INFLUENCE OF PENICILLIN ALLERGIC REACTIONS ON VENEREAL DISEASE CONTROL PROGRAMMES*

BY

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Penicillin, in spite of other would-be contenders, is still the drug of choice for the treatment of both syphilis and gonorrhoea; and yet it is responsible for from 70–90 per cent. of all drug reactions encountered (Welch, Lewis, Weinstein, Boeckman, 1957; Casgrain, 1961; Tirlea and Angleseiscu, 1961). Indeed it is by far the commonest cause of drug allergy (Lowance, 1960; Maha, 1961), producing the most anaphylaxis (9 per cent. fatal), the most exfoliative dermatitis (10 per cent. fatal), and the most angio-oedema with respiratory involvement (13 per cent. fatal)—see Welch, Lewis, Weinstein, and Boeckman (1958).

The reactions to penicillin are many, and include toxic, microbiogenic, and allergic side-effects (Idsøe, Guthe, and Willcox, 1957; Guthe, Idsøe, and Willcox, 1958). Apart from local toxicity—especially with benzathine penicillin, which with some preparations nearly one-half of patients treated have experienced local pain (Krugman and Ebin, 1958)—penicillin is a remarkably non-toxic drug and it is almost impossible to administer a lethal dose by a single injection.

The possibility that some of the newer penicillins may affect the bone marrow has, however, been suggested (McElfresh and Huang, 1962), and some workers (e.g. Boyd, Boyd, and Brown, 1960) have postulated that certain reactions, including anaphylaxis and others generally attributed to allergy, are in fact toxic in nature in hypersusceptible subjects.

The microbiogenic effects of the Herxheimer reaction (therapeutic shock) and therapeutic paradox during the treatment of syphilis are really a testimony to the efficacy of the antibiotic. Bacterial resistance to penicillin has not so far occurred in respect of T. pallidum (Turner and Hollander, 1957), but is a potential problem in gonorrhoea (this is regarded as beyond the scope of this paper). Superinfection with other penicillin-insensitive organisms (e.g. Staphylococci, Monilia, etc.) is a side-effect common to all antibiotics and will not be considered further.

The most important reactions to penicillin are the immediate and late allergic reactions, which include anaphylaxis, urticaria, angio-oedema, and dermatitis (see, amongst many others, Dobson, Jillson, and Lobitz, 1957; Zimmerman, 1958; Willcox, 1959). Other rarer reactions include fixed drug eruptions (Verma, 1959); pachymeningitis (Farmer, Echlin, Loughlin, Breakey, and Duvoisin, 1960), purpura (Warwick, 1960); gangrene (Yeh Fang, 1958), and massive intestinal haemorrhage (Maha, 1961; Subhiyah, 1961). Not all the so-called allergic reactions are side-effects of penicillin; some may be due to the combined procaine (see Fernström, 1959; 1960a), particularly immediate reactions with tinnitus, dizziness, metallic taste, paraesthesiae, and acute mental disturbance (Hoigné and Schoch, 1959; Björnberg, 1959; Grounds, 1960), although, unlike the anaphylaxis which such reactions may resemble, there is no circulatory collapse (Björnberg and Selstam, 1960).

It is anaphylaxis from which fatalities may result which commands the greatest attention: of all allergic reactions it is the greatest potential inhibiting factor on a venereal disease programme. It has been stated that only two deaths from penicillin sensitivity were recorded during the first 9 years of penicillin usage, but from 1953–54 onwards increasing numbers came to be reported from the countries in which penicillin had been most widely used (Kern and Wimberley, 1953; Babione, 1956; Rajam and Rangiah, 1956; Guthe and others, 1958; Idsøe and Wang, 1958), although other cases may have occurred elsewhere at an earlier date (Chiang Shih-yü, 1957).

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By 1957 it was estimated that over 1,000 deaths from anaphylaxis to penicillin had occurred in the USA (Peters, Henderson, and Prickman, 1957).

At first serious anaphylaxis was rare following penicillin given orally, but in recent years an increasing number of cases has been recorded (Fraser, 1958; Balson, 1960; Miller, 1960; Todd, 1960), including a few fatalities (Levine, Perri, and Anthony, 1960) even in children (Mason, 1957). Anaphylaxis has even occurred from the use of lozenges containing penicillin (Gullatt, 1957) and of rectal suppositories (Halpern, 1960).

To-day fatalities are still occurring (Schweiz. med. Wschr., 1958; Schiff and Davis, 1961) and are being experienced in countries not previously troubled by them (Subhijah, 1961). It has been estimated by the Mexican Society of Allergists that in Mexico there was one death daily from penicillin allergy (Mallén, 1960)—although this would seem to be an extravagant estimate. The publicity such cases have engendered has interfered with the development of programmes aimed at venereal syphilis (WHO, 1958; Idsøe and Wang, 1958). Opposition has been offered to the routine administration of penicillin to adult populations for the eradication of non-venereal treponematoses, e.g. pinta (Mallén, 1960). The risk of fatalities certainly represents a legal hazard to the practitioner and several fatal cases of anaphylaxis have been the subject of law-suits (Rosenthal, 1958).

