apparatus, or patients' refusal to avail themselves of surgery. Finally, no death occurred in this group other than among those treated conservatively because of some serious incidental condition.

Summary

The total incidence of fractures of the femoral neck during two years is analysed.

The inevitable increase in incidence, which is applicable generally, is calculated.

Additional staff and accommodation will probably be required for this contingency.

The suggested segregation of female patients is discussed.

Problems in treatment and disposal are outlined.

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SULPHAEMOGLOBINAEMIA

A REPORT OF FIVE CASES

BY

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Cyanosis in warm skin, in the absence of obvious disease of the cardiovascular and respiratory systems and of polycythaemia, calls for spectroscopic examination of the blood, and in a proportion of such instances either methaemoglobin or sulphaemoglobin, or both, may be identified.

Methaemoglobin consists of oxidized haem linked to native globin, and is present in traces in normal erythrocytes, in which an enzyme system constantly reduces any methaemoglobin. This enzyme system is probably defective in congenital methaemoglobinaemia. Sulphaemoglobin, in contrast, is invariably a pathological product. Its exact chemical constitution is unknown, but it is thought that a sulphur atom has been incorporated in the pyrrole components of the haem molecule and that the mode of linkage of the haem to the globin moiety is altered. There is no intracellular mechanism for the reconversion of sulphaemoglobin to haemoglobin, nor can reconversion be effected by any known drugs. Sulphaemoglobin remains in the erythrocyte, an irreversible product of haemoglobin metabolism and a harmless though inert pigment, until the cell is destroyed, and there is no evidence that the formation or retention of sulphaemoglobin shortens the average life span of the cell. The only ill effect that can be attributed to it is anoxia, due to the immobilization of oxygen-carrying haemoglobin in the form of an inert pigment.

Both pigments are identified by the presence of an absorption band in the red part of the light spectrum—

the methaemoglobin band at 625–655 millimicrons, and the sulphaemoglobin band at 615–630 millimicrons. The absorption band of methaemoglobin is dispelled when a few drops of 5% potassium cyanide are added to the laked blood. This procedure leaves the absorption band of sulphaemoglobin unchanged, but it disappears on adding hydrogen peroxide alone.

In the human subject sulphaemoglobinaemia may follow the ingestion of compounds belonging to two groups: (1) nitrogen-containing compounds such as potassium nitrate, sodium nitrite, or nitroglycerin; and (2) aromatic amino-compounds, such as the sulphonamides or the aniline derivatives acetanilide and phenacetin.

Many cases of sulphaemoglobinaemia due to drugs have been reported in recent years, and the following five patients present few new features, but several aspects of their histories merit discussion.

Case 1

A spinster aged 70 came into hospital on October 26, 1951, complaining of feverishness and of pain in the right iliac fossa and in the back for two weeks. She was accustomed to taking saline aperients regularly, and her bowels were more constipated than usually. She had taken only a few aspirin tablets for the pain.

She was febrile, pale, ill, and not cyanosed. The fingers were clubbed. A blood count showed: Hb, 11.9 g.% (Sahli); red cells, 3,860,000 per c.mm.; P.C.V., 40%; M.C.V., 104 cubic microns; M.C.H.C., 29.75%; white cells, 9,200 per c.mm.; E.S.R., 73 mm. in one hour (Westergren). The urine showed a trace of albumin, no excess of urobilin, and no other abnormality. Clinical and radiological examination suggested a resolving pneumonia, and acute osteomyelitis of vertebrae D 12 and L 1 was diagnosed later. Both conditions resolved with antibiotics.

Aspirin was prescribed for her pain. On October 31 she was cyanosed, and spectroscopic examination of the blood showed a well-marked band in the red due to sulphaemoglobin. On December 17 sulphaemoglobin was still present in a 1 in 20 dilution of blood, examined in a 1 in. (2.5 cm.) thickness. On January 7, 1952, during chloramphenicol therapy, the patient developed loose stools from which type-specific *Bact. coli* (beta type) was grown. The diarrhoea stopped on January 16, and five days later no sulphaemoglobin was detected in a 1 in 5 dilution of blood. The patient went home on March 5.

She was readmitted in October, 1952, with gastric carcinoma. There was no cyanosis, and no sulphaemoglobin was detected.

Case 2

A widow aged 66 had suffered from a duodenal ulcer for 16 years, and was admitted on October 12, 1953, following a haematemesis. She had been subject to headaches most of her life, and had taken an occasional "askit" powder to relieve them. For a year her headache had been very severe and persistent, and her weekly consumption of powders had been two to three dozen. At night she took two compound codeine tablets. For 16 years she had regularly taken a powder thrice daily after meals, which was prescribed by her doctor to prevent her ulcer pain and to keep her bowels regular. For six to seven months she had had paraesthesiae of the hands and feet.

