Comparison of incidence in biracial communities may also be fallacious if access to hospital and opportunities for full clinical and laboratory assessment are more limited for the negro than for the white on account of local social or economic circumstances. The picture is further complicated by the difficulty of establishing complete racial purity in the modern West Indian or American negro. All of our patients presented essentially negroid characteristics; but it cannot be affirmed with any certainty that there had been no admixture of white, Chinese, or Indian blood. For practical purposes, however, it can be said that they were typical and representative of the negro in the West Indies to-day.

These are aspects of the disease that clearly require careful and detailed analysis and constant awareness of the tendency for preconceptions to persist as misconceptions. For the reasons stated comparison with incidence rates from other hospitals is likely to be unrewarding. In our hospital, however, it is certainly significant that all our patients were diagnosed in the period from January, 1958, to June, 1960, whereas this diagnosis had been made only once in the previous five years (in a white American female). It was during these two and a half years that particular attention was being directed towards the study of two disorders commonly seen in Jamaica, which show some features of pernicious anaemia. These are the megaloblastic anaemia of infancy, which has been shown to be due to a dietary insufficiency of folic acid (MacIver and Back, 1960a, 1960b), and an unusual neuropathy of unknown aetiology, the neurological features of which are very similar to those of subacute combined degeneration of the spinal cord (Cruickshank, 1961). We have thought that it is this detailed study and increased awareness of these and allied disorders that account for the increasing frequency with which the diagnosis is being made locally, and not an increasing incidence.

Summary

Clinical and laboratory details are given on 10 negro patients with pernicious anaemia admitted to the University College Hospital in Jamaica in the 30 months from January, 1958, to June, 1960. All showed the usual clinical and laboratory features of pernicious anaemia; and in the patients on whom these tests were carried out the Schilling test and gastric biopsy findings were characteristic. Anorexia and loss of weight were conspicuous features.

It is thought that the rarity of this disease in the negro has been overemphasized and that hospital statistics may be misleading in this respect.

The literature on pernicious anaemia in other parts of the tropics is briefly reviewed. There is evidence that, in addition to the basic gastric lesion, dietary and economic factors may play a part in the genesis of the disease.

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THE SYMPTOMS OF HYPERPARATHYROIDISM*

BY

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For practical purposes the presence of a complication is needed to call attention to the diagnosis of primary hyperparathyroidism, but, particularly in recent years, patients have been seen whose initial complaint has not been due to either of the well-known complications of kidney stone and bone disease.

The parathyroid glands were discovered in 1880 by Sandström in Sweden; their relation to the calcium level of the blood was demonstrated by MacCullum and Voegtlin (1908). Von Recklinghausen (1891) described the generalized bone disease of osteitis fibrosa cystica, and Askanazy (1904) found a parathyroid tumour in a patient dead from this disease. Later, enlargement of the parathyroid glands was also noted in rickets and osteomalacia (Erdheim, 1907, 1914), and it was assumed that the parathyroid tumours in von Recklinghausen's disease were secondary to the bone disease. Schlagenhaufer (1915), however, suggested that the reverse might be true, though it was not until July 30, 1925, that Mandl, in Vienna, explored a patient's neck, and with removal of a parathyroid tumour the bone condition improved (Mandl, 1926). Hyperparathyroidism was then considered to be synonymous with von Recklinghausen's disease of bone.

Albright *et al.* (1934) pointed out that renal stones were often found in patients with hyperparathyroidism (in 42 of 83 patients reviewed) and that the renal lesions could occur without the classical bone disease. Later it was also noted that osteoporosis might occur without bone cyst formation. Cope (1944) reviewed 78 cases and showed that, in fact, renal disease was more common than bone disease, a finding confirmed by a paper from the Mayo Clinic (Keating and Cook, 1945). Cope (1957) recorded clinical types of primary hyperparathyroidism as shown in Table I. It will be noted that one patient had neither bone disease nor renal stones.

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TABLE I.—*Clinical Types of Primary Hyperparathyroidism. 175 Patients at the Massachusetts General Hospital (1932–57)*

Complication		No.	Percentage
Bone disease	Classic	48	27
	Osteoporosis	7	4
	Osteoporosis and renal stones	30	17
No bone disease	Renal stones	81	52
	Peptic ulcer and renal stones	8	
	No renal stones	1	

69% with renal stones.