**Prevention of Allergic Reactions**

In the prevention of allergic reactions to penicillin it has been repeatedly emphasized that penicillin should not be given except on sound therapeutic or prophylactic indications and particularly that the local use of penicillin should be discouraged, as its use in local ointments, compresses, instillations, and aerosols, etc., has in many cases led to sensitization when penicillin was used for fresh conditions at a later date (Tirlea and Angelesco, 1961).

The taking of a careful history before administering penicillin and the use of an alternative when previous upset to it, or other allergy—particularly asthma—is recorded, will do much to prevent serious reactions, although anaphylaxis can occur even in persons who apparently have not had previous penicillin—possibly from hidden sources, e.g. milk, syringes, virus vaccines, and cross-sensitization with other fungi (Rosenthal, 1958; Siegel, 1959). It is also very important to have adrenalin and other drugs and the means of their administration readily at hand for the prompt treatment of anaphylaxis should it occur (Taggart and Greaves, 1960).

The above measures have been fairly widely adopted in recent years and appear to have reduced the fatality rates from anaphylaxis from about 28 per cent. (Welch, Lewis, Kerlan, and Putnam, 1953) to about 9 per cent. (Welch and others, 1958).

Other measures, less widely adopted, include the keeping of patients in the clinic for 30 minutes after an injection (Brown, 1960; Brown, Simpson, and Price, 1960), and the use of test doses of oral penicillin (Brown, 1956), or other drugs in combination with penicillin, and of skin and serum tests in an attempt to detect penicillin sensitivity in advance.

As has been indicated, fatal cases of anaphylaxis can occur even after oral administration. Although some authors (e.g. Graciansky and Grupper, 1961) have claimed that the simultaneous use of steroids will reduce the incidence of Herxheimer reactions, cases of anaphylaxis to penicillin have occurred in patients on steroid therapy (Bernstein and Lustberg, 1957). The simultaneous use of antihistamines has been stated not to reduce the incidence of reactions (Sciple, Knox, and Montgomery, 1959, 1960) although others (e.g. Brown, Simpson, and Price, 1961) consider that they reduce the risk.

Some authors (e.g. Brown, 1956; Cazort and Johnston, 1957) urge the use of skin tests which, although not of great help in detecting delayed reactions, are considered by some to be serviceable in indicating potential anaphylaxis (Steele and Hijazi, 1959; Fernström, 1960b—see also Lancet, 1957; Gerber and Colle, 1961). Negative skin tests still offer no complete assurance that anaphylaxis may not occur (Teigland, 1957; Fernström, 1960b) and positive reactions do not indicate that anaphylaxis is inevitable.

If skin tests are made, scratch and conjunctival tests are recommended rather than intradermal tests (Schiff and Davis, 1959; Steele and Hijazi, 1959), for fatal or severe cases of anaphylaxis and cases of precipitate labour and stillbirth (T’ao Jen and Sung Chieh, 1958) have followed the giving of minute quantities of penicillin by intradermal testing (Wang, 1957).

Although the scratch and conjunctival tests can produce a result in 15 to 20 minutes (Steele and Hijazi, 1959), and it has been stated that approximately only 1 per cent. of patients will be denied therapy by this means (Smith, 1957), their mass use in a syphilis control programme at once poses the difficult problem of what to do with the accumulating numbers of positive reactors, e.g. in Taiwan, where 0·5–2 per cent. of positive reactors were obtained (WHO, 1958).

In more recent years anti-penicillin antibodies have been studied by haemagglutination techniques
(Epp, 1959; Bird, 1960; Harris and Vaughan, 1961) and specific anti-penicillin antibodies have been found. The thrombocytopenic index and other tests have also been studied (Heijer, Nilzen, Skog, and Solberger, 1960). The findings with such tests have not so far proved adequate in the detection of potentially anaphylactic persons. Newer tests, e.g. the basophil reaction, are under investigation and are said to be more promising (Shelley and Juhlin, 1961).

Thus far, therefore, sensitivity tests have had no wide application in venereal disease clinics. In dealing with communicable diseases like syphilis and gonorrhea, speed is essential, so that any test which is developed in the future will have to be swift and easy of performance on a "while-you-wait" basis to be of maximum service to the venereologist.

Implications of Penicillin Allergic Reactions in the Control of Syphilis and Gonorrhea

Important questions from the standpoint of venereal disease control are:

1. How frequent are penicillin reactions in patients with venereal disease?
2. How often are they serious or fatal?
3. To what extent do they interfere with the treatment of the patient or with venereal disease control as a whole?
4. Is the problem increasing?

