albumin concentration in the oedema fluid lies in their indication that blood capillary permeability remains unaltered in uncomplicated lymphoedema. Pathological processes, such as inflammation, which render the capillary wall abnormally permeable produce extravascular fluids that have an electrophoretic pattern resembling closely their parent serum. Fig. 3 includes the electrophoretic pattern of fluid obtained from a slightly inflamed bursa, and it can be seen that all components of the plasma protein are represented. It was also observed that in the electrophoretic pattern of oedema fluids containing less than 2.5 g. of protein per 100 ml. the β-globulin band was a prominent feature and second only to albumin in intensity. It is probable that this band is due to the iron-binding globulin (siderophyllin or transferrin). This substance has a molecular size only slightly larger than that of albumin, and has been found in nephrotic urine (Neale, 1955).

Discussion

An important function of the lymphatic system is to remove protein molecules from the tissue spaces. Lymphatic insufficiency interferes with this function, and we have shown (Taylor *et al.*, 1957) that plasma proteins are removed abnormally slowly from the subcutaneous tissues in lymphoedema. On these grounds it can be expected that oedema fluid in lymphoedema will contain an abnormally high quantity of protein. The investigation presented here confirms this, and the results are in general agreement with the observations of Drinker *et al.* (1934) on four patients, Watson (1953) on five patients, and Crockett (1956) on 10 patients with lymphoedema.

The Starling hypothesis (Starling, 1896) of tissue-fluid formation depends on the high protein content of the plasma to provide an osmotic force sufficient to promote absorption of tissue fluid into the vascular bed at the venous end of the capillary loop. In lymphatic insufficiency the small quantity of plasma protein that normally leaks through the capillary wall will accumulate in the tissue spaces. This extravascular protein then exerts an osmotic pressure in opposition to that of the plasma protein, and in consequence absorption of water from the tissue spaces is impaired. If the disturbance is great enough, water will be retained in the tissues and clinical oedema will be produced. A measurement of the colloid osmotic pressure made on the oedema fluid from one of our patients gives an indication of the magnitude of the abnormal extravascular osmotic force. This fluid contained 2.5 g. of protein per 100 ml. and had a colloid osmotic pressure of 14 cm. of water as measured by the method of Rowe (1954). The plasma colloid osmotic pressure is normally 36 cm. of water (Landis, 1934), and it can be seen that the osmotic force of the extravascular protein is of such a magnitude as to influence the hydrodynamic balance considerably. In these circumstances water will be retained in the tissue spaces until dilution and rising tissue tension restore equilibrium.

Summary and Conclusions

Oedema fluid from the legs of 38 patients with chronic primary lymphoedema was examined for protein content. Values ranging from 1 to 5.5 g. per 100 ml. were found, the mean level being 2.8 g. per 100 ml. The A./G. ratio was found to be increased in the oedema fluids, and electrophoresis showed that the large-molecule protein fractions such as α_2-globulin were retained inside the blood capillary wall. It is concluded that lymphatic failure results in an accumulation of protein molecules in the tissue spaces and that water retention and oedema are produced by this abnormal extravascular osmotic force. Capillary permeability is unaltered in uncomplicated lymphoedema.

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REFERENCES

Crockett, D. J. (1956). *Lancet*, **2**, 1179.
Drinker, C. K., Field, M. E., Hein, J. W., and Leigh, O. C. (1934). *Amer J. Physiol.*, **109**, 572.
Kinmonth, J. B., Taylor, G. W., and Harper, R. K. (1955). *Brit. med. J.*, **1**, 940.
—— —— Tracy, G. D., and Marsh, J. D. (1957). *Brit. J. Surg.*, **45**, 1.
Landis, E. M. (1934). *Physiol. Rev.*, **14**, 404.
Neale, F. C. (1955). *J. clin. Path.*, **8**, 334.
Pappenheimer, J. R. (1953). *Physiol. Rev.*, **33**, 387.
Rowe, D. S. (1954). *J. Physiol.*, **123**, 18P.
Starling, E. H. (1896). Ibid., **19**, 312.
Taylor, G. W., Kinmonth, J. B., Rollinson, E., Rotblat, J., and Francis, G. E. (1957). *Brit. med. J.*, **1**, 133.
Watson, J. (1953). *Brit. J. Surg.*, **41**, 31

TREATMENT OF FAT EMBOLISM WITH HEPARIN

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Aird (1949), writing of fat embolism, states that "most patients who suffer from fat embolism probably recover, but those in whom the diagnosis is made during life usually die." Faced with a severe case of this condition in 1956, one of us (R. H. S.) consulted the Department of Pharmacology of the University of Birmingham and was advised to try the use of heparin. This patient recovered, and heparin has since been used successfully in two further cases.