Presentations from Renal Stones and Bone Disease

The presentation leading to the diagnosis of primary hyperparathyroidism is most commonly due to renal stones, which give rise to pain or urinary infection, or symptoms from secondary impaired renal function or hypertension. Occasionally, nephrocalcinosis or the finding of kidney stones on incidental plain *x*-ray film may lead to investigation for this disease. Between 2 and 8% of renal-tract stones appear to be caused by hyperparathyroidism (Cope, 1957; Hodgkinson and Pyrah, 1958).

Bone disease consisting of osteoporosis (not just decalcification, as so often stated), with or without cysts and tumours, may be of varying degree. The early symptom may be indefinite pain, often attributed to "rheumatism," "arthritis," or "neuritis," and well described by Mandl's (1926) historic record of a Viennese street-car conductor. He wrote: "The present illness

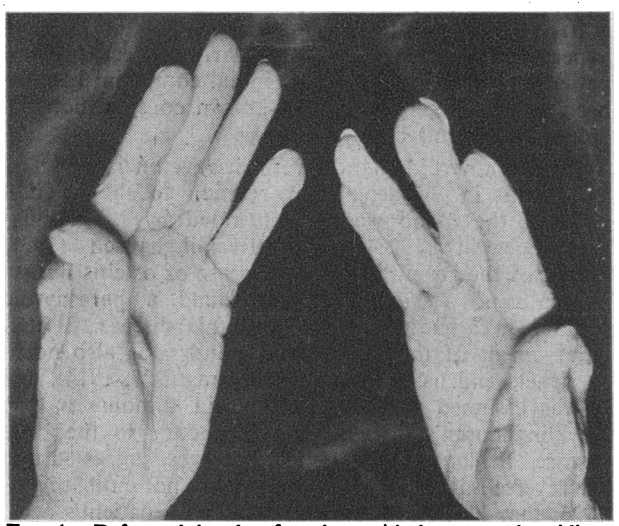

FIG. 1.—Deformed hands of patient with hyperparathyroidism, showing beaking of thumbs and finger-tips.

began five years ago with a from day to day increasing tiredness and feeling of pain in the pelvis and lower extremities. The pains were increased by all bodily efforts, sneezing, coughing, defaecation, etc. In the course of months the suffering so increased that the patient had to be pensioned." These pains may disappear within hours of removal of the hyperfunctioning parathyroid tissue. A pathological fracture may occur, or bone deformities such as collapse of vertebrae leading to shortening in stature, "pigeon-breast" deformity of the chest, or alteration in the shape of the hands (Fig. 1). Tumours, particularly in the jaws, metacarpals and metatarsals, and ends of long bones, may be reported on as benign giant-cell tumours. Every epulis is not due to hyperparathyroidism, but this diagnosis must be considered with each, so that a presentation may result from a visit to a dental department.

Anaemia and leucopenia may occur as a result of marked fibrosis of the bone-marrow in hyperparathyroidism with bone disease, and anaemia is also frequent in the presence of complicating renal disease. The anaemia may respond to iron (Albright and Reifenstein, 1948).

Atypical Presentations

Albright noted that renal stones were common in patients with hyperparathyroidism and might occur in the absence of bone disease. Now patients with hyperparathyroidism are being recognized who present with symptoms other than those from renal stones or bone disease. Clinicians have for many years been aware of these other symptoms in patients presenting with renal stones or bone disease, but only recently have these become the clue to diagnosis and not a secondary clinical aid to diagnosis. It is the question of the other symptoms setting the doctor the task of investigating for hyperparathyroidism. Often the investigation may then reveal kidney stones or bone disease, but more and more patients are being diagnosed who have neither of these. It is remarkable, on reviewing the records of patients with proved hyperparathyroidism, how many had been to their doctors with suggestive symptoms, admittedly often vague, before, say, the attack of renal colic which had led to the diagnosis.