These questions are considered below in the light of recorded reports in the literature and of the experience of two venereal disease clinics, one a large clinic in London (St. Mary's Hospital), and the other a smaller clinic situated at Windsor about 25 miles from London.

At the former no less than 108,311 new patients were seen during the period 1945–61, of which it is estimated that some 35,000 have been treated with penicillin (32·4 per cent). Sample series of 226 cases of syphilis and 200 cases of gonorrhoea in which penicillin was used during 1960–61 are also reviewed.

At the latter the reactions to penicillin of 895 patients given 7,300 injections of the antibiotic during the years 1946–56 (Willcox and Fryers, 1957) are compared with those of a further 314 patients given 877 injections in 1959–61—an overall total of 1,635 penicillin-treated patients receiving detailed study.

Incidence of Penicillin Reactions

Rates of allergic reactions to penicillin quoted in the literature vary between 1 and 53 per cent. depending particularly on methods of observation and recording, criteria of definition, and on the nature of the treated group. From 1 to 10 per cent. is common (Cortes, 1960; Arif, 1961; Moore and Woody, 1960), although figures of only 1 to 2 per cent. are recorded in large series of patients (Babione, 1956; Bernstein and Houser, 1959; McFarland, 1958; Med. J. Austr., 1959; Willcox, 1958). In some series minor reactions not reported by the patients are likely to have been ignored. A frequently quoted figure is 2 per cent. of children, 5 per cent. of non-allergic adults, and 15 per cent. of allergic patients (Brown, 1956; Kandar, 1959).

Reaction rates in over 74,000 patients with venereal disease quoted in the literature between 1955 and 1961 have generally been low (Table I).

The relationship between the incidence of reactions and the number of injections has been noted by many authors (see Willcox and Fryers, 1957; Brown and others, 1961; and Table IV). This is reflected also in a direct relationship with dosage, duration of therapy, age of the patient, and also of diagnosis (Table II).

Thus, in the author's data from the Windsor clinic, the incidence of allergic reactions in patients treated with multiple injections for syphilis was ten times that observed in the treatment of gonorrhoea in which single injections were usually given. The
close relationship of allergic reactions with the number of injections is shown in Table III.

Table III

<table>
<thead>
<tr>
<th>No. of Injections</th>
<th>Total</th>
<th>Reactions</th>
<th>Cumulative per cent.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1,635</td>
<td>12</td>
<td>0-73</td>
</tr>
<tr>
<td>2-4</td>
<td>871</td>
<td>11</td>
<td>1-27</td>
</tr>
<tr>
<td>5-9</td>
<td>652</td>
<td>23</td>
<td>3-53</td>
</tr>
<tr>
<td>10-19</td>
<td>420</td>
<td>16</td>
<td>3-81</td>
</tr>
<tr>
<td>20 or More</td>
<td>123</td>
<td>7</td>
<td>5-69</td>
</tr>
<tr>
<td>Total</td>
<td>1,635</td>
<td>69</td>
<td>4-22</td>
</tr>
</tbody>
</table>

Thus, of 1,635 venereal diseases patients treated with penicillin, there were 69 possible allergic reactions (4·22 per cent.). The incidence was lowest (0·73 per cent.) after the first or single injection and the cumulative percentage of reactions rose virtually in a straight line as the number of injections was increased.

Reaction rates following single or multiple injections reported by other authors are shown in Table IV.

Table IV

<table>
<thead>
<tr>
<th>Author</th>
<th>Date</th>
<th>Reaction Rate Percent.</th>
<th>No. of Cases</th>
<th>No. of Fatalities</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Single Injection</td>
<td>Multiple Injection</td>
<td></td>
</tr>
<tr>
<td>Brown and Others</td>
<td>1961</td>
<td>0·53</td>
<td>6·6</td>
<td></td>
</tr>
<tr>
<td>Smith, Kamp, Olansky, and Price</td>
<td>1956</td>
<td>0·19</td>
<td>7·4</td>
<td></td>
</tr>
<tr>
<td>Wilcox and Fryers</td>
<td>1957</td>
<td>0·0</td>
<td>9·0</td>
<td></td>
</tr>
<tr>
<td>Sciple and Others</td>
<td>1959</td>
<td>0·48</td>
<td>10·2</td>
<td></td>
</tr>
<tr>
<td>Tung and Others</td>
<td>1957</td>
<td>—</td>
<td>7·4</td>
<td></td>
</tr>
<tr>
<td>Morton</td>
<td>1957</td>
<td>—</td>
<td>—</td>
<td></td>
</tr>
</tbody>
</table>

Reaction rates of approximately 0·5 per cent. or less may thus be expected after single injections, whereas with multiple injections rates of 6–10 per cent. may be encountered.

