REFRESHER COURSE FOR GENERAL PRACTITIONERS

SERUM REACTIONS AND SERUM SENSITIVITY TESTS

BY

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The present low incidence of diphtheria, the mildness of scarlet fever, and the increasing use of sulphonamides and antibiotics in the treatment of acute infections have all combined to reduce the number of patients treated with serum. Many practitioners in consequence have little or no experience in the use of serum, and are unfamiliar with the manifestations of serum allergy. Furthermore, the diversity in the advice given by various authors on the performance and interpretation of the different types of serum "sensitivity tests" has produced much confusion. In order to illustrate this point the following have been abstracted from authoritative publications.

Harries and Mitman.¹—"Sensitivity is revealed by an intradermal or ophthalmic test. . . . Unfortunately [tests for hypersensitivity to serum] are not reliable . . . there is no exact parallelism between dermal and general (constitutional) hypersensitivity." Nevertheless, full descriptions are given. The intradermal test for hypersensitivity ("the one regarded as most reliable") is discussed in detail. "The ophthalmic or conjunctival test is less sensitive," and "some regard it as inaccurate and dangerous. The scratch test is the safest." In desensitization, or, more correctly, hyposensitization, "clinical practice consists in injecting very small graduated doses of the serum." The intradermal route is advised in testing subjects with a history of previous administration of serum. It is also discussed as a first stage in the special precautions for asthmatics.

Joe.²—"Cases which give a history of previous serum administration should have a preliminary injection of 0.5 ml. of the therapeutic serum subcutaneously. If no reaction occurs within half an hour, then the full therapeutic dose should be given by the appropriate route. . . . In cases which present a history of asthma or allied conditions, or of reaction to previous serum administration, the procedure is more elaborate." Methods of giving doses of diluted serum subcutaneously are described. "When the reaction becomes minimal, a small dose should be given intramuscularly, before administering the remainder by this route. . . . To prevent anaphylactic accidents . . . intracutaneous injections or conjunctival instillations of diluted serum" have been used "for the detection of hypersensitive individuals." They are "uncertain guides, and it is doubtful if at present their routine application has any practical advantage."

Ratner.³—"In determining serum hypersensitivity the scratch test with 'concentrated liquid serum may give a dependable reaction. . . . The intracutaneous test is reliable.' The ophthalmic or conjunctival test is 'valuable.' 'We may briefly summarize the procedure preliminary to serum administration as follows: (a) Detailed history. (b) Intracutaneous test. (c) Ophthalmic test.' (d) If the decision is to administer serum, inject a few minims intravenously or subcutaneously before proceeding with the full amount." There is a long discussion about the difficulties and defects of the skin tests, but it is noteworthy that neither the intracutaneous nor the ophthalmic test is dismissed summarily as not worth performing.

Queries and Minor Notes.⁴—"While the skin test technique has minimized the incidence of acute reactions, 'its limitations in

avoiding delayed serum sensitivity are recognized." Reference to the foregoing publication by Ratner is then recommended at the end of the note.

Banks.⁵—"If serum is essential . . . in cases of asthma or infantile eczema . . . commence with a dose of 0.1 ml. of 1:100 dilution subcutaneously and proceed with three doses, each increased tenfold over its predecessor, subcutaneously every half-hour. . . . In minor allergic conditions . . . give one injection of 0.25 ml. as a trial dose subcutaneously and then wait two hours. This is a test for general sensitivity; if there is no general reaction in that time the full dose may be given intramuscularly. Intradermal and conjunctival sensitivity tests are unreliable as test of general sensitivity both in a positive and negative sense."

Parish.⁶—"In view of the unreliability of the intradermal and conjunctival reactions, 'the safest course is to give a small dose, for example, 0.1 or 0.5 ml. of a 1:10 dilution of serum in sterile saline, by the same route as that which is chosen for the main dose. If no disturbing symptoms appear within half an hour the main injection may then be given very slowly.'"

Cruickshank.⁷—"Before giving an injection of antiserum . . . the doctor should inquire about a personal history of asthma or hay-fever, particularly from contact with horses, or any family or personal history of allergic disorders. If in doubt an intradermal injection of 0.1 ml. of the serum diluted 1:100 should be given; this will produce a local wheal and erythema reaction in a sensitized person, who may then be partially and temporarily desensitized by repeated small injections of the serum."

