SOME PROBLEMS OF HYPERPARATHYROIDISM*

BY

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In view of the increasing interest in and knowledge of hyperparathyroidism, both primary and secondary, I have decided not to bore you nor myself with a detailed review of the subject, which of course I would have had to put carefully together with full acknowledgments and not a foot in the wrong place. I propose to omit altogether consideration of its more commonplace aspects. (Good recent reviews are those by Munson, 1960; Rasmussen, 1961; Keynes, 1961; Pronove and Bartter, 1961; Rasmussen and Reifstein, 1962.) I will discuss only a few selected matters of particular interest, not hesitating to speculate somewhat dangerously while doing so. I will quote a great deal of data obtained from the work of my colleagues at University College Hospital, to whom I am deeply grateful. In particular do I appreciate the ever-willing help of Mr. D. R. Davies, who has had so often to intervene for us in difficult and dramatic circumstances and who has done the operations on 76 of the 80 patients successfully dealt with. I would first, however, mention that some general lessons as well as particular ones can be learnt from the close study of this remarkable gland. One can note how this study can be most effective in unspecializing the specialist, how pure science and pure clinical observation and trial have interacted

with great mutual advantage, and how in consequence the sick have benefited.

Importance of Plasma Calcium Levels

On the question of diagnosis of primary hyperparathyroidism I have only a few points to make. The prime importance of total plasma calcium levels is now generally recognized, so that a total calcium is now the first routine test to demand. The more time-consuming ionized-

calcium determination (Rose, 1957) remains a valuable additional help when total calcium abnormalities are marginal, when plasma protein abnormalities are present, and when renal failure is severe. We stress again the importance with borderline cases of obtaining blood for total calcium in the fasting state. It is even more important to use minimal venous occlusion, since some subjects are most sensitive to this factor (Fig. 1). Indeed, we now (since 1958) always determine plasma specific gravity (by the copper-sulphate method) so as to correct if necessary for an artifactual high protein produced by the high venous pressure. The rough rule is that for every unit in the third decimal place of the specific gravity above 1.027, 0.25 mg. of calcium per 100 ml. must be subtracted from the total calcium, and vice versa. However, our graphs still show total calcium uncorrected in this way, with comment when necessary about abnormal proteins, since much of our data antedates this wise routine precaution.

Many patients, especially for some curious reason in Belfast (McGeown and Morrison, 1959), are being reported with variable levels of total calcium, presumably because of variable activity in their parathyroid tumour. Data from a case of our own are shown in Fig. 2, although the effect is less than shown if correction

FIG. 1.—Effect of venous occlusion on plasma specific gravity and total calcium. Corresponding plasma from five normal people are marked with the same numbers. The sphygmomanometer cuff was left on the arm at 100 mm. Hg. Specific gravity was measured by the copper-sulphate method. Note the great variability between different subjects. The same subject behaves consistently on repeat experiments (taken from Philpot, 1958).

FIG. 2.—Mrs. Mildred W. Plasma calcium levels on a patient whose parathyroid operation had to be delayed. No treatment was being given during this time. It is noted that part of the fall in total calcium shown is due to a corresponding fall in plasma specific gravity.

for specific gravity is made; and one wonders about results from centres which do not determine this. Nevertheless repeated determinations over a few months may be worth while if facilities are available and if the clinical indications are strong enough. It can still be

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stated, however, that one quite normal value for total calcium obtained with impeccable technique makes the diagnosis most unlikely. Determining the plasma calcium with the patient on a low phosphate intake or when taking aluminium hydroxide may be a useful method of raising it to less ambiguous levels, and is

FIG. 3.—Mrs. Mabel B. Primary hyperparathyroidism. The graph shows the reciprocal changes in plasma calcium on artificially lowering and raising her plasma phosphorus. Correction for specific-gravity changes would be small and would not alter the curves appreciably. It is obvious also that such a patient will manifest large fluctuations in total calcium according to the phosphate content of her diet.

especially effective when renal failure is present (Fig. 3). We no longer do diagnostic tests based on urine calcium output, since so many false positives and negatives occur. A recent refinement described by Pronove, Bell, and Bartter (1961) sounds worthy of further trial.

