Editorial

Severe shock, in some cases resulting in the death of the patient, due to the administration of penicillin is a rare phenomenon. In England and Wales there were eight deaths due to penicillin sensitivity in two years.[1] These deaths are nevertheless tragic and are becoming more common. The nature of penicillin shock is imperfectly understood. Reactions to penicillin can be divided into two types — the immediate and the delayed. The immediate reactions are the dangerous ones and account for nearly all the deaths due to penicillin. Typically the symptoms begin within fifteen minutes of the dose of penicillin being given. Penicillin shock is characterised by extreme dyspnoea, urticaria, cyanosis and circulatory collapse. It exhibits a close resemblance to anaphylactic shock and to the severe or fatal reactions which may occur following the administration of many other drugs.

Aetiological similarity between anaphylaxis and immediate drug reactions has been accepted even though the majority of drug reactions cannot be shown to involve an antibody — antigen response. Nearly always the patient who is hypersensitive to penicillin has had penicillin previously. In accounts of thirty-two severe or fatal reactions we have found that thirty cases had given a past history of receiving penicillin — in all these thirty-two cases the patient had been asked specifically whether or not he had had penicillin before. Of thirty-one cases seven gave a history of allergy. This proportion is larger than that in the general population. Kern and Wimberley[2] estimate that one in seven of the general population is an allergic subject. They believe that penicillin hypersensitivity is acquired and that an allergic subject is more likely to acquire it than a normal one. They also point out that during the first nine years in which penicillin was used there were two deaths due to it in the next eighteen months there were fifteen. It may be that with widespread use of penicillin all allergic subjects will become hypersensitive to penicillin.

Penicillin shock thus shows clinical similarity to anaphylaxis, most of the cases have had a previous sensitising dose and allergic subjects are particularly liable to both types of shock. But it may be thought that only proteins can cause anaphylactic shock. There is evidence that certain drugs induce hypersensitivity by uniting with protein molecules in the patient's body. Aspirin and sulphonamides will not produce a local reaction in the skin of sensitised patients unless the drug is first mixed with the patient's or normal serum.[3] In 1931, Oriel showed that an aspirin-proteose complex, isolated from the urine of a patient sensitive to aspirin, would produce a cutaneous reaction not produced by aspirin alone.[4] Aspirin, sulphonamides and quinine give no dermal response but will do so if applied to the mucosa of the mouth for twenty to thirty minutes. So far no one has shown that penicillin will unite with body protein in this way. There is, however, evidence that penicillin sensitive patients have antibodies to penicillin in their blood,[5, 6, 7, 8, 9].

If severe penicillin reactions are of the nature of anaphylactic shock, then something of practical importance, relevant to this discussion, may be learned from the experiences of doctors using sera and the anaphylactic reactions resulting from sera. Laurent and Parish advise that a doctor should differentiate between testing for local serum sensitivity by intradermal or conjunctival tests and for general sensitivity by subcutaneous or intramuscular test doses. They believe that whereas serum rashes occur in about 5% of patients, deaths occur in only one in fifty thousand to two hundred thousand.[10] Here is seen again the differentiation between the delayed non-fatal reactions which are common and the immediate severe ones which are rare. The skin test is not a reliable way of detecting those patients who may suffer severe shock. Harries and Mitman point out that there is no exact parallelism between dermal and general constitutional hypersensitivity.[11] Joe considers these tests to be uncertain guides and doubts whether their routine use has any practical advantage.[12] Ratner, admitting their defects, considers them worth doing.[13] Banks believes that a small injection subcutaneously is a better test for general sensitivity than a dermal or conjunctival test.[14] Parish recognises the unreliability of intradermal and conjunctival tests. He advises that the safest course is to give a small dose of diluted serum by the same route as that chosen for the main dose. You should then wait thirty minutes and if no reaction has occurred give the main dose slowly.[15] Later we will quote evidence casting similar doubts on the reliability of skin and eye tests for general penicillin sensitivity.