It is thus hardly surprising that some doctors take no precautions at all, whereas others perform some form of sensitivity test in cases selected on the basis of the answers to a few stock questions; a few practitioners are unduly cautious and tend to overdo the preliminary testing, even performing tests (such as the intradermal or conjunctival) that are of little practical value as guides to general sensitivity.

The purpose of this article is to endeavour to dispel some of the existing confusion about so-called sensitivity tests. We shall seek to differentiate between (a) testing for local serum hypersensitivity—namely, the intradermal injections, conjunctival instillations, scratch tests, etc., with diluted or undiluted serum which are made shortly before the parenteral injection of a main or larger dose of serum; and (b) the trial or test doses (used in testing for general reaction)—namely, small amounts of serum given subcutaneously or intramuscularly before the administration of larger doses.

In assessing the risks of serum therapy it will be remembered that the complications are infrequent. Serum rashes of all types, often mild and unimportant, have a case incidence of about 5%; and fatal anaphylaxis occurs, according to various authorities, perhaps once in 50,000 to 200,000 administrations of serum. The incidence of serum anaphylaxis may not have been appreciably affected by modern processing, whereas that of serum sickness has been progressively reduced. The latter used to be 40 to 60% with native (crude or unconcentrated) serum; the introduction of ammonium or sodium sulphate concentration reduced it to 20 to 30%, and enzyme treatment or refining reduced it still further to about 5%. The rashes seen nowadays are almost invariably mild and transient, but cannot be entirely eliminated, as the refined product is still a foreign protein preparation to which some persons have become sensitized either naturally or by some artificial means, such as previous injections of serum.

¹ Harries, E. H. R., and Mitman, M., *Clinical Practice in Infectious Diseases*, 1951, 4th ed., pp. 35, 43, 47. Livingstone, Edinburgh.

² Joe, A., *The Acute Infectious Fevers*, 1947, p. 266. Churchill, London.

³ Ratner, B., *Allergy, Anaphylaxis and Immunotherapy*, 1943, pp. 472, 481. Williams and Wilkins Co., Baltimore.

⁴ Queries and Minor Notes, *J. Amer. med. Ass.*, 1951, 147, 1090.

⁵ Banks, H. S., *The Common Infectious Diseases*, 1949, p. 75. Arnold, London.

⁶ Parish, H. J., *Bacterial and Virus Diseases*, 1951, 2nd ed., pp. 21, 88. Livingstone, Edinburgh.

⁷ Cruickshank, R., *British Medical Journal*, 1952, 1, 212.

Types of Reaction

The following is a short and simplified classification of the reactions which may follow the parenteral administration of serum.

Severe Anaphylactic Shock.—This is an immediate reaction attended with fall in blood pressure (as shown by an imperceptible or very low-tension pulse), dyspnoea, and loss of consciousness, with or without rash or oedema. It comes on typically in a few minutes, or more gradually, and with less intensity from half an hour to two hours after the injection. It may prove fatal if not adequately treated.

Serum Sickness.—This is a syndrome made up of pyrexia, urticaria and other rashes, oedema of the tissues, and joint pains. It occurs in two forms, the common (so-called *delayed*) serum sickness after an interval of seven to twelve days, and the *accelerated* serum sickness after three to four days. (This second form is typically seen in persons who have had a previous serum injection.)

Local Hypersensitivity or Local Anaphylaxis Analogous to the Arthus Phenomenon in Animals.—Marked swelling and induration occur, and, later, sloughing of the skin and subcutaneous tissues, and even of the muscular tissues. The reaction is often the result of faulty management. It is apt to develop when repeated serum injections are being given, particularly when an injection is given while the patient is already suffering from serum sickness due to a previous injection. More than one dose need not be given at the same site, as was formerly believed.

Thermal Reaction.—There is sudden pyrexia with a severe chill or rigor. This is not due to serum hypersensitivity and occurs mostly after intravenous injection. It is probably caused by pyrogens produced by certain dead bacteria in the processing of certain batches of serum or in various solutions for injection. (The batch numbers, which should always be recorded whenever serum is injected, should be mentioned in a report to the manufacturers, who should be invited to comment on experiences elsewhere.)

