drainages, removal of foreign bodies, closure of deep layers of cheek wounds, the accurate suture of lips, the immediate replacement of displaced fractured nasal bones, zygomatic bones, and orbital margins, and the repair of torn eyelids. In many instances the patients with these injuries could not have reached an advanced base hospital till three days later.

It needs little imagination to appreciate the value of the trinity at this level, not only singly but in conjunction on the same patient.

As field ambulances had fostered field surgical units, so likewise casualty clearing stations fostered the trinity. There were sometimes difficulties of accommodation in one casualty clearing station for the extra theatres and personnel. The drawbacks were always overcome and the trinity remained undivided. It is doubtful, however, if the specialties could have worked so closely together had their teams not been split. The trinity would then have been too cumbersome for any of the foremost casualty clearing stations to accommodate in addition to the general teams.

The chest specialty was not made so advanced, although, had there been a sufficiency of chest teams, the experiment of placing a team at the same level as the trinity might have been tried. The policy with only one team "in the field," as distinct from the base, was to place the field unit with a suitable advanced general hospital. Theoretically it was at a site where it could hold patients for six weeks. In practice it could not hold them all because of the other heavy demands upon such a hospital. But it could hold the serious ones. Haemothorax and its possible infection constitute the most important complications of chest wounds. Removal of foreign bodies and the treatment of complications are better performed, if possible, with the greater facilities of a general hospital in the matters of x rays, theatres, laboratories, and nursing. What the field surgeon contributed to the chest specialty was the closing of sucking wounds, débridement of others, and aspiration of haemothoraces after 48 hours. Only occasionally was anything more indicated.

(To be concluded)

SENSITIVITY TO LIVER EXTRACT

BY

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AND

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The purpose of this communication is to stress the not uncommon occurrence of allergic reactions to intramuscular liver therapy, their alarming nature on occasion, and the practicability of desensitization.

Since Schlesinger (1930) first drew attention to the occurrence of reactions to liver therapy we have been able to find in the literature records of less than a hundred cases of allergic reactions to oral, intravenous, and intramuscular liver therapy. When the widespread use of liver extracts throughout the world is considered, such a small number of reported cases would appear to indicate that allergic reactions to liver extracts are rare. Delikat (1943) had 14 cases of sensitivity to liver therapy among 200 cases of pernicious anaemia, and records in detail three severe cases. Of 60 consecutive cases of pernicious anaemia admitted to our wards during the past five years, four (6.6%) have subsequently developed reactions after one to three years of maintenance therapy. Barfred (1942) reports 19 cases showing allergic reactions among a total of 49 treated with intramuscular liver extracts—an incidence of approximately 40%. It should be pointed out, however, that Barfred was using experimental extracts which were often neither purified nor concentrated, and hence were given in large amounts (5 to 10 c.cm.).

We have been able to find only two papers in the British literature devoted to the subject of allergic reactions to liver therapy. Andrews (1941) records one case and Delikat (1943) three cases in detail. The most significant British reference is contained in a letter to the *British Medical Journal* by Morgans (1943)—a few weeks after Delikat's article—record-

ing the only fatality ever published from a reaction to an intramuscular injection of liver extract. In 1936 Ungley, Davidson, and Wayne, in an investigation of the clinical efficacy of the original Dakin and West preparation (anahaemin), mentioned that reactions to intravenous therapy occurred in two cases.

Reactions to liver extract may be classified as primary—i.e., those occurring after the first liver injection; and secondary—i.e., those which appear for the first time after weeks, months, or years of parenteral therapy.

Primary reactions are not due to acquired sensitivity, but are an immediate response of the body to the parenteral injection of foreign material. Such reactions were much more common when liver extracts were given by the intravenous route (Castle and Taylor, 1931; Murphy, 1932). The use of the intramuscular route and the purification and concentration of liver extracts have resulted almost in their complete disappearance. Disagreeable effects reported include pyrexia, collapse, shivering, vertigo, flushing, headache, and dyspnoea (Strauss and Castle, 1932; Schlumm, 1932; Strandell and Hammar, 1932).