It has been suggested from time to time that procaine in procaine penicillin or given with penicillin may be the cause of some of the reactions. A patient may be sensitive to both drugs. Morgan reports a case who gave a history of being sensitive to procaine. The patient was given penicillin alone and developed a severe reaction with recovery.[16] Lewis points out that five hundred thousand units of procaine penicillin contains two hundred mgm. of procaine. If this amount were injected by accident into a vein it could produce the symptoms of procaine poisoning. These are central stimulation and convulsions.[17] We feel that these differ from those of penicillin shock. Lewis does not doubt that most reactions after penicillin are truly due to the penicillin. Handford and Richiutti, using procaine penicilliin in oil (procaine 120 mgm./cc.) intravenously in laboratory animals to four times the ordinary human dose produced no ill effects. When the dose was increased above this level, symptoms developed due to oil embolism.[18] It would seem that procaine is rarely the cause of these reactions so far as its poisonous properties are concerned. Of course procaine can itself produce shock in individuals sensitive to it and this shock would be indistinguishable from penicillin shock.

If we accept penicillin shock as being fundamentally due to the same causes as anaphylactic shock, not as a proven fact but as a satisfactory hypothesis on which we can base our future actions when faced with this grave danger to one of our patients, then some knowledge of anaphylaxis should be of assistance to us.

In animals the sensitising dose may be very small and may be given by any route. Several days or weeks must elapse before the anaphylactic state is established. To produce shock the dose given must be large and must be given into a vein. This is necessary in experimental work, since the experiments demand that the shock will be induced with certainty. It may be that a small number of the animals would go into shock if the second dose were given by a route other than intravenously. Since in man only one patient out of every fifty to two hundred thousand develops shock when the second dose is given, it would obviously be difficult to prove in the laboratory animals that shock is never produced by non-intravenous administration. We must not infer that penicillin shock is due to accidental intravenous injection.

The antigen used for the second dose must be a protein or a protein united to a simpler chemical substance. The whole antigen, or the simpler chemical substance (in our hypothesis this is penicillin) must be identical to or closely similar to the sensitising agent. The main symptoms of anaphylactic shock come on within a few minutes. They are caused by contraction of smooth muscle and damage to capillary endothelium. They vary in different animals — in the guinea pig the stress falls on the smooth muscle of the bronchioles — in the dog on the smooth muscle of the hepatic veins — in the rabbit on the smooth muscle of the pulmonary arteries.

The substance which is mainly responsible for these effects is histamine. Other substances in addition to histamine play an important part in producing anaphylactic shock. Since we have no way at present of reversing the effect of these other substances, we cannot expect antihistamines alone to reverse the rapid deterioration in the condition of our patients suffering from penicillin shock. Antihistamines, given to laboratory animals in induced anaphylactic shock, produced a significant decrease in the severity of the symptoms and the mortality. They did not suppress the shock altogether. It has been shown that the degree of shock in animals is proportional to the amount of histamine in the blood and lymph and that recovery coincides with its disappearance.

Whatever may be the cause of penicillin shock and however interesting it may be to revise our knowledge of it, we all want to know what is the best attitude to adopt towards this menace. Firstly we should not abandon the use of penicillin. Penicillin is still one of the most valuable and safe of the antibiotics. Severe reactions are rare and deaths rarer still. The amount of penicillin used in the world to-day is measured in hundreds of tons annually. In 1956, patients in the United States swallowed forty tons of penicillin and probably three times as much as that was administered to them by injection.[19] In a survey of 95 hospitals with 51,000 beds, Welch *et al.* found 59 cases with 19 deaths.[20] There are obvious indications for the use of penicillin, the drug saves many lives and if its use were abandoned it is almost certain that more lives would be lost from disease than would be saved by preventing penicillin shock. Doctors should also know that it is possible to be held to be negligent if penicillin is not given when its administration is strongly

indicated. In a case in England [21] in 1955, a patient sustained a compound fracture of the radius and ulna. Penetration of the skin was very slight. The attendant doctor did not give the patient any penicillin. Gas gangrene developed and the arm had to be amputated. The doctor said that he did not give any penicillin because the skin penetration was slight and because he had had several patients who had become sensitised to penicillin. Expert evidence was given that the administration of penicillin in such cases was now an established practice and its omission difficult or impossible to defend. The judge made a finding of negligence.

