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SYSTEMIC REACTIONS IN SPECIFIC ANTIALLERGIC TREATMENT

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General reactions which may appear in conjunction with allergic diagnosis and antiallergic treatment are usually divided into two groups, the systemic reactions and the constitutional reactions. An allergic systemic reaction may develop into a constitutional reaction, but generally subsides with proper treatment. As a third group, mention may be made of the abdominal reaction, though in its pure form this is an extremely rare occurrence.

The allergic systemic reaction appears within the first 10 minutes after the injection of the antigen; its first symptom is an intense local reaction at the site of injection with streaky lymphangitis extending up the arm (it is taken for granted that diagnostic and therapeutic antigen injections are always given into the forearm, see later). The patient then complains of itching of the eyes, the conjunctivae become injected, the face congested and, gradually, universal redness and urticaria develop. At this stage the pulse is hard and the blood pressure normal. The physician should interfere at this moment, and the reaction will then soon subside with adequate treatment. If the symptoms are neglected, the patient will have oedema of the face and fauces, dry cough owing to oedema of the mucous membrane in the respiratory tracts, and gradually a typical attack of asthma develops. So far the condition can generally be rectified, and sometimes the patient

improves spontaneously, but this is a possibility one should never consider. The patient is now in danger of passing on to the phase of shock: the patient, congested so far, now turns greyish pale, possibly greyish cyanotic, the pulse becomes small and feeble and may not be perceptible, the blood pressure falls, involuntary evacuation of excreta occurs, and death may occur owing to circulatory collapse with cerebral anoxia.

This form of shock, occurring after an allergic systematic reaction, can and should usually be avoided. As already mentioned, the picture appears in the course of the first 10 to 15 minutes after the injection of antigen, and develops comparatively slowly during the next 10 to 20 minutes. It is ushered in by such characteristic prodromal signs that any alert physician can interfere in time.

The allergic constitutional reaction, which starts with symptoms of shock, including a rapid fall in the blood pressure, develops so acutely that it cannot always be managed to institute treatment before the injury is irreparable. It passes off with extreme suddenness, and death may occur in a few minutes.

If the cause of the shock is an intravenous antigen injection, the symptoms appear in from $\frac{1}{2}$ to 1 minute, but in other cases, as in the systemic reaction, they do not occur until about 10 minutes after the injection of antigen. There are few or no prodromal symptoms; the patient suddenly turns greyish pale, the pulse is hardly perceptible, breathing becomes shallow, the patient becomes unconscious and may develop clonic convulsions, in many cases there is involuntary evacuation of excreta, and death may occur in a few minutes.

It may seem astonishing that the disaster may occur so soon in an otherwise healthy patient. It should, however, be borne in mind that there occurs a more or less complete paralysis of the musculature of the capillaries, and that the muscle capillaries have a surface area of about 6300 square metres, which is about 3000 times the body surface; and it has been calculated that, if there were no antagonistic forces in the capillaries, the total plasma volume would be able to

pass into the tissues in the course of 10 seconds (11). Therefore there is nothing to prevent the death of a patient of capillary shock in a few minutes.

The abdominal type.—In Quincke's oedema, gastro-intestinal forms may sometimes be seen which may be difficult to diagnose and have induced surgeons to perform laparotomy in several cases. The allergic systemic reaction may also, though seldom, appear in the guise of the acute abdomen. The shocked patient complains of violent constant abdominal pain, or pain started by attacks, and the abdomen may be hard and tense. Sooner or later, universal urticaria or oedema of the face generally occurs, but in the purely abdominal phase the diagnosis may be difficult to establish if the possibility is not realized.

INCIDENCE

With regard to the incidence of *the allergic systemic reaction*, this is illustrated by three publications from the University Hospital, Copenhagen. In 1943 M. Schwarz (9) found from 1 to 10 per cent. of systemic reactions in testing and treatment with inhalation allergens. Flensburg (3) (1950) found 26 per cent. of systemic reactions in treatment with bacterial antigens. E. Henriksen (6a), in his thesis (1951), tabulated the nature of side-effects in examination and treatment of asthmatics.