How often are Penicillin Reactions Serious or Fatal?

Reported fatalities from penicillin in venereal disease patients are low (Table V), i.e. one per 78,002 patients treated.

Included in Table V are the author's own data. At St. Mary's Hospital, of 108,311 new patients seen between 1945 and 1961 (76,919 male), 37,124 (34·3 per cent.) had syphilis or gonorrhea. Excluding those treated with other drugs, largely on research schedules, an estimated total of 35,000 patients was treated with penicillin and there were no fatalities. At Windsor, among 895 patients treated between 1946 and 1956, there was one delayed fatality from dermatitis (Willcox and Fryers, 1957), and among 314 patients treated between 1959–61 or in the intervening period there was none. In total this implies one death per 78,000 cases treated, which is literally one death or none at all in a lifetime of professional experience for most venereologists.

Table V

<table>
<thead>
<tr>
<th>Source</th>
<th>Author</th>
<th>Date</th>
<th>No. of Cases</th>
<th>No. of Fatalities</th>
</tr>
</thead>
<tbody>
<tr>
<td>USA, 1960</td>
<td>Brown and Others</td>
<td>1961</td>
<td>100,000</td>
<td>1</td>
</tr>
<tr>
<td>USA, 1959</td>
<td>Brown and Others</td>
<td>1961</td>
<td>35,406</td>
<td>0</td>
</tr>
<tr>
<td>USA, 1961</td>
<td>Sciple and Others</td>
<td>1959</td>
<td>4,337</td>
<td>0</td>
</tr>
<tr>
<td>Norway, 1946–59</td>
<td>Gjessing</td>
<td>1960</td>
<td>55,231</td>
<td>0</td>
</tr>
<tr>
<td>UK, 1946–56</td>
<td>Wilcox and Fryers</td>
<td>1957</td>
<td>385</td>
<td>1</td>
</tr>
<tr>
<td>UK, 1945–61</td>
<td>Present paper</td>
<td>1964</td>
<td>35,314</td>
<td>0</td>
</tr>
<tr>
<td>WHO (17 countries), 1952–56</td>
<td>Wilcox</td>
<td>1958</td>
<td>626,551</td>
<td>9</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td>852,024</td>
<td>11</td>
</tr>
</tbody>
</table>

If the incidence of total reactions was between 1 and 10 per cent. for each fatality, there would have been between 858 and 8,580 milder reactions. Large-scale data (Brown and others, 1961) have shown that only about one-sixth or less of non-fatality reactions are anaphylactic in nature, most of the remainder being due to urticaria and angio-oedema. Only about one-third of the anaphylactic cases are severe or even moderate in degree.

Fatalities are very few in relation to the vast amount of penicillin used. Gjessing (1960) reported no fatalities after the use of 4·6 billion units of penicillin for venereal disease patients in Norway, and Babione (1956) observed none in an issue of 3,453 billion units over a 3-year period to the US navy.

Is the Problem of Penicillin Sensitivity Reactions Increasing?

The dramatic impact of the spate of cases of fatal anaphylaxis reported in the early fifties led clinicians to suppose that the problem of penicillin reactions was an increasing one. A number of authors (e.g. Brown, 1956; Peters and others, 1955) have suggested that the incidence is increasing even in children (Maha, 1961), an annual increment of 1 per cent. per year having been suggested (Brown, 1956).

As it has been stated that immediate reactions are more likely in those who have received penicillin on an earlier occasion (Med. J. Austr., 1959), the immediate reaction rate should be related to the proportion of the treated population who have previously had penicillin.
However, although it has been shown (Willcox and Fryers, 1961; Brown and others, 1961) that there is an increased incidence of reactions in patients who have had penicillin previously compared with those who have not, the apparent increase (from 5.95 per 1,000 in 1954 to 9.71 per 1,000 in 1959 in the data of Brown and others, 1961) was considered likely to have been due largely to an increasing awareness of reactions, and to the practice of retaining treated patients in the clinics for 30 minutes during the later year. It must be remembered that under current practice those who are most likely to show a reaction, i.e. those who had a reaction on a previous occasion, are usually not now given any opportunity to contribute and the difference between “penicillinized” and “non-penicillinized” persons is less striking than otherwise might be the case.

Certainly, in the author's personal data, there is no evidence of an increase in the incidence of reactions—indeed if anything the opposite (Table VI).

