LEADING ARTICLE
THE IMPLICATIONS OF FATAL PENICILLIN ANAPHYLACTIC REACTIONS

By G. O. Horne

Although penicillin has been in use for thirty years, and has proved to be one of the least harmful effective drugs ever produced, its side-effects are not yet completely understood. One of the side-effects, acute anaphylactic shock (which is usually fatal), is a source of great anxiety to doctors all over the world, and especially in those regions where the relative cheapness of penicillin makes it the drug of choice in a wide range of diseases in which its effectiveness persists. Unfortunately, the shadow of a "penicillin death" hangs over all doctors who use the drug, and especially over those general practitioners who have no organization behind which to shield themselves in the event of such a tragedy occurring in their practices.

The problem has been aggravated rather than helped by the development of a so-called "prospective skin test", which was supposed to reveal hypersensitivity to the drug, and so provide a means of avoiding serious reactions. Unfortunately, the medical and the legal professions have both become confused over the application of this test, and, in view of the serious implications of the problem especially in this part of the world, a review of the current situation is presented here.

INCIDENCE

The most comprehensive and authoratative review of the nature and frequency of allergic side-effects of penicillin is the report by the World Health Organization published in 1968 (Idsϕe *et al*, 1968), although the report admitted the unreliability of much of the data analysed. It stated that studies in different countries reported an incidence of reactions ranging from 0·7 to 10 per cent. In the anaphylactic type of reaction the range was about 0·0015 to 0·04 per cent, with a fatality rate from shock of 0·0015 to 0·002 per cent. Death has occurred following a test intradermal injection of penicillin (Idsϕe *et al*, 1968; Mozhaev, 1971; Assem and Vickers, in Press; various references quoted later in this article); after a test "scratch" (Dogliotti, 1968); after an accidental scratch with a needle contaminated with penicillin (Wirth, 1963); and after the administration of oral penicillin (Idsϕe *et al*, 1968; Spark, 1971).

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There is little information available about the incidence of allergic penicillin reactions (including the fatal anaphylactic type) in Singapore and Malaysia, but there is no reason to believe that it should differ much from other similar areas of the world. Development of allergy as a result of such factors as hidden penicillin contacts (e.g. drug-factory workers) or milk and milk-products may occur less often in this region, but some popular traditional Chinese asthma powders are known to contain penicillin powder, as do some local animal feeds.

However, there is no doubt that for various reasons the local incidence of fatal penicillin reactions is higher than is commonly believed. Gwee commented on the relatively low estimated incidence in Singapore, and suspected a considerable degree of under-reporting (Gwee, 1972). It is likely that only those cases reaching the Coroner's court see the light of day—and then usually at the expense of a nightmare for the doctor involved.

HISTORICAL

It is difficult to understand how the almost pathological obsession with the importance of a routine prospective skin test for penicillin has become established in Singapore and Malaysia, where in some quarters it seems to be considered almost a charm against disaster, if not against litigation.

Over many years, among the most widely read medical publications, the skin test has repeatedly been described as "unreliable and risky" or even roundly condemned (for example, leading articles in the *British Medical Journal* in 1964 and in 1968, and a special article on drug toxicity in the general practitioners' "bible", the *Practitioner* (Hughes, 1965); similarly, in popular standard textbooks, such as "Current Diagnosis and Treatment" (Brainerd *et al*, 1968; Krupp *et al*, 1971).

In 1964 The Malacca Agricultural Medical Board issued a medical circular in which it stated: "There is no reliable test for the sensitivity [to penicillin] which leads to these serious reactions . . . " (The Malacca Agricultural Medical Board, 1964).

The WHO Report of 1968 stated: "Routine penicillin skin testing prior to penicillin administration cannot, however, be generally advocated at present . . . "; and there is still no evidence to the

contrary available. In scientific publications, in many languages all over the world, the same verdict has been expressed time after time, and it is not possible to find a single reliable authority that supports the routine use of a prospective skin test.

Neither is there any justification for the tendency which has become established in this region over the years to conclude that, when a patient dies of penicillin anaphylaxis, the doctor who gave the penicillin is guilty unless he can prove the contrary. But the fact that the two phenomena (the faith in a skin test and the doctor's fear of being blamed) appear to have developed coincidentally suggests that they may have influenced and even perpetuated each other. However, the medical profession generally may have contributed to the development of this predicament because of its failure to be unanimous about the explanation of penicillin deaths and the measures that should be taken to avoid them—as it appears to be equally unable to be unanimous about other life and death matters with medical implications (such as cigarette smoking and blood cholesterol levels).