Secondary reactions to oral, intravenous, and intramuscular liver therapy have been described. They are undoubtedly of an allergic nature. In support of this contention are the eosinophilia, the latent period between the primary injection and the onset of symptoms, the clinical features, including bronchospasm and the characteristic skin reactions, and the response to adrenaline. Sensitivity can be passively transferred to a normal individual from the sensitive individual by the Praetorius-Küstner technique (Grün, 1934; Lasch, 1936; Criepe, 1938; Pache, 1939; Jones, 1939; and ourselves in 2 cases). The sensitivity has been shown to be specific to the organ from which the extract has been prepared rather than for the species of animal concerned (Criepe, 1938; Pache, 1939; Jones, 1939; Scarlett and Macnab, 1942).

During the past ten years one of us has had referred to him approximately 40 patients with reactions to parenteral liver therapy, 21 of whom have been investigated during the last two years. Of these cases 15 were so severe that they were admitted to hospital for investigation and desensitization.

A study of the literature shows that sensitivity has occurred to all the leading brands of liver extract. On the continent of Europe, campolon in Germany and pernaemon in the Netherlands appear to be often incriminated, while in America reticulogen and Lederle extracts are those chiefly mentioned. In our experience anahaemin and campolon are the commonest offending extracts, but we have also had cases sensitive to other British extracts and to Continental and American products. The frequency with which reactions are reported to such highly purified extracts as reticulogen and anahaemin indicates clearly that the causation of the reactions does not correspond to the degree of purification and concentration, but rather to the chances of sensitivity occurring from extracts which enjoy the greatest popularity in the various countries.

When such sensitivity is established to a particular liver extract, injections of a different extract may be given in some cases without any reactions. Thus on occasion we have had patients sensitive to anahaemin or campolon who tolerated reticulogen well. Such patients, however, tended to become sensitive to reticulogen in a period of weeks or months. In general, however, our experience suggests that if a patient shows marked reactions to one liver extract, sensitivity will extend to all liver extracts.

The reaction generally occurs within 5 to 30 minutes after injection. In many reported cases, and 9 out of 19 of our cases investigated during the past two years, there have been periods of interruption of therapy lasting in some instances for several months, with the reactions appearing shortly after the resumption of treatment but not after the first injection of the new course of treatment. Another important feature is that once the reactions have appeared they usually increase in severity after successive injections.

Types of Reaction

A study of the literature reveals that almost every type of allergic reaction has been observed in cases sensitive to liver therapy. The commonest reactions, in our experience, are

flushing, tachycardia, erythema, and localized urticaria. Reactions vary much in severity, from the mild features mentioned above to generalized urticaria, severe bronchospasm, vomiting, rigor, hyperpyrexia, severe nasal and ocular discharges, substernal pain, collapse, and angioneurotic oedema. One or more of these manifestations were present in each of our cases. Allergic manifestations not observed by us but reported by other workers include swelling of the lymph nodes, hemiplegia (Kaufman *et al.*, 1943), and repeated uterine haemorrhages (Gardner, 1938).^{*} Sensitivity may reach such an extreme degree that even the injection of 0.1 c.cm. of liver extract given intradermally for the purpose of making a skin test has brought about severe flushing, bronchospasm, and tachycardia in one of our cases.

Skin Tests

Opinion regarding the value of skin tests for assessing the presence and degree of sensitivity in allergic diseases is sharply divided. No less an authority than Rackemann (1943), in a paper dealing with the problems of allergy, concludes that "skin tests have lost some of their glamour." It is well recognized that a patient may give a positive skin reaction to pollen or to tuberculin and yet not be suffering from hay-fever or active tuberculosis. Similarly, patients who have been receiving liver extract are not infrequently positive to a skin test and yet show no reactions to parenteral liver therapy. This was found by us in 16 of 52 cases of pernicious anaemia. Conversely, it is known that skin tests may be negative in allergic conditions, and yet severe allergic reactions may occur to parenteral injection of the specific allergen. Thus Bullowa (1937) reported 8 fatal cases of anaphylaxis to antipneumococcal serum, in all of which previous skin tests for sensitivity were negative. In two of our cases with extremely severe allergic reactions skin tests were negative, later becoming positive in one case when urticaria developed as an additional feature to bronchospasm. Despite these limitations, our experience suggests that it is worth while doing skin tests, since we have found in the majority of cases that the degree of the skin reaction bears some relation to the severity of general sensitization and the reactions which result. Moreover, if general reactions follow the skin test it may be concluded that the patient is extremely sensitive.