The rarer forms of serum reactions such as radiculitis and neuritis are not considered here.

Treatment of Serum Reactions

In the treatment of *anaphylactic shock* (as distinct from prevention, which is discussed later) adrenaline (0.5 to 1 ml. of 1:1,000 solution) should be given at once intramuscularly, and repeated if recovery is not rapid. (If delay is to be avoided—and this point is all-important—a syringe and adrenaline should always be at hand before injections are given). Antihistamine drugs given by intramuscular injection in full doses are also very useful, and are clearly indicated if urticaria or oedema develops. The patient should be kept recumbent, with the head low, and warmed with hot-water bottles and blankets, or by an electric blanket if one is available.

The treatment of *serum sickness* includes good nursing, soothing lotions, such as calamine to the skin, and antihistamine drugs by mouth for one to three days, or, in the more serious cases, by injection. Cortisone has recently been recommended.

Thermal reactions subside in 15 to 20 minutes. The patient should be kept warm until the disturbance is over, and should be given an injection of adrenaline if his pulse flags.

Avoidance of Anaphylaxis

This is the outstanding and fundamental problem. While anaphylaxis may occur in patients who have been injected previously with serum, it is observed more often in those who are intensely sensitive to horse serum and who are being injected for the first time. Many of these patients give a history of asthma or infantile eczema, or, more rarely, some other allergic manifestation, hereditary or acquired. In addition to these two categories, "accidents" have occurred quite unexpectedly in some rare cases with no history of either previous serum administration or allergic diathesis.

The degree of the shock varies directly with both the dose of serum and the rate of absorption into the general circulation, two important points which give a clue to the methods of prevention and control described below.

Sensitivity Tests

Intradermal Tests.—The use of intradermal tests for hypersensitivity of the skin is based on the assumption that the degree of general or constitutional sensitivity can be inferred from the results: this assumption is often quite unsound. It is important that this should be appreciated, for the method is widely used. A usual test is the intradermal injection of 0.2 ml. of a 1:10 or 1:100 dilution of normal horse serum or of the serum to be administered. Sometimes even undiluted serum is used, either as the first dose or as a final intradermal check of safety, before the injection of the main dose by some other route. A large local wheal or redness over a wide area, with some swelling, is sometimes an indication of allergy. But it is useful to recall that any local trauma may produce wheals in some subjects—for example, in dermatographia. Injections of quite innocuous substances may also produce reactions of various kinds. It is therefore not surprising that many experienced clinicians have found the intradermal method unreliable, and have ceased to recommend it. The real value of any test is best estimated by practical experience; by this criterion intradermal testing for sensitivity fails in a high proportion of cases. Some patients have reacted locally to the preliminary test without giving any sign of a general reaction either to a trial or test dose or to the subsequent full dose. On the other hand, patients who showed no local reaction have occasionally developed violent general allergic reactions to the main injection: some have even died, and an attempt has then been made to blame the serum instead of the faulty procedure adopted.

One of us (H. J. P.) has often received letters reporting that undiluted serum, which is still sometimes given intradermally or subcutaneously for sensitivity tests, had caused *local* reaction which led to the withholding of ordinary doses of serum for prophylactic or therapeutic purposes. This matter deserves further consideration, for not only doctors but also their patients have been misled and have refused injections which might well have been life-saving. Apart from the vagueness of some local reactions that are due to trauma, certain flushes observed even when serum is given superficially by the subcutaneous route may be due solely to a cresolic preservative.

Ophthalmic or Conjunctival Tests.—The instillation of a drop of serum, usually diluted 1:10, has been abandoned for several years by most people—but not by all—as a test for general hypersensitivity. Injection of the vessels, itching, and lacrimation are said to constitute a positive reaction. Like the intradermal test, the ophthalmic test is misleading as an indication of general sensitivity. A further disadvantage is the occasional occurrence of severe and dangerous local reaction, sometimes involving swelling of the eyeball and considerable pain.