The pharmacological basis of the treatment is the effect *in vivo* of heparin "clearing" lipaemic plasma—that is, rendering translucent plasma which has become opalescent after a fatty meal (Hahn, 1943). French, Robinson, and Florey (1953) suggested, therefore, that the fat globules present in the blood of patients suffering from fat embolism might be similarly lysed, reducing the risk of infarction.

As a result of experiments with the heparin treatment of artificially induced fat embolism in rats, Gardner and Harrison (1957) came to the conclusion that a clinical trial of heparin in human fat embolism would not be justified. They found that, in their animals, heparin both accelerated death and increased the number of deaths after fat embolism. In view of these findings we present below three human cases in which heparin was successfully used. Despite the view of de Takáts (1945) that there may be regression of symptoms to complete recovery, no matter how serious the initial symptoms, these three were of such severity that we would otherwise have expected them all to be fatal.

Case 1

A soldier aged 23, a pillion passenger on a motor-cycle, received a closed fracture of the mid-shaft of the right femur on May 15, 1955. This was treated by extension, with a Steinmann pin through the tibial tuberosity, on a Thomas splint. No blood transfusion was given at this stage. On the evening of the 16th his temperature was 101.6° F. (38.7° C.), but the pulse and respirations were normal. On May 17 his temperature was 102.8° F. (39.3° C.), pulse 86,

and respirations 20. Pneumonia was suspected and penicillin, 300,000 units six-hourly, was started by intramuscular injection. On May 19 there was dullness on percussion of the left side of the chest compared with the right, and numerous rales were heard at the left base. Next day the patient was drowsy and complained of headache; dyspnoea and slight cyanosis were present, with blood-stained sputum. The chest moved freely, but rales were still present at the left base. The optic fundi showed small haemorrhages in the right retina, and petechial haemorrhages were present in both supraclavicular fossae.

Chest *x*-ray examination on May 20 showed: "Portable film compatible with extensive fat embolus of lungs. No *x*-ray evidence of left rib fractures." The urine examined the same day contained no fat globules. Report on sputum: "There are fairly numerous fat globules measuring up to 30 microns in diameter. This is said to be an invariable finding in fractures of marrow bones." A diagnosis of fat embolism was accepted, and the fracture was relegated to second importance.

On May 20 aminophylline, 3 gr. (0.2 g.), was given intravenously, together with heparin, 12,500 units intravenously, in the morning. A further 25,000 units of heparin was given intramuscularly that night. Next day aminophylline, 3 gr. (0.2 g.) four-hourly, was given orally, together with heparin, 25,000 units intramuscularly, at 6 p.m. A clotting-time estimation done just before this injection was reported as 6 minutes. On May 22 a further 25,000 units of heparin was given. The patient's condition remained critical for some days, but by June 1 he had so improved that open reduction and plating of the fracture was carried out and a plaster-of-Paris case was applied. *X*-ray examination on September 30 (13 weeks after the plating operation) showed union so advanced that a walking-calliper was fitted. There was considerable swelling of the calf and foot, and the knee was stiff. The calliper was finally discarded on April 23, 1956. By June there was 90 degrees flexion at the knee-joint; the thigh and leg had no swelling. The patient was back at civilian work and was able to take part in all reasonable activities.

Case 2

A man aged 40, involved in a motor-cycle accident, received multiple laceration, a closed but grossly comminuted fracture of the left femur, and an open fracture of the left tibia and fibula. There was no head injury. Two pints (1,140 ml.) of blood was given, the fractured tibia reduced and plated, and a Steinmann pin inserted through the tibial tuberosity for extension of the fractured femur. Two days later he became collapsed and mentally confused. He was incontinent of urine and had purpuric spots on the upper chest and the shoulders. A portable *x*-ray film of his chest on this day "failed to reveal any gross pulmonary pathology."

