that one is probably dealing with a changing situation and that the absence of venous abnormalities at any time in the natural history of the disease does not imply their absence throughout its development.

Summary

In 23 patients with clinical primary lymphoedema starting in youth (lymphoedema praecox) the venous drainage of the affected leg has been investigated by venography and by venous-flow and venous-pressure studies. Eleven of the patients showed evidence of obstruction of the left common iliac vein, probably by the right common iliac artery. Lymphangiography was performed in 10 cases, and clinical lymphoedema was seen with both abnormal and normal lymphangiographic appearances.

The manner in which a raised venous pressure could influence the onset of lymphoedema is discussed.

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Some Experiences in Managing Sickle-cell Anaemia in Children and Young Adults, Using Alkalis and Magnesium

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Sickle-cell anaemia is due to an inherited defect in haemoglobin synthesis. The solubility of sickle-cell haemoglobin is lowered in the deoxygenated state. As the haemoglobin comes out of solution it forms spindle-shaped tactoids—the basis of the sickling phenomenon. Although the oxygen tension may become low enough in most tissues to induce a significant amount of sickling, this is not a constantly recurring process because, as Allison (1956) demonstrated, it requires time for deoxygenation to produce sickling, so that usually the circulating cells have become reoxygenated before this has occurred. Sickling is enhanced by acid *p*H. When the red blood cells become sickle-shaped the viscosity of the blood is increased and so the blood flow, especially in small vessels, diminishes (Harris, Brewster, Ham, and Castle, 1956). This effect, which in due course will lead to sludging, causes further deoxygenation of the blood and fall in *p*H, and so a vicious circle begins which ends in actual intravascular clotting of the blood. This is the cause of most of the symptomatology of the disease.

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It is not possible to alter the fundamental metabolic defect that gives rise to this abnormal haemoglobin, but what has been attempted is to try to interfere with the blood-clotting processes to make infarction less likely and to try to prevent acidosis and so to minimize intravascular sickling and sludging.

In attempting to interfere with the blood-clotting processes, something had to be found that would be economical on a large scale and not require constant supervision as do coumarin compounds. From earlier work it was known that magnesium would compete with available calcium and delay blood-clotting *in vitro* (Greville and Lehmann, 1944), and these observations were extended by work *in vivo* which showed that blood-clotting processes could be delayed and that this could be measured as a prolongation of the thrombin-generation time (Anstall, Huntsman, Lehmann, Hayward, and Weitzman, 1959 ; Huntsman, Hurn, and Lehmann, 1960). This treatment was often begun with intravenous magnesium sulphate because it had the further advantage of causing vasodilatation. This seemed to improve blood-flow where sludging was occurring and so dramatically relieve ischaemic pain. To minimize the effects of acidosis alkalis were given ; sodium bicarbonate seemed the most suitable.

The following case reports show how these lines of treatment were evolved.

Case 1

A Greek boy had had frequent painful crises and was diagnosed in Athens as a case of sickle-cell anaemia at the age of 9 years. When he came to London (aged 12) for further studies he was still having painful crises lasting a few days. He had the typical build of a child with sickle-cell anaemia, with a relatively large skull, small body, and long limbs, being 54 in. (137 cm.) tall and weighing 65 lb. (29.5 kg.). He was clinically anaemic and slightly jaundiced. The heart was somewhat enlarged and at the apex there was a soft systolic murmur. The liver was just palpable and the remainder of the physical examination revealed nothing abnormal. Diagnosis was established by electrophoresis of his haemoglobin. His parents similarly were shown to be heterozygotes.

Haematological Findings.—Electrophoresis of haemoglobin: Hb S 92%, Hb F 8%. Haemoglobin 7–8 g./100 ml. Reticulocytes 20–30%. Serum bilirubin 2–3 mg./100 ml. Sickling easily demonstrated. Increased osmotic fragility. ^{51}Cr-labelled red-cell survival time, half-life eight days.

During an initial period of observation in hospital he had two slight attacks of pain, and occasionally blood was found in his urine. He was treated with magnesium citrate and peptone as the amino-acid carrier to help absorption (see Anstall *et al.*, 1959). There was no significant change in the haemoglobin values, reticulocyte counts, or the red-cell survival time, showing that no change had occurred in the basic haemolytic process. His thrombin-generation time was increased by four to five minutes though other coagulation tests were unaltered.

