EMERGENCIES IN GENERAL PRACTICE

SERUM AND ANAPHYLACTIC REACTIONS

BY

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Almost any protein material or organic compound, by combining with body proteins, may produce severe allergic reactions. Although the use of serum and consequently the reactions from serum have been considerably reduced, these reactions still occur, and new treatments have brought new hazards. There are no more distressing emergencies than those which result from one's own treatment; their avoidance is most desirable, while their prompt recognition and treatment are essential.

It is not the purpose of this paper to discuss reactions to those substances which are used only occasionally and which only very exceptionally cause reactions, but rather to those substances which the practitioner may well use often in the course of his work. Nor is the value, or otherwise, of serum sensitivity tests dealt with, as this subject was fully discussed by Laurent and Parish in a previous refresher course series.*

There are three main types of reactions: local reactions, anaphylactic reactions, and serum sickness.

Local Reactions

An area of local redness at the site of injection of an allergenic substance is not unusual and therefore gives rise to no concern, but when such reactions are large the gap between a local and a general reaction is being narrowed, and this must be remembered if further similar injections have to be given.

Anaphylactic Reactions

Anaphylactic reactions always come on soon after the injection of the allergen, sometimes immediately, and the earlier the reaction the more likely is it to be severe and dangerous. A reaction occurring within a few minutes of the injection will be severe, and possibly fatal, while a reaction occurring after thirty minutes to an hour, although it may be quite troublesome, is rarely, if ever, dangerous.

The earliest symptoms of severe and dangerous anaphylactic reactions may be sweating, a feeling of heat throughout the body, a generalized pruritus, or an urticarial rash rapidly becoming generalized; an irritating cough, dyspnoea and wheeziness, a choking sensation, substernal oppression, or a feeling of constriction in the chest; retching or vomiting with cramp-like pains in the abdomen, sometimes diarrhoea, occasionally severe abdominal distension; and/or headache, giddiness, or sudden unconsciousness, in some cases followed by convulsions; while acute circulatory collapse and death may occur rapidly. The pulse is at first of good volume, slow and bounding, but in the dangerously ill patient it becomes rapid, weak, and thready, and there is a marked fall in blood pressure.

Serum Sickness

In serum sickness the symptoms occur only after a definite incubation period, usually six to twelve days, commonly ten days. Symptoms may be mild or severe. They consist of fever, skin eruptions, glandular enlargement, and arthritis, often in this order. The fever ranges from 99 to 104° F. (37.2 to 40° C.). Skin eruptions are the commonest manifestation, the large majority being urticarial weals or, in the

severer cases, angioneurotic oedema. A morbilliform type of rash is also fairly common, and different parts of the body may present different appearances at the same time. The scarlatiniform type of rash occurs infrequently. When generalized angioneurotic oedema occurs the urine may contain albumin, but rarely blood. The presence of albumin need not cause undue concern, for after the serum disease has subsided the albumin disappears.

When severe pains in the joints occur it is almost always towards the end of the illness, and although these are a fresh and sometimes frightening addition to the patient's symptoms they usually herald the last phase, when the acute stage is nearing its end. In the more severe reactions there may be difficulty in swallowing and a feeling of a heavy lump behind the sternum, while cramp-like abdominal pains, with or without diarrhoea or vomiting or both, are also not uncommon and may last for several days.

Stiffness of the joints, especially after use, and an urticarial type of skin reaction after pressure may persist for weeks and sometimes for many months. One of my own patients, six months after his penicillin reaction, still developed pain and swelling of the feet and ankles after a brisk walk, and was unable to use his hands for heavy manual work.

Neurological complications are rare but of special interest. The commonest is an affection of the brachial plexus or part of the brachial plexus, resulting in a scapulo-humeral paralysis. The patient often complains of neuritic pains in the shoulder regions, and these are followed fairly rapidly by a flaccid paralysis with the usual tenderness and hyperaesthesia. Recovery usually occurs within six months.