Cortisone Differential Test

An important help in differentiating the hypercalcaemia due to primary hyperparathyroidism from that due to sarcoidosis, to vitamin D overdose or sen-

sitivity, and often from that due to malignancy is the test with cortisone (Dent, 1956). This arose out of the work that had been done on sarcoidosis partly by clinicians who were using cortisone therapy (Gleckler, 1956) and partly by two groups working simultaneously and independently in a more detailed study of the calcium disorder (Anderson, Dent, Harper, and Philpot, 1954; Henneman, Dempsey, Carroll, and Albright, 1956). In primary hyperparathyroidism the hypercalcaemia usually remains constant or may even rise a little on giving a standard 10-day load (50 t.d.s.) of cortisone (Fig. 4); in most of the other conditions it rapidly begins to fall to normal or may even reach normality during the test, to bounce up again after the cortisone has been withdrawn.

May I stress that most of the work using this test was done with cortisone itself and not with its various substitutes, most of which have been especially synthesized and chosen so as to have different activities on mineral metabolism? There is no reason I know of to expect, say, equivalent doses of prednisone to have identical actions on calcium metabolism. Doctors who insist on using the latest and most fashionable corticosteroid substitute do so at their own peril. There is no need to do the test if bone disease is present, as in this case the bone x-ray films give the diagnosis of hyperparathyroidism and the only differential diagnosis concerns whether it is primary or secondary, a situation I will deal with later. We have had two false negatives with the test in trials on two other patients whose data are omitted from Fig. 4. In one of these patients a

"response" to the cortisone (Fig. 5) led to some months' delay in parathyroid surgery, although in retrospect it appears to have been due to a sphygmomanometer artifact (Fig. 6). Meanwhile we were giving her cortisone as an out-patient, thinking she probably had sarcoidosis. After a prolonged trial on doses rising to 150 mg. a day the hypercalcaemia remained (Fig. 5) and operation was then advised and a tumour found and removed.

Of more potential importance are the two standard cortisone tests done on the other patient (Fig. 7). Although she had classic radiological signs of hyperparathyroidism she had elsewhere been given large doses of vitamin D before admission as it had been thought that her bone disease was secondary to her considerable degree of renal failure. There were also other odd features present, so we did a cortisone test in case she really had secondary renal hyperparathyroidism with hypercalcaemia due to vitamin-D intoxication. Rather

FIG. 4.—Plasma calcium levels during our standard cortisone test on 13 patients, subsequently proved to have primary hyperparathyroidism. This is our total experience to date of this test except for the patients mentioned in Figs. 5, 6, and 7. The patient with the lowest calcium levels had low plasma proteins requiring the addition of about 1 mg. of calcium to the lower readings. The fluctuations during the test were probably due to a sphygmomanometer artifact, as we later showed that he manifested this effect grossly. This experience four years ago made us subsequently determine plasma specific gravity on all specimens for calcium determination.

FIG. 5.—Miss Alice B. The fall to normal of her total calcium was taken at the time (January, 1958) to mean that she had not got a parathyroid tumour, but when subsequent cortisone treatment on a long-term basis did not maintain this normal calcium, exploration was undertaken and a tumour found.

to our surprise both calcium and phosphatase levels fell during the cortisone load, to rise again after it. We repeated it with the same result. There was no sphygmomanometer artifact here. Another patient with bone disease had had cortisone for different reasons before coming to us and may have had a similar response

FIG. 6.—Miss Alice B. The curve for total calcium was originally thought to show inadequate reciprocation with the aluminium hydroxide and sodium phosphate, the plasma phosphorus (not presented here) showing the expected wide fluctuations. The cortisone test (not included among those in Fig. 4) showed a fall to normal within the usual 10 days. Specific gravities were determined then. They were unusually variable, but we did not then know how to correct for them properly. In preparation for this lecture the figures were again reviewed and our current specific gravity correction was applied. The corrected calcium curve shows adequate reciprocation and an inadequate response to cortisone, both typical of primary hyperparathyroidism.

that sudden stopping of the cortisone at the end of the test is unwise owing to adrenal suppression? It should be tailed off slowly over a week at least. Likewise parathyroid operation is unwise immediately after, unless cortisone cover is given. In one case

FIG. 7.—Mrs. Florence G. It is seen here that both standard cortisone tests resulted in a fall to normal of her total calcium with subsequent rebound. This patient had marked osteitis fibrosa with raised alkaline phosphatase levels, these latter also falling a little each time with the calcium. See text for further discussion.

