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UNTOWARD PENICILLIN REACTIONS

T. GUTHE, M.D.
O. IDSÖE, M.D.
R. R. WILLCOX, M.D.

Venereal Disease and Treponematoses Section,
World Health Organization, Geneva

SYNOPSIS

The literature on untoward reactions following the administration of penicillin is reviewed. These reactions, including a certain number of deaths which have been reported, are of particular interest to health administrations and to WHO in view of the large-scale programmes for controlling the treponematoses which are now under way—programmes affecting millions of people in many parts of the world.

The most serious problems are anaphylactic sensitivity phenomena and superinfection or cross-infection with penicillin-resistant organisms, and the reactions involved range in intensity from the mildest to the fatal; the incidence of the latter is estimated at 0.1-0.3 per million injections. The authors point out that with increasing use of penicillin, more persons are likely to become sensitized and the number of reactions can therefore be expected to rise. The best prevention against such an increase is the restriction of the unnecessary use of penicillin.

BACKGROUND AND PERSPECTIVE

To date, more than 400 antibiotic substances have been evolved—products of bacteria, of actinomycetes, and of fungi, and antibiotically active agents biosynthesized by plants, derived from animal sources, or synthesized by the chemist. Not only has the discovery of antibiotics brought about a revolutionary advance in the control of infectious diseases in human medicine and public health, but antibiotics have also contributed significantly to success in agriculture and veterinary medicine (e.g., control of infectious diseases in cattle, growth stimulants in animals, plant pathology, food preservation and processing, etc.). The over-all importance of antibiotics is shown by the magnitude of their production, which now outranks that of all other medicaments added together. Some 50% of the value of the world's pharmaceutical production is thus represented by these drugs. By 1953 more than 600 tons of penicillin, streptomycin

and broad-spectrum antibiotics had been produced (Pratt & Dufrenoy, 1953); in 1955, the world production of penicillin alone exceeded 500 tons. The great increase in production is illustrated by the fact that in 1943, the first year of commercial production of antibiotics in the USA, only 29 pounds of crude penicillin were produced, while by 1956 crystalline antibiotics were being manufactured at the enormous rate of 1 500 000 pounds yearly (Welch, 1957).

When this perspective is kept in mind, it is not surprising to note not only that health workers have become aware of the preventive and curative impact of antibiotics on health and disease but also that the actual and potential undesirable effects of antibiotics both from the point of view of individual medication and in regard to the public health have gradually been recognized. Although there has been much speculation on the long-term effect of antibiotics, it appears impossible as yet to discuss their potential broad influences on the environment, resulting from their wide use in the human, the animal and the plants worlds. Nor is sufficient knowledge available to consider their ultimate influence on social and economic problems, such as may result from the prolongation of life and the increase of populations which could tax the production of the earth (Pratt & Dufrenoy, 1953). A great deal of knowledge has, however, accumulated on the usefulness of antibiotics in the control of infections and on certain aspects of untoward reactions in man following their use.

The present paper is limited to a study of the nature and extent of the untoward reactions which may occur following the most commonly used present-day antibiotic: penicillin. Such reactions in individual patients have attracted considerable attention because of the occurrence of certain local and systemic manifestations. Fatal reactions have also been reported. These reactions are of interest to doctors generally in view of the current general use—and misuse—of penicillin. They are of interest also to health administrations and to the World Health Organization in view of their importance in public health programmes, particularly in the large treponematosis control programme now under way which involves millions of people in many parts of the world.

The Development of Penicillin

The knowledge of the antibiotic properties of micro-organisms can be traced back to tribal magic, folklore and primitive medicine, when advantage was apparently taken of the healing effect sometimes observed in the treatment of sores, boils and other infections following the use of mouldy bread, spoiled food, excreta and other natural products. It was only, however, when micro-organisms were discovered in the nineteenth century that the value of microbial products as curative agents or as sources for useful drugs could be more systematically explored.

Pasteur & Joubert in 1877 first recognized the clinical potentialities of antibiotics as therapeutic agents in disease, the antagonistic effects of certain bacteria against anthrax bacilli being reported by Pasteur in 1878. Tyndall (1881) described the bactericidal effect of " penicillin-producing " moulds introduced into bacterial cultures; Cornil & Babes (1885) conceived the role of chemical inhibitors in neutral antagonistic bacterial systems, and Vuillemin introduced the word " antibiosis " for these phenomena in 1889. In 1897, Duchesne showed that *B. coli* and *Salmonella typhi* could, when mixed with *Penicillium* mould, be injected intraperitoneally with impunity. In 1900, Emmerich & Saida found that the ferment (pyocyanase) produced by *Pseudomonas pyocyanea (Bacillus pyocyaneus)* was destructive for other micro-organisms *in vitro* although local applications and injections failed to substantiate this *in vivo*.

In spite of this early work, however, a clear idea of antibiotic therapy did not develop. The era of chemotherapy, with the development of Salvarsan, commenced instead.