Cope (1957), for instance, has recorded the story of a New Yorker, aged 45, who felt lackadaisical and without his usual energy while performing a desk job in the Navy during the second world war. The patient ascribed this to the uprooting of his wartime job, but on return to his old life he continued to feel out of sorts. It was then noted that he had a prominent right thyroid lobe, and in 1946 a partial thyroidectomy was performed without the finding of any disorder of the thyroid gland. He was better for three months, but then lapsed into his state of lack of energy; all he wanted was to sit and do nothing. In 1949 he changed his doctor, who found nothing abnormal on physical examination. The examination, however, included the Sulkowitch test for calcium content of the urine, and this showed a raised concentration. The doctor then asked for tests of the fasting serum calcium and phosphate levels to be performed, and received the news that the calcium level was raised at 12 mg., with the phosphate at 2.5 mg./100 ml. That night the patient called him in with an attack of left-sided abdominal colic and later passed a stone. The diagnosis of hyperparathyroidism was confirmed by the removal of an adenoma, but would have been made in the absence of renal symptoms.

Fatigue appears to be one of the symptoms of hypercalcaemia, which is the cause of other symptoms from which hyperparathyroidism may be diagnosed. These include muscular weakness, hypotonia, bradycardia, lassitude, loss of appetite, chronic constipation, polyuria,

TABLE II.—*Symptoms of Hypercalcaemia*

Fatigue	Muscular weakness
Lassitude	Hypotonia
Headache	Bradycardia
Loss of appetite	Chronic constipation
Mental disturbance	
Keratitis	
Polyuria	Polydipsia

polydipsia, keratitis, headache, and mental disturbance (Table II). Dyspepsia, pancreatitis, and other endocrine disease may also lead to the diagnosis of hyperparathyroidism.

The clues to the diagnosis of hyperparathyroidism in 230 patients at the Massachusetts General Hospital are shown in Table III (Cope, 1960). 16% were not due to renal stones or bone disease, but this figure probably should be higher, since the series dates from 1932 and is weighted by the earlier emphasis on bone disease.

TABLE III.—*Clues to Diagnosis of Hyperparathyroidism. 230 Patients at the Massachusetts General Hospital* (1932–59)

Bone disease	63 (27%)	Hypertension	3 (1%)
Renal stones	130 (57%)	Mental disturbance	2 (1%)
Peptic ulcer	19 (8%)	C.N.S. signs	3 (1%)
Pancreatitis	4 (2%)	No symptoms	2 (1%)
Fatigue	4 (2%)		

Presentations from Hypercalcaemia

The symptoms of hypercalcaemia are mainly vague, as already outlined, and may suggest Addison's disease or, in the case of polyuria and polydipsia, diabetes insipidus. A typical history has been related by Albright and Reifenstein (1948). A woman of 59 was first seen with fatigue and sleeplessness. Two years later she was admitted to hospital for a mastoid operation, and it was noticed that she had a large fluid intake between 4 and 7 litres a day; the blood-pressure was 160/100. On investigation five years later for these symptoms, when tests for diabetes insipidus were negative, the serum calcium level was found to be 12.4 mg. and the serum phosphate 2.4 mg./100 ml. There was a normal I.V.P. and no bone disease was seen on *x*-ray examination. The kidney function was impaired, but this improved after the removal of a parathyroid adenoma. (This is the patient already noted in Table I without bone disease or renal stones.)

At the Massachusetts General Hospital I saw two patients in 1958 with mental disturbance and hyperparathyroidism. The first patient was an elderly man with a large head suggestive of arrested hydrocephalus. The psychiatrist thought that the large head suggested hyperparathyroidism and asked for a serum calcium determination. The level was raised, and later a parathyroid adenoma was removed; the patient's mental state improved. The same psychiatrist, a few months later, saw a young woman with an atypical psychosis, and, remembering the first patient, asked for a test of serum calcium, which was found to be raised. After further investigation a parathyroid adenoma was removed. This patient, who had neither bone disease nor renal stones, then became rational. Nielsen (1955), who first described psychic disturbances with hyperparathyroidism, has reviewed five patients whose psychic symptoms disappeared after parathyroidectomy. Occasionally acute hyperparathyroidism, with hypercalcaemia, may give rise to coma, vomiting, dehydration, high fever, and tachycardia (Mandl, 1947; Albright and Reifenstein, 1948). One sign of hypercalcaemia is band keratopathy where there is a grey, granular, and superficial opacity limited to the paralimbal region on either side of the cornea (Walsh and Howard, 1947; Cogan *et al.*, 1948).

