number of previous workers mentioned above. Two questions immediately arise—Where has the retained magnesium collected? And how has this retention been brought about?

Magnesium does not accumulate in the extracellular fluid, for there is no rise in the serum magnesium. On the contrary, serum magnesium tends to fall, indicating a movement of magnesium out of the extracellular space. It could move into the cells or, alternatively, be deposited in the bones. Tibbetts and Aub (1937) found that the ratio of magnesium retention to calcium retention was greater than the ratio of magnesium to calcium in bone and concluded that some of the retained magnesium had been taken up by the soft tissues. This is a valid inference only if bone were of constant composition, which it is not. New bone crystals are smaller and consequently contain relatively larger hydration shells than old bone crystals. Moreover, it is thought (Neuman and Neuman, 1957, 1958) that much of the bone magnesium is held in these hydration shells. It follows that the Mg:Ca ratio of new bone would be expected to be higher than that of old bone. This explanation is supported by the finding of Shohl (1939) that the Mg:Ca ratio of bone rises after parathyroidectomy. Our own muscle biopsies are insufficient to offer direct evidence, but two of the cases had normal muscle magnesium before operation—refuting, in these cases, any suggestion of muscle depletion requiring restoration.

Prior to parathyroidectomy, bone resorption is occurring faster than bone replacement, with resulting thinning of bone. The magnesium liberated by this excessive resorption is in part used again to form new bone, but the surplus is lost from the body. Once the parathyroid tumour is removed, bone resorption slows up, while bone formation continues unabated. A fall in extracellular magnesium is a natural consequence.

Comparison of balances before and after operation indicate that the chief change which occurs is a fall in the urinary magnesium in the post-operative phase. This can be accounted for by the reduction in serum magnesium. The excessive losses pre-operatively, however, require further explanation. It should be stressed that this is by no means a constant finding; Cases 1 and 4 in the series reported here showed a very slight negative magnesium balance, and Bassett and Van Alstine (1935) described a case which was in a positive balance pre-operatively. The often-encountered negative balance can, however, be explained by the increased filtered load of calcium in the kidneys. This increase will lead to increased loss of magnesium because of competition for a common transport reabsorptive mechanism (Hanna *et al.*, 1960). The same conclusion can be drawn from studying the effect of magnesium infusion and magnesium supplement on urinary calcium in Cases 2 and 7 in this series. If the magnesium intake is not high enough, this obligatory increase in urinary loss will lead to a negative magnesium balance.

From a practical point of view it is important now to recognize that hypomagnesaemia with its associated dangers (Hanna *et al.*, 1960) is likely to occur after parathyroidectomy. Further, it seems from this limited series that oral supplements are sufficient to prevent a fall of serum magnesium and should therefore be given prophylactically in the post-operative period.

Summary

Primary hyperparathyroidism is sometimes associated with a negative magnesium balance because of increased urinary loss. This increase in urinary loss may be explained by an increase in the filtered load of calcium in the kidneys.

Parathyroidectomy in hyperparathyroid subjects produces: (a) lowering of plasma magnesium level, and (b) a positive magnesium balance.

These changes can be explained by the uptake of magnesium by bone.

The findings do not justify the proposition of a "primary" action of the parathyroid hormone on magnesium metabolism.

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INCIDENCE OF HYPOTHYROIDISM IN THE ELDERLY

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In the past two and a half years we have been impressed by the high incidence of hypothyroidism seen in patients attending this geriatric department. The purpose of our paper is to illustrate this.

Material and Methods

During a period of two and a half years 93 patients attending the geriatric department were thought to be suffering from hypothyroidism. From these, 58 patients have been selected whom we regard as unequivocally hypothyroid. The material of this paper is derived from our observations on this group of 58.

Each case was carefully assessed clinically on the basis of a specially prepared form. Most cases were subjected to one or more laboratory tests. The accompanying Table shows the tests employed and the number of patients examined by each test. Apart from five patients

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seen by one of us (W. H. L.), all were seen and examined by both authors.

