abundant amyloid deposition and focal calcification within amyloid (Fig. 3). In some areas the tumour was more anaplastic, forming ill-defined round masses of tumour cells, with many vacuoles but little or no amyloid; in these areas it resembled the tumour found in the cervical lymph node biopsy. Secondary deposits of medullary carcinoma were found in the cervical lymph nodes, a matted mass of nodes in the upper mediastinum, the pleura, throughout the grossly enlarged liver, and in the vertebral marrow. The left lobe of the thyroid was small, with a single small white nodule (0.4 cm. diameter) (Fig. 4) which proved to be a medullary carcinoma with abundant amyloid. In view of the scarcity of amyloid in the secondary deposits elsewhere, the solitary nature of this nodule, and the previously reported instances of bilateral medullary carcinoma, it was considered that this was a second primary tumour. Two normal parathyroids were found. The pancreas was rather autolysed, but the islets appeared normal. Both adrenals were enlarged (Fig. 5); the left (14 g.) contained a central soft rounded brown tumour (2.5 cm. diameter). The right adrenal (9 g.) showed a central collapsed partly cystic tumour (1.5×1 cm.). Both on microscopy were benign phaeochromocytomas (Fig 6), the right one being largely degenerate but also containing a small secondary deposit of medullary carcinoma.

In the *alimentary tract* the duodenal and colonic diverticula were confirmed; the villi had lost their epithelium but were not flattened. The intestinal nerve plexuses were normal.

The only significant abnormal finding in the urogenital tract was in the bladder. This showed two diverticula, and on section the muscle in places formed whorls and nodules in an abnormal growth pattern.

In the *respiratory tract* the trachea was deviated to the left, and both lungs were moderately overweight. Widespread large and small pulmonary emboli were present, with scattered infarcts, but no significant infection was found.

The *skeletal system* showed bony ankylosis of cervical dorsal and lumbar vertebrae.

There were no relevant findings in the *cardiovascular system*, nor, apart from secondary carcinoma, in the *reticuloendothelial system*. The *central nervous system* could not be examined, because necropsy permission was limited.

Pathologist's Diagnosis

(1) Bilateral primary medullary carcinoma of thyroid, with widespread secondary deposits.
(2) Bilateral phaeochromocytomas of adrenals.
(3) Diverticula of intestinal tract and bladder.
(4) Massive pulmonary emboli.
(5) Ankylosing spondylitis.

Discussion

Dr. COPE: This is a fascinating case. So far as I can gather the medullary carcinoma of the thyroid is a form which has been recognized only in the last 10 years. We did not diagnose it, except in so far as we called for a biopsy. Dr. Williams diagnosed it, and he is our expert on this disorder; we hope