Presentation from Peptic Ulceration

It is probable that peptic ulcer is clinically significant in hyperparathyroidism. Dyspepsia is common, and St. Goar (1957), who made the comment that hyperparathyroidism was a "disease of stones, bones and abdominal groans," found that 4 out of 45 patients (8.8%) had peptic ulcers, and 16 out of the 45 had gastro-intestinal symptoms (nausea, vomiting, anorexia, weight loss, abdominal pains, and constipation). At the Mayo Clinic 24% of patients with primary hyperparathyroidism had proved peptic ulceration, and more had symptoms suggestive of this (Lee *et al.*, 1955). Most of the ulcers are duodenal ulcers. The patients who should particularly be screened for hyperparathyroidism will be those with peptic ulcers and renal stones. Parathyroidectomy has been shown to promote healing of some of the ulcers.

A patient whose story is remarkable was a girl of 19 who was admitted to the Massachusetts General Hospital with a haematemesis requiring the transfusion of 1.5 litres of blood. A barium-meal examination showed a duodenal ulcer. The residents had been told of the association of peptic ulceration and hyperparathyroidism and urged to investigate all patients whose peptic ulcers were strange (thus a girl of 19 with a duodenal ulcer which bled sufficiently to require blood transfusion). In the ward, and on the first visit to the out-patient department, the serum calcium was normal, but at the next visit the determination was repeated. This time it was raised and she was readmitted for investigation. There was no bone disease or renal stones, but the biochemical findings favoured hyperparathyroidism. At operation Dr. Cope removed an early parathyroid carcinoma.

Presentations from Pancreatitis and Pancreatic Lithiasis

Nephrocalcinosis is a familiar complication of hyperparathyroidism, but only recently has pancreatic calcification and recurrent pancreatitis become recognized as another complication of this disease. Cope *et al.* (1957) reported two cases and reviewed five more from the literature. Their second patient was a woman of

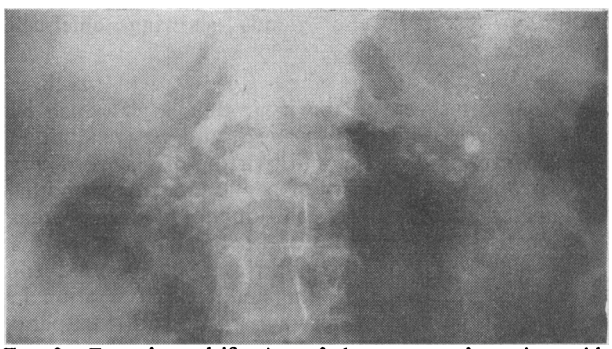

FIG. 2.—Extensive calcification of the pancreas in patient with hyperparathyroidism. (By permission of Dr. A. W. Spence.)

62 with a three-year history of epigastric distress who was admitted with acute pancreatitis. Despite medical and surgical treatment she continued to have recurrent episodes of pancreatitis. On the fourth admission a serum calcium estimation was 14.4 mg./100 ml.—the estimation was made as a routine test, hypocalcaemia being so often a complication of acute pancreatitis. The raised serum calcium led to exploration of the neck, with the finding and removal of a parathyroid adenoma. After this she had no more symptoms suggestive of pancreatitis. Hoar and Gorlin (1958) have since reported a further example of hyperparathyroidism presenting with acute pancreatitis, and we have at present a patient at St. Bartholomew's Hospital in whom exploration has revealed a parathyroid tumour. Her pancreas shows extensive calcification (Fig. 2) and she has had, in retrospect, recurrent attacks of pancreatitis. Primary pancreatic lithiasis is a rare condition, but, when encountered, efforts should be made to investigate the patient for hyperparathyroidism, which is almost

certainly a more common cause of pancreatitis and pancreatic calcification than the few records would suggest.