(Case 2 quoted by Dent and Harper, 1962). For this and other reasons we advised operation, and Mr. Davies duly found and removed a very large parathyroid adenoma. It seems important to check further the possibility that such patients with osteitis fibrosa may sometimes react differently to cortisone from those without.

We no longer do cortisone tests routinely when the clinical evidence seems clear enough to exclude other causes of hypercalcaemia, but it remains useful in doubtful cases. With hesitation may I recall the well-known fact

described in the standard literature the patient had his cortisone (200 mg. a day for six days) stopped suddenly and a neck exploration on the day after. He died suddenly and "unexpectedly" four days later. We have also had one probably false positive with the cortisone test. This was in a patient with known sarcoidosis, whose hypercalcaemia only partly fell with cortisone. Mr. Davies was asked to do a diagnostic operation and found four normal parathyroid glands. In another similar previous patient (under Professor M. Rosenheim), who died of uraemia before we were presented with a very difficult decision, a parathyroid tumour as well as sarcoidosis had been found at necropsy. This remarkably difficult double diagnostic situation has been described before (Snapper, Yarvis, Freund, and Goldberg, 1958; Burr, Farrell, and Hills, 1959), and gives food for thought.

Phosphate Abnormality

The study of phosphate abnormalities remains a helpful additional diagnostic aid, but the various tests are far less specific than are measurements of plasma calcium (Pronove and Bartter, 1961), especially in the very many patients who have idiopathic hypercalciuria, and who are unfortunately the people who most commonly come into the differential diagnosis (McGeown, 1957). These latter patients are not always used as controls by those who campaign in favour of the phosphate tests. Normal plasma phosphorus and normal renal tubular reabsorption, however, in the presence of good renal function together comprise suggestive but not final evidence against a diagnosis of primary hyperparathyroidism, but the reverse is not true. We do not therefore routinely measure renal phosphate handling.

It is relevant here to recall that the seemingly pure parathyroid hormone prepared by Rasmussen is now shown to increase phosphate excretion as well as to raise plasma calcium. The crude commercial extracts previously available had shown such variable actions on phosphate excretion as to suggest the presence of variable quantities of impurities with phosphate activity (Dent, 1954; Munson, 1955). Some authors had even doubted that the pure hormone had phosphate activity at all. Rasmussen's findings, however, are not surprising in the face of the clinical evidence to the effect that diminished renal tubular reabsorption of phosphate is nearly always found in primary hyperparathyroidism. The non-specificity of the phosphate action may well account for the fact that many workers who had used this criterion for their assay method had failed in their efforts to isolate the pure hormone. We are proud to think that Rasmussen began his isolation work in our laboratory (Rasmussen and Westall, 1957) and that he has throughout firmly held to our view that all assays should be based primarily on calcium-raising action.

Clinical Features

There have been few clinical developments concerning specific physical signs helpful in diagnosing primary hyperparathyroidism. However, the evidence is now overwhelming that the disease is quite common, so that a high index of suspicion needs to be developed in order to ferret out patients whose presenting signs are probably of greater variety than in most other known diseases. "Stones and bones" will remain the mainstay of diagnosis, but nevertheless more and more instances are

coming to light of new associations with other diseases, such as with pancreatitis (Mixer, Keynes, and Cope, 1962), peptic ulceration (St. Goar, 1957), psychosis (Fitz and Hallman, 1952), Cushing's syndrome (Raker, Henneman, and Graf, 1962), thyrotoxicosis (Frame and Durham, 1959), and Zollinger-Ellison syndrome (Summerskill, Code, Hallenbeck, and Priestley, 1961). Table I shows the diseases we found associated with our own series of 80 patients at U.C.H. We also have an instance of hereditary hyperparathyroidism proved in three members of a family and likely in a fourth who is now dead. In this family there is no suggestion of any aspects of the polyglandular syndrome or other medical complication.