**TABLE VI**

**PENICILLIN REACTIONS IN A SMALL CLINIC** (Windsor)

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>1946-56</th>
<th>1959-61</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of</td>
<td>No.</td>
</tr>
<tr>
<td></td>
<td>Patients Treated</td>
<td>Reactions</td>
</tr>
<tr>
<td>Syphilis</td>
<td>366</td>
<td>33 9.1</td>
</tr>
<tr>
<td>Gonorrhoea and Other Conditions</td>
<td>529</td>
<td>10 1.9</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>895</td>
<td>43 4.8</td>
</tr>
</tbody>
</table>

If reactions are related to previous penicillin administration it would be expected that there would be no further increase in incidence once the saturation point of “penicillinization” has been reached, or once the proportion of “penicillinized” persons had become stabilized.

Indeed in some areas, e.g. Igloo, North Dakota, where over 99 per cent. of a small community were shown to have received antibiotics, almost complete saturation appears to have been achieved (Nolen and Dille, 1957). At present, in London, approximately 70 per cent. of male venereal disease patients have had penicillin previously, the figure for females who tend generally to fall into a lower age group being somewhat less (Table VII).

These figures compare with 76.5 per cent. for males and 57.1 per cent. for females in a study of 275 venereal disease patients in London undertaken in 1958 (Willcox, 1959). The average age for female patients attending venereal disease clinics (24.3 years in the latter study) tends to be lower than that of males (29.5 years).

**TABLE VII**

**PREVIOUS PENICILLIN ADMINISTRATION TO VD PATIENTS**

<table>
<thead>
<tr>
<th>Source</th>
<th>Diagnosis</th>
<th>Sex</th>
<th>Total Cases</th>
<th>Previous Treatment Known</th>
<th>Previous Penicillin</th>
</tr>
</thead>
<tbody>
<tr>
<td>London, 1960-61</td>
<td>Syphilis and Gonorrhoea</td>
<td>M</td>
<td>429*</td>
<td>364</td>
<td>258 70.9</td>
</tr>
<tr>
<td>Windsor, 1959-61</td>
<td>Venereal Disease</td>
<td>M</td>
<td>863</td>
<td>579</td>
<td>411 71.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>F</td>
<td>454</td>
<td>343</td>
<td>164 47.8</td>
</tr>
</tbody>
</table>

* Average age 29.3 years

**How far do Penicillin Reactions interfere with a Venereal Disease Control Programme?**

While it cannot be denied that the publicity engendered by fatalities from penicillin may interfere with the development of a mass venereal disease programme (WHO, 1958), it is not usually the fatalities amongst venereal disease patients which brings this about but rather those occurring in the population at large, especially when the antibiotic is being indiscriminately used. Amongst venereal disease patients fatalities have been shown to be excessively rare. They are particularly rare if a history is taken of previous upset due to penicillin or of other allergy, and if alternative drugs (e.g. the tetracyclines) are used when a positive history has been obtained.

The frequency with which such a history may be obtained and alternative drugs may be necessary is shown in Table VIII.

**TABLE VIII**

**CONTRA-INDICATIONS TO PENICILLIN THERAPY IN VENEREAL DISEASE PATIENTS, 1959-61**

<table>
<thead>
<tr>
<th>Patients</th>
<th>No.</th>
<th>Per cent.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>1,317</td>
<td>922</td>
</tr>
<tr>
<td>Previous Treatment Known</td>
<td>28</td>
<td>5</td>
</tr>
<tr>
<td>Previous History of Allergy</td>
<td>33</td>
<td>3.58</td>
</tr>
</tbody>
</table>

Of the 922 patients (Windsor) concerning whom information was available, previous allergy to penicillin had been noted in 28 (3.04 per cent.). As the number known to have had penicillin was 575, the rate of allergy in those known to have had the antibiotic was 4.87 per cent. The reactions included one case each of vomiting, nausea, fever, faintness, and dizziness, eleven of urticaria (restricted to the injection site in one case), four of angio-oedema,
three of dermatitis or eczema, and three of local sensitivity from ointment or eye drops. In two cases the reported reactions were not classifiable: in one of these the patient stated that the leg swelled afterwards and he could not walk properly for 6 months, and in the other that the leg went blue and he was told not to have penicillin again.

Five patients (0·54 per cent.) gave a history of allergy other than to penicillin; one was asthmatic, three suffered from flexural eczema or dermatitis—in one patient with aortic syphilis this was generalized from chlorothiazide—and one had had a rash from streptomycin. Penicillin had been given previously in only one of these five cases. Thus, in the total group of 922 venereal disease patients, a decision to withhold penicillin was considered in 3·58 per cent.

Possible sensitivity to penicillin is a negligible problem in venereal diseases other than syphilis. For non-gonococcal urethritis and trichomoniasis penicillin is not used as it is ineffective. For gonorrhoea there are many other effective antibiotics (streptomycin, the tetracyclines, spiramycin, erythromycin, actinomycin, chloramphenicol, etc.) which can easily be substituted whenever an allergic history is obtained. With single injections of penicillin reactions are few. Indeed of 200 male patients with gonorrhoea treated in 1960 (68·5 per cent. of whom had had penicillin before), there was only one case of reaction (urticaria at 3 days). i.e. 1·5 per cent. of those treated.

