FIG. 1.—November 1, 1955. 1=0.3 ml. of $\text{Al}(\text{OH})_3$ -treated patient's plasma (1 in 5), 0.3 ml. of patient's serum (1 in 10), and 0.3 ml. of patient's platelet suspension. 2=0.3 ml. of $\text{Al}(\text{OH})_3$ -treated patient's plasma (1 in 5), 0.3 ml. of normal serum (1 in 10), and 0.3 ml. of normal platelet suspension. 3=0.3 ml. of $\text{Al}(\text{OH})_3$ -treated normal plasma (1 in 5), 0.3 ml. of patient's serum (1 in 10), and 0.3 ml. of normal platelet suspension. 4=Normal reaction.

did not occur in the tube containing 0.2 mg. of protamine sulphate (normal clotting, 0.12–0.14 mg.). The administration of protamine sulphate intravenously temporarily corrected the signs of haemorrhagic diathesis.

All these experiments revealed the existence of a "heparin" or "heparin-like" circulating anticoagulant.

A thromboplastin generation test performed a week later (November 8) showed a slight change for the better (Fig. 2): although there was some clinical improvement, the haemorrhagic diathesis still existed. On November 15 the test showed that the formation of thromboplastin had become normal (Fig. 3), and the clinical findings of a haemorrhagic diathesis had disappeared. The patient was discharged at his own request on November 28, 1955.

FIG. 2.—Patient's reaction. November 8.

FIG. 3.—Patient's reaction. November 15.

Discussion

The defect in thromboplastin generation, the prolongation of the coagulation time, heparin clotting-time, prothrombin time, and antithrombin time, and *in vitro* correction of the abnormal findings by the addition of protamine sulphate and toluidine blue, and finally the result of the protamine titration method of Allen *et al.*, show that the circulating anticoagulant in this case is heparin or a heparin-like substance. The fact that one ampoule of protamine sulphate, when injected intravenously, temporarily corrected the prolonged coagulation time and prothrombin time confirmed these findings.

It is well known that heparin activates antithrombin and the clearing factor, and inhibits the conversion of prothrombin to thrombin. Douglas (1956) showed that heparin prevents the utilization of A.H.G. and labile factor, and thus prothrombin is not consumed.

In one of our previous publications (1957) we (Ulutin and Sestakof, 1957) recorded that heparin, when injected intravenously, inhibits the formation of thromboplastin in the thromboplastin generation test of Biggs and Douglas (1957).

Summary

A haemorrhagic diathesis manifesting itself by bleeding from the gums, subcutaneous haematomata, subarachnoid haemorrhage, and epistaxis developed in the course of chronic nephritis. The cause of this haemorrhagic diathesis was a heparin-like circulating anticoagulant. The literature concerning the existence of such an anticoagulant and hyperheparinaemia are briefly reviewed.

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IMMEDIATE SENSITIVITY REACTION TO POLIOMYELITIS VACCINE

BY

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Untoward reactions to poliomyelitis vaccination are uncommon, and it is generally agreed that poliomyelitis vaccine is exceedingly safe to use. Although the vaccine has been administered many thousands of times, both in this country and the U.S.A., reports of unpleasant sequelae have been few. Nevertheless, from the reports that are available, it is clear that allergic reactions may occur. Usually the skin is involved, but general systemic upsets have also been described. In most cases traces of penicillin in the vaccine have been suspected of being the sensitizing agent.

Most of the reported cases of allergy to poliomyelitis vaccine have occurred in the U.S.A. Zimmerman (1958) described the cases of six patients, all with a previous history of sensitivity to penicillin, who developed urticaria or bullous dermatitis a few days after vaccination. Each patient responded to penicillinase therapy and did not react when a penicillin-free vaccine was subsequently administered.

Stroud *et al.* (1958) reported 12 cases of cutaneous eruptions following poliomyelitis vaccination. The eruptions were described as urticarial, eczematous, or psoriasiform, and one, or possibly two, of the patients were sensitive to penicillin. Erythema multiforme was noted by Chervinsky (1957) in a young girl two weeks after vaccination; and 0.1 ml. of the vaccine intradermally a month later was followed in five days by joint pains, swelling of the eyelids, and an erythematous eruption. The case of a one-year-old girl who developed angioneurotic oedema an hour after poliomyelitis vaccination was described by Clyde (1956). Red "splotches" appeared over her body, and the site of the injection became red and swollen. She had no ill effects when, later, penicillin-free vaccine was given.