Treatment of Anaphylactic Reactions

Before any therapy by injection is given, adrenaline should be near at hand; before any potent antigenic substance is used, adrenaline, intravenous aminophylline, and an intravenous antihistaminic, together with the necessary syringes, should be made instantly available. Immediately reaction occurs 5 to 10 minims (0.3 to 0.6 ml.) of adrenaline (1:1,000) should be injected subcutaneously. If practicable, a tourniquet should be applied above the site of the sensitizing injection, where a further 3 to 5 minims (0.2 to 0.3 ml.) of adrenaline should be injected. The dosage of adrenaline varies according to the severity of the reaction, and frequent doses may be necessary. In worsening cases the dose should be repeated in ten minutes or so and local massage used to help to expedite absorption. Intravenous adrenaline in a strength of 1:1,000 is contraindicated because of its danger.

In those cases not responding to adrenaline intravenous aminophylline and/or an intravenous antihistamine should be given. The intravenous aminophylline (0.48 g. in 20 ml.) should be given slowly over five to ten minutes. I have several times had most satisfactory results with this therapy. Intravenous antihistaminics—diphenhydramine hydrochloride, 50 mg., or promethazine hydrochloride, 25 to 50 mg.—must also be given very slowly. If intravenous therapy is impracticable intramuscular therapy with an antihistaminic (dosage and solutions are the same as for intravenous therapy) and/or aminophylline (0.5 g. in 2 ml.) is advisable.

Treatment of Serum Sickness

Antihistaminics and ephedrine, $\frac{1}{2}$ gr. (32 mg.) three times a day or as required, are the drugs most commonly used.

*British Medical Journal, 1952, 1, 1294.

In patients confined to bed the hypnotic effect of diphenhydramine hydrochloride, 25 mg. three or four times a day, or promethazine hydrochloride, 25 to 50 mg. at night with 10 mg. once or twice a day, is helpful; in severe cases larger doses, 50 mg. up to six times in twenty-four hours of the former or 50 to 75 mg. at night with 25 mg. once or twice a day of the latter, may be indicated. For those who are ambulant antihistaminics causing drowsiness might be reserved for use at night. During the day chlorcyclizine hydrochloride, 50 mg., or phenindamine, 25 mg., may be given as required.

In severe and persistent cases which do not respond to the above measures, corticotrophin (A.C.T.H. gel) 60–80 units or cortisone 25–50 mg. six-hourly may well be indicated and are very effective. Intravenous hydrocortisone gives promise of being the most rapid form of hormonal therapy. Before considering corticotrophin or cortisone it is well to exclude the presence of a contraindication, especially a history of gastric or duodenal ulcer or of tuberculosis.

Immunization to Tetanus

In the same way as diphtheria has been reduced to a rare disease by active immunization, so can tetanus be reduced. Certainly all allergic individuals should be given tetanus toxoid, which carries for them no special risk. L. Unger gives each of his patients a card to carry with them certifying that he or she is highly allergic and has received tetanus toxoid. "In case of injury," it reads, "*do not give tetanus antitoxin*; please inject instead 0.5 ml. of tetanus toxoid."

Administration of Horse Serum

Before serum is given inquiry must be made of any previous serum therapy, of any known sensitivity to horse-dander or horse serum, and of any personal or family history of asthma, infantile eczema, hay-fever, urticaria, or food or drug allergies.

When there is a negative history intramuscular serum is, for all practical purposes, safe, but observation for half an hour afterwards is always advisable. If there has been previous serum therapy a trial dose of 0.2 ml. of the serum is given half an hour before the full intramuscular dose.

Ideally, allergic subjects should not receive serum, but when necessary those without special sensitivity to serum or horse-dander should be given 0.2 ml. of the serum diluted one in ten subcutaneously, followed in half an hour by 0.2 ml. of the undiluted serum, followed in a further half an hour by the full dose and the usual post-injection observation. Never give intravenous serum before intramuscular serum has been tried—the interval between the two is ideally two hours. (The above is essentially an abstract from the article by Laurent and Parish.)