Following treatment he had no further pains or haematuria, and ran an afebrile course for the next six months. There was one exception, when he had an aplastic crisis associated with a rigor up to 106° F. (41° C.), the haemoglobin level falling to 5 g./100 ml. and reticulocytes to 0.5%; but this was, surprisingly, an entirely pain-free episode.

He returned to Greece on this regime and was well supervised. Three years later he came back for review, having had only one slight attack of pain during the whole of this time. He had grown well, weighed 95 lb. (43.1 kg.) and seemed in excellent health. His haematological findings were basically the same: Hb 8 g./100 ml., reticulocytes 20%; ^{51}Cr-labelled red-cell survival time, half-life eight days.

Case 2

A boy of 14 from St. Kitts was admitted to hospital with painful priapism. He was a known case of sickle-cell anaemia. Hb S only was found on electrophoresis. His mother was a sickle-cell-trait carrier, his father was not available for study, and his brother is Case 3. He was 58 in. (147 cm.) tall and weighed 72 lb. (32.7 kg.). He was anaemic and jaundiced, and had considerable pain. His heart was enlarged and there was an apical systolic murmur; the liver was palpable 2 in. (5 cm.) below the costal margin. Otherwise physical examination showed nothing abnormal.

Haematological Findings.—Electrophoresis of haemoglobin: Hb S only found. Haemoglobin 7–8 g./100 ml. Reticulocytes 8–18%. Serum bilirubin 3.3–6.3 mg./100 ml. ^{51}Cr-labelled red-cell survival time, half-life six days.

Opaque gall-stones were seen on plain *x*-ray examination of the abdomen. Initially he was given Dindevan (phenindione) with little effect. On the third day 1 ml. of 50% magnesium sulphate was given intravenously; this relieved his pain within three-quarters of an hour. He was then maintained on magnesium citrate and Oxoid peptone carrier, and although the urine was not always alkaline he steadily improved. The Oxoid peptone was not always well tolerated and he has been difficult to keep under adequate supervision, but after two years his mother reported that he was well. Haematological tests were repeated after the first three months, while under hospital supervision, and there was no change in the haemoglobin level, reticulocyte values, or the ^{51}Cr-labelled red-cell survival time.

Case 3

The younger brother of the above patient (Case 2) had a very typical history of painful swollen fingers as a young child and later suffered from frequent attacks of fever and bone pains. He came to this country when he was 9 years old, by which time the attacks were becoming less frequent, but he was having severe crises about once a year and minor episodes once a week. When admitted for study aged 12¼ years he was 53 in. (134.5 cm.) tall and weighed 61 lb. (27.7 kg.), and had the typical bodily configuration of a child with sickle-cell anaemia. He was anaemic and slightly jaundiced. The heart was enlarged and there was an apical systolic murmur; the liver was palpable, but otherwise examination showed nothing abnormal.

Haematological Findings.—Electrophoresis of haemoglobin: Hb S 98%, Hb F 2%. Haemoglobin 7.2–8.9 g./100 ml. Reticulocytes 10–20%. Haemoglobin solubility (Itano) 0.25 g./l. Serum bilirubin 2–3 mg./100 ml.

After a period of observation in hospital, during which time he had frequent headaches and vague abdominal pains, he was given sodium bicarbonate, 10 g. t.d.s., equivalent to a total of 1 g./kg./day. During the next six weeks his urine was always alkaline and he was entirely free of pain. Blood *p*H was 7.44, P_{CO_2} 40 mm. Hg, plasma bicarbonate 26.3 mEq/l. He was then given magnesium glutamate, but could not tolerate a sufficient quantity to keep his urine alkaline, and on occasion there was a return of symptoms. He was discharged on bicarbonate therapy. Supervision of this family was not entirely satisfactory as they came from a broken home and the mother had to go out to work. During the next year he was admitted on four occasions, each time because of severe pain. The first was associated with an attack of tonsillitis, the second with a urinary infection, the third with pneumonia, and on the fourth, although no obvious infection was discovered, he developed obstructive jaundice. The urine on admission was acid on three occasions and neutral once. Except for the last admission the urine rapidly became alkaline and the pain was quickly relieved either by increasing the dose of bicarbonate to 10 g. q.d.s. on one occasion or by ensuring that he took the prescribed dose, 10 g. t.d.s.