TABLE I.—Other Associated Diseases Not Easily Relatable to Immediate Complications of Primary Hyperparathyroidism

Zollinger-Ellison syndrome ..	1	Pulmonary tuberculosis ..	4
Ankylosing spondylitis ..	1	Steatorrhoea ..	1
Acute gout ..	3	Rheumatoid arthritis ..	2
Depressive psychosis ..	1	Periculous anaemia ..	2
Osteomalacia ..	1	Thyroid cancer ..	1
Diabetes ..	1	Idiopathic osteoporosis ..	1
Thyrotoxicosis ..	2	Pancreatitis ..	4
Cushing's syndrome ..	1	Gall-stones ..	2
Acromegaly (without hyper-	1	Alzheimer's disease ..	1
insulinism) ..	1		

Because of the difficulties of clinical diagnosis in a common disease it is not surprising that more and more instances of purely accidental diagnosis are being reported (Randall and Keating, 1958; Riggs, Jones, and Randall, 1962). In many of these an x-ray examination performed for another purpose revealed a renal stone or bone cyst which then led to the obvious further tests. Our U.C.H. series also includes many instances of this but is particularly unusual in that we also have 10 instances in which the plasma calcium was determined for reasons far less reasonable. When it was found to be raised the further necessary tests were done. These remarkable situations are shown in Table II. Obviously such accidental diagnoses provide further evidence for the commonness of the disease, as one could hardly stumble on them like this unless there were plenty lying around the place.

Aetiology

With regard to the question of aetiology very little new has appeared, and that has been mostly destructive.

We have produced evidence from our department (Dent, Hartland, Hicks, and Sykes, 1961) that previous low dietary calcium intake is not usually correlated with development of parathyroid tumours, nor with the genesis of the bone disease when it occurs (Fig. 8). This is at variance with the very plausible theory of Albright and Reifstein (1948). However, one of our adult patients

FIG. 8.—Pre-operative calcium intake in patients with primary hyperparathyroidism (taken from Dent, Hartland, Hicks, and Sykes, 1961). Reproduced by permission of *Lancet*.

TABLE II.—Ten Unusual Reasons for Plasma Calcium Determination in Patients Later Shown to Have Primary Hyperparathyroidism (None had Renal Stones, and Only Case 12 had Osteitis Fibrosa—That Very Early)

- Case 2.—Her doctor phoned to say that his patient had sciatic pain and that an x-ray examination had revealed that the lumbar vertebrae "were dissolving away." We advised plasma calcium determination among other things. We later saw the x-ray films and considered them normal.
- Case 12.—Long-standing ankylosing spondylitis. Bone biopsy showed osteoporosis consistent with her long immobilization. Plasma calcium done as part of routine work-up when patient again reviewed.
- Case 22.—The x-ray diagnosis elsewhere of "osteitis fibrosa" had led to the determination of plasma calcium. She had marked rheumatoid arthritis and corresponding bone changes. We did not consider there was any sign of osteitis fibrosa.
- Case 30.—The patient forced her general practitioner and then ourselves to arrange her admission to hospital, which we were most reluctant to do. She diagnosed her own back-ache as being due to renal colic from cystinuria "which she had caught from her husband," a genuine cystinuric long under our care. Her urine and intravenous pyelogram were normal, but as we were about to discharge her the plasma calcium and phosphorus results came through from the laboratory. They had been determined without our knowledge or approval by our house-physician, who "thought he would be asked for it."
- Case 33.—This patient with depressive psychosis was extensively investigated with negative results over some years. On subsequently reviewing the notes a registrar ordered the plasma calcium, "as that seemed about the only investigation not yet done on her." (She has recovered normal mentality over a four-year follow-up.)
- Case 45.—This patient injured her foot, which was x-rayed and thought to be osteoporotic. Plasma levels were done and were typical of primary hyperparathyroidism without bone disease. In retrospect the foot findings do not appear to be relevant.
- Case 54.—This patient had marked idiopathic osteoporosis, fully confirmed subsequently and wrongly interpreted as a manifestation of hyperparathyroidism.
- Case 55.—This patient had eczema of many years' standing. The registrar had heard that sometimes this was due to unrecognized low plasma calcium and therefore ordered the investigation.
- Case 70.—This woman had a severe acute progressive gastrointestinal upset. All obvious investigations being normal, the despairing physician obtained a large blood specimen and submitted it to the laboratory with the instruction to "do everything."
- Case 73.—Fully diagnosed Alzheimer's disease present. The registrar ordered the plasma calcium as he thought some of her symptoms resembled those due to hypocalcaemia.