A clinical diagnosis of fat embolism was made, and treatment with heparin, 4,000 units intravenously four-hourly, plus aminophylline, 0.2 g. intravenously four-hourly, was begun, and continued for 48 hours. On the day after treatment was begun the injured thigh was grossly swollen and bruised, due obviously to bleeding at the fracture site, and this was the main factor in limiting the duration of heparin treatment to two days. Rapid improvement in the general condition occurred, and by the eighth day after the accident the patient's condition was back to that of the first day. Union of the two fractures was delayed, the femur taking nine months and the tibia fifteen. He did not resume work for a further six months owing to stiffness of the left knee-joint.

Case 3

A man aged 19 received an open oblique fracture of the mid-shaft of the right tibia and fibula while playing football; there was no other injury. Surgical toilet and reduction were performed within a few hours of admission and a full-length plaster-of-Paris case was applied. Three days later he became drowsy and cyanosed, with a temperature of 100° F. (37.8° C.). There was no cough and the chest was clear; the wound showed nothing abnormal. Within a few hours a physician found "some patchy consolidation—rales mainly in the right base zone. No tracheal displacement. Rapid breathing. Temperature 100° F. (37.8° C.), pulse 130. Fairly profuse petechial rash on neck and shoulders. Semi-stupor without localizing neurological signs. Optic disks: no evidence of fat embolism here." Urine taken at this stage was subsequently reported to contain no fat droplets and a blood culture was negative. A clinical diagnosis of fat embolism was accepted and treatment with oxygen and penicillin was begun. Heparin, 12,500 units intravenously followed by 25,000 units intramuscularly twice daily, and aminophylline, 0.5 g. intravenously six-hourly, were given for three days. At the end of this time there was marked improvement in the general condition and no bleeding at the fracture site occurred.

Portable *x*-ray film of the chest on the sixth day after injury showed: "Increased transverse diameter of the heart, especially left ventricle. The lung fields appear to be clear." The serum total lipid fatty acid+cholesterol= 505 mg./100 ml. (normal) on the same day.

On the 18th day after the accident a Steinmann pin was inserted through the os calcis for extension, and a plaster-of-Paris case was applied. Union of the fracture was complete and the plaster-of-Paris was removed at the 19th week. Rehabilitation was slow, and at the 10th month, when the patient was discharged, there was still some stiffness of the foot.

Comment

The treatment with heparin of three patients whose fractures were complicated by the occurrence of fat embolism is reported. Unfortunately the diagnosis in each case was made on clinical grounds only, but this was largely because it was considered to be so clear. The dosages of heparin employed were those used in deep calf-vein thrombosis, and, although the records of clotting-time are not available, it was raised considerably in each case. The shortness of the course given—that is, three days in each—is noteworthy. Haemorrhage at the fracture site, delayed union, and more than usual joint stiffness after conventional treatment of the fracture were noted. The latter complication is possibly due to the forced neglect of physiotherapy in the early days after injury, when the general condition of the patient is so poor.

Summary

Three patients with severe fat embolism, all of whom might have been expected to die, recovered after treatment with heparin.

It is suggested that heparin treatment is worthy of further trial in this serious condition, and that a controlled series of cases would be justified.

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References

Aird, Ian (1949). *A Companion in Surgical Studies*, p. 25. Livingstone, Edinburgh.

de Takáts, G. (1945) In *Textbook of Surgery* edited by F. Christopher, 4th ed., p. 248. Saunders, Philadelphia.

French, J. E., Robinson, D. S., and Florey, H. W. (1953). *Quart. J. exp. Physiol.*, **38**, 101.

Gardner, A. M. N., and Harrison, M. H. M. (1957). *J. Bone Jt Surg.*, **39B**, 538.

Hahn, P. F. (1943). *Science*, **98**, 19.

Volume II of the *Manual of the International Statistical Classification of Diseases, Injuries, and Causes of Death* (Seventh Revision) has now been published by the World Health Organization, Geneva. It contains alphabetical indexes to the terms used in volume I, which was reviewed in the *Journal* of January 11, 1958 (p. 94). Both volumes are obtainable from H.M. Stationery Office, price 35s. the set.