Scratch Test.—This test is also unreliable, and is of only historical interest. The usual technique was to place on the skin a small drop of serum, or of equal parts of serum and glycerin, and to scratch through the drop with a Hagedorn or other needle. A positive reaction was erythema or an urticarial wheal developing within 30 minutes. This crude method permitted great irregularities in the amount of serum absorbed from the scarified area. When a scratch was made through a drop of 50% glycerin on a second area as a control the accuracy of the test was not materially improved, in spite of the over-confidence of many users.

Trial Doses.—These are preliminary subcutaneous injections of small doses (0.1 ml., or preferably 0.2 ml., of serum or of a serum dilution) which are not given with the purpose of observing a local reaction of any kind. They are meant to be absorbed slowly into the general circulation. We prefer to call them "trial doses" rather than "sensitivity tests" or "desensitizing doses." The conception that a patient can be "desensitized" by numerous graduated injections, either intradermal or subcutaneous, at short intervals, without causing a reaction is probably illusory and in practice probably impossible. The absence of reaction

to any dilution or dose probably means that the patient was never hypersensitive. With the method of preliminary small subcutaneous injections, the patient's *general reaction* to a small dose of serum is first tried before he is given a large dose. The essence of the procedure is to introduce the serum into the general circulation slowly, in small amount, so that should an anaphylactic shock develop it would be almost certainly mild and respond rapidly to the usual therapeutic measures. The method is rational and is not based on any local tissue reaction which may or may not be significant. It has been extensively used by one of us (L. J. M. L.) for over 25 years in daily practice, and also by many colleagues and others. We have found it valuable and safe. It is the method we recommend in cases of suspected serum allergy.

Recommended Procedure

In the ordinary straightforward case two questions must be asked: (1) Has the patient had serum before? and (2) Has he suffered from asthma or infantile eczema? The answer to the second question may be supplemented by further inquiries about other allergic manifestations, hereditary or acquired.

If the answers are negative the required dose of serum may be given intramuscularly for prophylaxis or treatment. (The intravenous route is discussed below.) The patient must be kept under observation for half an hour. If no untoward effects are noted within this period it can be assumed that nothing dangerous will subsequently develop.

If he is sent home the fact should be mentioned that in a few instances some local or general rash may develop, usually seven to ten days after injection. The doctor should ask to be informed of this or any other unusual event. If the patient or his relatives are not forewarned of the possibility of a delayed serum reaction there may be undue alarm in the household and serum may come into some disrepute. We know of instances where permission for the use of tetanus antitoxin has been refused for other patients, in view of the publicity accorded to a generalized serum rash which had developed in a friend or neighbour and about which the doctor knew nothing.

If there is a history of a previous injection of serum, a small trial dose (0.2 ml.) of undiluted serum is injected subcutaneously. A volume of 0.1 ml. is sometimes recommended for this purpose, but is rather small for most syringes in general use to-day. The doctor must keep the patient under observation for half an hour; if no general symptoms develop, the full dose of serum may then be given intramuscularly as required for prophylaxis or treatment. Once again observation for half an hour is necessary. If the patient is sent home at the end of that time he should be warned about the possibility of an accelerated serum reaction, with the appearance of rashes, in about three to four days.

If there is a history of allergic asthma or infantile eczema this will necessarily start a train of other questions, in order to ascertain the severity and frequency of the attacks and their relationship to other forms of allergy in the patient or his family. (From 50 to 70% of allergic patients have an allergic family history.) There may be difficulties in obtaining an accurate history, but the attempt should be made to get an impression of the patient's allergic background. In general, most attention will be paid to asthma in the older subject and to infantile eczema; Britton has pointed out that allergic eczema is commoner below the age of 5 years, and that after this age eczema tends to be replaced by asthma. Of the other allergic disorders, hay-fever, food idiosyncrasies, and eczema other than infantile are much less important, since they are rarely associated with a dangerous degree of sensitivity.

Ideally, asthmatic patients and those with infantile eczema should not receive serum at all, as the risk of anaphylactic shock is considerable. In the case of asthmatics, active immunization with diphtheria and tetanus toxoids is particularly important, in order to obviate the emergency use of any

serum. Experience has shown that injection of these prophylactics is rarely associated with untoward reactions in young subjects of allergic diathesis.