It was in 1929 that Fleming made his classic observation that when staphylococci were in the proximity of a *Penicillium* mould they underwent lysis. He named the substance responsible " penicillin ". In 1932, he reported that filtrate or broth cultures of the mould containing penicillin had been used locally in the treatment of a number of indolent wounds and considered that, in view of its innocuous action upon leucocytes, penicillin appeared to be superior in value to applications of potent chemical antiseptics. In 1931, also, a further advance in the field of antibiotics was made by the isolation of a bacillus (*Bacillus brevis*) from soil, which led to the isolation of gramicidin (Dubos, 1944).

In 1932, Clutterbuck, Lovell & Raistrick, stimulated by Fleming's discovery, attempted to extract penicillin from culture filtrates but concluded that the substance obtained was too " labile " for clinical use. Although Paine in Sheffield in the same year (quoted by Florey et al. 1949) had also successfully used penicillin (Fleming's own culture) in the treatment of staphylococcal skin infections and in babies with ophthalmia neonatorum, Fleming reluctantly concurred with these conclusions and the use of penicillin was restricted to differential culture in the laboratory until 1941.

In the meantime, Chain and his colleagues (1940) had isolated a more concentrated penicillin and had used it against various infections in laboratory animals. A year later Abraham et al. (1941) described its successful use in ten patients with severe pyogenic infections which had proved resistant to sulfonamide therapy. The antibiotic era had begun. Florey then visited the USA, following which the manufacture of penicillin was soon begun on a commercial scale. It was not long before Mahoney, Arnold & Harris (1943) had successfully treated four humans with syphilis with penicillin.

Penicillin Preparations Suitable for the Routine Treatment of Treponematosis: Emergence of Sensitivity Reactions

The period 1942-45, when there was rapid development of the processes for improving potencies, purity of yields and clinical effectiveness, has been described as the " golden era of penicillin " (Smith & Walker, 1951).

The early penicillins were amorphous powders of low unitage per milligram. Even so, the antibiotic was remarkable in being non-toxic to man and, in comparison with the arsenic and bismuth treatment of long duration then in use, provided safe and rapid therapy in syphilis. As such, it was welcomed by the medical services of the armed forces of the Allied Powers.

By 1945, the scope of reported reactions from penicillin had already broadened. An increasing number of penicillin reactions of some type, usually mild, were reported. These included urticaria, angio-oedema, erythemata, vesicular eruptions, erythema nodosum, convulsions and anaphylaxis. To venereologists, however, these seemed trivial in comparison with the arsenical dermatitis, encephalitis, agranulocytosis and other serious and truly toxic complications of metallotherapy to which they had previously been accustomed.

As pointed out by Herrell (1945), the general view was that the reactions noted were easily recognized and easily controlled. None endangered life, and none, for all practical purposes, required " a great deal of the intelligent physician in its management ".

It was then found that the amorphous penicillins at that time in use contained a number of fractions, G, F, K and X, and that the G fraction was more effective in rabbit and human syphilis than the other fractions mentioned. This led to the manufacture of pure sodium penicillin G (benzyl penicillin), which came on the market in 1946. With the introduction of pure benzyl crystalline penicillin G, the incidence of side-effects was reduced.

In 1947, Kolmer wrote that in the whole realm of chemotherapy no other compound or group of compounds, except streptomycin and a few other antibiotics, combined such low toxicity and so few side-effects with such high therapeutic activity as did penicillin. Both penicillin and streptomycin stood out as the greatest therapeutic agents yet discovered and were much less noxious for man than the sulfonamide compounds. Even so, contact dermatitis in those handling the drug and atopic dermatitis which sometimes exfoliated were reported by numerous investigators. Severe conjunctival allergy to local penicillin was also recorded, as were generalized pruritus, erythema multiforme and herpes simplex. Serum-sickness-like reactions—in which symptoms could be immediate or delayed, and included giant urticaria, fever and arthralgia—had already been reported in the literature. Even more significant were reports of cases of severe asthma, anaphylaxis

and anaphylactic purpura due to penicillin sensitivity. The complete picture of allergy was now emerging.

Meanwhile, the introduction by Romansky & Rittman in 1945 of penicillin in oil-beeswax (POB)—a repository calcium penicillin preparation—which permitted the use of only one daily injection in the treatment of syphilis, was welcomed by syphilologists all over the world and was in routine use for a few years. During this period, urticaria was the most common side-effect reported. The urticaria was often local at the sight of injection and sometimes local sterile abscesses developed suggesting the Arthus phenomenon. Pain and induration at the site of injection were also noted.

The principal disadvantage of penicillin in oil-beeswax, however, was not the reactions experienced by the patient but the inconvenience encountered by the doctor or nurse who had to draw up into the syringe a viscous, butter-like substance which was difficult to handle.