On his fourth admission he had a severe headache associated with a rigor and vomiting. No obvious cause was found for this crisis, in which he remained very drowsy and ill for nearly a week. During this time the signs of obstructive jaundice developed, which no doubt accounted for some of the difficulty in getting him to take adequate alkali. Intravenous sodium bicarbonate and citrate were used, but great difficulty was encountered in keeping the urine alkaline, and he continued to have severe headaches, backaches, and abdominal pain. His haemoglobin fell to 4 g./100 ml. and he was given a transfusion. A few days later he again became confused and drowsy, and complained of backache. The urinary output fell, and on the next day he was dyspnoeic, had a raised venous pressure (2 cm.), enlarged liver (12 cm. below costal margin), and crepitations at both lung bases. At this point the boy was desperately ill; he did not respond to digitalis, nor did he pass urine after a mersalyl injection.

During the first 12 hours of this crisis he passed 400 ml. of urine; during the next 12 hours 100 ml. was obtained by catheter; and no further urine was passed during the next 10 hours. At this point he was given 2 ml. of 50% magnesium sulphate intravenously. Three hours later he passed 150 ml. of urine. He was given the same dose intravenously four-hourly for 12 hours, during which time he passed 2 litres of urine with dramatic relief in his symptoms. Treatment was continued orally with 6 ml. of 70% magnesium glutamate six-hourly for five days, and then 2 g. of sodium bicarbonate six-hourly. No further trouble was encountered in keeping the urine alkaline, and the boy made fairly steady recovery to his usual health. It was felt that this treatment had improved the blood-flow through the kidneys and prevented infarction, thus relieving this crisis associated with anuria.

Case 4

A Nigerian girl aged 11 with sickle-cell anaemia became blind and disorientated after an operation. This state continued until she was given 50% magnesium sulphate intravenously every six hours for three days. By the next day her vision and mental state had improved; final recovery was complete. This case has been reported in detail (Lewin and Goodell, 1962).

Case 5

This patient, a young woman aged 21 and weighing 7 st. 12 lb. (50 kg.), had slight jaundice and moderate anaemia. Since the age of 7 years she had suffered from recurrent attacks of pain,

low-grade fever, and anaemia. Three years ago she was proved to be a case of sickle-cell thalassaemia. A splenectomy performed in Nairobi had had little effect. Examination showed nothing abnormal except for the splenectomy scar and a soft apical systolic murmur.

Haematological Findings.—Electrophoresis of haemoglobin: Hb S 92%, Hb F 8%, no Hb A_2 found. Haemoglobin 9–11 g./100 ml. Reticulocytes 3–10%. Bilirubin 1–2 mg./100 ml. Her father showed increased Hb A_2, her brother increased Hb A_2 and foetal haemoglobin, and her mother was a sickle-cell-trait carrier. A brother aged 15 had died after an operation.

Her first admission, caused by an attack of pain in the lower arm, was for a few days. The pain settled in two to three days on 0.5 g. of magnesium sulphate intravenously, given eight-hourly, and sodium bicarbonate 10 g. eight-hourly by mouth. A few months later her right thigh became painful and swollen. This was not relieved by magnesium sulphate intravenously, but the pain settled slowly though the swelling remained. Two weeks later she had a pulmonary infarct. She was extremely ill on admission. Her urine was acid and remained so for some four to five days. Pain in the chest was not relieved by intravenous magnesium sulphate; it was in the nature of a pleuritic pain and settled in the next few days, symptomatic relief being obtained with pethidine. The acute phase of this illness lasted some 10 days, but it was nearly seven weeks before the lung abscess which developed had resolved. She had two further admissions—one because of a painful arm, and the other because of pains all over her body associated with a urinary infection. The first of these episodes was promptly relieved by intravenous magnesium sulphate. The second settled over the next few days on sulphonamide treatment, though it was not obviously affected by magnesium sulphate or bicarbonate.

The patient returned to Kenya and was reported to be keeping well on the sodium bicarbonate regime. She has recently married.

Case 6

A boy of 9 years from Sierra Leone had had swollen painful fingers since the age of 6 months, and later had prolonged crises with pain in his limbs and jaundice about once every six months. His sister is Case 7. His maternal grandmother had sickle-cell anaemia, his mother died of the disease in childbirth, and his father is a carrier.

On examination he weighed 68 lb. (30.8 kg.) and was 53 in. (134.5 cm.) tall. He was jaundiced and anaemic, and there was an apical systolic murmur in his heart. The liver was palpable, and there were scars of healed ulcers on his legs.

