W. GLYN OWEN:
DIFFUSE MESOTHELIOMA

FIG. 1

FIG. 2

FIG. 3

FIG. 4

FIG. 5

C. E. DENT AND L. WATSON:
HYPERPARATHYROIDISM AND CANCER

with these fibres. On the other hand, Cartier (1952) mentioned two cases of diffuse mesothelioma from a Canadian chrysotile mine.

It is clear that evidence of exposure to asbestos may assist in the diagnosis of diffuse mesothelioma and that a careful occupational history should be obtained in cases of prolonged chest pain or recurrent pleural effusion of obscure origin. The presence of hyaluronic acid in serous effusions is said to provide confirmatory evidence, and a simple screening test is available for the detection of this substance (Wagner *et al.* (1962). No pleural or peritoneal fluids have been available for examination in this series.

Summary

Seventeen cases of diffuse mesothelioma occurring in the Merseyside area were investigated and evidence was sought of exposure to asbestos dust.

An account is given of the clinical features of diffuse mesothelioma, and in 12 cases the pathological findings at post-mortem examination are described.

Difficulties of histological diagnosis are discussed and the histological appearance of the tumours described.

Exposure to asbestos had occurred in 14 (82%) of the 17 cases examined, and asbestos bodies were seen in seven out of 10 specimens of lung tissue examined.

It is concluded that exposure to asbestos is a major factor in the causation of diffuse mesothelioma.

ADDENDUM.—Since this paper was submitted two further papers (Enticknap and Smither, 1964; Hourihane, 1964) have been published, both dealing with the subject of mesothelioma and asbestos.

I am grateful to the surgeons of the Liverpool Thoracic Surgery Unit for permission to study the medical records of cases under their care, and to Dr. Edith M. McConnell for searching the files of the Liverpool Cancer Control Organization. I am indebted to Dr. H. McClean, Dr. Rachel M. Rawcliffe, Dr. P. J. Taylor, Dr. H. E. Vickers, and Dr. A. S. Woodcock for making available post-mortem records and for sending blocks of tissue from their cases. My thanks are due to Dr. F. Whitwell and Dr. J. A. Campbell for their constant encouragement, and to Dr. J. C. Wagner, of the M.R.C. Pneumoconiosis Research Unit, who first suggested the investigation and who has helped me at many stages. The work could not have been carried out without the enthusiastic assistance of Mr. A. Robertson, who devoted much time to the preparation of the histological material.

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Hyperparathyroidism and Cancer

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[WITH SPECIAL PLATE]

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The cause of hypercalcaemia in a particular patient can usually be established with great certainty. This has been emphasized in several reviews, including those of Albright and Reifenstein (1948), Thomas *et al.* (1959), and David *et al.* (1962), and such has been our experience in this unit.

A difficult problem still arises in the differential diagnosis of hypercalcaemia when more than one of the known causes is present in the one patient, a situation which seems to occur more often than it should. Case reports of these associations include hyperparathyroidism and thyrotoxicosis (Bortz *et al.*, 1961; Jackson *et al.*, 1961), hyperparathyroidism and sarcoidosis (Burr *et al.*, 1959), hyperparathyroidism and Paget's disease (Kohn and Myerson, 1961), and hyperparathyroidism and cancer (Hellström and Ivarmark, 1962).

We are reporting our findings from a severely hypercalcaemic patient, who proved to have both a primary carcinoma of the cervix uteri and primary hyperparathyroidism due to parathyroid adenoma.

Case Report

A married woman aged 37 was admitted to University College Hospital in August 1962. She was the mother of six children, whose ages ranged from 17 years to 3 months. She had few complaints. She had been a little more tired than usual since the beginning of her sixth pregnancy and perhaps a little thirsty. When six months pregnant she slipped and fell from a bus and was admitted to Redhill Hospital because of abdominal pain, which quickly settled down. She soon felt very well but was found to be anaemic, with a haemoglobin of about 50%. She was given two blood transfusions, each of 2 pints (1,140 ml.) and discharged. Three months later she came into labour, which was rather prolonged, lasting about 25 hours and terminating with the aid of vacuum extraction. This was unusual for her, as she had previously had quick and easy labours at home.