Each case was treated with L-thyroxine. The initial dose for almost every case was 0.1 mg. daily, increased by 0.1 mg. at fortnightly intervals, until they were taking a total of 0.2–0.3 mg. daily. Most of the cases were treated as out-patients. All out-patients received their tablets from the hospital dispensary. For the first six to eight weeks of treatment, all out-patients were seen fortnightly and thereafter at approximately monthly intervals. The body weight and clinical picture were recorded before treatment and at each attendance. All

Tests Employed

Tests Employed	Cases Examined
Haemoglobin	56
Erythrocyte sedimentation rate (E.S.R.)	43
Serum cholesterol	56
Electrocardiogram (E.C.G.)	57
Basal metabolic rate (B.M.R.)	34
24-hour thyroidal radioiodine (¹³¹ I) uptake	47
Serum protein-bound iodine (P.B.I.)	8

cases were photographed before and after four to six months' treatment. E.C.G., serum cholesterol, E.S.R., and haemoglobin estimations were repeated serially.

Serum cholesterol estimations were made by the method of Zlatkis, Zak, and Boyle (1953) as modified by McIntyre and Ralston (1954): 290 mg./100 ml. has been taken as the upper limit of normal.

The basal metabolic rate was estimated on in-patients and out-patients, using a Benedict–Roth machine; the method described by Robertson (1944) and the British Standards of Robertson and Reid (1952) were employed.

The thyroidal radioiodine uptake 24 hours after a test dose was used. This test was carried out at the Christie Hospital, Manchester, as was the estimation of serum protein-bound iodine.

Diagnostic Criteria

The diagnosis of hypothyroidism in our 58 cases has depended on the following criteria:

1. Response to replacement therapy with L-thyroxine. This has applied to 51 of the 58 cases (7 patients died before their response to treatment could be assessed). Response to treatment was judged on weight loss in 51 cases, relief of symptoms and signs in 51, facial change (assessed by serial photograph) in 51, fall in serum cholesterol in 28 (54%), and alteration in E.C.G. in 38 (74%).

2. Pre-treatment B.M.R. A value of –15% or less was found in 23 (67%) of the 34 cases examined in this respect.

3. Pre-treatment ¹³¹I uptake of less than 20% of administered dose; this was found in 31 (66%) of the 47 cases so assessed.

4. Serum P.B.I. levels of less than 3 µg.; seven of the eight cases tested before treatment met this criterion.

5. The use of a "diagnostic index" (Wayne, 1960) based on the presented signs and symptoms, devised in the department of Professor E. J. Wayne, Glasgow University (Wayne, personal communication, 1960).† We have applied this to 51 cases and have found a confirmatory score (15 or more) in 33 (64%). Eighteen cases fell into the "equivocal range" (Wayne, 1960), the individual scores ranging from 7 to 13. The remaining seven cases were not scored, as these patients were too ill to report their symptoms.

†We have found this index valuable, since it indicates quantitatively the number of signs or symptoms of hypothyroidism which are present in a given case.

6. Post-mortem examination carried out in 13 cases; 4 of these patients died in hypothermic coma.

Analysis of Cases

We would emphasize that the disease was severe in most of our cases, judging severity by the degree of physical disability, mental inertia, and social dependence caused. The results of specific treatment in general were striking, despite the high average age and high incidence of arteriosclerosis.

Fig. 1.—Results of tests.

The test results are shown in Fig. 1. The symptoms and signs of hypothyroidism are diffuse, and it is impossible to present the overall clinical picture of a large series of cases in a simple manner without reference to some form of clinical index. We feel that the application to our cases of Professor Wayne's scoring technique approximates to an external clinical assessment, particularly as it has been applied retrospectively and as we have been conservative in our scoring.

Cases Showing Confirmatory "Index"

Cases 1 to 4 were all clinically obvious cases of myxoedema, and when first seen were judged too ill to warrant the delay in subjecting them to special investigations. Of the remaining cases showing a confirmatory index, Cases 12 (see below), 13, 18, and 19 showed non-confirmatory values for B.M.R. and/or ¹³¹I uptake.

Case 13.—A woman aged 75. Although clinically a definite case of hypothyroidism, all tests were negative. Her "index" scored 15. After two months' treatment she showed improvement in her symptoms and signs. She subsequently discontinued her thyroxine and had a clinical relapse. Treatment was started again, her symptoms and signs regressing once more. Thirteen months after her initial attendance she developed a cerebral thrombosis. After death the thyroid gland weighed 8.5 g. and histologically showed marked fibrosis and small round-cell infiltration.

Case 18.—A man aged 79 presented with dyspnoea on exertion and severe anaemia (haemoglobin 47%). Despite

his anaemia the B.M.R. was -12% . Serum P.B.I. was $2.4 \mu\text{g./100 ml.}$; "diagnostic index" 18. He responded well to treatment, his haemoglobin ultimately rising to 89% . Prior to treatment he was virtually confined to a chair. At the time of writing he was an active man.