On admission she was slightly cyanosed. The haemoglobin was 4.2 g.% and R.B.C. 2,070,000 per c.mm. The urine showed green to Benedict's solution; no albumin or excessive urobilin. Next day sulphaemoglobin was detected in a 1 in 75 dilution of blood. Its concentration slowly declined, and on December 3 it was detectable only in 1 in 20.

A barium-meal examination on November 17 showed an ulcer deformity of the duodenal cap but no crater. The patient improved slowly, but the blood urea was constantly raised. Pyuria occurred in late October, and it was thought that renal function was impaired by chronic pyelonephritis. The patient returned home on December 29.

She was readmitted on June 9, 1954, following a further haematemesis. Her headaches had persisted but she had taken only aspirin for them, as instructed. She was not cyanosed, and no sulphaemoglobin was detected.

Case 3

A married woman aged 49 was admitted on March 18, 1954, for restabilization of diabetes mellitus, which she had had for four years. She had occasional headaches, and for six months had had paraesthesiae of the feet and legs. For about three months she had had pruritus vulvae with ulceration. For many months she had taken two or three askit powders a day, not to relieve pain but for their "tonic effect."

She was pale and not cyanosed. The haemoglobin was 9 g.%, R.B.C. 4,100,000 per c.mm., and W.B.C. 19,200 per c.mm. The blood was examined spectroscopically on account of the history of regular consumption of powders, and sulphaemoglobin was present. It was still detectable on April 6 in blood diluted 1 in 7.

Case 4

This patient, a woman aged 58, separated from her husband in 1936, had no children, and lived alone. She had a history of psoriasis in childhood, and of three "nervous breakdowns." She had recurrent varicose ulceration, and dressed the ulcers herself, but had neglected them recently. She had taken askit powders regularly for two years, usually three or four a day, but at times nine or ten. She had been accustomed to taking one for occasional headaches all her life, but in the past two years she took them not so much to relieve pain as to "buck her up" if she felt depressed. For several years her face had been puffy.

She was admitted on March 12, 1954, because of post-"influenzal" asthenia and constipation. She was cyanosed, dyspnoeic, and extremely weak, and had a puffy "moon face." The signs of congestive cardiac failure were present, and gravitational ulcers almost encircled the lower thirds of the legs. The pulse rate was 100; B.P. 120/50 mm. Hg. Crepitations were heard at the lung bases; knee- and ankle-jerks were absent. The anal sphincter was lax, and the rectum filled with scybala and a foul watery fluid. A blood count showed Hb, 6.3 g.%; red cells, 2,060,000 per c.mm.; P.C.V., 24%; M.C.V., 116 cubic microns; M.C.H.C., 26%; white cells, 11,700 per c.mm. The serum showed no sign of haemolysis. The red cells were normal in size and shape, and were slightly deficient in haemoglobin.

The sulphaemoglobin absorption band was seen in a 1 in 80 dilution of blood. The marrow was normoblastic and active. The W.R. was negative. The urine showed albumin, R.B.C., and red-cell casts; no excessive urobilin.

Penicillin injections were given and the ulcers dressed with eusol. On March 14 a bottle of packed red cells was given. Vitamin therapy was begun and an olive-oil enema and nightly liquid paraffin were ordered. The facial oedema steadily diminished. She refused further blood transfusion and resisted all attempts at venepuncture; at times she refused other therapeutic measures such as enemata, and was morose and difficult throughout her stay in hospital. On March 25 sulphaemoglobin was detected in 1 in 50; most of the decrease was attributable to dilution by the transfused blood. It was detected in 1 in 40 on April 6, 1 in 10 on April 29, and not at all on May 19.

The anaemia improved rapidly with oral iron therapy, and the ulcers healed. On April 22 the patient was allowed up. She had no spontaneous bowel movements during her rest in bed, and frequent enemata were given. The patient went home on June 5.

Case 5

A coal-miner aged 42 was referred by his doctor because of cyanosis. He had had rheumatoid arthritis for six years, but had been working regularly for the past five years despite some pain. Every fortnight for five years his doctor had prescribed 100 powders for him, containing aspirin, phenacetin, and codeine. He admitted that he took them "more as a habit than anything." For two weeks he had been taking three askit powders a day, unknown to his doctor.

He had cyanosis, with no dyspnoea even when he ran, and no cardiac or gross respiratory disease. Rheumatoid changes involved both hands, both feet, and the right elbow. Chest x-ray examination showed no abnormality, and the E.S.R. was 55 mm. in one hour (Westergren). The blood contained sulphaemoglobin.