If it is necessary, in view of the gravity of the infection, to give serum to asthmatic or eczematous children, the method of the small trial dose, with slow absorption, is absolutely essential. The subcutaneous route of injection is preferred to the intramuscular, the slower absorption from the subcutaneous site and the more superficial location of the serum being obvious advantages. The following scheme of injections is suggested for these cases: (a) Give 0.2 ml. of a 1:10 dilution of serum subcutaneously. (b) Keep the patient under close observation for half an hour. (c) If there is no general reaction, give 0.2 ml. of undiluted serum subcutaneously. (d) Once again observe the patient for evidence of general sensitivity for half an hour. If there is no general reaction within half an hour the patient will not subsequently develop really severe anaphylaxis. (e) If there is no general reaction, give intramuscularly the full dose of serum required for prophylaxis or treatment. (f) Once again keep the patient under close observation for half an hour. (g) If he is being sent home he should be warned of the possibility of delayed serum sickness.

In cases of doubtful asthma or allergic diathesis the scheme of injection will depend on the urgency of the illness. If the treatment is not urgent the doctor may proceed as for a known asthmatic. If it is urgent he should follow the method advised for those with a history of a previous injection of serum.

Finally, the question arises whether serum can be given with safety after anaphylaxis has occurred. Fortunately there is seldom any difficulty, provided the doctor waits till the blood pressure is normal and rashes (if any) have subsided after dosage with an antihistamine drug. This should take up to six hours. The trial dose is then repeated, and if there is no reaction after half an hour the full dose may be given.

Intravenous Injection of Serum

The intravenous route of administration merits separate discussion. Although this is by far the most dangerous route for allergic subjects, it may be invaluable for therapeutic purposes, since it ensures that the highest possible concentration of the serum should be immediately available. It saves much time in dealing with an acute infection which may have had all too long a start.

Before the intravenous route is used the preliminary procedures described above for an intramuscular injection should always be carried out. It is neither wise nor safe to give an intravenous injection of serum (whatever the result of the skin-sensitivity test) as a first step in treatment and without a preliminary intramuscular injection that has been tolerated by the patient. Ideally, two hours should elapse between the intramuscular injection and the intravenous injection. In cases of great urgency, however, as in severe diphtheria or tetanus, this interval can and should be shortened, with only a slight risk, but never to less than half an hour. There is no case so urgent that any further reduction of this period would make all the difference in the outcome of the infection. The time of waiting is not wasted; it allows the patient to recover from his journey, and his attendant to get ready the syringe, adrenaline (which should have been available from the start of serum therapy), blankets, hot-water bottles, etc. The delay also allows time for the serum taken straight from the refrigerator to warm up to room temperature; it is not a good plan to warm it in hot water. The doctor should give the injection very slowly, preferably through as fine a needle as possible, and he should be prepared to stop the injection at once if there is any sign of distress. The patient must always be recumbent for the injection and for at least one hour afterwards.

We would reiterate that the trial dose with slow absorption is the main safeguard against dangerous anaphylactic reactions. It may be likened to putting a person first in shallow water to know whether he can swim. When it is

discovered that he can, then only is he plunged into deep water. Serum anaphylaxis can be fatal on rare occasions, but the experienced clinician will generally save his patient. On the other hand, serum sickness may be a troublesome but never a dangerous disease, and there are no fatalities except from ill-conceived treatment.

Conclusion

Whenever serum is injected, whatever the route, the patient should be kept under observation for at least 30 minutes afterwards, with a syringe and adrenaline 1 : 1,000 ready for emergency use.

Intradermal, conjunctival, and scratch tests for the detection of serum sensitivity are unreliable. The small "trial dose," given subcutaneously, is preferable, and should be used in all patients with a previous history of serum injections or allergic conditions.

Serum should never be given intravenously unless a preliminary intramuscular injection has been tolerated and all preparations have been made beforehand for treating shock.

Next Refresher Course Article.—"Clinical Effects of Exposure to Heat and Sunlight," by Professor B. G. Maegraith.

THE PROBLEM OF THE AGED SICK AS SEEN BY THE GENERAL PRACTITIONER*

BY

MORTIMER O'SULLIVAN, M.B., B.Ch.