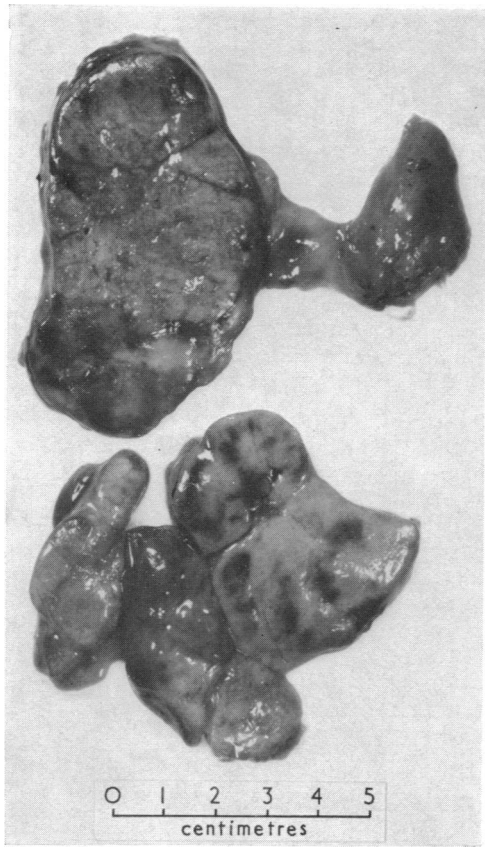

FIG. 1

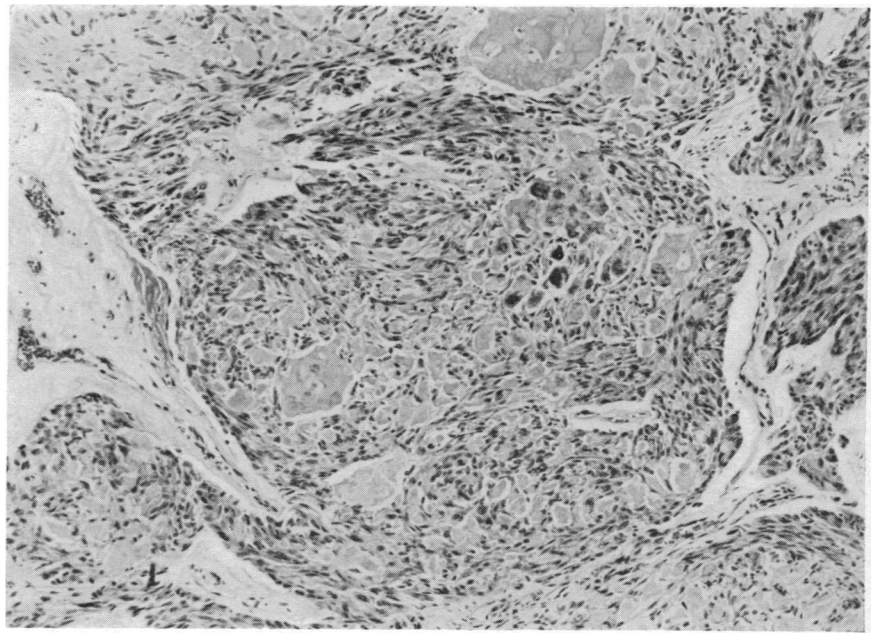

FIG. 2

FIG. 1.—Thyroid, with right lobe transected to show a massive well-circumscribed tumour, and mediastinal lymph nodes also replaced by tumour.

FIG. 2.—Medullary carcinoma of right lobe of thyroid. Note the abundant amyloid deposition. (H. and E. ×105.)

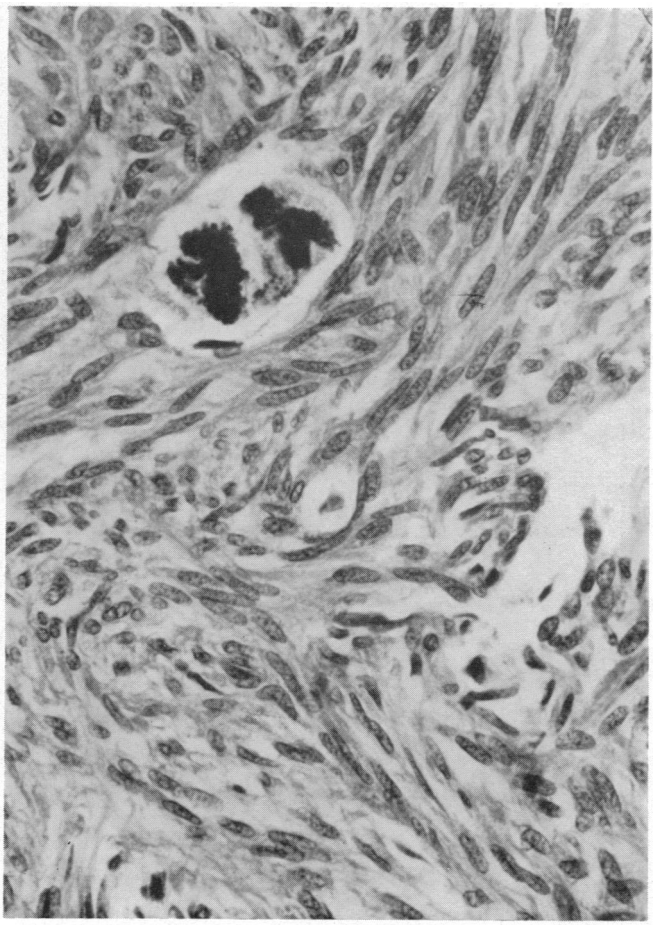

FIG. 3.—High-power view of the same tumour. The dark granular material is calcification within a deposit of amyloid. The carcinoma shows predominantly a spindle-cell pattern. (H. and E. ×440.)

