It is of interest that the haemorrhagic episodes recorded occurred in several varieties of megaloblastic anaemia—Addisonian pernicious anaemia, megaloblastic anaemia of pregnancy, malabsorption due to steatorrhoea, and megaloblastic anaemia associated with primidone administration. This supports the conception that thrombocytopenia is part of the dyshaemopoietic state produced by lack of vitamin B_{12} or folic acid and is not an independent feature. Other factors may have contributed to the haemorrhagic tendency, but unfortunately they were not investigated in any detail in our patients. Hypoprothrombinaemia has been described in pernicious anaemia. In itself it is unlikely to be severe enough to account for haemorrhage (Warner and Owen, 1942), but it can form a contributory cause. Where intestinal malabsorption exists lack of vitamin K may likewise contribute to a bleeding tendency.

These cases are reminders that post-partum blood loss, epistaxis, haematemesis, haematuria, and confluent purpura can have as their basis a megaloblastic anaemia. Thrombocytopenia is a significant factor in accounting for the bleeding and, like the anaemia, is corrected by vitamin B_{12} or folic acid. The condition is initially critical and usually calls for blood transfusion before haematinics can take effect.

Summary

Nine cases of haemorrhagic emergencies found attributable to thrombocytopenia associated with various forms of megaloblastic anaemia are described. Eight of the patients required blood transfusion and subsequently recovered on vitamin-B_{12} or folic-acid therapy. One responded to vitamin B_{12} but died with a coronary infarction.

We are indebted to the following physicians and obstetricians for access to their patients and records: Professor L. J. Davis, Dr. A. H. Imrie, and Dr. E. G. Oastler, of the Royal Infirmary, Glasgow, and Dr. W. Armstrong, of Robroyston Hospital, Glasgow.

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ABSORPTION OF FOLIC ACID AND D-XYLOSE AS TESTS OF SMALL-INTESTINAL FUNCTION

BY

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The urinary excretion of the pentose D-xylose after an oral dose of 25 g. is widely employed as a test of intestinal absorption (Helmer and Fouts, 1937). A folic-acid absorption test in the form of either a urinary excretion test (Girdwood, 1953) or a tolerance-type test (Chanarin, Anderson, and Mollin, 1958) is less widely employed because microbiological assay methods are required for the measurement of the vitamin.

In investigating patients with megaloblastic anaemia due to folic-acid deficiency, patients were encountered in whom the only evidence of intestinal malabsorption was a test showing impaired folic-acid absorption. In two of these patients the diagnosis of idiopathic steatorrhoea was established by the finding of villous atrophy on jejunal biopsy, but biopsy was normal in four other patients. It is likely that folic-acid deficiency in turn aggravates intestinal malabsorption, and this may be reversed by folic-acid therapy. This appears to be the case in tropical sprue, for after treatment with folic acid tests of intestinal function show a return towards normal (Darby, 1947). Similarly, administration of a folic-acid antagonist interferes with the absorption of xylose in the rat (Zamcheck, 1960). Thus not only may evidence of intestinal malabsorption be minimal but it may be transient. Under these circumstances it would be advantageous to be able to estimate the absorption of D-xylose and folic acid at the same time and under the same circumstances.

This paper reports the results of estimating the serum levels and the urinary excretion after oral doses of folic acid and xylose, given together, in normal subjects and in patients with intestinal malabsorption.

Materials and Methods

Folic-acid Solution.—A solution of folic acid containing 2 mg./ml. was prepared in N/5 NaOH.

Estimation of Folic Acid.—Folic acid was estimated by microbiological assay using *Streptococcus faecalis* (A.T.C.C. 8043) as the test organism. The culture medium was that described by Toepfer, Zook, Orr, and Richardson (1951). A widely used commercial dehydrated medium proved unsatisfactory for serum assay, giving recoveries of folic acid added to serum which varied from 140 to 200%.

Estimation of Xylose.—This was by the method of Roe and Rice (1948), barium hydroxide and zinc sulphate being used as a protein-precipitant in serum estimation.