It is in syphilis and the other treponematoses therefore that the biggest problems arise. Reactions to penicillin have occasioned little concern in the vast campaigns against treponematoses mounted by the World Health Organization, particularly those against yaws and the endemic treponematoses in the course of which over 36 million persons have now been treated with penicillin (WHO, 1962). The populations concerned are predominantly children in whom the incidence of reactions is lower than in adults, and they are usually persons from backward areas whose previous opportunities of exposure to penicillin have been slight (Idsoe and others, 1957). Moreover, many of the patients are Negroes in whom reaction rates are lower than in other races (Brown and others, 1961). The problem is therefore virtually confined to campaigns against venereal syphilis or to those involving the adult populations of towns.

**Influence of Penicillin Reactions upon the Treatment of Patients with Venereal Syphilis**

Of 229 male patients with syphilis seen in London in 1960–61, whose average age was 30·1 years and of whom 57 were Negroes, 121 (52·8 per cent.) were known to have had penicillin previously and four were believed to have been allergic to it (urticaria 2; unstated 2). This represented 3·3 per cent. of those who had had penicillin but only 1·75 per cent. of the whole group. One of these patients was a treated case and no more treatment was given, one was given a 10-day course of penicillin without trouble, and two (0·87 per cent. of the entire group) were treated with tetracyclines instead. There were no cases of previous allergy from other reasons, but one patient later developed a dermatitis from sulphonamides.

Penicillin was given to 226 of these patients by multiple injections, either of procaine penicillin or procaine penicillin with aluminium monostearate daily, or of the latter preparation twice weekly. Excluding Herxheimer reactions, suspected allergic reactions to penicillin were noted in seventeen cases (7·52 per cent.). The reaction rate was only 1·77 per cent. among the Negroes compared with 9·57 per cent. for the remainder. This finding is in accord with those of other authors (e.g. Brown and others, 1961).

Of the seventeen reactions noted, one patient fainted immediately after the injection, one developed a profuse petechial rash at 3 days, ten had urticaria alone (two at 6–7 days, six at 8–14 days, one at 25 days, one at 56 days), one had urticaria and angio-oedema at 14 days, two had angio-oedema at 9 and 12 days respectively, one had dermatitis at 10 to 18 days (although this patient had also had local treatment for scabies), and in one the reaction was unspecified (although he had already received 7·2 mega units penicillin). In no case was the reaction life-threatening.

Thus, in all but four patients (1·77 per cent. of those receiving penicillin), the reaction took more than a week to appear. Thus, even in cases likely to have reactions, the majority may have been given a minimal curative dose of a repository penicillin before the reaction is evident.

In the current series, of 226 receiving penicillin, 208 received 6 mega units or more and eighteen (7·96 per cent.) less than this amount. However, in the majority of these eighteen cases, the amount of penicillin given was small because the patient defaulted rather than because of reaction. Of the seventeen patients showing reaction, the amount received was less than 6 mega units in only five (2·2 per cent. of the entire treated group), and four of these patients had received 3·0, 3·6, 4·4, and 4·8 mega units respectively. Only one patient (the one who fainted after the first injection of 0·9 mega units) received an amount of penicillin unlikely to
have been beneficial to the syphilitic condition. Thus, even in this series of patients with venereal syphilis treated with multiple injections, 97.8 per cent. received a curative dose of penicillin.

Because many allergic reactions to penicillin take time to develop (see also Bjornberg and Selstam, 1957; Tung and others, 1957; McFarland, 1958), and because the incidence of reactions increases with the number of injections, it is desirable to use the single or double injection techniques with long-acting benzathine penicillin or procaine penicillin with aluminium monostearate, so that if a reaction occurs a minimal curative dose will already have been given. This gives added force to the policy of using the so-called "epidemiological" dose of repository penicillin in the treatment of infectious syphilis as a protection to the patient and the community, should he default after only one injection.

However, it is felt that, because of the risk of serious reactions, penicillin should be given to adults in developed urban areas only on the responsibility of an attendant physician who can ensure that the available methods of preventing and alleviating them can be effectively applied. As even a mass campaign in an urban area is usually conducted from a fixed centre, this affords no particular difficulty. It is fortunate that, in mass campaigns against the treponematoses in the under-developed rural areas where medical men are at a premium, allergic reactions to penicillin have so far been of little concern although the situation is being closely watched.

By and large the author agrees with the views of others such as McFarland (1958) that allergic reactions offer no serious deterrent to the use of penicillin where indicated. The fatalities have been rare in relation to the vast amounts of penicillin used (see Gjessing, 1960)—as low as 1.8 reactions per billion units (Babione, 1956).