During the puerperium investigations revealed that the plasma calcium level was raised, as was the plasma alkaline phosphatase, while the plasma phosphorus level was abnormally low. At this stage the patient insisted that she was free of symptoms and that she should be allowed to leave hospital in order to look after her family. In August she returned for a post-natal follow-up examination, when the S.H.O. (Mr. A. R. F. Williams) thought that the

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cervix was somewhat too firm in consistency and too irregular in outline. There were no other abnormalities on pelvic examination. A biopsy showed the presence of anaplastic squamous-cell carcinoma of the cervix uteri.

She was admitted at once to the metabolic ward at University College Hospital, still with no real complaints. Examination revealed some old interstitial keratitis in both corneae, coarse irregular scarring of the tongue, and a few irregular clefts in the soft palate. The liver edge was just palpable and firm in consistency, but clinically the liver was not enlarged. The pelvic findings were unchanged and there were no other abnormal physical signs. An additional piece of history elicited at this stage was that she had suffered from "eye trouble" as a very young girl and had had a course of injections for this.

Initial Investigation

Plasma total calcium 14.4 mg./100 ml. (ionized fraction 9.4 mg./100 ml., complexed fraction 0.7 mg./100 ml., protein-bound fraction 4.3 mg./100 ml.); plasma phosphorus 2.9 mg./100 ml.; plasma alkaline phosphatase 19 K.A. units; plasma total proteins 6.7 g./100 ml. (plasma-protein electrophoresis showed a slight decrease in the albumin fraction with a definite increase in gamma-globulin); serum bilirubin 0.4 mg./100 ml.; plasma urea 17 mg./100 ml.; plasma sodium 140 mEq/l.; plasma potassium 4.7 mEq/l.; plasma chloride 108 mEq/l.; plasma bicarbonate 24.5 mEq/l.; 24-hour urinary calcium 603 mg.; 24-hour urinary phosphorus 880 mg.; haemoglobin 13.0 g./100 ml.; E.S.R. 21 mm. in one hour. Chemical and microscopical examination of a clean specimen of urine revealed no abnormality. W.R., Kahn, Reiter, and treponemal immobilization tests were all negative.

Skeletal x-ray films were normal except for the hands, where there was some minor erosion of the terminal phalanges and a suggestion of subperiosteal resorption in the middle phalanges (Special Plate, Figs. 1a and 2a). These changes were thought to be consistent with hyperparathyroidism, but were so slight as not to be diagnostic. An intravenous pyelogram was normal.

Course and Progress

The patient was seen by Professor W. C. Nixon, who confirmed the diagnosis of squamous carcinoma of the cervix uteri, stage 1

FIG. 1.—Metabolic data. Note that no changes in the plasma levels occurred with the patient's radium implantations in August 1962. They all became normal after parathyroidectomy, the alkaline phosphatase as usual being the last to become normal.

progressing to stage 2. The cancer was treated by means of two radium implantations. Each implant was left in position for four days and the second was inserted seven days after the first. While the implants were in position she was given nitrofurantoin 100 mg. four times daily. There were no complications during this treatment and it was thought that a good result had been achieved.

Blood calcium and phosphorus levels were determined about twice weekly throughout the investigation, and these are shown together with some other data in Fig. 1. They did not alter significantly during the radium therapy or in the following week, but during these three weeks of observation the plasma alkaline phosphatase fell slowly to 16 K.A. units.

She was then put on a constant diet containing 1,159 mg. of calcium and 1,465 mg. of phosphorus daily, and calcium and phosphorus balances were determined for two consecutive six-day periods. These showed that she was in approximate balance. The urinary calcium varied between 525 and 618 mg./day during these two periods, when the faecal calcium was 671 and 594 mg./day respectively, giving a slightly negative balance of about 50 mg./day in each period. These results, together with phosphorus balances, are shown in Fig. II.

FIG. 2.—Calcium and phosphorus balances. The patient is in approximate balance for both these elements, showing marked overabsorption from the gut and excessive urinary excretion. This partition of excretion is commonly found in hyperparathyroidism. It is not modified by cortisone treatment.