Procedure.—Patients were saturated with folic acid by giving one or more parenteral doses of 15 mg. of folic acid, the last injection being given 36 hours before the test. Control subjects were given 10 mg. of folic acid by mouth 36 hours before the test. Breakfast was withheld from ward patients, but control subjects were usually tested after a "light breakfast" (coffee and

toast). Xylose (0.3 or 0.4 g./kg. body weight) was dissolved in 250 ml. of water and a solution of folic acid (40 μg./kg. body weight) was added. The solution was given orally after collecting an initial blood sample; further blood samples were collected after one and two hours. All urine passed in the next six hours was saved. The folic-acid and xylose concentrations of the serum samples and the urine was estimated.

Subjects Studied.—Observations were made on: (1) Eighty-four normal subjects who were members of the hospital and laboratory staff. (2) Sixty-one patients with idiopathic steatorrhoea, 80 tests being carried out on them. Twenty-six of these patients were studied at Hammersmith Hospital (Chanarin and Mollin, 1959, unpublished observations). All but two excreted more than 6 g. of fat a day. Jejunal biopsy carried out on 44 of these patients, including two with normal fat excretion at the time of observation, showed either partial or total villous atrophy. (3) Twenty-two patients with "regional ileitis." Nineteen of these had undergone a laparotomy and had had a portion of ileum resected. The amount removed was less than 2 ft. (60 cm.) in three patients and was more extensive in the rest.

Results

Folic Acid Absorption Test

Results with this test carried out during the last four years are shown in Table I and Fig. 1. The results show a clear distinction between normal subjects, the peak serum folic-acid level being 51 to 142 μmg./ml., and patients with idiopathic steatorrhoea, the serum levels ranging from 0 to 44 μmg./ml.

The peak serum folic-acid concentration was below the normal range in all but 3 of the 22 patients with regional ileitis. These three had minimal involvement of the ileum, two of them being apparently well after resection of 1 and 2 ft. (30 and 60 cm.) of gut respectively.

Not only was the mean peak serum folic-acid level in the patients with idiopathic steatorrhoea and regional ileitis significantly less than in control subjects, but in idiopathic steatorrhoea it was significantly less (17 μmg./ml.) than the peak in patients with regional ileitis (35 μmg./ml.), the value of P being less than 0.001.

Urinary excretion of folic acid was below the normal range in 18 out of 19 patients with idiopathic steatorrhoea. In the remaining patient, although the amount of folic acid excreted in the urine was normal, the serum folic-acid levels one and two hours after the oral dose were 36 and 27 μmg./ml.—that is, well below the range found in normal subjects.

The urinary excretion of folic acid was an unsatisfactory method of detecting intestinal malabsorption in regional ileitis, being within the normal range in 7 out of 13 patients. Four of these patients, however, had abnormally low peak serum folic-acid levels (17, 30, 31, and 49 μmg./ml.).

TABLE I.—*Peak Serum Folic-acid Concentration and Urinary Folic-acid Excretion After a Single Oral Dose of* 40 μg./kg. *of Body Weight*

	Peak Serum Concentration (μmg./ml.)			Urinary Excretion (% of Dose)		
	No.	Range	Mean	No.	Range	Mean
Normal subjects	84	51–142	91±3·3*	28	12–44	28±1·8
Idiopathic steatorrhoea ..	80	0–44	17±1·4	19	0–17	4±1·0
Regional ileitis ..	22	12–83	35±4·0	11	5–22	13±2·1

* Standard error.