Applying the fatality rate of 1 in 78,000 cases to the 1,323,677 cases of syphilis and 2,388,638 cases of gonorrhoea reported by US State Health Departments for the fiscal years 1952-61, would give an anticipated total of 47 fatalities in 10 years. Whether this approach realise the author does not know, but no such numbers have apparently been recorded in the literature although doubtless some cases of venereal disease are treated by general practitioners and the reactions that occurred might not be reported. It is interesting by comparison to observe that in 15 years 340 young Americans have been killed playing American football (Blonstein, 1962); this would average 226 deaths over a 10-year period and would appear to indicate that the problem of deaths from American football might be 4.8 times greater than the possible fatality rate from penicillin sensitivity reactions in venereal disease patients. Few of us would discourage our sons from playing football because of this risk. We should therefore have even less fear of their being treated by penicillin should they unfortunately contract venereal disease!

In England and Wales, where 37,716 cases of syphilis and gonorrhoea were treated in venereal disease clinics in 1960, the estimated number of fatalities from penicillin would be approximately 0.5 of a case. There were 527,532 deaths from all causes in 1960, so that less than one-millionth of all deaths would be due to penicillin given in venereal disease clinics. Some comparisons with deaths from other causes (Table IX) show that there were, for example, 3,000 times as many deaths from accidental poisoning in 1960 than the number estimated from penicillin in VD clinics, indicating that the problem is relatively insignificant and that there is a need for a sense of proportion.

<table>
<thead>
<tr>
<th>Cause</th>
<th>No. of deaths</th>
<th>Multiple of Deaths from Penicillin in VD Clinics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penicillin in VD Clinics</td>
<td>(estimated) 0.5</td>
<td>1</td>
</tr>
<tr>
<td>Gout</td>
<td>18</td>
<td>36</td>
</tr>
<tr>
<td>Aircraft Accidents</td>
<td>48</td>
<td>96</td>
</tr>
<tr>
<td>Water-transport Accidents</td>
<td>176</td>
<td>352</td>
</tr>
<tr>
<td>Homicide and Injury inflicted by Others</td>
<td>234</td>
<td>468</td>
</tr>
<tr>
<td>Railway Accidents</td>
<td>254</td>
<td>508</td>
</tr>
<tr>
<td>Accidental Poisoning</td>
<td>1,500</td>
<td>3,000</td>
</tr>
<tr>
<td>Suicide</td>
<td>5,118</td>
<td>10,236</td>
</tr>
<tr>
<td>Road Vehicle Accidents</td>
<td>6,740</td>
<td>13,480</td>
</tr>
</tbody>
</table>

**Summary and Conclusions**

(1) Allergic reactions to penicillin, which is the drug of choice for the treatment of both gonorrhoea and syphilis, are reviewed. Penicillin is the commonest cause of drug allergy, and cases of anaphylaxis, which may prove fatal, are naturally of serious concern.

(2) The prevention of penicillin reactions is considered. The practice of taking a careful history of previous upset to penicillin, or of other allergy, and of giving an alternative antibiotic if indicated is endorsed, as is the necessity of having the appropriate measures of resuscitation available should anaphylaxis occur. The policy in some areas of keeping patients in the clinic for 30 minutes after an injection of penicillin is noted and other possible methods of prevention are reviewed.
Skin, serum, and other tests to detect allergy have not so far been generally regarded accurate enough or simple enough to perform to be of value in a mass venereal disease control programme. Current developments in this field are receiving close attention.

(3) The incidence of penicillin reactions in venereal disease patients has generally been low. Collected data of over 74,000 cases has shown a reported incidence of less than 1 per cent. but such rates were encountered with single injection techniques. When multiple injection techniques are used in the treatment of syphilis, reaction rates of 6.6 to 10.2 per cent. have been reported. Reaction rates are lower in Negroes than in other persons.

(4) Fatalities (from anaphylaxis and other causes) are very rare in relation to the vast amounts of penicillin used. It is estimated, from a collective survey of 858,024 venereal disease patients treated with penicillin, that there was one death per 78,002 patients treated, which implies an average of one death or less in the professional life-time of most venereologists.

(5) With the increasing use of penicillin, it might be expected that the incidence of penicillin reactions would increase. However, once the degree of "penicillinization" of the population has become stabilized and is no longer increasing, and provided the drug is withheld from suspected allergic subjects, the evidence suggests that the problem of allergic reactions in venereal disease patients is not one that continues to increase in magnitude.

(6) Penicillin is not used in the treatment of nongonococcal urethritis or of trichomoniase. Many other effective antibiotics can be used in gonorrhoea in suspected allergic subjects. Allergic reactions have so far proved of little importance in mass campaigns against the endemic treponematoses, in which the largest numbers of those treated are usually "unpenicillinized" children in underdeveloped rural areas who are given single injections. The greatest threat of allergic reactions to penicillin lies in the treatment of venereal syphilis in adult urban populations.