When there is a history of previous serum and horse-dander sensitivity, preliminary testing should be with 0.05 ml. of 1:20 serum subcutaneously with a few minims of adrenaline followed by half-hourly injections of small but increasing doses of serum (0.1, 0.2, 0.5, 1, 2, and 4 ml., until the total amount has been given) either with a few minims of adrenaline with each dose or with adrenaline every hour or as necessary.

Skin Testing and Hyposensitization of Allergic Patients

Severe anaphylactic reactions from skin testing do occur, especially in the highly allergic individual. It is therefore advisable to carry out skin tests by the prick method before doing any intracutaneous tests.

If a known allergen can be avoided hyposensitization should only rarely be advised. Hyposensitization is widely practised for hay-fever and with other inhalant allergens causing asthma. The initial dose should be one-tenth of that which just produces a definite positive intracutaneous reaction.

The injections are given subcutaneously, usually every few days or weekly. If any constitutional reactions occur, subsequent dosage must obviously be considerably reduced

and great care taken in subsequent increases. It is also important that any local reaction should be looked for and reported to the doctor before the next injection is given. If there is a local reaction the size of half a crown or more the next dose should be reduced to that which produced no reaction previously and subsequent increases in dosage made more gradually. The patient should be asked if he has a cold or sore throat or any other illness, for the presence of influenza or sore throat or other infection reduces the patient's tolerance to the allergen and it is as well temporarily to reduce the dose to at most one-tenth of that previously given, or even to omit the injection. After the infection has cleared the dose should be rapidly increased again. The dose should not be increased if the interval since the last injection is two weeks and should be reduced if the interval is over four weeks. The patient must be strongly advised not to leave the doctor's surgery for at least thirty minutes after any injection. As has already been pointed out, a reaction coming on half an hour or more after the injection is not likely to be dangerous, but one which comes on sooner usually requires immediate treatment.

It is vitally important when allergenic substances are being given that the label on the bottle should be carefully read and fully understood. If a nurse is giving such injections the doctor should check the bottle and the dose in the syringe; if a doctor has several bottles of different strengths for hyposensitization, only one at a time should be given to the nurse and the others kept under his personal care.

Another reason for constitutional reactions is too rapid absorption of the allergen, due either to the injection having been given in error intravenously or to "seepage"—that is, the rapid entrance of the allergen into small vessels pierced by the injecting needle. To minimize these possibilities, before any injection the plunger should always be pulled back and a momentary pause made to see that no blood appears. After the injection has been given firm pressure should be applied with a cotton swab immediately and for a few moments so that "seepage" into dilated vessels is unlikely. Patients should be advised against strenuous exertion for a few hours after the injection.

Reactions Following Penicillin

Severe anaphylactic reactions and death following penicillin therapy are, unfortunately, being reported with increasing frequency. The symptoms, the same as those already described under anaphylactic reactions, often come on with dramatic suddenness; the more violent reactions begin within minutes, or even seconds, of the injection. Post-mortem findings have recorded acutely distended emphysematous lungs, oedema of the glottis, and in some cases mucoid secretion in the bronchi and bronchioles.

These reactions occur more often in allergic than in non-allergic persons—that is, in those with a history of asthma, hay-fever, or of food, inhalant, or drug allergies. Those who had previous reactions from penicillin are especially at risk, particularly those with previous accelerated or immediate reactions.

Before injecting penicillin it is important to find out if the patient has had any previous penicillin therapy, any untoward incidents in connexion with penicillin, or any allergic illnesses. I do not, however, agree with the withholding of penicillin when indicated in an asthmatic unless there has been a previous reaction to penicillin.