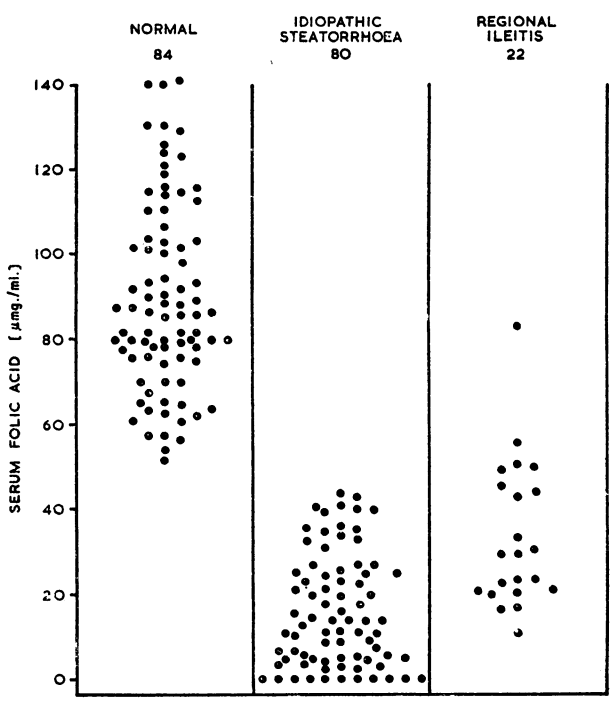

FIG. 1.—Peak serum folic-acid concentration after an oral dose of 40 μg. of folic acid per kg. of body weight in 84 normal subjects, 61 patients with idiopathic steatorrhoea (80 tests), and 22 patients with regional ileitis.

Xylose Absorption Test

When D-xylose was used at a dose level of 0.3 g./kg. of body weight (Fig. 2, Table II) there was considerable

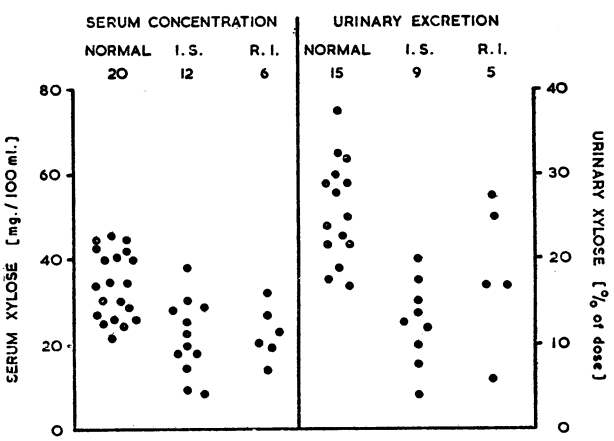

FIG. 2.—Peak serum xylose concentration and urinary excretion of xylose after an oral dose of 0.3 g. of xylose per kg. of body weight in 20 normal subjects, 12 patients with idiopathic steatorrhoea (I.S.), and six patients with regional ileitis (R.I.).

TABLE II.—*Peak Serum Xylose Concentration and Urinary Xylose Excretion After a Single Oral Dose*

	Peak Serum Concentration (mg./100 ml.)			Urinary Excretion (% of Dose)		
	No.	Range	Mean	No.	Range	Mean
Dose 0·3 g./kg. of Body Weight						
Normal subject ..	20	22–46	35±2·3*	15	17–38	26±2·3
Idiopathic steatorrhoea ..	12	9–38	22±3·3	9	4–20	13±2·2
Regional ileitis ..	6	14–33	23±5·2	5	6–27	19±5·1
Dose 0·4 g./kg. of Body Weight						
Normal subject ..	21	32–67	45±3·0	14	13–31	23±2·2
Idiopathic steatorrhoea ..	12	0–27	15±2·5	10	0–17	8±1·7
Regional ileitis ..	6	28–54	42±8·6	6	13–37	24±5·6

* Standard error.

overlap between the peak serum xylose levels of normal subjects and two groups of patients tested. When the urinary excretion of xylose was measured at the same dose level the excretion in seven out of nine patients with idiopathic steatorrhoea was below the normal range.

Increasing the oral dose of D-xylose to 0.4 g./kg. resulted in a clear distinction in the peak serum xylose levels between normal subjects and patients with idiopathic steatorrhoea (Fig. 3). There was little difference, however, between the peak xylose levels in normal subjects and patients with regional ileitis. The urinary excretion of xylose was equally satisfactory in distinguishing the normal group from idiopathic steatorrhoea, only one patient with idiopathic steatorrhoea overlapping with the normal.

Comparison of Folic-acid and Xylose Absorption

In 100 combined xylose and folic-acid absorption tests the peak serum folic-acid level and the peak xylose level coincided in 75 tests.