Technique of Skin Tests

We inject intradermally 0.05 c.cm. of undiluted liver extract into the volar surface of the forearm just below the crease of the elbow-joint, with a saline control at the same level. We accept as a positive reaction a wheal of 15 mm. or more, developing in 15 to 30 minutes. Pseudopodial extensions from the wheal occur in practically all patients who are very sensitive. The size of the surrounding red areola is of little significance. Pache (1939) reported positive intradermal reactions to liver extract in a dilution of 1 in 1,000,000. As severe generalized reactions may occur to the skin-test dose of 0.05 c.cm., adrenaline should always be at hand in case of emergency.

Treatment

We have arbitrarily divided sensitive patients into two classes for treatment: (1) those with mild symptoms, and (2) those with severe constitutional reactions. It is permissible in mild cases to attempt to control the reactions by injecting three minims of 1 in 1,000 adrenaline hydrochloride concurrently with the liver preparation. In some cases this may be sufficient without any alterations or additions to treatment. In other cases satisfactory results may be obtained by reducing the quantity injected to one-half or one-quarter of the dose which produced a reaction and decreasing the periods between injections by a quarter or a half. Adrenaline may be given at the same time. After a few weeks on this treatment the dosage and the intervals between injections can be gradually increased to the desired maintenance levels.

The following measures have been recommended as adjuvants for the reduction of sensitivity, but proof of their value is wanting: (1) calcium orally and parenterally (Lasch, 1936; Gigante, 1939); (2) injections of parathyroid to raise the blood calcium (Lasch, 1936); (3) histamine in gradually increasing

doses to produce histamine refractoriness (Corelli, 1935); (4) histaminase, a supposed inactivator of histamine (Taylor and Hilger, 1941). The latter workers claimed that histaminase, given orally, not only prevented reactions but also reduced or abolished positive skin sensitivity, precipitin reactions, and passive transference of sensitivity. When the histaminase was discontinued, reactions and positive sensitivity to skin tests recurred. We have been unable to obtain histaminase to test the accuracy of these claims. It should be noted that Rackemann (1943), in a discussion of the value of histaminase in preventing allergic manifestations in general, states that its efficacy is doubtful.

Barfred (1942) claimed that the preparation of liver extract with butyl alcohol removed a considerable part of the factor causing allergic reactions. Accordingly we asked British Drug Houses Ltd. to supply us with a sample of anahaemin which had been extracted with butyl alcohol. The material was tested on two cases sensitive to anahaemin, and, in both, reactions occurred of a degree and a type similar to those produced by the standard anahaemin. In addition, when the butyl alcohol was evaporated and the residue dissolved in water its intradermal injection failed to give positive skin reactions in the two cases referred to above. Accordingly we are unable to confirm Barfred's claims.

Severe Cases

Patients who are suffering from dangerous allergic reactions must either replace parenteral liver therapy by oral ingestion of whole liver, liver extract, or hog-stomach preparations, or submit to desensitization. Desensitization has been recommended and carried out by Grün (1934); Krantz (1938), and Delikat (1943). Increasing doses of the liver extract were given subcutaneously or intramuscularly at intervals of days or weeks. The method which we have found satisfactory in 17 severe cases, including two desensitized by Dr. L. J. Davis, Lecturer in the Department of Medicine, is as follows:

The degree of sensitivity is assessed by the history of the severity of the generalized reactions and by the response of the skin and the patient to an intradermal test of 0.05 c.cm. of the liver extract to be used. If any generalized reaction occurs to this test, desensitization should be started with a smaller quantity of liver extract, such as 0.01 c.cm. In the great majority of cases 0.05 c.cm. was found to be a suitable initial dose. With the initial and all subsequent injections, 0.2 c.cm. of adrenaline hydrochloride (1 in 1,000) is given. The dose of liver extract is doubled every half-hour and the route of the injection is changed from the intradermal to the subcutaneous when the 0.4-c.cm. dose of extract has been reached, and to the intramuscular route at the 1-c.cm. dose. It is our experience that if a reaction is going to occur during desensitization it generally follows the 1-c.cm. dose. In this event the same dose is repeated in half an hour, and if no reaction occurs the dose is increased to 1.5 c.cm. and finally to 2 c.cm. of extract at half-hourly intervals. In the majority of cases desensitization is secured in three to five hours. Thereafter it is advisable to repeat the final dose (2 c.cm.) daily for three days without the addition of adrenaline. Weekly doses of 2 c.cm. are now given for six weeks, and finally maintenance therapy is continued by a single injection once every two, three, or four weeks. We advocate the daily and weekly injections mentioned above because we have found that there is a tendency for sensitivity to recur if the interval between the initial course of desensitization and the next injection is delayed for two weeks or longer. Although Kaufman *et al.* (1943) advise that the intervals between injections for maintenance treatment should not exceed one week, since otherwise sensitivity will recur, this has not been our experience, as we have at the present time 14 patients who have been desensitized and who have maintained a normal blood level for one to two years without a recurrence of sensitivity on an intramuscular injection of 2 c.cm. of anahaemin monthly. Attention has already been drawn to the frequency with which a history was obtained of sensitization occurring subsequent to breaks in the continuity of treatment. Accordingly it is essential that intervals between injections should on no account exceed four weeks.

Conclusion

We would advocate desensitization for patients allergic to liver extract rather than the alteration of treatment to the oral ingestion of liver or hog-stomach preparations, since it is generally agreed that parenteral therapy is cheaper and more effective than oral therapy. Desensitization is, however, a potentially dangerous procedure unless carried out under strict supervision by someone experienced in the danger of anaphy-

^{*} Since the preparation of this paper a case showing uterine bleeding as a manifestation of allergy to liver extracts has come under our care.

lactic reactions. This danger is greatly increased if the patient is seriously debilitated or is suffering from cardiovascular disease. A potent solution of adrenaline hydrochloride and a sterile syringe must always be at hand; and 0.5 c.cm. should be given immediately any signs of an allergic reaction occur.

Summary

The nature and frequency of reactions to parenteral liver therapy and the significance and technique of skin tests for sensitivity are discussed.

The successful desensitization of 15 cases with severe reactions is reported, with a description of the method employed.

We wish to express our thanks to those of our colleagues on the staff of the Royal Infirmary, Edinburgh, who have permitted us to investigate cases of sensitivity under their charge. One of us (J. G. M.) was in receipt of a Bursary in Medicine from the National University of Ireland during part of this investigation.

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EXPERIMENTAL TRAUMATIC SHOCK

BY

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The aetiology of traumatic shock still eludes final proof. All are agreed that a reduction of blood volume underlies the state of shock, but the mechanism whereby this reduction occurs is still obscure.

Traumatic shock has been investigated by clinicians and experimentalists, and many important facts have been established. There is, however, a fatal tendency to mix indiscriminately the facts of clinical shock with the facts of experimental shock, and a tendency to mix deductions from one type of experimental shock with shock produced by quite unrelated means. As a result of loose inference the problem of shock is to-day more difficult than it has ever been, and as much time must be spent in "debunking" the literature as in tackling the facts of the problem itself. Before the gaps between the various aspects and manifestations of shock can be bridged by a single theory the truth of each aspect must be firmly established. It is the purpose of this paper to concentrate exclusively on experimental traumatic shock produced by mechanical trauma to a limb.