From the general practitioner's point of view the aged sick are usually those persons who require more or less constant medical supervision and a considerable amount of personal attention. They are mostly visited in their homes, but those who can, even with an effort, attend during surgery hours are encouraged to do so. For the general practitioner there is no clear dividing line between the chronic sick proper and the aged infirm. This classification is of importance to us only when the question arises of removing them from their homes. Before and after they should become the responsibility of either the hospital or the local health authority the general practitioner has usually to look after them for a considerable time.

Speaking as a middle-aged general practitioner, one is thankful that all the aged do not come under one or the other category. Most of the over-seventies are hale and hearty. But when a doctor has worked in the same district for a number of years his patients grow up with him, with the result that the older he gets the more aged sick he has to look after.

In the last quarter of a century the face of medicine has changed. Osler's remark that "pneumonia is the friend of the aged" is no longer true. Since the advent of the antibiotics the chance of death from natural causes has decreased, and at the same time the improvement in anaesthesia and surgery has greatly reduced the risks of operation.

Types of Aged Sick Encountered

As is to be expected, most of the aged sick are suffering from some degenerative process. In my present list of

chronic cases I find the majority to be those of cerebral arteriosclerosis or of encephalopathy—patients with severe headaches, mental degeneration, irritability, retinal haemorrhages, senile cataract, transient paralysis, and a condition which, to me, seems to be on the increase, vertigo. The next largest group may be classified as coronary arteriosclerosis and hypertensive failure: this class varies from the impaired myocardium as the result of coronary thrombosis to the senile cardiac asthmatic. Next there are the arthritics—the chronic cases of rheumatoid arthritis and of osteoarthritis, both making their victims house-fast. Cases of chronic bronchitis and of pulmonary heart disease breaking down several times a year are always present. I have four cases of hemiplegia, three of disseminated sclerosis, two of paralysis agitans, and four of other forms of paralysis. There are five cases of inoperable carcinoma, four cases of chronic tuberculosis which require visiting, two cases of heart failure from rheumatic disease, one case of pituitary tumour, and one man with senile prostate who refuses operation and has had to be trained to catheterize himself, with all its attendant sequelae and complications. There are two mental cases, both women, who in spite of their delusions (they have been in hospital many times) make a laudable effort to run their homes but are always a worry. There are two cases of hysteria, in both of which one can produce a hemianaesthesia at will. I find that hysteria in the aged is a not uncommon symptom. Finally there are five senile cases, all over 90, with nothing much wrong except that they are physically and mentally enfeebled.

Reasons for the Problem

Perhaps Job was the first recorded case of a chronic sick person. Certainly there have always been aged sick. The problem has become acute (mainly in the urban areas), principally for the following reasons.

1. *People Live Longer.*—If you survive long enough you are almost certain to get on a chronic sick list. About ten years ago I assisted at an operation for the local removal of a carcinomatous breast in a woman of 96. The operation was necessary because the growth had begun to fungate. The patient survived for four years.

2. *Absence of the "Handy Woman."*—A generation ago there were in each of the poorer streets of a district one or two of this type of female. They attended at the time of birth, carrying pails of hot water. They would sit at night with a sick person. The more efficient gave an enema if required, and they finally did the washing and laying out after death. Very many of them were retired "gamps," and, although neither home helps nor nurses, combined the duties of both.

3. *Housing.*—The housing situation to-day reflects directly on the young and indirectly on the old. Gone are the days when the family had means and accommodation to care for aged relatives and servants past the age of service. Few young couples lucky enough to have a house are now able to start married life without having an aged relative thrust on them. As children come along there is no longer enough accommodation for them all; domestic friction arises, and so begins the trail of events which leads to the demand for hospital beds.

4. *Tendency to Avoid Responsibility.*—Because weekly contributions are paid to the State there is a feeling that it is the duty of the State to nurture and nurse, and that the care of the aged is no longer the responsibility of the family.

Home Treatment

I would like here to emphasize—and I think that most general practitioners would agree—that any service dealing with the aged should be so designed as to make it easier

*A paper read to the Middlesex Medical Society at the West Middlesex Hospital, Isleworth, June 14, 1951.