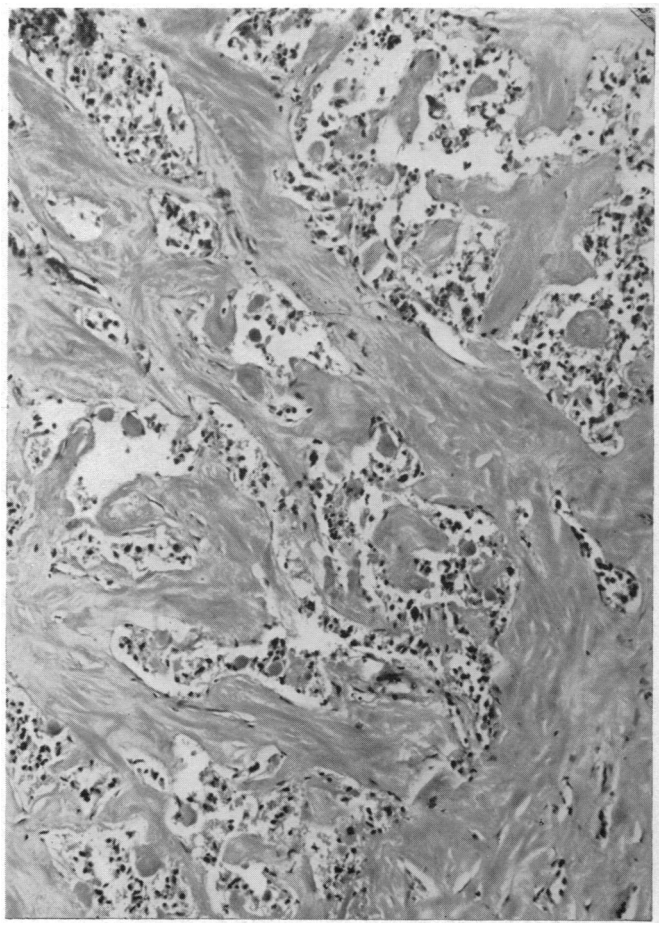

FIG. 4.—Tumour from left lobe of thyroid. This is also a medullary carcinoma with abundant stromal amyloid, and is probably a second primary tumour. (H. and E. ×110.)

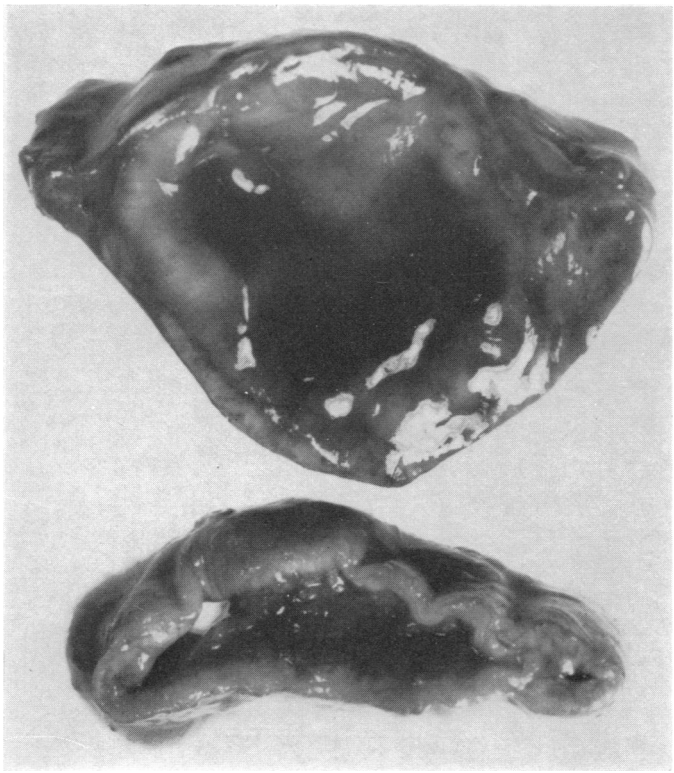

FIG. 5.—Both adrenals bisected to show bilateral phaeochromocytomas. (×3.3.)