He was sent home and instructed to avoid all tablets unless prescribed by his doctor, who was asked to avoid prescribing phenacetin.

Discussion

Acetanilide and phenacetin have often been followed by sulphaemoglobinaemia (Morgan and Anderson, 1940; Lazarus, 1945; Brandenburg and Smith, 1951), and constipation has appeared to facilitate the formation of the pigment in many cases. Finch (1948) postulated that an oxidizing drug and either constipation or a sulphur-containing medication were necessary for the production of sulphaemoglobinaemia. In the present series four patients had taken phenacetin, and two of these were constipated, and the fifth patient had been taking magnesium sulphate for constipation. *In vitro*, sulphaemoglobin is easily produced by the addition to laked blood of hydrogen sulphide and *para*-aminophenol, a possible breakdown product of phenacetin in the body (Campbell and Morgan, 1939). *In vivo*, *para*-aminophenol or a related compound may act upon red cells along with hydrogen sulphide absorbed from the bowel. Such absorption would be increased by intestinal stasis, and one might suggest that the sulphide content of the bowel is increased by sulphate medicaments, since *Bact. coli* is known to reduce sulphate to sulphide.

Brandenburg and Smith (1951) noted that a large percentage of their 62 patients with sulphaemoglobinaemia were neurotic. In the present small series neurotic tendencies were observed in all four patients who took analgesics.

The analgesic of choice with the four patients was the askit powder, which, incidentally, is manufactured locally. Its appeal is twofold: 0.55 g. (8.25 gr.) of aspirin and 0.4 g. (6 gr.) of phenacetin endow it with potent analgesic properties, and 0.11 g. (1.7 gr.) of caffeine citrate provides significant cerebral stimulation, even without the other 0.1–0.2 g. of caffeine in a cup of tea. (The corresponding quantities in the B.P.C. tablet are 4½ gr. (0.29 g.) of aspirin, 3½ gr. (0.23 g.) of phenacetin, and ½ gr. (32 mg.) of caffeine.) The attraction of askit to the neurotic patient is undoubtedly the stimulant effect, mild though it is. Of the 62 cases of sulphaemoglobinaemia described by Brandenburg and Smith (1951), at least 44 were due to analgesic preparations containing caffeine, and Morgan and Anderson (1940) recorded a case of habituation to a tablet containing acetanilide, phenazone, and caffeine. They also pointed out that true addiction implies physical dependence on a drug, and this has not been demonstrated in the case of antipyretics or caffeine; nor did any of the present patients develop any symptoms which could be attributed to withdrawal. Their dependence had been purely psychic, and habituation is the more correct term than addiction. However, the same type of personality is liable to become a true addict, and this danger must be recognized before one prescribes alternative treatment.

Anaemia is not a usual accompaniment of sulphaemoglobinaemia, but four of the present patients were anaemic. The cause of the hypochromic anaemia in Cases 1 and 3 was not clearly established; Case 2 had a bleeding duodenal ulcer, and Case 4 a chronic superficial infection and haemo-

dilution due to water retention caused by salicylates. In none of the cases was there any evidence of haemolysis.

Treatment followed the usual lines: the offending drug was withheld and aspirin alone was given to relieve any slight pain; constipation was relieved by enemata and liquid paraffin; severe purgatives were avoided lest hyperaemia of the intestinal mucosa facilitate absorption of hydrogen sulphide and perpetuate the sulphaemoglobinaemia. Blood transfusion was required for Case 4 because of anoxia, and appeared almost life-saving. No specific treatment is of any avail. Treatment of the concomitant diseases was not altered by the presence of sulphaemoglobin, and no sequelae attributable to sulphaemoglobin were noticed.

Summary

Five cases of sulphaemoglobinaemia are described. One case followed the administration of magnesium sulphate as an aperient and the other four cases were due to analgesic preparations containing phenacetin. The presence of caffeine in such preparations is thought to induce habituation, particularly in neurotic personalities. Anaemia was present in four of the cases, but was not attributable to sulphaemoglobinaemia. The principles of treatment are enumerated.