Haematological Findings.—Electrophoresis of haemoglobin: Hb S 94%, Hb F 6%. Haemoglobin 6–8 g./100 ml. Red cells showed sickling. Reticulocytes 10–18%. ^{51}Cr-labelled red-cell survival, half life 6.3 days. Serum bilirubin 2–3 mg./100 ml.

He was treated with sodium bicarbonate 0.7 g./kg./day. While under hospital supervision his urine was always alkaline, and the crises that caused his admission settled within a few days; thereafter he was free of pain. Since returning to Sierra Leone, supervision has not been so good, but his father has tried to keep his urine alkaline. In nine months he has had only one short-lived crisis, but for the first time in his life was able to live normally.

Case 7

The sister aged 11 of the above patient (Case 6) used to have frequent crises, but for the past four to five years these had been getting less severe. During the last year she had been troubled with recurrent leg ulcers. She weighed 91 lb. (41.3 kg.) and was 59 in. (150 cm.) tall. She was a little anaemic and had a shallow ulcer 2 by ½ in. (5 by 1.3 cm.) on the outer aspect of her right leg; otherwise, examination showed her to be essentially normal.

Haematological Findings.—Electrophoresis of haemoglobin: Hb S 91%, Hb F 9%. Haemoglobin 7–10 g./100 ml. Reticulocytes 5–15%. ^{51}Cr-labelled red-cell survival time, half-life 11 days. Serum bilirubin 1–2 mg./100 ml.

She, too, was given sodium bicarbonate 0.6 g./kg./day, and has been entirely free of all pain for nine months, and her ulcers have healed.

Discussion

Initially it was felt that the important aim of treatment should be to prevent intravascular clotting. Although this could be achieved by heparin or the coumarin compounds, careful supervision would be essential, and therefore use of these drugs on a large scale would not be practical. From earlier work it was known that magnesium could compete with calcium ions in the blood and interfere with the blood-clotting processes. Also by giving it with an amino-acid it became a practical form of oral treatment. The first patient was treated orally with magnesium citrate and a peptone amino-acid carrier, and has been in good health for a number of years. The remarkable feature about this boy was not anything that could be measured in the laboratory, but the enormous clinical improvement in his well-being and the very fact that he remained virtually pain-free for so long. This was something he had never experienced before. He also weathered an aplastic crisis in which his haemoglobin fell to 5 g./100 ml. without the associated hypoxia beginning the vicious circle that would have ended in an attack of ischaemic pain.

Case 2 demonstrated the dramatic effect of intravenous magnesium sulphate, which came on within less than an hour of the injection, with complete relief of the pain. This treatment could not have affected any thrombosis that had already occurred—it did not relieve the pain of the deep-vein thrombosis in Case 5—but relief must have been due to the improved blood supply to and from the affected area. It is known that magnesium can cause a vasodilatation (Haury, 1939a, 1939b), so where blood is flowing extremely slowly, owing to the sludging of sickled cells, vasodilatation will cause an increased blood-flow and thus will improve oxygenation of the affected part, and hence the relief of ischaemic pain and return of function. This was demonstrated by the return of sight in Case 4, the relief of pain and anuria in Case 3, and the relief of ischaemic bone pains in Cases 2 and 5.

During the long follow-up of the first case a similar regimen was tried on adult volunteers, but it was the exception rather than the rule for this therapy to be so well tolerated. Prolongation of the thrombin-generation time was found to be rather variable even in adults. Other amino-acid vehicles were tried, even some specially prepared magnesium glutamate. For large-scale practical use, however, they were all too unpalatable.

An inevitable result of magnesium citrate therapy was to make the urine alkaline at all times. So it was decided to find out whether or not crises could be as successfully averted merely by the prevention of acidosis. The next case was therefore tried on enough sodium bicarbonate to keep the urine alkaline at all times. In Case 3 the patient was symptomless when under close supervision: whenever he was readmitted in pain it was found that his urine was no longer alkaline. Cases 6 and 7 were also kept free from crises while on bicarbonate therapy. It was felt that the bicarbonate regimen was just as effective as the magnesium citrate; it was also more palatable and much less expensive. The first patient has now been put on to bicarbonate treatment with no deterioration in his well-being. The difficulty with this treatment is to ensure that the children take the required dose regularly at least three times a day; the need is even greater when they are not well, at which times the dose should be increased if the urine becomes acid.