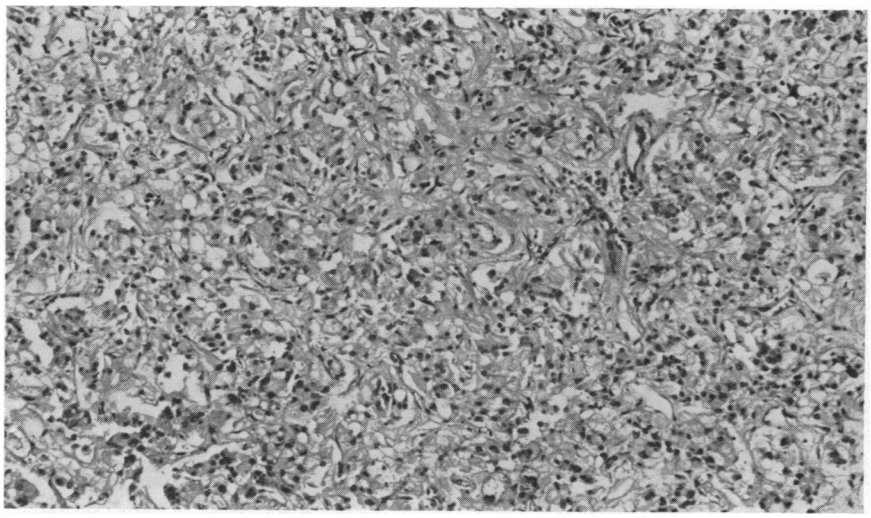

FIG. 6.—Phaeochromocytoma of left adrenal. The tumour shows the typical packeted arrangement of regular large cells with abundant granular cytoplasm. (H and E. ×105.)

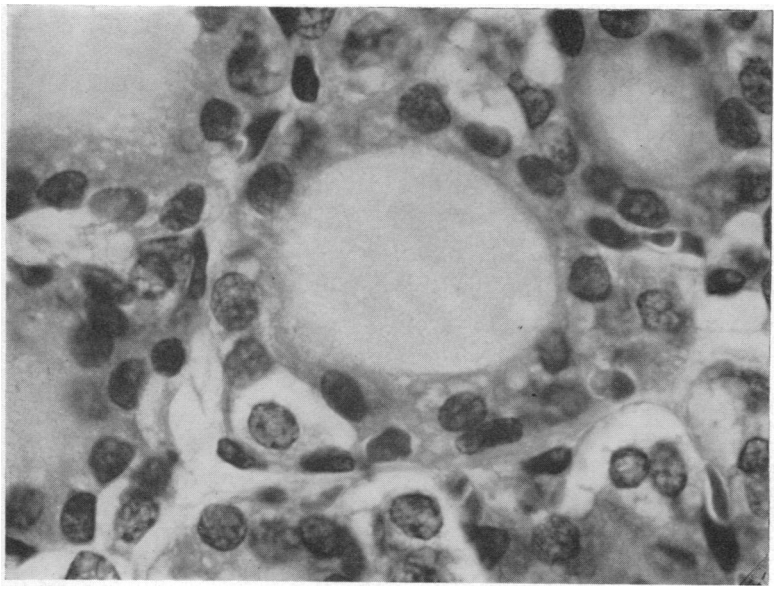

FIG. 7.—High-power view of a thyroid from an aged rat. The parafollicular cell is seen as a cell with pale cytoplasm separated from the colloid by the darker cytoplasm of the follicular cells. (H. and E. ×910.)

to hear a lot more about it from him in due course. We diagnosed the presence of malignancy clinically by two of the classical criteria, increasing dysphagia, and the appearance of a lymph node which was an obvious metastasis.

Cause of Diarrhoea

We did not, however, realize there was any link between this medullary carcinoma and the symptom of persistent diarrhoea. The association between medullary carcinoma and persistent diarrhoea is, I believe, a discovery made by Dr. Williams himself. Certainly we found no other cause for it; I do not think for a minute the diverticula were an adequate cause—there was no infection, and there was very rarely any occult blood. There was no other local cause, and I think Dr. Williams must be perfectly right in suggesting that there was a humoral cause for this intestinal hurry, which the patient undoubtedly had right through to the colon. At no time did we as clinicians consider a phaeochromocytoma, and even in retrospect there was no evidence of it. He never had any cardiovascular episodes, any episodes of paraesthesia, of pallor, of headaches, of paroxysms of hypertension, and never was any raised blood pressure recorded, so far as I am aware. The vanillyl mandelic acid test, which was done after we knew the diagnosis at the suggestion of Dr. Williams, was at the upper limit of normal, but not high enough to give us any real clue. Some of you may have seen the very opportune paper in the *British Medical Journal*[1] about this particular association of medullary carcinoma with phaeochromocytomas and its familial incidence. It is interesting that this particular patient had a mother who, when we last heard, was still alive at the age of 89 but had an enlarged thyroid and had complained of diarrhoea for many years of her life. Obviously it was not a death-dealing disorder in her case. The wife and three brothers were alive and they were all well. The patient's father had died at the age of 61 with what was described as congestive cardiac failure. One can only speculate whether that was in any way related to a phaeochromocytoma. We do not even know if he had a goitre. There are many points of interest here, the thyroid aspects, the reasons for the diarrhoea, and the question of diverticula as a possible alternative cause for the diarrhoea.