The first British report was by Fowden (1958), who described the case of a 12-year-old boy, known to be penicillin-sensitive, who developed severe frontal headache, anorexia, lethargy, and a sparse itchy rash, later becoming vesicular, a few hours after the injection of British vaccine. Bronchospasm developed three days later. Three cases with marked local reactions of poliomyelitis vaccination were reported by Burrowes (1959). Two were known to be sensitive to penicillin.

In the following case a nurse, who was sensitive to penicillin and, to a less extent, streptomycin, developed angioneurotic oedema and mild shock after injection of 1 ml. of poliomyelitis vaccine; and 41 days later a similar reaction followed the intradermal injection of 0.1 ml. of the vaccine.

Case Report

A nurse aged 24 received 1 ml. of poliomyelitis vaccine (American: Pare, Davies) intramuscularly at the hospital where she was employed. Within five minutes she felt a generalized itch, particularly about the eyes, which became irritable and watery, and which began to swell. A severe colicky pain developed in the lower abdomen and, with it, a strong desire to micturate. The swelling of the eyes progressed until she could hardly see, and she had a feeling of "water behind the eyes" (? conjunctival oedema). During this time she felt "queer"; had a throbbing sensation in her ears; and felt faint, sweaty, and "far away." On the point of collapse she was put to bed.

On being examined shortly thereafter she was found to be flushed and restless, her eyes almost closed by periorbital oedema. Seventeen minims (1 ml.) of adrenaline hydrochloride 1:1,000 was immediately given subcutaneously, and this gradually resolved her symptoms. She became less restless, and the throbbing in her ears and the abdominal pain disappeared. The periorbital oedema did not increase, and she felt better. Three hours later, apart from a feeling of weakness, she felt well. There was still general flushing of the skin, but the periorbital oedema had begun to subside. Twenty-four hours later she had returned to normal apart from some puffiness about the eyes. It is worth noting that for a period of 24-hours before the injection, and on the morning of the injection, she had taken antihistamine tablets for a mild irritation of the hands produced by detergents.

Because of the potential danger of contracting poliomyelitis in her work it was decided that, despite this reaction, her immunization should be completed. Accordingly she was referred to the local authority's special clinic. This clinic has been functioning in Glasgow for the past year, and to it are referred those patients who wish to be vaccinated against poliomyelitis but who suffer from, for example, asthma, eczema, hay-fever, or allergic conditions.

Forty-one days after her initial vaccination the patient reported to the special clinic. A course of small doses was

planned, each to be given at weekly intervals, as past experience had shown that this technique was the safest with allergic subjects. To this end, 0.1 ml. of poliomyelitis vaccine (American: Pitman-Moore) was given intradermally in the left forearm. Within two minutes a weal developed at the site of injection, surrounded by an area of erythema. Over the next half-hour this weal grew to a size approximately $2\frac{1}{2}$ by $1\frac{1}{2}$ in. (6.4 by 3.8 cm.) and the erythema covered most of the forearm. At the same time—that is, about two minutes after the test dose—the patient complained that her eyes were irritable, and on examination they were seen to be watering, with reddening of the palpebral conjunctiva.

Gradually her eyes became puffy, and over the next 10 to 15 minutes periorbital oedema developed and increased, until the right eye was closed and the left eye almost closed. During this time there was marked conjunctival oedema and the eyes watered profusely. Five minutes after receiving the injection she stated that she felt warm, unwell, and nauseated, and that there was a buzzing in her ears. Restlessness, agitation, and marked trembling of the hands were noted; her face was flushed and her pulse had risen to 120 a minute. She was given 6 minims (0.35 ml.) of adrenaline hydrochloride 1:1,000 subcutaneously and 8 mg. of chlorpheniramine maleate ("piriton") orally, and a few minutes later a further six minims (0.35 ml.) of adrenaline hydrochloride was given.

Within 5 to 10 minutes the patient became more settled. The nausea and the buzzing in her ears disappeared and she felt better. She still complained of being warm and, in fact, there was a general erythema which persisted for at least another hour. Approximately half an hour after the test dose urticaria was noted on her wrists, upper arms, and upper thighs. The periorbital and conjunctival oedema began to subside one hour after the test dose; and after two hours, although the right eye was still obviously swollen, there was only slight puffiness of the left (see photograph).

Photograph taken two hours after a test dose of 0.1 ml. of poliomyelitis vaccine had been given.

At this stage the weal and the erythema of the left forearm began to subside. As she now appeared well and no longer complained of any ill effects, she was sent home by car and advised to rest.

On examination, five hours after the injection, her eyes were still slightly puffy but most of the swelling had disappeared, as had the general erythema, the urticaria, and the weal on the forearm. She returned to duty next day, when examination revealed no abnormality apart from slight oedema of the eyelids.