Case 19.—A woman aged 66. Failure to record a confirmatory B.M.R. in this case was due to severe cardiac dyspnoea. Her ^{131}I uptake was 27% . All other tests were positive and her "diagnostic index" 25. She responded well to treatment.

Cases Showing Non-confirmatory "Index"

It will be seen from Fig. 1 that only two cases showing a non-confirmatory index had poor supporting laboratory evidence.

FIG. 2

FIG. 3

FIG. 2.—Case 50. Photograph before treatment. FIG. 3.—Case 50. Photograph after treatment.

Case 50.—A woman aged 77 was a very definite clinical case (Fig. 2). Serum cholesterol was 520 mg./100 ml. , ^{131}I uptake was 23% . B.M.R. was not done. "Diagnostic index" was 13. Her response to treatment was striking (Fig. 3).

Case 51.—A woman aged 72 gave a definite history of exophthalmic Graves's disease as a young woman. She had been treated with radiotherapy at the Manchester Royal Infirmary. Her ^{131}I uptake was 21% . "Diagnostic index" was 13. She showed a very satisfactory response to treatment.

Post-mortem Results

As already indicated, 14 of these patients died, and post-mortem examination was carried out on 13. Full details of our findings will be published elsewhere.

Post-mortem examination on Cases 6, 10, 12, 13, 52, 53, 56, and 57 failed to reveal any thyroid tissue. A résumé of each of the remaining five cases is given below.

Cases 5 and 14.—Women aged 69 and 70 respectively. Post-mortem examination showed in both cases very small thyroid glands replaced by fibro-fatty tissue.

Case 54.—A man aged 81 had severe aortic stenosis, angina decubitus, and recurrent congestive heart failure. Clinically we thought him to be myxoedematous, although there was no laboratory confirmation. In view of the severe cardiac damage thyroxine was not given. While an in-patient he developed irreversible hypothermic coma. At post-mortem examination only a remnant of thyroid tissue was found, which showed gross fibrosis.

Case 55.—A woman aged 79 was admitted to hospital in irreversible hypothermic coma. At post-mortem examina-

tion the thyroid was small and histologically suggested Hashimoto's disease.

Case 58.—A woman aged 79 was admitted to hospital in a moribund state, due to an acute coronary thrombosis. At post-mortem examination the thyroid was very small and histologically showed marked fibrosis and small round-cell infiltration.

Incidence of Hypothyroidism

Of the 58 cases of hypothyroidism in this series, five had been treated in the past for hyperthyroidism, either surgically or by radiotherapy. The remaining 53 cases were thought to be suffering from primary hypothyroidism. The age distribution of these 58 cases is shown in Fig. 4; the average was 70.3 ± 6.8 years. There were 9 males and 49 females. The age-and-sex distribution of these patients has been compared with that of the 3,417 (1,857 females, 1,560 males) new patients seen in this department during a period of two and a half years. The age distribution closely follows that of the total cases seen in the department, but there is a preponderance of females (5:1) over males in the sex distribution. Of these 3,417 cases, 17 suffered from hyperthyroidism and 58 from hypothyroidism. The incidence of hyperthyroidism was therefore 0.5% and of hypothyroidism 1.7% of new cases seen.

Discussion

Critchley (1931) has stated: "The subject of old age has never been a popular one with the medical profession. Among both savage and civilized people a certain lack of interest, and even of sympathy, is associated with the infirmities and maladies of the aged. Problems of diagnosis and of therapy tend to be neglected, to the detriment of the individual and still more of the community." Although a normal process of ageing remains to be defined, many people believe that age alone is responsible for all sorts of symptoms and signs. It would seem that hypothyroidism is one disease

FIG. 4.—Age distribution of 58 patients with hypothyroidism.

commonly confused by patients and doctors with "the normal ageing process." However, Starr (1955) has commented: "Old people are not normally hypothyroid; middle-aged people should not be allowed to become hypothyroid." In approximately 90% of the cases in our series, the general practitioners referring the case did not suspect hypothyroidism. Most were sent as examples of heart failure, cerebral thrombosis, anaemia, or bronchitis, with a few labelled simply as "senile."