Diarrhoea and Thyroid Tumours

Dr. WILLIAMS: The relationship between the thyroid and the diarrhoea is based on a study of a large number of cases which I collected together with Professor Doniach and Dr. Brown from various London hospitals; we collected them mainly to look at the pathology of this type of tumour. In going through the records it became apparent that a surprisingly large number of them showed diarrhoea. The diarrhoea correlated with the extent of the tumour, in that very few patients with tumour localized to the neck had diarrhoea, and a very high proportion of patients with widespread tumour had diarrhoea. Also, in four patients there was evidence that when the tumour was resected the diarrhoea improved, in two of them to recur again when the widespread tumour recurred. Putting these observations together it seems likely that there was a humoral factor linking the tumour with the diarrhoea. The other points which made this a likely possibility are the resemblance that this tumour bears to certain other hormone-secreting tumours like carcinoids. This resemblance is both histological and histogenetic, as there is evidence to suggest that this tumour does not arise from the ordinary follicular cells of the thyroid but from a second type of thyroid cell, the parafollicular cell. This cell has a number of different possible functions, among them the production of calcitonin; in the sheep this cell has been shown to contain 5-hydroxytryptamine (5 H.T.).

We therefore have a tumour of a cell which is potentially capable of making 5 H.T., and which is likely to have a humoral function unrelated to thyroxin. The nature of the humoral factor leading to diarrhoea is another point. Despite the fact that this tumour may occasionally make 5 H.T., this does not seem to be the cause of the diarrhoea. Slightly increased 5-hydroxyindolacetic acid excretion was found in two out of the seven cases where we've had a chance of testing urine. In one case we found a raised level of kallikrein in the tumour. Kallikrein is the enzyme secreted by carcinoids which releases small chain polypeptides from their precursor kininogen, an alpha-2 globulin. We have since failed to find kallikrein in several other tumours, so I think there must be some other factor, and we are now investigating various other possibilities.

Professor C. BOOTH: What about calcitonin? If this tumour is derived from the cells which secrete calcitonin, why doesn't this tumour secrete calcitonin?

Function of Thyroid Cells

Dr. I. MCINTYRE: May I comment here? The thyroid is really two separate endocrine glands: the A cells, secreting the iodothyronins; and the C cells, which normally secrete calcitonin. This is reasonably well established now, both biochemically and immunochemically. Now, I would like to ask Dr. Williams whether he thinks this tumour arises from a third cell type within the thyroid, or whether he thinks it arises from the C cells. I think it's better to use the term "C cells" for the calcitonin-producing cells, because they cannot be described simply as parafollicular, as their position varies from species to species.

Dr. WILLIAMS: That question is best answered by reference to a photomicrograph of thyroid tissue (Fig. 7). This is a high-power view of a rat thyroid gland. It shows the follicles full of colloid and lined by follicular cells. In the centre is a second type of cell with a clear cytoplasm. The follicular cells link together to separate this clear cell from the colloid, and I think that should immediately make one suspect that its function is unrelated to the production of colloid or thyroxin. In the sheep these cells have been shown to contain 5 H.T., while in other animals the cells with a similar morphological position have been shown to contain calcitonin. Now, to answer Dr. McIntyre's comment. We can compare the thyroid to the pancreas. In some species of fish the islet cells line the ducts between the duct epithelium and the basement membrane, whereas in mammals they form the distinct cell groups known as the islets of Langerhans. Similarly in some species, for example the rat, the second type of thyroid epithelial cells lie between the follicular cell and the basement membrane, while in others, particularly the dog, they form "thyroid islets" of solid cells lying between the follicles. These cells may have a variety of different functions. Two of the functions that are known are that in some animals they can make 5 H.T., and that in others some at least of the cells can make calcitonin and therefore can be known as C cells. A C cell is defined in terms of production of calcitonin. Maybe there are several different types of epithelial cell in the thyroid apart from the follicular cell. I don't think at present we really have enough evidence to answer the question of whether there is a cell type for each hormone produced.

Dr. I. GILLILAND: Are they necessarily homogenous cells, these "islets of Williams"? Even morphologically they differ from one place to another.

Dr. WILLIAMS: I prefer to let Professor Pearse answer that question.

Hypercalcitonaemia

Dr. COPE: May I ask Dr. McIntyre if it is yet known what the symptoms are of hypercalcitonaemia, and whether we may not perhaps be missing the world's first calcitonin-producing tumour?