When Schwartz gave such a wide margin of variation as from 1 to 10 per cent., this was due to several facts. The technique of testing and treatment plays a great part. If tests are performed uncritically with potent extracts, there will be a relatively high incidence of systemic reactions. With scratch tests there will be fewer systemic reactions, *ceteris paribus*, than with intra-dermal tests. If desensitization is performed according to a fixed schedule up to a certain high antigen concentration, a greater number of systemic reactions will appear than in the case of individualized treatment or with the so-called small dosage treatment. If a vigorous local reaction following the last injection is neglected, there is a risk of a

systemic reaction which might have been avoided etc. The nature of the allergy also plays a part. Pollen allergics rather often develop systemic reactions, because they generally have a very pronounced allergy to pollen, or perhaps because pollen is an especially potent antigen. This is illustrated by Furstenberg & Gay's publication (4) in which they mention that they have seen 75 cases of severe shock in 29,547 pollen injections, but only 2 cases following 7,744 injections of other antigens.

In the Allergy Consultation of the Medical Outpatient Department, the University Hospital, Copenhagen, it is estimated that there are from 10 to 20 systemic reactions in from 100,000 to 150,000 injections per year.

With regard to the incidence of the *constitutional reactions*, i.e. the really dangerous cases, there are exactly the same possibilities of variation as in the case of the systemic reactions. In 1927 Vander Veer & Spain (10) saw 96 constitutional reactions in 14,280 pollen injections; Waldbott & Ascher (12) had 141 cases in 51,036 pollen injections. In Copenhagen, Schwartz (1943) found 5 cases of constitutional reaction in the course of treatment of 183 allergics, about half the number being asthmatics. In Henriksen's series from the same clinic there was only 1 case of constitutional reaction in testing and treatment of 538 patients, all of whom were asthmatics. With the technique that has now been developed at the Allergy Consultation there are only few actual constitutional reactions, hardly more than 1 or 2 per year, and chiefly in patients allergic to pollen and animal hair.

The purely *abdominal type* is very rare; the writer considers that he has observed only 2 cases of this nature.

With regard to the incidence of *fatal constitutional reactions*, reference may be made to surveys by E. Henriksen (6b), O. Midttun (7), Salén & Björnstjerna (8), and Vaughan & Black (11). Without doubt the great majority of fatal cases are published and altogether the literature hardly contains more than 75 cases of this nature. This figure includes

28 patients who died after injections of serum and antitoxin, and several cases of death following bee-stings, administration of aspirin and quinine, injections of penicillin and novocaine etc. The number of published fatal constitutional reactions following allergic diagnosis and treatment hardly exceeds 20, and this figure includes the Scandinavian cases most recently published (1). Twenty cases is of course a great number, but it should be viewed on the background of the enormous number of antigen injections given per year all over the world¹. In the Allergy Consultation of the University Hospital, Copenhagen, where, broadly speaking, from 1 to 1½ million antigen injections have been given since 1941, there have been no fatal reactions.

TREATMENT

The allergic systemic reaction.—As soon as the symptoms begin to appear a rubber-tube tourniquet is applied proximal to the site of injection to compress the extremity. Diagnostic and desensitizing injections should always be given into the forearm, so that the tourniquet may be applied to the upper arm, thus producing an effective arrest of the circulation from the rest of the body. When the tourniquet has been applied, 0.5 ml of a 1 per mille adrenalin solution is administered at the site of injection of the antigen, and a similar dose is injected into one of the lower extremities. If the reaction is not extremely violent, this dose of adrenalin of 1 ml will suffice,

¹ Assuming that there are 5 million patients with hay fever in the U.S.A. (Feinberg (2) states from 5 to 7 million), and supposing that only 1 per cent. of these become desensitized, then, if each patient receives 40 injections, 2 million injections per year are given in the U.S.A. to patients with hay fever only. Furthermore, an estimate should be made of the number of desensitizing injections to other patients in the U.S.A. and to allergics all over the rest of the world. The 20 fatal cases date back to 1911 when desensitization was introduced. The 20 deaths should therefore be considered in relation to hundreds of millions of injections—perhaps even more.

and the troublesome side-effects of adrenalin seen in the case of higher doses are avoided.

In a few minutes the patient will declare that he feels better; the tourniquet is then replaced by a blood pressure cuff, and the tension is kept between systolic and diastolic pressure. If the patient still feels better, the cuff is deflated, but should be left on the arm to be inflated again in the case of signs of recurrence of the symptoms.

When the patient feels free from symptoms, he should be urged to remain in the consulting room for another hour. If he is still feeling well, he should be given an antihistamine tablet and enjoined, when discharged, to keep quiet the rest of the day.