Cortisone was then begun in a dosage of 50 mg. eight-hourly and continued for 12 days, while two further six-day balance studies were made on the same diet. There was no real change in the balance picture. The urinary calcium remained above 600 mg./day and the faecal calcium was 679 and 598 mg./day, giving a slightly more negative calcium balance of 168 mg./day in the first cortisone period; but the negative balance was again about 50 mg./day in the second cortisone period. During this time the calcium and phosphorus levels remained substantially unchanged in the plasma. Indeed, there was a slight rise in the plasma calcium level.

At the end of the cortisone test the balance studies were stopped, but hydrocortisone was substituted in an equivalent dose (40 mg. eight-hourly) and the blood levels were investigated for a further 13 days. The plasma calcium fell only slightly during this time, to 13.3 mg./100 ml., while the plasma phosphorus levels remained unchanged.

During the administration of corticoids she developed dyspepsia and epigastric pain which was characteristic of peptic ulceration. The stools were found to be positive for occult blood, and a barium meal examination revealed the presence of a duodenal ulcer. Hydrocortisone was therefore reduced during the next five days to 10 mg. b.d. and she was given some magnesium trisilicate, which relieved the pain and dyspepsia.

A careful search was now made for the presence of any secondaries, since it was thought that all the evidence was in favour of a diagnosis

of primary hyperparathyroidism with minimal bone disease provided that secondary carcinoma could be reasonably excluded. Professor Nixon reported that the response of the primary carcinoma to treatment was satisfactory and that there was no clinical evidence of secondaries in the pelvis. Systematic examination did not reveal any signs of secondaries elsewhere. The plasma alkaline phosphatase level had remained between 14 and 18 K.A. units throughout, and bone x-ray films did not show any evidence of secondaries, the only abnormalities seen being those already described in the hands, which were thought to be radiological evidence of minimal hyperparathyroid bone disease. Although the edge of the liver was still palpable the organ was not enlarged clinically. Bromsulphthalein retention was found to be normal (4% after 45 minutes) and liver biopsy was also normal.

The final assessment was clinical. After three months of close observation her clinical condition was unaltered. She was no better and no worse. There had been no loss of weight, and no evidence of any kind had appeared to suggest either the presence of secondary carcinoma or that the primary cancer had been inadequately treated. We therefore diagnosed primary hyperparathyroidism.

Operation.—On 24 October 1962 Mr. D. R. Davies explored the neck and removed a parathyroid adenoma weighing 1.5 g. He also demonstrated the presence of three normal-sized parathyroid glands. Histological examination showed that the adenoma was of the chief-celled type and confirmed the normality of the other three.

Two days after the operation the plasma calcium level fell to 8.6 mg./100 ml. while the plasma phosphorus rose to 3.8 mg./100 ml., and during the next 10 days the plasma calcium level fell slowly to 7.6 mg./100 ml. She was given dihydrotachysterol 4 mg. on the first day, 2 mg. daily for two days, then 0.25 mg. once daily and discharged from hospital. Two weeks later she looked and felt very well; her only complaint was of occasional mild tingling in the hands and feet. The plasma calcium was found to be normal, and when the same result was obtained two weeks later dihydrotachysterol was stopped.

In April 1964 she was still very well. The plasma calcium and phosphorus have remained normal and the plasma alkaline phosphatase has fallen slowly to 7 K.A. units. In addition the slight changes noted in the hands had resolved completely and her hand x-ray films were normal (Special Plate, Figs. 1b and 2b). There was no evidence of any cancer recurrence either at the primary site or elsewhere. We would like to redetermine her calcium balance, but for the moment this procedure does not seem to be justifiable and, furthermore, the patient prefers to avoid readmission if possible.