Dr. McINTYRE: Unfortunately we can't measure calcitonin in serum. I think one would predict that the symptoms would be impaired resorption of bone and would be rather similar to the kind of picture which one might see in marble bone disease. Dr. Doyle and Dr. Foster showed that if calcitonin is given to animals for long periods the equivalent of "rugger jersey" spine is produced. So the long-continued over-secretion of calcitonin might produce impaired resorption of bone with "rugger jersey" spine and osteopetrosis. With a short history like this I don't think one would be able to detect bony changes. We need a means of measuring calcitonin in the blood.

Professor BOOTH: You don't think the calcification that Dr. Williams showed us in the amyloid tissue or in the ligaments in relation to the ankylosing spondylitis could have anything to do with this?

Dr. McINTYRE: I think it could, Professor Booth, but we just don't know.

Dr. WILLIAMS: If there was calcitonin production by the tumour would one not expect parathyroid hyperplasia secondary to this? I have seen one case of medullary carcinoma which at necropsy had unexplained parathyroid hyperplasia.

Thyroid C Cells

Professor BOOTH: Professor Pearse, have you anything further to add on the C cells?

Professor A. G. E. PEARSE: They have a number of characteristics, over a wide variety of species or genera, and in no single case are all the characteristics present. The electron-microscopic appearance is the one which is most uniform, and they can be seen very easily in electron micrographs of rat thyroid. The problem is to find C cells in the human thyroid. The classical method of showing them is by the Cajal silver stain which was used by Nonidez in 1931. The cells were first seen by E. C. Baber, who was an ear, nose, and throat surgeon in Brighton. He described them in 1877, and they should be called Baber cells if you use a name at all. A second method of showing them works in every animal in which I have tried it, but I have not tried it in man. This is because it is necessary to inject an amine-precursor, such as 5-hydroxytryptophan (5 H.T.P.). This is taken up and converted by the C cells to 5 H.T. Normally the cells don't manufacture 5 H.T., so I must take exception to Dr. Williams's statement on that point. There is no evidence that they manufacture it, only that they will if you give them a chance. C cells which have taken up 5 H.T.P. and converted it to 5 H.T. can be shown by the so-called fluorescent amine technique. One cannot ethically give a human being a large dose of 5 H.T.P. in order to show the C cells. However, one can do it with radioactive 5-H.T.P.; an easier way of doing it, perhaps. Only in the sheep and perhaps the horse are the C cells known to have 5 H.T. in them normally. There is one further method of showing them up. In many animals they contain high levels of α-glycerophosphate dehydrogenase. With a fluorescent antibody technique, using anti-pig calcitonin, the C cells of the pig and also of the dog show the fluorescent label. This indicates that calcitonin is stored in the C cells (C for calcitonin).

Professor BOOTH: Are they specific medullary cells, or do all medullary cells show this?

Professor PEARSE: We don't use this term except in the case of the human carcinoma. There are specifically interfollicular cells, but in most animals, as you've heard, they are part of the follicle wall. Not every cell that is interfollicular is a C cell; there are other cell types between the follicles, some of which might form a tumour.

Dr. COPE: Does a medullary carcinoma take up this particular antibody?

Professor PEARSE: We have never tried it—we haven't got enough to waste on human cases. In the normal human thyroid it is very difficult to find any C cells, even with the α-glycerophosphate dehydrogenase technique. I believe, although the article in the *B.M.J.*[1] said that these cells could not be detected in the human thyroid, that, in fact, they can be.

Professor BOOTH: What we've got, then, are some cells which may produce calcitonin, and Dr. Williams believes these cells are the origin of this tumour. We've now got to ask what the relation is between this tumour and the tumour of the adrenal.