Presentations from Other Endocrine Disease

Underdahl *et al.* (1953) published a paper entitled "Multiple Endocrine Adenomas: a Report of 8 Cases in which the Parathyroids, Pituitary and Pancreatic Islets were Involved." Besides their own patients they reviewed 14 more with tumours of two or three of these glands. Zollinger and Ellison (1955) described a syndrome with four main characteristics—gastric hypersecretion and hyperacidity, severe peptic ulceration (often atypical), and a non-insulin-producing islet-cell tumour of the pancreas. The tumours of the pancreas were often multiple and many were malignant. Up to date at least 75 cases showing the Zollinger–Ellison syndrome have been described, and about a quarter of these had other endocrine tumours, including tumours of the parathyroids. Thus patients with other endocrine disease may on investigation show hyperparathyroidism.

Cope *et al.* (1958) published a paper on a new form of parathyroid hyperplasia with enlargement of all four parathyroid glands which they called "primary chief-cell hyperplasia." Four of the 10 patients had tumours of the pancreas and pituitary gland. One of these was a woman of 46 who gave a history of renal colic in 1954, and two operations for severe peptic ulceration in 1954 and 1957. At the second operation a nodule was removed from the pancreas which proved histologically to be a non-insulin-producing islet-cell adenoma. Because of this the possibility of hyperparathyroidism was considered and diagnosed. At operation in 1958 four enlarged parathyroid glands were found and subtotally resected, the glands showing chief-cell hyperplasia.

Another of the patients, a man aged 45, had had three operations for severe peptic ulceration, after which he had a generalized convulsive attack and was readmitted with confusion, headache, and blurring of vision. There was a strong family history of peptic ulceration, and his daughter had had two islet-cell tumours of the pancreas removed in 1953. She also had a history of passing a few small stones in 1952, and was investigated for hyperparathyroidism, with the finding, at operation in 1953, of primary chief-cell hyperplasia of the parathyroids. Because of this the father was investigated for hyperparathyroidism, which was proved at operation in 1953. His bones showed osteoporosis, and he was a tense, gloomy individual. An *x*-ray examination showed enlargement of the sella turcica due to a chromophobe pituitary tumour, and later he underwent a total gastrectomy because of further haematemesis. At this operation no pancreatic tumour was discovered, though on his recent death the pancreas showed at least 10 small islet adenomas (Cope, 1960).

Summary

The symptoms of hyperparathyroidism have been outlined, with emphasis on those not due to renal stones or bone disease. Hyperparathyroidism is more common than supposed, and cases are being missed, even when some of the presentations mentioned are remembered.

Investigation for hyperparathyroidism because of "other symptoms" may reveal kidney stones or bone disease, which would later possibly have given symptoms themselves. In this case the diagnosis of hyperparathyroidism may only be delayed, but this will be after a longer period of ill-health and perhaps increasing irreversible damage. More and more cases, however, are being diagnosed without renal stones or bone disease, and more than 15% of patients with hyperparathyroidism are now being detected without these being the clue to diagnosis.

The atypical presentations may be from hypercalcaemia, when the symptoms are often vague—fatigue, weakness, loss of appetite, constipation, polyuria, polydipsia, headache, and mental disturbance—and from peptic ulceration, pancreatitis, and other endocrine disease.

The basis of this paper is the experience obtained during 16 months which I spent at the Massachusetts General Hospital and Harvard Medical School as a Nuffield Fellow working under Dr. Oliver Cope, to whom I should like to extend my thanks and admiration.

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"Considerable progress has been made [in the U.S.A.] in the campaign to abolish the performance of painful experiments on animals by schoolchildren. The *Ladies Home Journal*, a very influential periodical, published a strong article condemning these cruel experiments and this was backed up by the *New York Daily News*. A body called the 1960 Science Achievement Awards for Students, which is under the aegis of the National Science Teachers' Association, has announced that it will not in future give awards for projects involving animal suffering. The Maryland Society for Medical Research has restated its decision not to offer animals to schools for painful experiments. In order to provide science teachers with a practical alternative to cruel experiments the Animal Welfare Institute, ever practical, has published a booklet called *Humane Biology Projects*. It contains sections written by experts on practical work which can be done by schoolchildren in the fields of ecology and conservation, bacteriology, animal behaviour, genetics, botany and physiology without causing animals to suffer." (*Annual Report and Accounts, July 1, 1959, to June 30, 1960*, Universities Federation for Animal Welfare.)