Dismissing the suggestion that penicillin should no longer be used, our next problem is to decide whether any test can be used to detect those patients who are likely to suffer a severe reaction if penicillin is given to them. We should ask our patients whether they have had penicillin previously. This is because we are expected to. It is better to assume that every patient has had penicillin. Even if the patient says he has never had any this may merely be because he has forgotten or he has had some without knowing that it was penicillin. We should certainly ask him about eczema, asthma and hay fever or any other allergy. Allergic patients are more liable to severe reactions than others. Above all we should ask him whether he has had a reaction to penicillin in the past. If he has had one then he is probably going to suffer another one if he is given penicillin. Every patient who survives a severe penicillin reaction must be told that another penicillin injection or tablet by mouth may kill him. Next we must ask ourselves, "Does this patient really need penicillin?" We found reports of ten cases who suffered severe reactions, with five deaths, in whom in our opinion pencillin was given unnecessarily. Many of the commonest conditions seen in practice really do not need penicillin. The common cold — the average case of acute tonsillitis — most sinus infections — eczema and dermatitis, all of these conditions have led to death from penicillin shock. A very large proportion of the deaths from penicillin, possibly 50% of them, would not occur if penicillin were to be given only when its use were clearly necessary.

The difficult question now has to be faced as to whether every patient should have a skin test for penicillin sensitivity before penicillin is administered to him. Many physicians believe that the evidence supporting the proposition that a positive skin test indicates that the patient is in the group of those liable to die from penicillin shock is so strong that the test should be done in all cases. They believe that lives can be saved by refusing to give penicillin to those with a positive skin test. Smith found twenty-five positive results to skin and conjunctival tests in thirteen hundred and sixty-five patients tested. Ten of these were known to have suffered penicillin shock with one death. [22] Williams states that penicillin skin tests will show a positive result in fifteen minutes in the vast majority of penicillin sensitive cases. [23] He agrees that a negative test will not indicate absence of sensitivity with certainty. There is strong evidence for this later statement. Idsoe, Wang and Wang, working in Taiwan, found that of twelve deaths, six had had

negative skin tests, the other six had had no tests done on them. [24] Further they found that of nineteen who survived severe penicillin shock, six had had negative skin tests, the others had had no tests done on them.

The tests used were a skin scratch through a drop of penicillin, 100,000 units/cc., an intradermal injection of 0.1 cc. of the same solution and a subcutaneous injection of 10,000 units. [24] Smith used a forearm scratch through a drop of procaine penicillin, 300,000 units/cc. [22] A positive result is a skin erythema of over 1 cm. diameter, a skin wheal and, if a drop of the procaine penicillin solution is placed in the eye, watering, redness and oedema. Williams advises much smaller doses for testing. [23] He advocates initial testing by prick or scratch methods using strengths of 5,000 to 10,000 units/cc. He also quotes authors who, even after a negative skin test, would start with very small doses of penicillin intracutaneously and work up gradually by eight steps to a full dose. We feel that such extreme caution, the whole testing process taking several hours, is impractical. The use of a single skin test is possible in most cases as a practical measure in Malayan conditions. The proportion of penicillin deaths which would be prevented in this way is unknown. We do not know whether the majority would be prevented. It would seem likely that in many patients the skin may be insensitive while at the same time internal organs may be sensitive. We are attracted by the logic and simplicity of Parish's opinion: "The safest course is to give a small dose, e.g. 0.1 or 0.5 cc. of a 1/10 dilution of serum by the same route as that chosen for the main dose. Wait thirty minutes and if no indication of sensitivity is noted, then give the main dose slowly." [15] Since the smallest dose to cause death in the literature is 5,000 units, so far as penicillin is concerned, the test dose by mouth or intravenously would have to be much smaller — say 500 units. Lastly the fact must be noted that patients having a course of penicillin injections have suffered severe reactions not at the first dose in the course but after subsequent ones. Thus of sixty-three cases in whom this observation was made, 52 suffered their reaction at their first injection, four at their second, three at their third, two at their fourth, one at his eighth and one at his ninth injection. We emphasise that each of these reactions occurred during one continuous series of injections. In order to avoid eleven of these reactions with four deaths, a reliable test for sensitivity would have to have been done before each injection, however long the course and however many the injections.