Relationship to Adrenal Tumour

Dr. WILLIAMS: Perhaps I should comment on that. Firstly, there is no doubt there is a relationship. I now know of 40 cases, either seen by myself or published, of carcinoma of the thyroid and phaeochromocytoma. In 30 of these the tumour of the thyroid is a medullary carcinoma, and in three of the others the description leaves very little doubt that it was a medullary carcinoma—that leaves only seven, and none of those seven was described as clearly a papillary carcinoma of the thyroid, which is the commonest type. So I think there is no doubt that there is a specific relationship between the two. Secondly, the phaeochromocytomas are commonly bilateral, and commonly the whole syndrome is familial, as the article by Ljungberg and his colleagues[1] illustrates. Now, one of the explanations put forward is inheritance of a pleotropic gene of incomplete penetrance—which I think I am right in saying is an explanation that will explain almost anything. I am not saying it's not true, but I don't see how one could possibly prove it. The thyroid carcinoma also seems on occasions to be bilateral, so I suppose that the genetic explanation is the most likely one. Why tumours of thyroid and adrenal medulla should occur together is much more difficult to explain. The only analogy is the multiple endocrine adenoma syndrome, in which tumours of pituitary, parathyroid, pancreatic islet, and adrenal cortex occur. This certainly is familial, and maybe there is a growth factor that controls all these endocrines. If that is the case one has to postulate a second growth factor that controls the parafollicular cells in the thyroid, the adrenal medulla, and possibly also controls the growth of some of the autonomic nervous system. In a small proportion of cases with carcinoma of the thyroid and phaeochromocytoma a wide variety of autonomic abnormalities is also found: ganglio-neuromatosis of the whole intestinal tract, also described in the bladder and the bronchus, and small mucosal neuromas of the eyelids, lips, and tongue. It is possible that there is a single factor controlling the growth of all these different tissues. We know now that there is a nerve growth factor, described by Levi Montalcini, that controls the growth of some nerves, and she has also found a skin growth factor. Thus it may be that there is an endocrine growth factor which is responsible either for the typical multiple endocrine adenoma syndrome or for this second type of syndrome with medullary carcinoma, phaeochromocytoma, and sometimes other neural abnormalities.

Professor BOOTH: Can we just get one thing clear—these are not overlapping syndromes—you're using the polyglandular one as a comparison.

Dr. WILLIAMS: I'm using the multiple endocrine adenoma syndrome as a comparison. To the best of my knowledge even in the more comprehensive studies of many families with the multiple endocrine adenoma syndrome phaeochromocytoma has never been recorded. To be absolutely honest even if confusing, there is an overlap in that parathyroid adenoma has been described in both. Four cases of medullary carcinoma of the thyroid and parathyroid adenoma have been recorded.

Clinical Course

Dr. COPE: I was just going to ask Dr. Williams whether in the light of his survey of these cases, and his peculiar knowledge of them, he could comment on the clinical course of these goitres. They are surprisingly slow growing for thyroid carcinomas generally, are they not?

Dr. WILLIAMS: There is a very great variability in prognosis. With some patients the survival is only a year or two, while the longest survivor that we've had in our series was 21 years. This patient was a man who died at the age of 42 who had had a thyroidectomy when he was 21. However, he had had a goitre before that, according to various reports either since birth or at least since the age of 8. With a tumour of the thyroid which is originating from a different cell type, it's not so surprising to find a spectrum of malignancy within that group of tumours—either relatively benign ones or relatively malignant ones.

Dr. GILLILAND: This must have been a most unusual man—there is a reference to his "having something in his abdomen makes him short of breath"—are these not hypertensive attacks he's having, or high blood pressure?

Dr. COPE: No, the blood pressure was never raised—I didn't see the point in giving innumerable figures. This "something in his abdomen making him short of breath" was in the last two or three days only. But he had a very large liver and he had two phaeochromocytomas. Maybe he knew he had one or the other.

Dr. GILLILAND: I am showing a case quite shortly—with Professor Welbourne—who had paroxysms only in the evening; this was missed for two years while she was in hospital because the attacks were never noticed during the day.

Dr. WILLIAMS: The phaeochromocytoma does not have to function, does it? A proportion of these patients can presumably go all through life and never have any symptoms at all.

Dr. GILLILAND: This patient, however, had a mild diabetes.

Professor J. GOODWIN: The diabetes and the diarrhoea might have been due to the phaeochromocytoma, might they not? I don't know quite why you attribute the diarrhoea necessarily to the carcinoma.

Dr. WILLIAMS: Because in a number of cases of diarrhoea and medullary carcinoma no phaeochromocytoma was found at necropsy. Also because the diarrhoea improved in some cases after resection of medullary carcinoma. I agree that phaeochromocytoma may occasionally present with extreme diarrhoea, but the link there is also humoral and unexplained so far as I'm concerned.

Professor GOODWIN: I think the "something in his abdomen making him short of breath" was pulmonary embolism.

We are grateful to Professor J. P. Shillingford and Dr. E. D. Williams for assistance in preparing this report, and to Mr. W. Brackenbury for the photomicrographs.