A comparison of the serum levels is shown in Fig. 4. Thus measurement of the serum folic-acid level provided a clear distinction between normals and idiopathic steatorrhoea, and measurement of xylose in the same specimen was equally decisive. However, whereas all the patients with regional ileitis had lower serum folic-acid levels than control subjects, measurement of xylose absorbed under the identical conditions showed little difference between the two groups. The results are essentially similar when the urinary excretion of the two substances are considered (Fig. 5).

The folic-acid absorption test was abnormal in all the patients who showed an abnormal xylose absorption. However, the folic-acid absorption was often abnormal when the xylose was within the normal range. This was frequently the case in patients with regional ileitis.

Discussion

Absorption of Folic Acid

The results show that the rise in the serum folic-acid level after an oral dose is an excellent test of the absorptive capacity of the small gut, ranking in this respect with a carefully performed fat balance test. Not only is the result always abnormal in idiopathic steatorrhoea, but the test shows evidence of abnormal function in all but the most mildly affected cases of regional ileitis. A similar conclusion was reached by Pitney, Joske, and Mackinnon (1960). On the other hand, when the urinary excretion of folic acid was used as an index of absorption the differentiation between normal subjects and patients with idiopathic steatorrhoea showed some small overlap and failed to differentiate between normal subjects and patients with regional ileitis (Chanarin, 1960).

Of the various methods available to test the absorption of folic acid, in our hands the measurement of changes in serum folic-acid levels after a small oral dose appeared the most satisfactory and the results more decisive than with either a urinary excretion or a balance method. Thus although normal subjects given 40 μg. of folic acid/kg. labelled with tritium absorbed 85% of the dose (Anderson, Belcher, Chanarin, and Mollin, 1960), and patients with idiopathic steatorrhoea absorbed only 29% even with the small number of cases investigated, these balance studies showed an overlap between normal controls and the patients with idiopathic steatorrhoea. All the patients with idiopathic steatorrhoea, however, had abnormal folic-acid absorption as judged by the serum levels. The superiority of the change in serum levels as an absorption test is probably due to the fact that malabsorption involves not only an absolute diminution in the amount absorbed but also a reduction in the rate at which the material being absorbed is transferred from the intestinal lumen across the mucosal

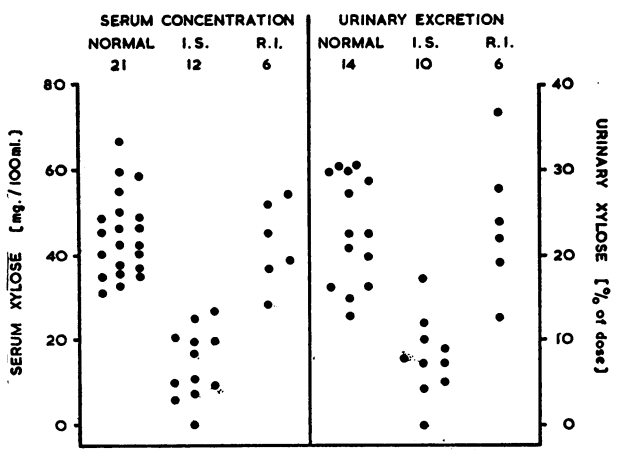

FIG. 3.—Peak serum xylose concentration and urinary excretion of xylose after an oral dose of 0.4 g. of xylose per kg. of body weight in 21 normal subjects, 12 patients with idiopathic steatorrhoea (I.S.) and six patients with regional ileitis (R.I.).

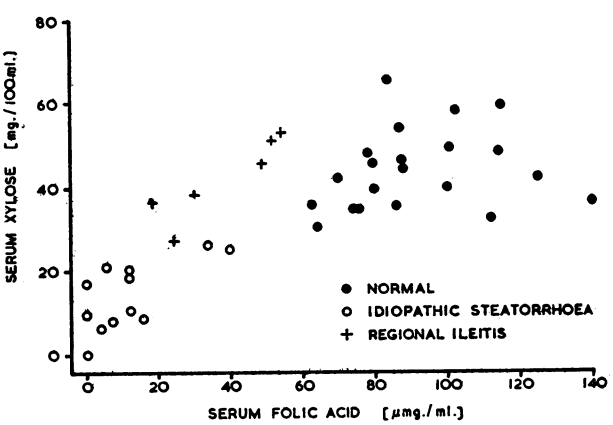

FIG. 4.—Comparison of peak serum concentrations of xylose and folic acid after a simultaneous oral dose of 0.4 g. of xylose and 40 μg. of folic acid per kg. of body weight in 21 normal subjects, 12 patients with idiopathic steatorrhoea, and six patients with regional ileitis.

