REFRESHER COURSE FOR GENERAL PRACTITIONERS

HAEMOPHILIA

BY

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Haemophilia is one of the best known of all the hereditary diseases, and, although not a very common affliction, it remains a major problem to the medical profession and a life-long burden to the sufferer. This article briefly presents the current views on the nature of the disease, its diagnosis and treatment, and the outlook for the haemophilic patient.

Inheritance

The gene responsible for haemophilia seems to lie in the X sex chromosome. The various patterns of inheritance to which the genes give rise are well known. A haemophilic man married to a normal woman does not transmit the disease to his sons, nor do they in their turn transmit the defect to any of their descendants, male or female; all the daughters of a haemophilic man married to a normal woman will, however, be carriers and capable of transmitting the disease (Fig. 1). If a carrier daughter marries a normal man half of their sons will be haemophiliacs and half of their daughters will be carriers (Fig. 2). Haemophilia can occur in a female only if she is the child of a haemophilic man married to a woman who is a carrier: instances of this rare combination have recently been described.

The sex-linked inheritance of haemophilia depends upon the gene for the disease being recessive. When the X sex

chromosome bearing the gene ($\bar{x}$) is combined with a normal X sex chromosome (a female resulting) the harmful effect of the gene is neutralized but the carrier state results. On the other hand, overt haemophilia results from the combination of the chromosome bearing the gene with a normal Y sex chromosome (a male resulting). The chromosome combinations resulting from the marriage of a haemophilic male to a normal female and of a normal male to a carrier female are illustrated in Fig. 3.

It is perhaps less well known that the classical pattern of inheritance—a boy with haemophilia having a maternal uncle or uncles or perhaps his maternal grandfather affected—is by no means always found. Indeed, out of 72 haemophiliacs studied by Merskey no family incidence could be proved in 34% of them, though in all other respects they were suffering from typical haemophilia. There are several possible reasons for an apparently negative family history: the members of the family may be widely scattered; the history they give may be incomplete; the disease itself may have been transmitted through several generations by carrier daughters, no haemophilic son having been born; or the disorder may conceivably be due in a particular patient to the occurrence of a fresh mutation.

Symptoms

The clinical signs and symptoms of haemophilia are not recounted in detail. An undue tendency to bleed, usually apparent in early life, is the cardinal symptom. Haemorrhage at circumcision may be the first sign. Later, bleeding or bruising following minor cuts or injuries or tooth extractions may be excessive and intractable; often deep bruising occurs apparently spontaneously, and haemorrhages into joints, leading to crippling deformity, are common and characteristic. Sometimes haematuria occurs, occasionally melaena, and more rarely, fortunately, haemorrhages into internal organs. Skin purpura is usually absent.

The manifestations of the disease vary from patient to patient, but are often remarkably constant in any one person. In one the joints cause most concern; in another it is frequent attacks of haematuria; in others it is repeated subcutaneous haemorrhages. Some claim that the seasons have a bearing on the severity of their symptoms; and a few state that certain drugs such as aspirin, penicillin, or aperients cause exacerbations. These variations and idiosyncrasies remain unexplained.

Haemophilia is fortunately not always an extremely severe disease. Some haemophiliacs may live almost normal lives and suffer little disability; in them the laboratory signs are usually also less marked. In the less fortunate the manifestations may be severe from birth and bring about death at an early age. On the whole the degree of severity tends to be uniform throughout an affected family, and throughout the life of any particular patient, if allowance is made for the periods of spontaneous improvement which are a feature of the disease.

Pathogenesis

In haemophilia the clotting mechanism of the blood is impaired. Most workers agree that the impairment is due to the absence or deficiency of a factor in the plasma which is essential for the formation of thromboplastin. This factor is a globulin, often referred to as "antihaemophilic globulin"; on plasma fractionation it is found in the

FIG. 1.—Transmission through an affected male (I₁) and carrier females (II₁ and II₂).

FIG. 2.—Transmission through carrier females (I₁ and II₁).

FIG. 3

fibrinogen fraction (Cohn's fraction I). All the other factors required for coagulation—the blood platelets, prothrombin, Factor V, Factor VII, calcium, and fibrinogen—seem to be qualitatively and quantitatively normal.

Diagnosis

The diagnosis of haemophilia is becoming more precise year by year. Often it can be tentatively made from the patient's clinical and family history. If there is also a markedly prolonged whole-blood clotting time the diagnosis becomes reasonably certain. The newer methods of studying blood clotting will provide corroborative evidence; for instance, the prothrombin-consumption index will show a failure to utilize prothrombin during clotting, and the thrombin-generation test will show delayed formation of thrombin. Significantly, too, it will be found that a small proportion of normal plasma (as little as 1 to 2%) added to the patient's plasma will markedly shorten the time his citrated plasma takes to clot after it has been recalcified. Typically, his skin-prick bleeding time will be normal and tests for naturally occurring anticoagulants in his plasma will be negative.