Despite the fact that experimental traumatic shock might be considered a threadbare field for research, there is no unanimous answer to the question, "Why does an animal under anaesthesia pass into shock when severe mechanical trauma is applied to the limb muscles?" This problem is purposely kept within narrow and artificial limits. Until the complete answer is known it is fatal to make analogies with the causes of shock after burns, of surgical shock in the presence of superadded disease, or of the complex mixture of oligæmic, neurogenic, psychogenic, and metabolic factors which contribute to the state of shock in the wounded soldier.

An attempt is made here to present an old experiment in a new light, and to emphasize the need to regard this artificial

problem as one which should be capable of complete experimental proof; then, and then only, can it be viewed in relation to the problem of shock in general.

The History of Traumatic Shock

Traumatic shock first aroused interest during the war of 1914-18 by the fact that it often supervened some time after the patient was wounded and after a mysterious latent interval during which he appeared quite normal. It was the nature of this latent interval which focused attention on shock. It was this which gave rise to the clinical entities described as "primary" and "secondary" shock.

By what was no more than a remarkable coincidence physiologists, notably Dale and Laidlaw (1918) and Dale and Richards (1918), were interested at this time in the pharmacological reactions of the comparatively new substance histamine, which seemed likely to open up new vistas in physiology. In a hurried piece of research undertaken during the war, when a solution was urgently needed, Cannon and Bayliss (1919) appeared to establish as a fact that so-called "secondary" shock was due to the action of a tissue toxin akin to histamine.

About ten years later Blalock (1930, 1934) started to publish the results of further investigations on the Cannon-Bayliss experiment, undertaken with a degree of patience probably unequalled in the history of experimental surgery. He failed entirely to find any toxic cause for shock, and produced many reasons explaining the death of the Cannon-Bayliss animal as the result of local fluid loss at the site of trauma. But many of the forms of shock encountered in clinical practice—i.e., after surgical operations, after head injuries, burns, etc.—seemed so obviously unrelated to haemorrhage that there was a tendency to reject Blalock's theories even for the conditions of his own experiments. This refusal to believe led to a determination to find some other explanation with a dangerous over-elaboration of experimental technique.

As regards the toxæmic theory of shock few new facts have emerged. The capillary phenomena following toxæmia produced by the introduction of crushed muscle into the peritoneum have been extensively studied by Moon (1938) and his collaborators, though it is doubtful whether this bears any relation to the conditions of the original Cannon-Bayliss experiment. Practically all recent variations of this latter classical experiment—notably the dialysis experiment of O'Shaughnessy and Slome—have failed to reveal any toxic substance in the blood stream.

There remained only the nervous pathway for secondary shock, and O'Shaughnessy and Slome (1935) believed that they were able to demonstrate such a condition in the absence of blood loss and toxæmia. It is to be noted in this connexion that at the time when Cannon and Bayliss did their original experiment neurogenic factors were in the public mind one of the most likely causes of delayed shock. But these workers, and later Blalock in a more extensive research, were entirely satisfied that this very obvious source was not a cause of experimental traumatic shock. It was only after excluding this possibility that there was any justification for assuming a toxic theory of shock. The experiments of O'Shaughnessy and Slome were extremely elaborate, and there could be but little surprise that shock resulted.

Finally, clinical experience now casts doubt upon the existence of "secondary" shock as a clear-cut entity. Modern battle and air-raid casualties tend to be shocked progressively from the time of reception of the wound. It is the exception rather than the rule for a patient to appear initially quite fit and later to pass into a state of shock for no apparent reason. The disappearance of the mysterious latent interval removes the original condition for which toxic theories were first invoked. The latent interval seen in 1914-18 might have been due to exposure to wet and cold for many hours after wounding—a state of affairs not commonly seen in this war, but one often commented on in the Special Reports of the Medical Research Council of 1917-18.

Cannon and Bayliss (1919) established as a definite fact that shock did not result if the femoral artery and vein were ligated before applying trauma to the thigh. This fact has never been questioned since, and Blalock carried the experiment a little