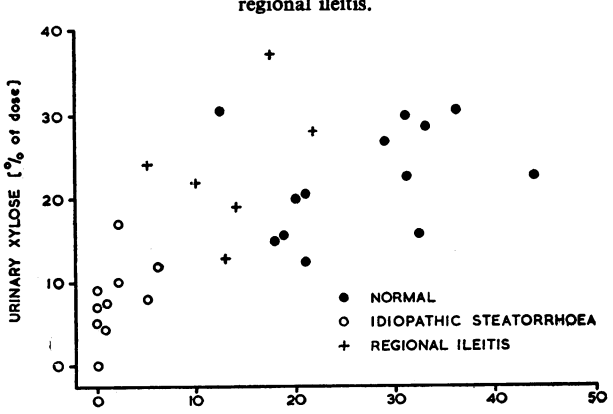

FIG. 5.—Comparison of urinary excretion of xylose and folic acid after a simultaneous oral dose of 0.4 g. of xylose and 40 μg. of folic acid per kg. of body weight in 13 normal subjects, 10 patients with idiopathic steatorrhoea, and six patients with regional ileitis.

cell to the plasma. Changes in the serum levels are more likely to be influenced by variation in rate of absorption than either a balance study or a urinary excretion method.

Absorption of Xylose

Since we were primarily interested in measuring serum levels as an index of absorption, the dose of D-xylose used in the xylose absorption test was adjusted to body weight. The change in serum levels of D-xylose after a standard oral dose of 25 g. has been studied and results showed a wide range in normal subjects which overlapped the values found in idiopathic steatorrhoea (Helmer and Fouts, 1937; Brien, Turner, Watson, and Geddes, 1952; Gardner and Perez-Santiago, 1956; Benson, Culver, Ragland, Jones, Drummey, and Bougas, 1957; Finlay and Wightman, 1958). With a dose of 0.4 g./kg. of body weight, however, the peak serum xylose concentration in control subjects was always greater than that found in patients with idiopathic steatorrhoea (Fig. 3).

The results with the 0.3-g. dose of xylose per kg. of body weight (Fig. 2) are of great interest. In the patients with idiopathic steatorrhoea the estimation of the urinary excretion of xylose appeared to give better results than the estimation of the peak serum level. Since the normal serum levels indicated that absorption was normal, the low urinary excretion suggested either an increase in the amount of xylose metabolized or a failure of renal excretion. There is in fact evidence that the renal excretion of xylose is delayed in idiopathic steatorrhoea. Butterworth, Perez-Santiago, Martinez de Jesus, and Santini (1959) found that in normal subjects 80% of the xylose appearing in the urine was excreted in the first five hours, whereas in five patients with untreated sprue only 55% of the material appearing in the urine was excreted in the same period. A similar observation was made by Fourman (1948). The delayed urinary excretion of xylose in sprue was confirmed by giving xylose intravenously. Thus the low urinary excretion of xylose in idiopathic steatorrhoea is due both to malabsorption and to a failure to excrete a substantial portion of the absorbed material in the five hours usually allowed for the test. This observation probably explains the abnormal xylose tests in pernicious anaemia (Helmer and Fouts, 1937; Butterworth *et al.*, 1959). In these conditions there is also delayed excretion of a water load (Wollaeger and Scribner, 1951; Taylor, 1954a and 1954b).

Another unsatisfactory feature of the xylose absorption test is the high incidence of gastro-intestinal upset. Benson *et al.* (1957) found that most of their subjects had at least increased peristalsis with borborygmi. Of our patients, 10% had acute diarrhoea within a few hours of the dose of xylose and at the same time invariably lost some urine. Inquiry, however, indicated that abdominal discomfort lasting as long as 24 hours was a common feature although the exact incidence was not recorded. Symptoms in our cases did not appear to be related to the size of the dose, although it has been suggested that these undesirable effects could be overcome by reducing the dose of xylose to 5 g. (Santini, Sheehy, and Martinez de Jesus, 1961).