Past History.—During her general training as a nurse the patient developed a sensitivity to penicillin and, to a lesser extent, streptomycin. Swelling of the eyes and a rash on the hands and wrists developed "many times" in this period, and this occurred only when she had to work with

the antibiotics, but especially with penicillin. Of her own volition she took to wearing rubber gloves and a mask when penicillin had to be administered, but this did not prevent her eyes from swelling. She also treated herself with antihistamines. She did not reveal her history of sensitivity before her first injection of poliomyelitis vaccine as she did not think there was any connexion between the two.

Commentary

In the preparation of poliomyelitis vaccine only 200 units of penicillin and 200 units of streptomycin, at most, are present in the original culture medium, and in the final product it is known that the concentrations are very much less. According to Zimmerman (1958), who wrote to the manufacturers concerned, the amount of penicillin present in 1 ml. of poliomyelitis vaccine is 3-10 units for Parke, Davies and less than 20 units for Pitman-Moore. In spite of the fact that these quantities are exceedingly small, they would still seem capable of producing anaphylactic reactions in sensitive subjects.

While the other components of poliomyelitis vaccine cannot be eliminated, it would seem, from the patient's past history of sensitivity to penicillin and streptomycin, that one or both of these antibiotics were responsible for the reaction. This would mean that she reacted to something in the nature of two units of penicillin and/or less than 20 units of streptomycin given intradermally.

Whether British vaccine is safer than American in this respect it is difficult to say. Perry (1956) stated that, while assay was difficult, the penicillin content of 1 ml. of British vaccine was in the region of 0.5 unit; Fowden's patient, however, reacted to the British vaccine, and at this stage it would seem unwise to consider any one vaccine superior to the other for penicillin-sensitive patients.

The potential danger to sensitized subjects of the traces of antibiotics in poliomyelitis vaccine was pointed out as early as 1956 (*Brit. med. J.*, 1956). This warning still holds true. For patients with a history of sensitivity to penicillin or streptomycin, poliomyelitis vaccine may produce sensitivity reactions. The recent decision to extend the age groups eligible for vaccination, has, if anything, increased the risk, as, according to Feinberg and Feinberg (1956), adults are potentially the more sensitive group.

Before poliomyelitis vaccine is administered it is essential that the patient (if a child, the parent) should be asked if there is a history of sensitivity to penicillin or streptomycin. If there is any doubt a test dose should be given intradermally. Particular attention should be paid to those who commonly work with these antibiotics. For those who are penicillin-sensitive a penicillin-free vaccine should be available similar to that obtainable in the U.S.A. and, if available, penicillinase should be administered before vaccination. The chief safeguard, however, is to ensure that the medical practitioner is aware of the potential risk to patients sensitive to penicillin or streptomycin.

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Reviews

MIDWIFE TO A UNIVERSITY

The Birth of Nigeria's University. By Kenneth Mellanby, C.B.E., Sc.D. (Pp. 263; illustrated. 25s.) London: Methuen and Co. Ltd. 1958.

Dr. Kenneth Mellanby has written a fascinating story of *The Birth of Nigeria's University* from the time when as "Principal Designate" he got lost in the bush at what was the chosen site for the new building at Ibadan until he handed over a remarkably going concern to his successor. The story, in fact, begins at an earlier date, and the first chapters tell of the origin of the college and Dr. Mellanby's introduction to the many problems involved. His uncle, the late Sir Edward Mellanby, told him, when the post was offered, that "you would be an idiot to accept." Fortunately for Nigeria this advice was disregarded, and in July, 1947, the designated principal flew out to West Africa for the first time. The difficulties were not small and the financial implications grew all the time. The author remarks that if the cost had not been originally greatly underestimated it is unlikely that the authorities would have undertaken the project. One conclusion from this piece of history is that it always costs much more than the experts say.

The chapter on the development of the medical faculty contains much of interest to medical readers. Skilful fostering by visitors from the University of London and the medical visitors under the Nuffield scheme has done much to raise standards (and a new hospital) much more quickly than seemed possible at first. It is interesting that, looking back, Dr. Mellanby thinks that Ibadan was a mistake as a site and that somewhere near Lagos would have been better. There is much detail in the volume for those concerned with university development, especially in overseas territories of the Commonwealth.

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VITAL STATISTICS

Elements of Vital Statistics. By B. Benjamin, B.Sc., Ph.D., F.I.A., F.S.S. (Pp. 352. 56s.) London: George Allen and Unwin Ltd. 1959.

A popular textbook of our predecessors in the field of public health and social medicine was Sir Arthur Newsholme's *Elements of Vital Statistics*. First published in 1889, and revised in 1899, it was brought up to date in 1923 by a completely new version written by Sir Arthur himself. Since then there have been many changes and much development both in the nature