LEGAL ASPECTS

The legal implications of penicillin anaphylactic deaths are completely different in Malaysia and Singapore, and may be summarized as follows:—

In Malaysia (Malayan Criminal Procedure Code, 1971) when the cause of death is known to the magistrate, and he is satisfied as to the cause of death, it is not his duty to find out how the death was caused, or who caused it or contributed to it; it is not his duty as coroner to express any views on criminal negligence, culpability or civil liability. Indeed, a recent circular from the Chief Justice of Malaysia (The Malayan Law Journal, 1973) took a magistrate to task for having "arrogated himself the right to say, of a doctor giving a penicillin injection which resulted in the patient's sudden death, that he was negligent. The verdict should have been confined strictly to the *cause of death*—anaphylactic shock as a result of the injection . . . ". The Chief Justice was referring to a press report of a case of the type under review here.

The situation is quite different in Singapore (The Statutes of the Republic of Singapore, 1970), where the law states:

> "If the Coroner is of opinion during the course of or at the close of any inquiry that sufficient grounds are disclosed for charging any person under the Penal Code with having caused or assisted in causing the death of the deceased person, he may issue his warrant for the apprehension and committal of that person to prison to be brought before a court to be prosecuted according to law and he may bind over any witness who has been examined before him in a recognizance with or without surety to appear and give evidence before that court."

This implies that a doctor involved in a coroner's inquest in Singapore in a case of this type could, at the discretion of the coroner, be charged.

At the conclusion of a "penicillin death" case in Telok Anson in 1969, in which the doctor was acquitted (without his defence being called), but only after literally years of anxiety on his part, on a charge of "causing death by a negligent act*", the Sessions Court President said: "In view of the expert evidence produced, I find that it is not necessary to give a test dose before giving an injection of penicillin as it can be unreliable and dangerous" (Straits Times, 1969). Unfortunately, a decision of a sessions court judge (contrary to some beliefs, e.g. Peter, 1969) is not binding in a high court, although it may be of persuasive value, and so a defending counsel might have to produce specialist evidence all over again in defence of his client.

The current medico-legal situation in Great Britain is reflected by a recent statement by the Deputy Secretary of the Medical Protection Society Limited, who is of the opinion that no precedent has been set there which would expect a test dose of penicillin to be given before the main injection (personal communication, 1973). He is extremely doubtful if in the foreseeable future any such contention could possibly be upheld even by eminent experts in the field of therapeutics. (He of course stresses the responsibility of the individual doctor in ascertaining, to the best of his professional ability, that there is no history of sensitivity to penicillin in any of its forms or preparations).

The medico-legal situation in the United States of America is implied in a recent leader in the *Journal of the American Medical Association* (Holder, 1970), which concluded: "Judicial discussions . . . regarding sensitivity tests have indicated without exception that they are so impractical and unreliable for general use that due care does not require them." The American Medical Association confirms that there has been no change in this view since then (personal communication, 1973).

*The actual charge read: "That you . . . on . . . caused the death of . . . by a negligent act not amounting to culpable homicide, to wit, by injecting penicillin into . . . without giving him a test dose and that you have hereby committed an offence punishable under Section 304A of the Penal Code" (Telok Anson Report No. 908/66).

As long ago as 1955 the Government of Taiwan issued an edict (Taiwan Province Health Edict, 1955) on the subject of serious (including fatal) reactions to penicillin. At that time it was making an all-out effort to curb the incidence of venereal disease, especially syphilis, but the campaign was apparently being sabotaged by doctors who were afraid that "penicillin deaths" might land them in prison. The Government medical department accordingly gave instructions that a skin test must be carried out in order to avoid accidents. Doctors were advised that if a sudden death occurred in spite of this precaution it could be considered "an act of God". The Judiciary and the police were informed of this policy, and newspapers were warned about reporting such cases in order to avoid any false advance verdict, and to ensure that the public was not given the wrong impression.

MEDICAL ASPECTS

Probably the foremost authorities on the medical aspects of penicillin allergy are Professor H. O. Schild and Dr. E. S. K. Assem (and their colleagues), of the Department of Pharmacology at University College, London, where this has been one of the major subjects of investigation for many years, and as a result of their, and other's work, the following conclusions are now virtually unassailable (Assem and Vickers, in Press):—

1. Skin tests for penicillin allergy (even when carried out by an expert in this field) are unreliable, potentially dangerous, and even potentially fatal.