with evidence of lifelong coeliac disease undoubtedly developed the picture of "primary" hyperparathyroidism, requiring surgical intervention (Davies, Dent, and Willcox, 1956), as if to suggest that the commonly occurring parathyroid hyperplasia secondary to the steatorrhoea could occasionally develop into one or more autonomous adenomas. It is possible that the immediate mechanism in this unusual case was that of calcium deficiency secondary to its malabsorption. We have now another such patient under investigation. We are accumulating suggestive data that this can also occur for the same reasons in chronic renal failure (Figs. 9 and 10), but as these patients do not usually survive long after a secondary hyperplasia has developed it will be difficult to obtain adequate confirmation. Indeed, the evidence in our two patients is far from convincing. Nevertheless it remains most reasonable to seek carefully for further causes of parathyroid hyperplasia in case they, too, can be found to precede the formation of autonomous adenoma. An obvious possible cause could be a temporary state of vitamin-D deficiency, since classical rickets, in my small experience, is usually associated also with x-ray signs of hyperparathyroidism.

Diagnosis by Surgery

This is not the place to discuss the difficulties of parathyroid surgery, nor the place of surgery in making a diagnosis. A parathyroid exploration is potentially too serious an operation to advise lightly as a diagnostic measure, especially as it would be likely to be needed only in a patient with ambiguously high normal plasma calcium levels, in whom the tumour, if any, may be quite small and difficult to find. If a tumour is found then of course the diagnosis is confirmed. However, finding fewer than four normal parathyroid glands proves nothing; and in one patient of ours an exploration in which four normal glands were found in their proper places in the neck did not exclude the diagnosis for at a second operation, at which the previous finding was again checked, Mr. Davies removing a large parathyroid

adenoma from her mediastinum (Rose, 1959). Papers such as that of Cope, Barnes, Castleman, Mueller, and Roth (1961), in which their failed parathyroid explorations are carefully recorded, are most welcome.

So far we have only twice advised diagnostic explorations, and in both Mr. Davies identified four normal parathyroid glands. In one the comatose hypercalcaemic patient was too ill for full investigations and the operation was done as a desperate gamble. The patient was eventually found to have a hypernephroma. The other patient is the one with sarcoidosis, unresponsive to cortisone, mentioned above. To complete the picture of our total U.C.H. experience we have one failure to find a tumour in a patient (Mrs. Emily P., mentioned below) and one clear medical misdiagnosis, a patient, the third in our series, who had sarcoidosis. This latter failure was the immediate stimulus for our using the cortisone test in later similar cases. We have now had 80 patients successfully diagnosed and explored, and have not yet been made aware of any diagnoses we have missed, although we daily await such news.