These more refined methods of studying blood coagulation are particularly useful in the mild or apparently anomalous cases of haemophilia in which the whole-blood coagulation time is normal or almost normal (20% out of 51 patients of Merskey's series) or where the family history seems to be negative. A decisive extension of these tests is to demonstrate that the plasma of a known haemophiliac fails to correct the defect in the plasma under test, whereas normal plasma succeeds in doing so. Here, however, a complication must be mentioned. Recent reports from Switzerland and America have referred to the existence of a "new" disease clinically closely simulating haemophilia but distinct from it. The disorder exists also in England and South Africa. A study of seven of these patients is reported on page 1378 of this issue, where it is shown that the disorder is due not to lack of antihæmophilic globulin but to lack of another quite distinct clotting factor ("Christmas factor"). The distinction between the two types of haemophilia can be made relatively easily in the laboratory. The importance of recognizing "Christmas disease" lies in its treatment, for the missing factor is not present in the fibrinogen fraction of plasma in which lies the antihæmophilic globulin effective in true haemophilia (see below).

Treatment

Although it cannot yet be said that an effective treatment for haemophilia is "just around the corner," the outlook is slowly becoming less bleak. A good deal can be done by the doctor to afford temporary and symptomatic relief, and the patient himself can help greatly in combating his disease.

The aim of the research worker, and the hope of the haemophiliac, is the permanent restoration to normal of the defective clotting mechanism, either by the administration of refined antihæmophilic globulin in harmless and effective form, by mouth if possible, or by some substance which would stimulate the production of antihæmophilic globulin within the patient himself (analogous perhaps to the effect of vitamin K on the formation of prothrombin). Some progress is being made in the isolation of antihæmophilic globulin; but unfortunately no substance is known which affects its production *in vivo*.

Effect of Blood or Plasma Transfusion

Antihæmophilic globulin is in fact administered whenever a patient receives a transfusion of whole blood or plasma, or is given an injection of human fibrinogen. Unfortunately, the effect on the coagulability of the patient's blood is transitory; it is greatest immediately after transfusion but diminishes rapidly, so that after 24 hours or so the benefit is negligible. Moreover, to obtain substantial and worth-while benefit large volumes of plasma have to be given. At present a really effective

treatment for an adult would entail intravenous injections of 400 to 500 ml. of plasma at least every other day, preferably daily. This regime is hardly practicable for any length of time and carries a remote risk of serum hepatitis, to say nothing of the possible development of a refractory state with consequent diminishing benefit from the transfusions. How often a refractory state develops is not yet known for certain; so far it has been observed chiefly in America.

Acute Haemorrhage

When haemorrhage is severe, no matter whether it is internal or external, transfusion is certainly indicated. The patient must, of course, receive blood only of the same ABO and Rh groups: ideally, he should be grouped in respect of the other blood-group systems also and blood chosen for him which matches his own as closely as possible, so that potentially dangerous reactions due to iso-antibodies that may have developed as the result of earlier transfusions may be avoided. Either whole blood or plasma may be used: if the patient's haemoglobin level is below normal, blood should be given; if not, plasma. Large volumes must be given: the plasma from 2 pints (1,140 ml.) of blood is the least amount necessary for an adult. If the haemorrhage persists the transfusion should be repeated. Laboratory control is desirable; measurement of the whole-blood clotting time is the minimum requirement. In a haemophiliac the clotting time should be normal or almost normal after a transfusion of 400 to 500 ml. of normal plasma; if it is not reduced by transfusion the reason may be that the patient is already refractory. In this case a transfusion of much larger volumes of blood should be tried.

Blood and plasma should be used as soon after being withdrawn as possible, at any rate within 24 hours, as antihæmophilic globulin in shed blood is labile. There seems, however, no reason to insist on the blood being absolutely fresh or to attempt direct transfusion. The citrate anticoagulant containing glucose used as a routine by the National Transfusion Service is suitable. Recently it has been suggested that heparin may be a preferable anticoagulant, but this needs confirmation.

Human fibrinogen (containing antihæmophilic globulin) is not yet available except on an experimental scale. When highly concentrated potent preparations can be prepared, the dried product may be used as a convenient substitute for fresh plasma.

Local Treatment of External Haemorrhage

Where the source of bleeding is accessible a haemostatic agent should be tried. Probably the best to use is thrombin, now available commercially in dried form, which on solution will clot fibrinogen in a few seconds; the thrombin solution should be applied direct to the bleeding surface under moderately firm pressure. Russell viper venom is also a powerful haemostatic agent. Neither thrombin nor the venom must of course be administered intravenously.