In our experience hypothyroid patients are almost always attractive people, and before the onset of their illness many of them were well known and liked in their circle for their mental and physical energy. When such people become "old" (hypothyroid) they are usually well supported by their relatives and friends, and this fact reduces their chance of recognition. There can be little doubt that many unrecognized cases of hypothyroidism are recorded as dying of uncomplicated cerebro-cardiovascular accidents. We have been unable to find a series in the literature which is comparable to ours in age distribution. This factor alone precludes a statistical comparison of incidence between our series and any of the published series. Our figures show a very high incidence of hypothyroidism (1.7% of new cases seen) in a relatively large sample of elderly people (3,417) referred to hospital in a period of two and a half years. It is of interest to note that we encountered more cases of hypothyroidism than hyperthyroidism; the ratio was 2.9:1.

Starr (1954) has suggested that the early stages of hypothyroidism are asymptomatic and has advocated estimation of serum P.B.I. as a routine screening test for all middle-aged and elderly patients. We attempted in every case to assess the duration of symptoms, but accuracy was not possible in this respect. The majority of cases indicated a duration of three to five years; as most of them had come to live with their symptoms the actual duration was probably much longer. It is interesting to speculate on the age at which our cases first became hypothyroid and whether adequate treatment with L-thyroxine from this point would have reduced or even prevented the arteriosclerotic complications which affected so many. We now have some experience of treating elderly hypothyroid patients who also exhibit evidence of myocardial insufficiency. A paper dealing with this subject is in preparation. In our opinion treatment of middle-aged or elderly hypothyroid patients should be undertaken with great care. If it is not possible for these patients to be seen frequently by a medical attendant and to rest physically during the initial few weeks of treatment, then treatment is best carried out in hospital. The decision to treat with thyroxine a middle-aged or elderly person showing signs of congestive failure or complaining of angina of effort should be taken only after the most careful assessment of cardiac and thyroid function.

Summary

Out of a total of 3,417 new patients referred to a geriatric unit during a period of two and a half years, there were 58 cases of hypothyroidism and 17 cases of hyperthyroidism. The incidence of hypothyroidism was 1.7% and of hyperthyroidism 0.5% of new cases seen. Details of diagnostic criteria and age distribution are given. It is suggested that hypothyroidism is a disease commonly confused with ageing.

Among others we would like to thank Professor E. J. Wayne, Glasgow University, for sending us details of his "clinical index" and for much helpful criticism of the paper; Dr. H. Jackson, Christie Hospital, Manchester, for estimating serum protein-bound iodine in our cases; Sister M. Seddon, who recorded most of the E.C.G.s; Mrs. M. Mansfield for technical assistance with B.M.R. estimations; Mr. Smith, department of medical illustration, Manchester Royal Infirmary, for his help in formulating Fig. 1; Mr. C. Richardson, department of photography, Oldham and District General Hospital, who took the photographs; and Mrs. J. Harrison for her clerical assistance.

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DIABETES MELLITUS AND PRIMARY CARCINOMA OF THE PANCREAS

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Primary carcinoma of the pancreas has often been reported in association with diabetes mellitus (Urmy, Jones, and Wood, 1931; Pygott and Osborn, 1937; Llamas and Molina, 1955). Marble (1934), in an extensive study of diabetes, regarded the relationship as purely fortuitous, a view supported by Joslin, Root, White, Marble, and Bailey (1946) and Lawrence (1955). Bell (1957), in a review of necropsy records, showed that cancer generally occurred less often in diabetics, with the exception of cancer of the pancreas, where the incidence was twice as great as in non-diabetics. We have recently observed a case of sarcoma of the pancreas in a patient who first attended the diabetic clinic 15 months previously. This led us to review the case records of all patients with proved neoplasm of the pancreas and of all patients suffering from diabetes seen in this hospital during the years 1955–9. We have found that certain types of diabetes are closely associated with this condition.

Results

Of 65 patients suffering from primary neoplasm of the pancreas in the period under review, 10 (15.4%) also had diabetes mellitus. Table I shows that the diagnosis was confirmed at operation in 53 cases (81%), a positive biopsy being obtained in 35 (53.8%). Necropsy was performed in 19 cases (29.2%). The mean age was 64.2 years (range 40–81 years) and the ratio males/females was 2.1/1.

The symptoms thought to be due to carcinoma are arranged in order of frequency in Table II. The insidious nature of the disease may be judged by the mean duration of symptoms—5.8 weeks (range 1 day—