REFERENCE

1 Ljungberg, O., Cederquist, E., and Von Studnitz, W., 1967, *Brit. med. J.*, 1, 279.

NEW APPLIANCES

New Urinary Diversion Appliance

Mr. H. B. ECKSTEIN, consultant surgeon, Queen Mary's Hospital for Children, Carshalton, Surrey, writes: With the rapidly increasing number of children surviving with myelomeningocele and hydrocephalus, the problem of urinary incontinence, and therefore urinary diversion, in childhood is becoming more important. Though a wide range of appliances are available for these patients, there is at present no completely satisfactory appliance.

The important features of an appliance for a urinary diversion either by an ileal conduit or by cutaneous ureterostomy are that it should be easy to apply and be easily cleanable and sterilizable; but since rubber bags cannot be cleaned properly and certainly cannot be sterilized adequately they should be either disposable or semi-disposable. It is impossible to clean and sterilize the outlet tap of the bag, and this should therefore not come in contact with the urine. The bag should contain a one-way valve to prevent reflux of urine on to and into the stoma when the patient is lying down.

With these basic conceptions in mind we have designed an appliance with plastic bags fitted with a slit valve and an external tap which will fulfil these criteria. We have tried these bags out on a number of children with considerable success. This appliance is manufactured by Eschmann Bros. & Walsh Ltd. and is now available through all appliance suppliers. While it may not be suitable for every single child, it is certainly an improvement on previously available models. The appliance is illustrated in Figs. 1–3 and is supplied initially in a basic set with replacement bags and flanges which are prescribable on E.C.10 forms.

It is marketed as the "Carshalton Appliance," and fitting instructions are enclosed with each set. Encrustation of the stoma, a common complication of ureteroileostomies in children, has been virtually eliminated by the use of a disposable bag.

I should like to express my thanks to my colleagues for their helpful criticisms and advice and to Mr. Peter Steer, of Eschmann Bros., for his patience and help in making the many modifications to produce the final product.

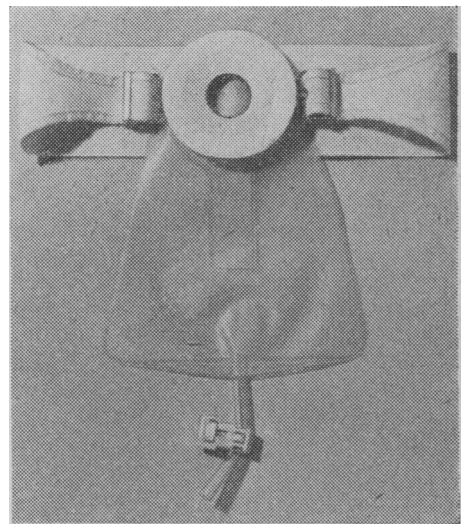

FIG. 2.—Assembled appliance.

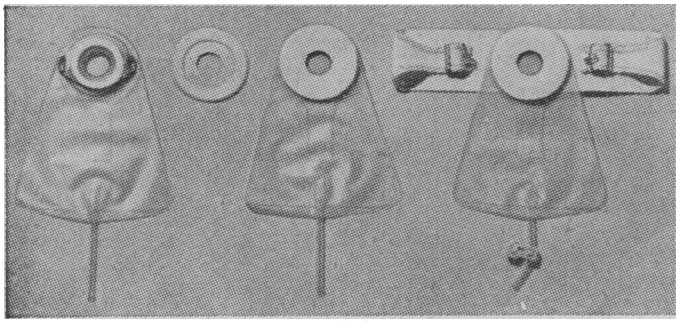

FIG. 1.—Different parts in assembly of appliance.

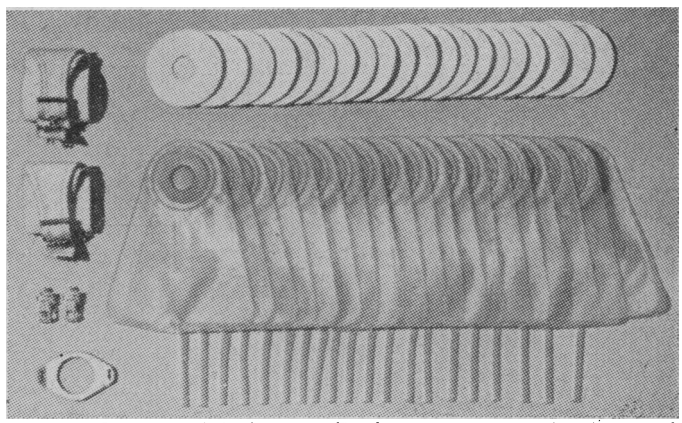

FIG. 3.—Contents of basic set. (Replacement set contains bags and adhesive flanges only.)