Discussion

We had considerable difficulty at first in making a diagnosis in a patient in whom hypercalcaemia had been accidentally discovered during hospital admission for unrelated reasons. Primary hyperparathyroidism seemed the most likely explanation when we first saw her as an out-patient and had confirmed the biochemical findings elsewhere of high plasma calcium, low phosphorus, and slightly raised alkaline phosphatase with minimal subperiosteal erosions in the phalanges (Special Plate, Figs. 1a and 2a). When a few days later we heard that the cervical biopsy showed anaplastic cancer we at once thought this a more likely explanation, for we are becoming very aware of the frequency of hypercalcaemia due to cancer (reviewed by Watson, 1963). The failure of the biochemical changes to reverse when the cancer was adequately treated could have been due to the presence of undiscovered metastases. These, however, did not reveal themselves during the time spent on investigation later.

The important next test was that in which we investigated the possible effect of corticosteroid on the plasma calcium levels. Both our standard load of cortisone and subsequently its equivalent of hydrocortisone failed to lower this appreciably. This result excluded sarcoidosis, vitamin-D intoxication, and various obscure conditions in which vitamin-D sensitivity seems to occur. It provided strong evidence against carcinoma as the cause of the hypercalcaemia, since in our experience most of such cases respond well to cortisone or, when liver damage is present, to hydrocortisone (Watson, 1964).

It was at this stage that the importance of her hand x-ray films (Special Plate, Figs. 1a and 2a) and slight rise in alkaline phosphatase became apparent. A liver biopsy and studies of liver function had shown normal results, so we could argue more firmly that the phosphatase result was not due to hepatic causes and that she had instead a mild degree of osteitis fibrosa with associated slight rise in phosphatase. We know that there is still disagreement concerning the earlier claim from this department that there are two distinguishable forms of primary hyperparathyroidism—one with osteitis fibrosa (or osteitis cystica) and raised alkaline phosphatase (>16 K.A.) units, and one with neither of these features which usually presents with renal stones and has other less clear distinguishing features (Dent and Harper, 1962; Dent, 1962). For instance, in a recent paper on primary hyperparathyroidism Hodgkinson (1963) disagrees with us, and quotes two patients "with bone disease" and normal phosphatase and seven "without bone disease" and raised phosphatase out of a total of 50 cases. We wonder about the radiological criteria he used, and perhaps we have not previously stressed the significance of quite minimal changes as shown in Figs. 1a and 2a (Special Plate).

We have had other patients with similarly slight radiological signs. In these, too, we have confirmed their specificity, since after removal of the parathyroid tumour the x-ray films have changed to normal coincident with a fall to normal of the phosphatase. Clearly, as increasing awareness makes for earlier and earlier diagnosis of primary hyperparathyroidism the number of such cases with minimal radiological signs is likely to increase. McGeown (1962), who agrees with us that there are two distinct types of primary hyperparathyroidism, describes that with bone disease as having a slightly raised phosphatase (up to 20 K.A. units) when the bone changes are minimal, or a higher phosphatase (>20 K.A. units) when the bone x-ray films show gross changes. This more cautious description may well be preferable to our original one.

It is a pity that renal phosphate-excretion studies have not proved helpful in the differential diagnosis of hypercalcaemia. In the presence of renal damage, as occurs in many patients with chronic stone formation, they are not too specific (McGeown, 1957). We are not aware of any systematic studies of phosphate excretion in patients with hypercalcaemia not caused by primary hyperparathyroidism, but we would expect them to be even less helpful here. We have seen hypercalcaemia—for instance, from vitamin-D overdosage—produce all types of renal tubular reabsorptive dysfunctions, from simple phosphate leaks to the fully developed "Fanconi syndrome" with, in addition, glycosuria, amino-aciduria, renal acidosis, potassium loss, and renal tubular proteinuria. Clearly we have to bear in mind that in any patient with hypercalcaemia there may be more than one cause operating or appearing to be operating. The situation may then have to be sorted out by dealing separately with each cause, as was done in our patient.

Summary

A case is reported in which hypercalcaemia was accidentally discovered during hospital admission for unrelated reasons. The patient was found later to have anaplastic carcinoma of the cervix uteri. It was at first difficult to decide whether her hypercalcaemia was due to the carcinoma or to primary hyperparathyroidism. The hypercalcaemia was unaltered by radium therapy to the cervix and later by our standard cortisone test. Furthermore, she had minimal subperiosteal phalangeal erosions and a slight rise in plasma alkaline phosphatase level. A diagnosis of primary hyperparathyroidism was therefore made. A parathyroid tumour was then found and removed.