(7) In the author's data relating to venereal syphilis in and around London, a previous history of allergy contra-indicated the use of penicillin in only 1.75 to 3.58 per cent. of cases, and the antibiotic could be used in 96.4 to 98.2 per cent. of cases. If multiple injections are used some reactions will be observed (7.5 per cent. of cases in this series), but the late occurrence of many of them will ensure that all but a few patients (2.2 per cent. in the series quoted) will have already received a curative dose of the antibiotic. This percentage may be even further reduced if more use is made of the massive first injection, the so-called "epidemiological" dose.

(8) It is therefore felt that the situation, in which the use of the less satisfactory alternative orally-administered tetracyclines has to be considered in only 4-6 per cent. of cases, and in which the prescribed penicillin schedules can be followed in 94-96 per cent. of cases, is not one which at present offers a serious threat to a treponematosis-control programme although continued vigilance is required.

REFERENCES

Reactions allergiques inattendues à la pénicilline et contrôle épidémiologique des maladies vénériennes

RÉSUMÉ

(1) L'auteur passe en revue les réactions allergiques à la pénicilline; celle-ci est le médicament de choix contre la gonorrhée et la syphilis, mais elle cause la plupart des allergies, et les anaphylaxies qui peuvent être fatales sont un sujet d'inquiétude.

(2) Afin de prévenir les réactions inattendues, il faut rechercher les antécédents de malaise du à la pénicilline ou d'autre allergie, donner un autre antibiotique aux suspects, et tenir toutes prêtes les mesures de ressuscitation. Dans quelques pays le malade est obligé de rester à la clinique pendant 30 minutes après l'injection. Les tests de la peau, du sérum, etc., pour la découverte de l'allergie ne sont pas encore assez exacts ou assez simples pour qu'on les emploie dans les grands programmes épidémiologiques antivénéériens. On suit de très près les progrès dans ce domaine.

(3) L'incidence des réactions inattendues chez les personnes atteintes de maladies vénériennes a été faible—moins de 1%. Pour 74,000 cas traités par une seule injection. Cependant, les régimes de plusieurs injections ont été suivis de 6,6 à 10,2% de réactions. Celles-ci sont moins nombreuses parmi les nègres que parmi les autres races.
PENICILLIN ALLERGIC REACTIONS AND VD CONTROL

(4) Les fatalités (dues à l’anaphylaxie ou aux autres causes) sont rares quand on pense aux énormes quantités de pénicilline qui ont été employées dans le monde. Dans une série de 858,024 malades traités, il y eut un seul décès sur 78,002 cas, ce qui veut dire une mort ou moins dans toute la vie professionnelle d’un vénéréologue.

(5) Avec l’augmentation de l’emploi de la pénicilline, on pourrait penser que les réactions deviendraient plus nombreuses, mais lorsque la “pénicillinisation” d’une population est stabilisée et pourvu qu’on refuse cet antibiotique aux personnes suspectées d’être allergiques, les données indiquent que le problème ne devient pas plus sérieux dans les cliniques antivénériennes du monde.

(6) On n’emploie pas la pénicilline contre l’urétrite non gonococcique ni contre la trichomoniase.

On peut se servir de plusieurs antibiotiques efficaces contre la gonorrhée chez les personnes suspectées d’être allergiques.

Les réactions ont eu peu d’importance dans les grandes campagnes contre les tréponématoses endémiques où la plupart des sujets sont des enfants qui habitent des villages où la pénicilline était inconnue auparavant et qui reçoivent une seule injection. Le plus grand danger est toujours le traitement de la syphilis vénérienne chez l’adulte dans les centres urbains.

(7) Un examen des données de l’auteur sur la syphilis vénérienne à Londres et aux environs révèle des antécédents d’allergie interdisant l’emploi de la pénicilline dans seulement 1,75 à 3,58% des cas; l’antibiotique fut employé dans 96,4 à 98,2% des cas. Quand on donne plusieurs injections on doit s’attendre à quelques réactions (7,5% dans cette série), mais leur développement est tellement tardif que la plupart des sujets ont déjà reçu une dose assez forte pour guérir. On peut encore réduire le pourcentage (2,2% dans cette série) de sujets non guéris par l’administration plus fréquente d’une première injection massive, dite “dose épidémiologique”.

(8) Il semble donc que, malgré la nécessité d’une surveillance prudente, ces réactions inattendues n’empêchent pas l’emploi épidémiologique de la pénicilline, puisqu’on peut suivre le régime prescrit dans 94 à 96% des cas, et qu’il ne faut administrer les tétracyclines orales qu’à 4 à 6% des cas.
Influence of Penicillin Allergic Reactions on Venereal Disease Control Programmes

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