Treatment

It would seem that the logical treatment of sickle-cell anaemia can best be considered under three headings (see also Lehmann, 1963).

1. *The Anaemia.*—The haemolytic anaemia of sickle-cell disease is no worse than any other inherited or acquired haemo-

lytic anaemia. It is clear that any additional stress to marrow function, such as infection, has to be treated promptly or, if possible, avoided. It is also accepted that subsidiary doses of folic acid prevent a deficiency that could occur as the result of the marrow working at an increased rate.

2. *Prevention of Sickling.*—As has been stated before, *in vitro* formation of sickle cells is the exception rather than the rule, even in sickle-cell anaemia. The fact is that sickling takes time, and so, if circulation is unimpeded, deoxygenated cells will become reoxygenated in the lungs before having changed their shape; hence the importance of preventing stasis. As it is known that sickling is enhanced by acid *p*H, it is essential to prevent acidosis. This can be achieved by providing a surplus of sodium bicarbonate *at all times* and thereby guaranteeing that there is sufficient alkali reserve to cope with acidifying processes. Sodium bicarbonate has been discussed as a possible treatment of sickle-cell crisis by Greenberg and Kass (1958), but in their hands had not been very beneficial. Nwokolo (1960), however, recommended it as a useful treatment. In our opinion its use would be in preventing acidosis, and thereby lowering the tendency to sickle, rather than in affecting any sickle cells once the crisis had set in.

3. *Painful Crisis.*—The mere formation of sickle cells does not do much harm. The risk arises only when they become wedged in small blood-vessels and interfere with the local circulation. The vicious circle of stasis, hypoxia, acidosis, and more sickling sets in, and while alkali may delay additional sickling it is the dislodgment of the sludged cells, with the prevention of firm clots by treatment with magnesium, that is required at this stage, for once the intravascular infarcts are firmly clotted the process is irreversible.

Magnesium, besides affecting the clotting processes, causes vasodilatation (Haury, 1939a, 1939b), and thus must help in dislodging sludged cells in partially clotting blood.

Although so small a number of cases can prove little, one cannot help but be impressed by the patients themselves, who had never been so free of pain as they have been since taking regular alkalis. Under adequate supervision and with prompt treatment of all infections these children and young adults were remarkably well. The practical problem was to educate their parents to maintain this supervision at home regularly. Whether the prolonged treatment with alkali will be tolerated as well as we have noted it to be in our patients must obviously depend on an efficient renal function to combat alkalosis. The amount of sodium bicarbonate required is in fact not very great and is, for example, well tolerated over many years by patients who take this salt habitually for treatment of indigestion.

To summarize the management of sickle-cell disease, patients should try to avoid acts which are known to have precipitated crises. Causes of hypoxia, such as chest infections, anaesthesia, air travel without adequate oxygen, causes of acidosis, infections, heavy meals, especially at night, violent exercise, exposure to undue cold, all seem to precipitate crises. Any underlying medical reason for the onset of the crises should be looked for and treated. In the treatment of the crises, pain should be relieved symptomatically by codeine or pethidine. Intravenous 50% magnesium sulphate solution (1–2 ml.) has been found to be useful as a vasodilator, and so often relieves this ischaemic pain. It can be repeated four- or six-hourly, but after 24 hours it can be satisfactorily replaced with magnesium glutamate by mouth. The dosage is 5–6 ml. of 70% magnesium glutamate diluted to 30 ml. with water, given four to six times daily between meals. If there is intestinal hurry the dose of magnesium glutamate should be lowered—usually no more than a decrease of 10–20% will be required. Ideally, acidosis should be prevented, but if it occurs it must be treated promptly. It seems that sodium bicarbonate in doses between 0.5 and 1 g./kg./day divided six- or eight-hourly will keep the urine alkaline. If the urine is always kept alkaline, crises become a rarity and attacks of pain are far less severe and much shorter lived. By this means people with sickle-cell disease can live a much more normal life with far less illness.

Summary

A combination of alkali and magnesium has been found helpful in the treatment of sickle-cell anaemia. Six cases are fully described. There was no effect on the haemoglobin level and red-cell survival time. The number of painful crises could, however, be reduced, and five of the patients were enabled to lead a normal life. The exception was one child whose home supervision of the alkali regime was not satisfactory.

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