Post-operative Findings

I will now quote some of our data from post-operative studies of patients in whom signs of hyperparathyroidism persisted after a neck exploration during which an adenoma may or may not have been removed (Figs. 11 and 12). We think that a temporary improvement in the signs following operation strongly suggests temporary damage to a tumour that has been left behind. This may be of great help in indicating the possible field for the second operation. When no change occurs post-operatively we think it is likely that the tumour left behind is situated far from the parts explored. It must be recalled that fluctuating hyperparathyroidism due probably to spontaneous haemorrhage or infarction of a tumour was described some years ago (Howard, Follis, Yendt, and Connor, 1953) and Mr. Davies has suggested to us that perhaps this could be produced at will by deliberate trauma applied in turn to various parts of the

FIG. 9.—Miss Dorothy J. On the basis of her first plasma levels and clinical history we made a firm diagnosis here of hyperparathyroidism secondary to chronic renal disease. During treatment with sodium bicarbonate she maintained a fair condition without, however, any definite improvement (she was described at this stage by Karani, 1955). Towards the end of 1954 she showed marked clinical deterioration of the bone disease with great increase in bone pains and collapse of vertebral bodies and loss of 2 in. (5 cm.) in height. This continued while we were wondering what to do next and while we were greatly puzzled by the rise in total plasma calcium. No vitamin D had yet been given. We are not quoting subsequent values, all similarly raised, which were obtained during vitamin-D therapy. When she died in uraemia a large parathyroid tumour (6.4 g.) was discovered with three normal-sized (together weighing 150 mg.) parathyroid glands. Her kidneys were scarred and weighed 29 and 34 g.

FIG. 10.—Mrs. May B. Total plasma calcium levels during her first follow-up elsewhere (Houghton and Pears, 1958) and since March, 1957, at U.C.H. No treatment with vitamin D was given during the periods shown here. The period from March, 1957, to April, 1960, is shown in Fig. 19. It is possible that she had hyperplasia of her four parathyroid glands on the basis of known renal damage of very long standing and that the slight later rise in total calcium was the indication that one of the glands was beginning to act autonomously. At operation she had a chief-cell parathyroid adenoma and three normal parathyroid glands.

FIG. 11.—Plasma levels of total calcium before and after neck operations. Mr. Arthur W.'s first operation was for the removal of a "cyst" in his left jaw, subsequently found to be an osteoclastoma. Pre-operative blood was available for analysis. The slow fall to normal of his total calcium followed by subsequent fluctuations was interpreted as a haemorrhage into a parathyroid tumour damaged at the first operation. This was confirmed at the second operation. Mrs. Lilian D.'s operation led to the discovery of one parathyroid adenoma and of only two normal ones. We interpreted the subsequent course of events as due to temporary damage to a second tumour, also in the neck. This was confirmed at the second operation. (Case described by Davis *et al.*, 1956.)

neck in patients suspected of having parathyroid adenomas, thus providing a method of locating them. His first attempt along these lines has been unsuccessful. I am afraid we have no other contributions yet with regard to the knotty problem of locating the tumour before the first operation.

We have something to add to the post-operative treatment of patients in whom successful removal of the adenoma has been carried out. It is surprising that so little is written on this important subject and that so much is unreliable. Albright and Reifstein (1948) stated that the tetany that so often follows operation is resistant to treatment with vitamin D and can be dealt with only by prolonged high calcium intake and in severe cases continuous intravenous calcium. Rasmussen and Reifstein (1962) repeat this statement in their recent comprehensive review. One international authority, reviewing one of our current patients who had severe renal damage and osteitis fibrosa, said that there would be no problem, post-operatively, of calcium absorption from the gut and that the patient would rapidly go into

FIG. 12.—Plasma levels of total calcium before and after neck operations. The first operation on Mrs. Grace W. revealed four normal parathyroid glands. This was confirmed at a second neck exploration, and it was then considered that lack of post-operative fall of the total calcium probably meant that a parathyroid tumour remained in a fifth gland beyond the field of the first operation. Her sternum was therefore split, and Mr. Davies found a tumour in her mediastinum. (Case described by Rose, 1959.) Mrs. Emily P.'s neck and mediastinum have been explored at two operations at U.C.H. without any temporary or permanent improvement in plasma calcium levels. We suspect there may be a parathyroid tumour at an ectopic site, as the diagnosis here is beyond dispute. Her follow-up data are shown in Fig. 17. Miss Bridget D. has a mother and brother confirmed to have parathyroid tumours. At her first operation a parathyroid adenoma was removed from her neck, only two other normal glands being identified. Her temporary response suggested that a second adenoma had been left behind near the previous operation site. This was confirmed at the second operation. Subsequent review of the slides suggests the histology of chief-cell hyperplasia. On follow-up her calcium has risen again to abnormal levels and a third operation has been carried out (May, 1962), showing adenoma formation, from a fragment of parathyroid previously considered normal.