Site of Absorption

It has been suggested that tests for the absorption of folic acid and xylose are tests of function of the upper gut (Avery Jones, 1959). An average meal probably contains less than 40 μg. of folic acid, and this may well be absorbed in the jejunum. In the folic-acid absorption test the dose of folic acid varies from 1,500 to 5,000 μg., and under these circumstances is probably not testing a physiological function of the upper gut. Disease of any portion of the small gut, if extensive enough, will produce an abnormal result in the folic-acid absorption test. In this series the results were abnormal in 19 out of 22 patients with disease of the distal ileum. Similarly there is evidence that xylose reaches the ileum in substantial amounts and can be absorbed from that site (Davidson and Garry, 1940; Benson *et al.*, 1957).

Finally, an abnormal xylose absorption was always accompanied by an abnormal folic-acid absorption. But the absorption of folic acid was frequently abnormal when the xylose test gave normal results. It would appear that the folic-acid absorption test is the more sensitive test of the two, and this difference becomes apparent when conditions other that idiopathic steatorrhoea are being studied.

Summary

The absorption of folic acid and D-xylose has been studied by following the serum concentrations and urinary excretion of these substances after a combined oral dose in normal subjects and patients with idiopathic steatorrhoea and regional ileitis.

The measurement of serum concentration appeared to be a better index of small-intestinal absorption than the urinary excretion for both folic acid and xylose. The folic-acid absorption test was abnormal in all the patients with idiopathic steatorrhoea studied and in 19 out of 22 patients with regional ileitis. The xylose absorption test was almost invariably abnormal in idiopathic steatorrhoea but was usually normal in regional ileitis. The reason for these differences is discussed. The folic-acid absorption test was always abnormal when the xylose test gave an abnormal result.

We thank Dr. P. Crome for helping us in carrying out many of the tests, and the physicians of St. Mary's Hospital, Paddington General Hospital, the Edgware General Hospital, Hammersmith Hospital, and Central Middlesex Hospital for allowing us to carry out studies on their patients.

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Medical Memoranda

Papilloedema and Polycythaemia

The high incidence of chronic respiratory disease in industrial areas is well recognized. Many of these patients eventually develop the clinical picture of chronic cor pulmonale, and in some this is complicated by moderate secondary polycythaemia.

In the following two cases of serious impairment of vision the simple procedure of venesection produced a dramatically favourable response.

CASE 1

A coach painter, born in 1919, attended the out-patient department in June, 1958, complaining of constant headaches and marked blurring of vision for the previous month. He had been under regular supervision since February, 1951, when chronic bronchitis and emphysema was diagnosed. His chest symptoms dated from the age of 3 years, and much of his school life was interrupted by recurrent attacks of bronchitis. Clinical examination in 1951 revealed finger-clubbing and central cyanosis. He had a moderate secondary polycythaemia. The red-cell count was 6,520,000 c.mm. and the haemoglobin 17 g./100 ml. A chest radiograph showed prominent vascular shadows to the lower lobes, but bronchography demonstrated only minimal irregularity of a few of the basal bronchi. The heart was not enlarged but the main pulmonary arteries were a little dilated. An electrocardiogram showed a p. pulmonale pattern. The first attack of congestive cardiac failure occurred in January, 1954. During the next four years he was treated at home and in hospital for a number of similar attacks, all of which responded well to mercurial diuretics. Frequent venesections were performed to control the polycythaemia. In spite of severe disability he was able to work for most of this period.