It will appear how important it is to give the injection into the forearm. Patients often want different sites of injection, but the physician should always insist on using the forearm. The thigh can only seldom be effectively compressed. Owing to the risk of neuritis it is generally considered a technical error to give hypodermic injections into the forearms. A spokesman of the insurance physicians (5) has said that, in the opinion of the insurance companies, it is a technical error to give injections into the forearm, and that he thought it was necessary owing to the risk of motor paralysis to warn doctors against hypodermic injections into the forearm. This view is also correct as far as all other injections (insulin, morphine etc.) are concerned. But the desensitizing injections form an exception and should always be given into the forearm owing to the treatment of possible constitutional reactions. It should be borne in mind in this connection that with a number of injections into the forearm running into 1½ million we have seen only one case of transient paresis, and no persistent cases, in the University Hospital, Copenhagen.

The allergic constitutional reaction is treated in principle on the same lines as the systemic reaction: application of a tourniquet proximal to the site of injection, and adrenalin injection(s). In such cases, however, a higher dose of adrenalin should at once be given into the lower extremity,

e.g. a dose of 1 ml. As soon as this has been done, a needle is inserted into a vein and fitted with a syringe containing a 1 per mille solution of adrenalin. An assistant or a nurse holds the syringe. It is important that the needle should be introduced into a vein before the veins collapse. At the least sign of unconsciousness, adrenalin should be injected intravenously, slowly or more rapidly according to the patient's condition and reaction.

Adrenalin should be given intravenously when vitally indicated, but should not be administered in this manner unless it is absolutely necessary, as it is one of the most unpleasant forms of treatment to which patients can be exposed. After a rapidly administered intravenous injection of adrenalin the patient feels as though he were going to explode. He is distressed, saying that he would rather die, and that his head is being blown up; he may actually run amuck and become quite unmanageable. Nevertheless the physician should not hesitate to use this form of treatment if it is considered necessary. In the writer's experience it saved the patient's life on two occasions, and he would certainly use it again if necessary.

If it is impossible to give an intravenous injection and if the patient is unconscious, adrenalin should be given into the heart.

It may be mentioned that other forms of therapy, especially intravenous injection of calcium, have proved rather ineffective in the case of constitutional reactions. In the Allergy Consultation of the University Hospital we have administered up to 30 ml of a 10 per cent. calcium solution intravenously without effect. The action of antihistamine preparations and of ephedrine is too slow to be of any use in the case of acute shock. In pharyngeal oedema, spraying with a 10 per cent. solution of adrenalin exerts a good effect. ACTH and cortisone cannot exert their effect during the short time that is decisive. In cases of hypertension theophyllamine intravenously can be used.

PROPHYLAXIS

What can be done to avoid allergic systemic reactions?

- (1) A number of obvious things may first be mentioned; even though they are obvious, they are nevertheless the factors which are most frequently overlooked.
 - (a) The antigen ampules should not be mixed up; the physician should take great care every time to convince himself that he is using the proper extract in the right dilution.
 - (b) The dose of antigen should be as prescribed. It must be urgently advised not to "take a short cut" by increasing the dose too rapidly.
 - (c) If a preceding injection has produced a persistent vigorous local reaction, the injection should not be given until the reaction has subsided.
 - (d) Care should be taken not to give the injection intravenously.
 - (e) The patient should be observed for at least 15 minutes after the injection of antigen.
 - (f) In titration of positively reacting allergens, tests with more than two allergens should not be made on the same day.
- (2) With regard to treatment with bacterial vaccines, reference may be made to page 140.
- (3) The patient should be enjoined not to appear for the antigen injection if he feels hot or has been exposed to exertion, for instance if he has had a Russian bath or has been playing tennis.
- (4) Certain patients are especially liable to develop systemic reactions, the so-called habitual shock patients. Such patients may be given an antihistamine preparation 30 minutes before each injection of antigen, and 0.2 ml of adrenalin should be added to each injection (this does not apply to the British Bencard extracts which contain adrenalin).
- (5) Certain allergens are inclined to produce systemic reac-

tions; this applies, for instance, to pollen. Therefore, if pollen allergy is suspected, tests should not be made with concentrated pollen extracts, but with concentrations not exceeding 1 : 1000. If egg allergy is suspected, still greater caution is called for.

SUMMARY

The clinical features and treatment of allergic systemic reactions are reviewed. Special importance is attached to adrenalin treatment. It is stressed that, owing to treatment of any allergic systemic reaction, the injections of antigen should always be given into the forearm.

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