2. The drug itself is the least satisfactory test agent, and is potentially the most dangerous.

3. An intradermal injection can lead to death even before any local reaction is visible.

4. The reliability of an intradermal test depends on the nature of the material used. The only safe test material commercially produced (penicilloyl-polylysine—"PPL")—which is not available in Singapore or Malaysia—gives about fifty per cent false negatives.

5. In order to obtain the maximum information, several different types of test material must be used, including a "control".

6. At least fifteen minutes must be allowed for any local reaction to develop, and considerable experience is required for correct interpretation of the results.

7. Even if all the appropriate antigens and proper techniques are used, potential anaphylaxis will not necessarily be revealed.

8. Oral and topical preparations of penicillin can lead to anaphylactic death.

9. There is cross-sensitivity (in the meaning under discussion here) among all the penicillin and semisynthetic penicillin preparations in current use; and, almost certainly (in spite of some of the manufacturers' claim to be contrary), to the cephalosporin preparations.

MEANS OF PREVENTION

If it is accepted—as it must be—that skin testing has no role whatsoever to play in the prevention of penicillin anaphylaxis death (unless very specialized facilities are available), reliance must be placed on the clinical acumen of the doctor, including, in particular, his patience (and the patience of his patients). If he does not know in detail the medical history, the only way he can try to avoid penicillin anaphylaxis is by very careful questioning. First, he must ask about previous topical, oral and parenteral administration of penicillin (and its allied preparations), and about any unexpected reactions to it. It is important to appreciate that the patient may not recall, or may be unaware, that he has ever received penicillin in any form, and that, if he ever had a "reaction", it was due to penicillin. Secondly, he must enquire about allergic conditions such as asthma, allergic rhinitis, and atopic dermatitis; again, the patient may not recall, or be unaware of, ever having had any of these. Having obtained all this information, the doctor must then weigh up the "pros and cons" of giving an injection.

Difficulties likely to be encountered in Singapore and Malaysia in eliciting this information include those associated with the intellect and sophistication of the patient; the degree of rapport it is possible to establish at the language level; and the time available for such questioning. The coroner in a recent case in Singapore (Straits Times, 1971) is reported as having said that "one must bear in mind that many people do not understand the niceties of medical terms. As such they may not be in a position to tell the doctor whether they are allergic to penicillin." Nevertheless, he added, "it is worthwhile for doctors to enquire from patients if they had suffered ill-effects from the drug before."

It is not only worthwhile, but *essential*, and this is where the question of professional negligence arises. If doctors are to be freed from the bogey of the current implications in Singapore and Malaysia of not giving a test injection they must be all the more diligent in reducing the danger of fatal anaphylaxis by every other possible means. These include (as well as taking a careful history) having a justifiable reason for using penicillin, keeping the

patient under observation for an adequate length of time after the administration of a penicillin injection, and having the necessary drugs and apparatus for resuscitation readily available.

After an injection of penicillin has been given, the only debatable outstanding matter is the period of observation which should follow. The WHO Report recommended that all patients after receiving an injection of penicillin should be retained in the clinic for half-an-hour. It was found that "almost half of the 151 anaphylactic reactions were explosive and appeared immediately after penicillin administration (in the French group, "the drama lasted 3 minutes maximum"), and in another 36 per cent reactions occurred within 15 minutes."

A medical specialist witness in a case in Kuala Lumpur is quoted in the press (Straits Times, 1972) as saying, "A penicillin shot was normally given after 10 to 30 minutes after the test dose . . . but there is no standard time. If a doctor should wait only five minutes, I would say it is a little too short, but it would not amount to neglect." O'Holohan (1973) recommends waiting "a full half-hour" after the skin test (0·02 cc.), and then waiting "another full half-hour before releasing the patient" (an example of the patient's patience!). On the other hand, The Malacca Agricultural Medical Board Circular of 1964 (already referred to) recommended that "any patient given a penicillin injection should be kept under observation for a quarter of an hour."

IMPLICATIONS OF THE PRESENT SITUATION

No matter how phlegmatic the doctor, and no matter how impersonal was the relationship between him and the deceased, the experience of a penicillin anaphylaxis death is inevitably distressing for the doctor at the personal level. Added to this is the possibility of a public enquiry, which is unlikely to escape headlines in the local press—which can be nearly as lethal to the doctor as the injection was to his (or her) patient. Only those who have been through the experience, or who have been closely associated with them (as friend or colleague, or as medical or legal adviser) can really appreciate the distress and sometimes the hardship that can result.