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nurses, biochemists, and dietitian of the metabolic ward for their invaluable help. The patient and her problem were kindly referred to us by Mr. J. C. Cuthbert.

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Venous Obstruction in the Aetiology of Lymphoedema Praecox

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[WITH SPECIAL PLATE]

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Allen (1934) defined lymphoedema as “a swelling of soft tissues which is the result of an increased quantity of lymph” and introduced the term “lymphoedema praecox” to denote primary lymphoedema in early life. He distinguished this from the familial congenital type of Nonne (1891) and Milroy (1892). The praecox form constituted 93 of Allen's 146 cases of primary lymphoedema. Kinmonth, Taylor, Tracey, and Marsh (1957) restricted the adjective “praecox” to those patients in whom the initial oedema appeared before the age of 35 years, and their series of 107 cases of primary lymphoedema contained 83 such patients.

The onset of swelling occurs spontaneously and often affects one leg only, as in 70% of Allen's cases. The oedema is more pronounced during long periods of activity, during menstruation, and in warm weather. There is usually progressive involvement of the entire limb. Early in the disease the oedema is soft, but later, as the protein content of the fluid increases, there is proliferation of fibrous tissue and the swollen limb will no longer pit on digital pressure. Although the course is often painless, attacks of lymphangitis may occur, and it is occasionally difficult to decide whether the initial incident was oedema or an inflammation, but a careful history usually allows the distinction to be made (Smith, Spittell, and Schirger, 1963).

Allen pointed out that lymphoedema praecox often begins during puberty and adolescence, and that it is much commoner in women. Among Allen's 93 patients with this form of lymphoedema, 65% were affected between the ages of 9 and 25 years and 87% were women. Kinmonth *et al.* (1957) and Schirger, Harrison, and Janes (1962) found a similar sex-and-age distribution in their large series. Adequate explanation for these two constant and striking features has never been presented. Minor trauma is frequently offered as a precipitating factor in lymphoedema, but there is no reason for this to occur more often either during adolescence or in the female sex. The answer to this problem must involve the basic nature of the disorder. The work of Kinmonth (1952) and Kinmonth, Taylor, and Harper (1955) on lymphangiography resulted in a description of the lymphatic vessels in primary lymphoedema

in 1957. Hypoplastic vessels occurred in 55% of patients, aplastic in 14%, and broad, tortuous, or varicose lymphatics in 24%; the phenomenon of dermal backflow was found as the only abnormal radiological feature in 6% of the series but was present in 22% of all patients in the group. This latter radiological appearance resulted from filling of the dermal lymph plexus distal to areas of imperfect lymph drainage. The importance of lymphatic vessel abnormality is clear, and these authors considered that their data supported the suggestion of Allen, Barker, and Hines (1946): “That it is possible that the entire explanation rests on a congenital under-development of the lymphatics.”

Little attention has been paid to the venous drainage in these extensive series of patients, although Aird (1950) and Boyd (1950) have drawn attention to the frequent occurrence of venous abnormalities among patients with clinical lymphoedema. It was with this in view and by the application of modern radiological and haemodynamic techniques that the following study was undertaken.

Materials and Methods

Twenty-three consecutive patients with lymphoedema praecox were studied. In all of them the oedema had begun before the age of 30 years. The details of age and sex together with other data are presented in the Table. It can be seen that 20 of the 23 patients are women.

In each patient the venous drainage from the limb was investigated by percutaneous femoral venography and venous flow and pressure measurements in the common iliac veins. Lymphangiography was successfully performed in 10 cases.

Venous-flow Studies

The continuous-injection-indicator-dilution technique described by Shillingford, Bruce, and Gabe (1962) and subsequently used by Pentecost, Irving, and Shillingford (1963) in the inferior vena cava was used to measure venous flow. A specially adapted No. 9 double-lumen cardiac catheter with a stainless-steel spray-tip was inserted into a median vein in the antecubital fossa under local anaesthesia and advanced under

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