strongly positive calcium balance. He needed, therefore, a high calcium intake as the mainstay of treatment. We disputed this with him hotly on the grounds that on account of the renal damage vitamin D would also have to be given and we later posted to him the results of our balance study shown in Fig. 13. The situation of our patient was indeed similar to that of the patient with secondary renal hyperparathyroidism described by Stanbury, Lumb, and Nicholson (1960). Their patient could not go into positive calcium balance after subtotal parathyroidectomy without large doses of vitamin D. Another authority was for a while treating his patients with a low calcium diet post-operatively. He argued that, while this might worsen the tetany temporarily, the

ensuing increased stimulus to the remaining parathyroid tissue would hasten its hypertrophy, so that in the long run the duration of the tetany would be less and the patient benefit as a result.

Our own views on post-operative management are strongly held and are as follows:

Post-operative Management

1. Very soon after the operation a suitable moment should be chosen to warn the patient of the possible signs and symptoms (especially depression) that may arise. Stress their invariably temporary nature and the fact that they signify cure of the hyperparathyroidism.

2. Hypocalcaemia is likely to be worse when there is much bone involvement and when the remaining normal parathyroid tissue is small and has had to be handled and biopsied a lot. Its duration is increased if there is renal failure or steatorrhoea.

3. The lowest levels of plasma calcium usually occur 4 to 10 days post-operatively. Maximal tetanic symptoms may precede the lowest calcium levels.

4. Before any hypocalcaemic symptoms are treated blood should be drawn for analysis and a subnormal plasma calcium confirmed. This

is especially important if all four parathyroids could not be found at operation. During this time the patient should be encouraged to drink as much milk or other high-calcium foods as possible.

5. From now on the treatment of patients with good renal function is entirely symptomatic. For severe symptoms not expected to last long intravenous calcium gluconate (20 ml. of 20% (Sandoz) given over 10 minutes) given once or twice daily will usually suffice. A continuous drip of 5% glucose containing calcium gluconate is more troublesome and can usually be avoided.

6. When hypocalcaemia is expected to last long (severe bone disease, renal failure, steatorrhoea) treatment with a form of vitamin D (D_2 , D_3 , or dihydrotachysterol) should be begun while the intravenous calcium gluconate is being tailed off. A good schedule of dosage is 8 mg. a day for two days, 4 mg. a day for two days, followed by 2 mg. a day from then on until the indications suggest a raising or lowering to be necessary. In nearly every case the vitamin D can be stopped in one to four months' time. Temporary hypocalcaemia without symptoms does not demand any treatment.

FIG. 13.—Mr. Joseph E. Metabolic data after removal of the parathyroid tumour. It is seen from his calcium balance that on two six-day collection periods he is unable to absorb calcium from his diet in spite of the fact that he had marked bone disease and a "hungry bones" phenomenon. A large loading dose of dihydrotachysterol (D.H.T.), later tailed off, quickly began to lower his faecal calcium, corrected the hypocalcaemia, and enabled us to increase the rate of his bone healing.

7. It is most important to follow plasma calcium and phosphorus levels about twice weekly post-operatively. The calcium gives the best measure of the success of operation and of the subsequent recovery of remaining normal parathyroid tissue. The phosphorus level usually remains low for some time after and does not help much in management. A rise to abnormally high levels suggests temporary hypoparathyroidism (unless it can be adequately explained as due to worse renal function) and means that therapy may be required to correct hypocalcaemia even if there is no bone disease present.

8. Temporary post-operative correction of calcium and phosphorus levels with subsequent return to pre-operative levels indicates that another parathyroid tumour has been left behind and is situated near the site of operation. No change in calcium and phosphorus levels means that a tumour remains far from the site of operation, or else that a misdiagnosis has been made.