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RISE OF SEDIMENTATION RATE AT LOW LABORATORY TEMPERATURE

ITS VALUE AS A LIVER-FUNCTION TEST

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Most authors believe that a high laboratory temperature increases and a low one decreases the erythrocytic sedimentation rate (E.S.R.). Temperature, however, has been shown to exert an inconstant effect on the E.S.R., and in many cases a higher fall is recorded at a lower temperature when the test is performed simultaneously in hot and cold atmospheres (Weingarten, 1946; Buttaro and Tosti, 1946). It was also observed by Weingarten that a greater fall at lower temperature occurred in those cases which had some hepatic damage. Gupta (1954) proved that the higher fall at a lower temperature is due to a qualitative change in the euglobulin fraction of the plasma proteins. Since most of the flocculation reactions that test the liver function depend on the euglobulin fraction of the plasma proteins (Dyke, 1947), it was thought worth while to investigate if such a simple observation could be used to determine the liver damage.

Material and Method

Cases having definite liver damage were selected for investigation. These included cases of cirrhosis and cancer of the liver, infective and amoebic hepatitis, and chronic malaria and kala-azar. Most of the malaria patients had an enlarged liver, and all had an enlarged spleen and fever for more than three months.

Blood was collected in the morning, the patient having been kept fasting overnight. The E.S.R. was carried out by the Westergren method at temperatures of 99 and 44° F. (37.2 and 6.7° C.) in an incubator and a refrigerator respectively. The readings were taken every ten minutes for a

period of one hour. If the E.S.R. was found more than 10% higher at 44° F. (6.7° C.) it was adjusted to be a higher fall in the cold—that is, a positive reaction for liver damage—while a greater fall at 99° F. (37.2° C.) was regarded as a negative reaction; and if the difference between the two readings was less than 10% the reaction was regarded as indeterminate.

After having observed a fairly large number of cases a comparative study was made with a number of well-established liver-function tests as controls. The control reactions were the Takata-Ara, thymol turbidity, hippuric acid synthesis, blood proteins, and the Weltmann. The tests were performed in 17 cases of cirrhosis, 10 cases each of infective and amoebic hepatitis, 12 cases of chronic malaria, and 4 cases of cancer of the liver.

The Takata-Ara, thymol turbidity, and intravenous hippuric acid tests were performed according to the technique described by Dyke (1947), and the Weltmann test as described by Tyagi (1947). Proteins were estimated in the beginning of our series by the biuret reaction (Harrison, 1947), but later on the "lumetron" photoelectric colorimeter was substituted.

Observation and Results

The results of the cases studied by the fractional estimation of the E.S.R. in the hot and cold chambers are given in Table I and those of the comparative study in Table II.

TABLE I.—Results of E.S.R. in Hot and Cold Temperatures

	No. of Cases	Positive	Negative
Cirrhosis	71	51 (72%)	20
Infective hepatitis ..	12	0	12
Cancer of liver ..	10	7 (70%)	2
Amoebic hepatitis ..	14	9 (64%)	5
Kala-azar	2	2 (100%)	0
Chronic malaria ..	19	15 (79%)	4

TABLE II.—Percentage of Positives with Various Tests

	No. of Cases	Thymol Turbidity	Takata-Ara	Weltmann Reaction	Hippuric Acid	Blood Protein	E.S.R. Hot and Cold
Cirrhosis	17	76%	82%	76%	88%	71%	76%
Infective hepatitis	10	90%	70%	50%	0%	50%	0%
Cancer liver	4	25%	100%	100%	50%	75%	75%
Amoebic hepatitis	10	50%	50%	50%	50%	25%	60%
Chronic malaria	12	66%	75%	83%	58%	75%	58%

It will be seen that 51 out of 71 (72%) cases of cirrhosis of the liver gave a positive result. Cases which showed a negative reaction were usually of long standing, some of five years' duration; and it could be concluded that in many of them the activity of the disease had come to an end. In 10 out of 20 cases which showed a negative reaction, the E.S.R. at the end of one hour was less than 20 mm., while the remainder showed a tendency towards a declining E.S.R., indicating that the activity of the lesion was waning. The positive results with other tests varied between 70 and 84%. It is of interest to quote the observations of Ernst and Dotti (1948), who while doing the thymol turbidity test on 33 cirrhotics found positive results in 22 (67%). They concluded that the compensated cirrhotics in whom there is considerable fibrosis with abdominal ascites, but in whom the remaining liver parenchyma is functioning adequately for bodily needs, do not show a rise of thymol turbidity. When, however, the remaining cells are damaged by an infection, or by a toxin, or by anoxia, then the thymol reaction becomes positive. The only three cases of alcoholic cirrhosis met with in our series gave completely negative results. It is interesting to note that Kunkel (1948) also got similar findings with the thymol turbidity and the cephalin-cholesterol flocculation tests, and in a large percentage of cases a negative reaction was consistently obtained with the two tests.

In amoebic hepatitis and abscess a high percentage of positives was obtained. Out of five cases which showed a negative