In June, 1958, he was admitted to hospital for further investigation. There was no evidence of a recent respiratory infection and he was not in congestive cardiac failure. The radiographic and electrocardiographic picture was that of right ventricular hypertrophy. Tests of pulmonary function indicated severe airway obstruction as found in generalized emphysema. Retinoscopy showed bilateral papilloedema. Both fundi exhibited grossly dilated and tortuous veins with haemorrhages and exudates. Lumbar puncture yielded a crystal clear fluid with a raised pressure of 250 mm. C.S.F. and a free rise and fall. Anticoagulant therapy and a number of venesections reduced the haematocrit from 70 to 52%, and there was a dramatic improvement in vision and in the fundal appearance. The vision of the right eye improved from 6/18 to 6/12 and of the left eye from 6/36 to 6/9. He was discharged from hospital, but died suddenly in an ambulance on his way to the out-patient department on November 29, 1958. A post-mortem examination was not made.

CASE 2

A housewife, born in 1929, attended the out-patient department in July, 1958, complaining of severe left temporal headaches, unsteadiness of gait, and hazy vision with diplopia. She had been under observation since November, 1956, when a diagnosis of cor pulmonale secondary to generalized bronchiectasis and emphysema was made. The history of productive cough and abundant purulent sputum dated back to whooping-cough at the age of 5 years; dyspnoea on effort first became evident in 1954. The haemoglobin at this time was 13.3 g./100 ml. Treatment consisted of postural drainage, chlortetracycline, and mercurial diuretics. Clinical improvement ensued but central cyanosis remained. In May, 1957, secondary polycythaemia was noted. The haemoglobin was 18 g./100 ml. and the haematocrit 62%. Pulmonary function tests revealed severe ventilatory disability. The forced vital capacity was 1,450 ml. and the F.E.V. 0.75 sec. was 500 ml.

She was admitted to hospital in July, 1958, with evidence of mild congestive cardiac failure. The heart was grossly enlarged. The fundi showed bilateral papilloedema. The retinal veins were dilated and tortuous. In other respects the central nervous system was normal. An electrocardiogram showed a sinus rhythm and the pattern of right ventricular hypertrophy. The resting arterial oxygen saturation was 51.5% and the carbon-dioxide tension measured 64 mm. Hg. The venous haematocrit was 63%. The cerebrospinal pressure was raised to 350 mm. C.S.F. but the fluid was normal. Treatment consisted of strict bed rest, low-salt diet, mercurial diuretics, and tetracycline. The oedema cleared rapidly, but the retinal changes persisted although the headaches were less severe. Venesections amounting to 45 oz. (1,280 ml.) were then carried out.

The haemoglobin fell from 16.7 to 15 g./100 ml. The vision improved and no papilloedema was evident three weeks later. Moderate tortuosity of the retinal veins persisted. From November, 1958, until her death on September 7, 1959, she suffered from attacks of paroxysmal nodal tachycardia. Signs of tricuspid incompetence were noted but gross signs of congestive cardiac failure did not recur. The haematocrit remained within the normal range, although studies of arterial blood gas showed evidence of severe hypoxia and hypercapnia. The final episode was a sudden right hemiplegia with temporary loss of consciousness.

Post-mortem examination revealed recent softening of the left internal capsule but no embolus was demonstrated. The heart weighed 450 g. There was marked right ventricular hypertrophy. The left atrium contained the remains of an ante-mortem clot. The lung showed bronchopneumonia and widespread bronchiectasis. A small tumour at the apex of the right lung had invaded the pleura. Metastases were present in the liver and both adrenal glands. Microscopical examination of the tumour showed an adenocarcinoma arising in an old tuberculous focus. Sections from other areas of the lungs showed congestion, emphysema, and patchy consolidation.

DISCUSSION

Both patients had the features of chronic cor pulmonale due to long-standing serious chest disease. In Case 1 papilloedema, haemorrhages, and dilatation and tortuosity of the retinal veins were associated with enough loss of visual acuity to cause the patient to fear for his eyesight. Otherwise there had been no detectable deterioration from either the cardiovascular or the respiratory standpoint and he had, in fact, carried on his usual restricted life until admission to hospital. In Case 2 no marked deterioration in the pulmonary or cardiac condition had occurred. The headaches, transient diplopia, dizziness, and papilloedema were suggestive of raised intracranial pressure.

Conn *et al.* (1957) reported the cases of two patients who were thought to have an intracranial space-occupying lesion, although it was finally established that the condition was secondary to cor pulmonale. Similar