9. Alkaline phosphatase levels should be followed every one or two weeks when they were raised pre-operatively. A fall to normal means that the bone disease is nearly healed and there is no likelihood of a recurrence of tetany. If vitamin D is being given this can usually be stopped. In some cases many months may elapse before this occurs.

10. Rarely, signs resembling tetany persist for a short time post-operatively when plasma calcium levels are nearly normal. This may be due to Mg lack and will then respond to intravenous $MgSO_4$. One should always bear Mg-lack in mind if a patient's mental and neuromuscular symptoms do not immediately respond to treatment of hypocalcaemia.

We note with interest that Jackson and Doncaster (1962) also recommend vitamin D as treatment for post-operative hypocalcaemia.

[The conclusion of this lecture, together with a list of references, will appear in our next issue.]

EPISODIC, POSTURAL, AND LINKED ANGINA

BY

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The realization that pains in the chest, independent of effort, sometimes lancinating and sometimes long-lasting and often situated below the left breast, were not of cardiac origin was part of the new look that cardiology assumed forty years ago. It did, however, promote the notion that by contrast anginal pain was of two broad kinds: a repetitive paroxysmal type related to effort or pains unrelated to effort that were recurrent and more and more persistent as a prelude to infarction of the heart. As to diagnosis, this did not generally remain long in doubt in either instance. Further, it has generally been accepted that if a patient has anginal pain that is independent of effort, then a sufficient grade of effort, notably locomotion, will surely provoke it.

We have been interested in studying and defining a third variety of angina which is clinically separate from effort angina and also from the worsening anginas (with or without effort) that terminate in overt cardiac infarction. We now bring together as a group those syndromes in which pain proved to emanate from the heart occurs sporadically, independently of exertion, often without any evident provocation and sometimes connected with posture. In this group of disorders the recurrent pains may appear at long intervals and without deterioration of effort tolerance over years. Sometimes attacks are related to cold or to emotional causes; at times they develop only in recumbency, and at times they are closely associated with a disorder that is not related to the coronary system or the heart at all, such as gall-bladder disease, cervical spondylitis, and gastro-oesophageal disorders.

Criteria, Definitions, and Aims

In making this study we have set ourselves certain conditions, definitions, and requirements. First, we do not seek to question the well-established neurogenic and non-cardiac basis of the "left submammary" pains. Secondly, we are not dealing with any syndromes that

cannot be shown at once or in time to have a basis in coronary artery disease. Such proof may appear in straight cardiography, in or out of the attack, or by cardiographic effort test, or by the ultimate development of cardiac infarction in circumstances that indict the earlier pains as anginal. Thirdly, we exclude from this study general myocardial anoxia due to extracardiac causes and anginal syndromes caused by non-coronary cardiac disease, such as aortic stenosis.

In considering disorders of the gullet, stomach, biliary tract, or the nervous system in connexion with angina, we emphasize that we are not concerned with differential diagnosis. Thus we are not interested to exonerate the heart in any particular disorder but to study patients who admittedly have a coronary disorder but who have, in addition, one of these other syndromes and to demonstrate how these maladies interact. Naturally we have in mind the well-established criteria of non-infarction angina—namely, that the pain is repetitive and of a pattern, even if at long intervals; that it is measured in minutes (not seconds); that it is often generally constricting rather than locally cramping; that its quality is frequently burning but never lancinating; that it has a distracting and disturbing quality, even if it is not a severe pain; and that it vanishes completely when the paroxysm is over, never being associated either in or after the attack with local tenderness.

Classification

For the purposes of this study we propose the following classification of angina independent of effort: (1) episodic angina (which may be nocturnal and then falls in group 2 (a)). (2) Postural angina: (a) nocturnal or decubitus, and (b) stooping. (3) Linked angina associated with (a) gastro-oesophageal and duodenal disorders and diseases, (b) gall-bladder disease, (c) cervical spondylitis, and (d) left submammary pain. (4) Status anginosus.