Skin testing as a means of excluding those at risk is not altogether satisfactory, for a negative skin test does not invariably exclude a serious reaction, nor does a positive reaction indicate that an anaphylactic reaction will always occur. In view of the difficulties and lack of precision inherent in skin testing, Siegal has suggested giving orally a penicillin tablet (50,000 units) ten minutes before the intramuscular injection. Another practical suggestion is to inject at first only a drop or two of penicillin and wait for

forty-five seconds before completing the injection, in order to try to avoid those particularly severe reactions that come on suddenly. Injecting in the arm rather than in the buttock is also recommended so that a tourniquet can be applied if necessary.

"Serum sickness" reactions following penicillin therapy are now widely known and recognized. The incubation period and symptoms are exactly the same as in the classical serum disease, and in the same way the severity varies widely. Although penicillin is non-toxic, its administration carries a risk of hypersensitivity estimated at 2-8%.

The indiscriminate use of penicillin is to be condemned, for reactions occurring when there is little indication for penicillin are indeed unfortunate, nor must we forget the possible sensitizing effect of initial injections. It has been suggested that procaine penicillin is more allergenic than crystalline penicillin, but some authorities are not of this view.

Reactions to Insulin

Severe generalized systemic reactions are very rare, and so far as I know death has not been recorded. Reactions usually consist of local redness and swelling with pruritus which may be quite troublesome but which usually subsides after a few weeks with the continuation of insulin. Anti-histaminic drugs are helpful, both prophylactically and for symptomatic relief, until spontaneous recovery occurs.

Reactions to Bee- and Wasp-Stings

The frequency of death from a bee- or wasp-sting is difficult to estimate, although such reports in the lay press are not unusual. The post-mortem findings are the same as those found in anaphylactic deaths from other antigens—laryngeal oedema and acute pulmonary emphysema. The early signs and symptoms are the same as those occurring in any severe anaphylactic reaction.

Successive reactions often become progressively worse; and those who are allergic to bee- or wasp-stings should be advised of this possibility. Every person who knows that he is allergic to bee- or wasp-stings should do all he can to avoid being stung. If this risk cannot be avoided, he should carry with him some tablets of ephedrine ($\frac{1}{2}$ gr.) or isoprenaline sulphate (20 mg.) and an antihistamine such as chlorcyclizine hydrochloride (50 mg.). If he is stung he should at once take one or two tablets of ephedrine (or half to one and a half tablets of isoprenaline) and one or two tablets of the antihistamine. Successful hyposensitization has been carried out in individual cases and a scheme of hyposensitization is given by Mueller and Hill.* Bee venom is an extremely potent antigen, and such procedures may well be left to experts. Further work is required on bee and wasp hyposensitization before the risks and benefits can be accurately assessed.

Miscellaneous Reactions

Reactions to vaccines prepared from chick embryos, such as most influenza, typhus, and yellow-fever vaccines, have been observed in individuals who are extremely allergic to egg; in these patients avoidance of such vaccines is necessary.

That occasional but rare reactions to local analgesics such as cocaine occur has long been recognized, and before carrying out bronchograms sensitivity tests are common practice.

Severe anaphylactic reactions following the injection of vitamin B have been recorded, and indicate the advisability, whenever practicable, of giving therapy by mouth rather than by injection.

Next article on Emergencies in General Practice.—
"Uterine Inertia," by Mr. Clifford Kennedy.

New Engl. J. Med.*, 1953, **249, 726.

MEDICAL BIRTHDAY HONOURS

The names of the following members of the medical profession were included in a Birthday Honours List published in *Supplements to the London Gazette* on June 9 :

G.C.V.O.

Sir HORACE EVANS, K.C.V.O., M.D., F.R.C.P. Physician to Her Majesty the Queen.

K.C.B. (Civil Division)

Sir JOHN ALEXANDER CHARLES, M.D., F.R.C.P., D.P.H. Chief Medical Officer, Ministry of Health, Ministry of Education, and Home Office.

K.B.E. (Civil Division)

Sir ALEXANDER STUART MURRAY MACGREGOR, O.B.E., M.D., LL.D., F.R.F.P.S., D.P.H. Medical Officer of Health for Glasgow from 1925 to 1946. For services to public health in Scotland.