In view of the widespread ignorance on the problem in this region, a doctor can be held to ransom by the relatives of a person who dies following an injection of penicillin by the threat of an action for negligence in the High Court, with all its attendant publicity. It is therefore obvious that, in order to avoid the unnecessary distress and hardship almost inevitably suffered by a doctor unfortunate enough to have a patient die of penicillin anaphylaxis, and, at least in Singapore, to avoid the possible castigations of a coroner (a doctor in such a situation should be legally represented), some action should be taken.

CONCLUSION

To give or not to give? The very frequent adaptation of the opening phrase from Hamlet's famous speech reflects the different types of dilemmas in which mankind finds itself. But surely, whether to give or not to give an injection of penicillin ought to be lifted above the level of a "doctor's dilemma". It should be possible to do this by the unqualified acceptance of indisputable medical and scientific evidence; provided always, of course, that the patient continues to be protected from professional negligence on the part of the doctor. It would be a tragedy if penicillin were to be virtually discarded at this stage of medical history because of an almost infinitesimal risk, even although this involves profoundly important implications for both patient and doctor.

However, it would surely be wrong to adopt the attitude of the correspondent in *La Presse Medicale* (Dupas, 1971) whose letter, with the typically French impassioned title, "Must we banish penicillin injections from current practice?", concluded dramatically that, because of the high incidence of reactions to penicillin (including his own experience), the drug should be confined to the treatment of endocarditis in hospital.

Nor is a more recently published argument (O'Holohan, 1973) acceptable: that "one penicillin injection can hardly be life saving today (with so many available alternative antibiotics) so why take the risk?" There is no merit in his subsequent argument that "if you must use penicillin injections in private practice, at least cover yourself by the skin test and at least half an hour to read the result. My advice is: do not use penicillin injections in private practice." The subsequent advice given in this article to pass the responsibility to the hospital, and the reasons for it, are of dubious morality, since the local hospital doctor is in no better position to ensure the avoidance of a fatal reaction than is the general practitioner: a skin test provides no more "cover" for a Government servant than it does for a general practitioner.

Nor are the implications of the "Taiwan Edict" acceptable—that if doctors follow its recommendations (to use a skin test) they will already have done their duty, and even if exceptional deaths occur the majority of such cases are inevitable (i.e. "an act of God"), and not the result of a deliberate act or mistake.

Penicillin must continue to be used, especially in developing countries, because of its efficacy in many conditions and of its relative cheapness. Chloramphenicol continued to be used extensively (even in "teaching" hospitals) for these very reasons for many years after its potential dangers were unequivocally established—but deaths from chloramphenicol were much less dramatic and seldom reached the headlines, and the doctors involved seldom reached the courts.

The topicality and urgency of the problem is illustrated by a recent local penicillin anaphylaxis death. In the Straits Times of 24th July, 1973, it was reported that a coroner's court in Singapore was told that a man died in an out-patient dispensary shortly after he had been given "a skin test with 40 units of penicillin". This was only a few months after the publication of an article in the Singapore Medical Association Newsletter, entitled "The Penicillin Dilemma" (Horne, 1973), which drew attention to the futility of a skin test, and which bluntly stated that penicillin itself is known to be the least satisfactory agent for the prediction of sensitivity to the drug, as well as being potentially the most dangerous. In the same newspaper on 27th July, the coroner (referring to the same case) is reported as lamenting, "Why is penicilloyl (*sic*), an effective test substance for penicillin (*sic*), not available in Singapore?" One reason is possibly its very high cost, but more likely it is hoped, because penicilloyl-penicillin is also known to be of very limited value in such a situation.

It is important to avoid seeking a hysterical solution to a situation that has developed in a hysterical kind of way, and to seek one that will allow doctors to continue to use penicillin at their professional discretion without the ever-present dread that, if they are unfortunate enough to be involved in an anaphylactic death—through no fault of their own—they run the risk of being pilloried and even blackmailed in the same way as some of their colleagues in Singapore and Malaysia have been in recent years.

It would seem to be imperative to have established some procedure which, whilst not protecting the negligent doctor, would avoid unjustifiable criticism and suffering in such cases. On the other hand, it would surely be wrong to arrange the law in such a way that a doctor must at least have made a show of having given a test dose solely to protect himself against litigation, irrespective of his real ability and conscientiousness—especially as it must now be accepted that the only type of test material he can administer (in Singapore and Malaysia, the drug itself) may be misleading and even lethal.

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