Doctors must make up their own minds as to the practice they will follow. The tests available are not reliable but they are better than nothing. We would suggest that the intramuscular injection of a small dose is likely to prove a better test for the presence of general constitutional hypersensitivity to penicillin than the skin tests are.

Penicillin shock occurs very suddenly and unexpectedly. Any doctor using penicillin may be faced with this catastrophe in his practice at any time. A few seconds to fifteen minutes after the dose of penicillin, symptoms indicative of respiratory obstruction, circulatory failure and urticaria occur. Any one of these may exceed the others in severity, all

are usually present. The shorter the period between dose and onset the higher the mortality. For example, of eighty-three cases in whom this period was less than fifteen minutes, seventeen died, whereas of thirteen cases in whom the period was more than fifteen minutes only one died. Death occurs within twenty to sixty minutes in most cases though a few have died after fourteen to sixteen hours.

Respiratory obstruction produces intense cyanosis and dyspnoea. The obstruction is caused partly by bronchospasm and partly by swelling of the throat, tongue and larynx. The pulse and blood pressure fail and rapidly become imperceptible. Extreme swelling of the face and widespread urticaria are common.

Despite the sudden onset and rapid progress of this condition treatment is available and may save life. But the doctor must be prepared beforehand. Treatment must be instituted at once. We think that the evidence favours the use of the antihistamines. As one example of many, we may refer to Humphrey's case. His patient, in severe penicillin shock was given 2 cc. of 2.5% Anthisan intravenously. Relief was noted to begin within fifteen minutes and the patient recovered.[25] Antihistamines may be given along with the injection of penicillin. Maslansky and Sanger give evidence that penicillin can be given safely, even to sensitised patients, if it is mixed with an antihistamine.[26] Lewis advises the use of adrenalin. This is given in a dose of 0.5 cc. intramuscularly and the needle left in.[17] Adrenalin, 0.1 cc. is given every minute until the attack begins to pass off. Penicillinase (Neutrapen, Burroughs Wellcome), given intramuscularly in a dose of 800,000 units has been reported to reduce the penicillin blood level to zero within one hour.[27] This drug has produced a satisfactory response in most cases within twenty-four hours and in others within two to six days. It has been used in delayed penicillin reactions but may have a place in reinforcing the effect of antihistamines and adrenalin in immediate reactions. A doctor working in his dispensary or in his patient's home may not be able to do more than use these antidotes. They should also be used in hospital. In addition the services of the anaesthetist should be called for. He should pass an endotracheal tube, give a relaxant and maintain positive pressure respiration until the patient recovers. Heyworth reports the successful treatment of a case in this way.[28] We feel that this last method should be used in every case if the necessary skill and equipment are available. The anaesthetist, more than any other member of a hospital staff, has the knowledge and experience of how to deal with respiratory failure, whatever may be the cause.

Lastly we suggest that those patients who have suffered from penicillin shock, begin to recover, but remain in coma or drowsy, should be treated as suffering from cerebral oedema due to the period of hypoxia. We suggest that these patients should be given 50% sucrose solution, sixty to ninety cc. intravenously. This solution has been used with success by us in other forms of delayed recovery from respiratory insufficiency.

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For an excellent dissertation on Anaphylaxis see: General Pathology, 1958, Edited by Florey, pp. 778 – 827, Lloyd Luke, London.

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