Knighthood

ALBERT ERNEST COATES, O.B.E., M.D., M.S., F.R.C.S., F.R.A.C.S. For services to the medical profession in Australia. DARC Y RIVERS WARREN COWAN, M.B., B.S., F.R.A.C.P. Honorary Consulting Physician, Royal Adelaide Hospital.

HAROLD ROBERT DEW, Sc.D., M.B., B.S., F.R.C.S., F.R.C.S.Ed., F.R.A.C.S., Professor of Surgery in the University of Sydney. For services to medicine in Australia.

GEOFFREY LANGDON KEYNES, M.D., F.R.C.P., F.R.C.S., F.R.C.O.G. Consulting Surgeon, St. Bartholomew's Hospital.

C.B. (Military Division)

SEYMOUR GROME RAINSFORD, D.S.C., M.D., D.P.H. Surgeon Rear-Admiral. Honorary Physician to the Queen.

ALBERT SACHS, C.B.E., M.D., M.R.C.P. Major-General, late R.A.M.C. Honorary Physician to the Queen.

C.B. (Civil Division)

WALTER ERIC CHIESMAN, M.D., F.R.C.P. Medical Adviser, H.M. Treasury.

C.M.G.

BENJAMIN KEITH RANK, M.B., M.S., F.R.C.S., F.R.A.C.S. Chief Plastic Surgeon, Heidelberg Military Hospital, Victoria, Australia.

ALLAN ROBERT STANLEY VICKERS, O.B.E., M.B., Ch.M. For services to the Flying Doctor Service in Australia.

C.B.E. (Military Division)

ALBERT FREDERICK COOK, O.B.E., L.R.C.P.&S.I., D.P.H. Air Commodore, R.A.F.

ALLEN LEPARD CROCKFORD, D.S.O., O.B.E., M.C., T.D., M.B., B.Chir. Brigadier, late R.A.M.C., T.A. Honorary Surgeon to the Queen. Secretary to St. Thomas's Hospital Medical School.

C.B.E. (Civil Division)

ROGER GILBERT BANNISTER, M.B., B.Chir. For services to amateur athletics.

PHILIPPE LESLIE CARO CARRIER, M.D., M.R.C.P., D.P.H. Senior Medical Officer, Home Office.

CHARLES WILLIAM ATKINSON EMERY, M.B., B.Ch. Principal Medical Officer, Ministry of Pensions and National Insurance.

MARY ESSLEMONT, LL.D., M.B., Ch.B., D.P.H. General Council Assessor to the University Court of the University of Aberdeen since 1947. President of the Medical Women's Federation, 1953-4. For services to medicine in Scotland.

RICHARD THOMAS BONDFIELD GREEN, M.D., D.Sc., D.T.M. Senior Bacteriologist, Institute for Medical Research, Federation of Malaya.

JOHN LEWERS GROVE, M.D. A prominent physician in Launceston, Tasmania.

JOHN ARTHUR LLEWELYN VAUGHAN JONES, M.B., Ch.B. Regional Medical Adviser, East and West Ridings Region, Yorkshire. For services to the Ministry of Labour and National Service.

WILLIAM CALDWELL McCLELLAND, M.B., Ch.B. For services to sport in Australia.

FREDERICK GRANTLEY MORGAN, M.B., Ch.B. Director, Commonwealth Serum Laboratories, Royal Park, Victoria, Australia.

FREDERICK WILLIAM ROQUES, M.D., M.Chir., F.R.C.S., F.R.C.O.G. Consultant in Gynaecology to the Royal Air Force. Obstetric and Gynaecological Surgeon, the Middlesex Hospital and the Royal Masonic Hospital. President of Section of Obstetrics and Gynaecology, Royal Society of Medicine, 1954-5.

MAX LEONARD ROSENHEIM, M.D., F.R.C.P. Professor of Medicine in the University of London and Director of Medical Unit at University College Hospital Medical School.