Other Forms of Treatment

As is natural in an intractable complaint, many different substances have been used either locally or systemically in an attempt to treat haemophilia. None has been proved to be of real benefit when subjected to carefully controlled tests. One remedy that has attracted attention in this country is the substance derived by Timperley from egg-white. On three separate occasions—before, during, and after the last war—the Medical Research Council has organized clinical trials of this substance in a number of different hospitals. In none of these trials was any evidence obtained that the patients benefited from the treatment.

Symptomatic Treatment

The treatment of the haemophilic patient's symptoms by means other than transfusion is largely a matter of applying common-sense principles of medicine. For example,

haematomata should be treated by rest and, if possible, by moderate pressure; pain by sedatives, though the possibility of drug addiction must be taken into account; carious teeth should be filled rather than extracted. Haemarthroses are a special problem: they should be firmly bandaged and not aspirated; later, radiant heat and skilled massage will help to preserve joint function.

Surgery in Haemophilia

It cannot be emphasized too strongly that operations on haemophiliacs should be avoided if at all possible. Thus abdominal emergencies are best treated conservatively—in any case they are often due to haemorrhage within the abdomen; septic conditions by antibiotics rather than incision; and cancer by radiation rather than operation. The extraction of carious teeth should be undertaken only if pain is intolerable, and it must always be carried out in hospital. Transfusions before and afterwards, the application of thrombin to the cavity, and local pressure will probably be necessary.

Operations have been carried out deliberately and successfully on haemophiliacs, but before the patient is on his feet again the surgeon usually wishes that he had never operated.

Social Implications

Patients with haemophilia need all the help and advice that the medical profession can give them in adjusting themselves to their disabilities. A haemophilic child is a particular source of worry, for minor degrees of trauma which would cause no injury to a healthy child often lead to widespread bruising or to haemarthroses. The child's parents must therefore shield him from harm so far as they can until he can look after himself. Fortunately, most haemophilic children learn to protect themselves at a comparatively early age. Schooling, however, presents a special problem. Ideally, the severely affected haemophilic child should be sent to a special school where he may avoid the normal rough-and-tumble, otherwise repeated absences are almost inevitable. Most haemophilic children experience intercurrent illness without undue upset, and in the absence of a practical specific treatment no special precautions can be taken. The seriousness of any operative intervention has already been mentioned.

The adult haemophiliac faces, and usually succeeds in overcoming, formidable problems. His ability to do a job of work and to keep the job is often jeopardized by the nature of his complaint and by repeated absences due to illness. Getting to and from work may be a continual source of anxiety, for the overcrowding and jostling at rush hours are a potent cause of haematomata likely to cause disability and absence from work. Naturally, he should be advised to take a sedentary rather than a manual job if this is possible and to obtain work close to his home. He may ask advice about marriage; if so, it should be clearly stated that, although any sons will be free of the disease, every daughter he has will be a carrier.

The mother of a haemophilic child deserves special sympathy. Her children are a constant anxiety to her; she feels responsible for their disabilities; and if she has another son she lives in fear that he too may prove to be affected. Nor at present can the daughter of a woman who is a carrier know whether or not she herself carries the trait. If this could be determined—and it is not possible as yet—then by voluntarily remaining childless she could help to diminish the incidence of the disease.

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SIR NORWOOD EAST AT 80

Another distinguished figure entering the ranks of octogenarians is Sir Norwood East, who celebrated his eightieth birthday on Christmas Eve. The evidence of the calendar cannot be gainsaid, but anyone hearing his vigorous speech at meetings of the Medico-Legal Society, the Society for the Study of Addiction, or the Psychiatric Section of the Royal Society of Medicine, of all of which he has in turn been president, would find difficulty in crediting him with fourscore years.

At a time when crime and its psychological background is attracting very much public attention, Sir Norwood East,

with fifty years' experience of the prison medical service behind him, has something perhaps more weighty to contribute than any other man in England. On the one hand, excessive claims are sometimes made for psychiatry in relation to the causation of crime and the treatment of offenders, and, on the other, there is a tendency in some quarters to dismiss psychological investigation and treatment as irrelevant. The division may to some extent be along the lines of doctor versus lawyer, but not exclusively so by any means. Sir Norwood East, with his balanced view, has done a great deal to bring about harmony and mutual understanding and to throw light into dark recesses. His book *Introduction to Forensic Psychiatry in Criminal Courts* was the first of its kind to afford a clear insight into the newer methods of dealing with offenders in prison. One subject on which he organized a large investigation comprehending 4,000 cases was on delinquency among adolescents, another theme much to the fore at the present time. He published his results in a book entitled *The Adolescent Criminal*. Many of his most valuable papers have been brought together in his books *Medical Aspects of Crime* and *Society and the Criminal*; in these will be found balanced judgments based on years of experience among criminals. His lectures on forensic psychiatry at the Maudsley Hospital have always been much appreciated by his students.

Sir Norwood qualified from Guy's Hospital in 1897 and joined the prison service two years later. He served at