The discovery by Buckwalter & Dickison in 1948 that procaine would combine in aqueous solution with penicillin to form procaine penicillin and its further adaptation by suspending it in peanut oil and gelling with aluminium monostearate resulted in a preparation (PAM) which is much easier to administer than POB and which, dose for dose, would at the same time give treponemicidal penicillin blood-levels for 24-26 hours. A nearly perfect long-acting penicillin preparation for the treatment of syphilis and other treponematoses was now available.

The PAM Era: Emergence of Problems of Anaphylaxis

In the years which followed, procaine penicillin with aluminium monostearate (PAM) became the preparation of choice for the treatment of syphilis throughout the world. It has remained so in most areas and the number of syphilitics treated with PAM during the ten years which have elapsed is beyond calculation. At the same time it was realized that PAM was an excellent potential weapon for the eradication of yaws as a very high percentage of cures can be obtained with but a single injection of an appropriate dosage of this long-acting penicillin preparation. The World Health Organization recommended its use, and in conjunction with the health administrations of the affected areas PAM treatment has been carried out on a large scale in the control of both yaws and endemic syphilis. By the end of 1957, no less than 80 million people had been examined in these treponematosis mass campaigns. Of these, 35 million had been treated with long-acting penicillin—the vast majority with PAM.

Although a few observers considered that the incidence and severity of penicillin reactions was increasing, that the urticaria which formerly was of little discomfort was often being replaced by reactions that simulated

serum-sickness of former days, and that an anaphylactoid phenomenon, with all that it portends, had made its appearance, many syphilologists expressed the opinion that the reactions were on a downward rather than an upward trend. An analysis of the literature related to penicillin production suggested a fall in the incidence of penicillin reactions (Kitchen et al., 1951). This is interesting since one would have expected a rise in the incidence of such reactions in view of the vastly increasing number of patients who had had the opportunity of becoming sensitized to the drug. It is possible that the use of the newer tetracycline antibiotics in persons known to be sensitive to penicillin, and more attentive care consequent upon an added awareness of penicillin reactions, may explain this development.

The first reported fatality from penicillin therapy (Wilensky, 1946), occurred in a man over 60 years old who developed vomiting, fever and a rash after having received penicillin for five days following a gastrectomy operation. His condition became steadily worse and resulted in death after three days. The second death was reported by Walbott in 1949 and occurred within three hours of a penicillin injection. There were thus only two deaths reported in the whole world during nine years of therapy.

The next 18 months told a different story as 16 more fatal anaphylactic cases were reported (Thomson, 1952; Higgins & Rothchild, 1952; Mayer et al., 1953; Siegal, Steinhardt & Gerber, 1953; Christenson, Hedrich & Shugmann, 1953; Stormont, 1953; Feinberg, Feinberg & Moran, 1953; and Kern & Wimberley, 1953, also reported a case recounted in 1952 by Curphey). It was generally agreed that there were a number of other cases which were never recorded in the literature. In addition, three fatal cases of exfoliative dermatitis had been reported by Rabinovitch & Smitkoff (1948), Barksdale, Frost & Nolan (1948) and by Langdon (1950). Moreover, lesions resembling erythema nodosum and erythema multiforme were more frequent (Kern & Wimberley, 1953).

By 1954, Hussar & Holley stated that 48 deaths from penicillin had been recorded, 39 of which in the years 1952-53. Moreover, Harkavy (1952) had reported two fatalities in patients with purpuric lesions and extensive visceral lesions due to penicillin reaction. The view that the urticarial weal, bronchial oedema and muscle spasm—which leave no trace—represent the sum of allergy to penicillin was no longer considered adequate (Kern & Wimberley, 1953). The incidence of periarteritis nodosa increased twelvefold after the introduction of sulfonamides, and the occasional case of prolonged penicillin reaction which proceeded to necrotizing arterial damage was now being reported. Also, cases recorded by Gold (1951) and by Walsh & Zimmermann (1953) suggested that penicillin sensitivity might be associated with the presence of lupus erythematosus (LE) cells in the bone marrow and LE factors in the plasma.

It has been suggested that all these phenomena of drug sensitivity, including the symptoms assigned to the various collagen diseases, would

sooner or later be shown to be due to hypersensitivity to penicillin (*J. Allergy*, 1953).

In 1953, a survey was conducted by the US Food and Drug Administration in 11 cities covering 95 hospitals with over 51 000 beds (Welch et al., 1953). In two years there were 59 anaphylactoid reactions, 19 of which were fatal; no such reactions had previously been reported. In addition, a drug company reported 25 cases with 5 deaths following penethamate treatment. The US Food and Drug Administration asked for the inclusion of a warning statement in brochures for parenteral, oral and aerosol penicillin and for penicillin recommended for instillation into body cavities:

> " The administration of penicillin in rare instances may cause acute anaphylaxis. The reaction seems to occur more frequently in patients with bronchial asthma and other allergies and who previously have demonstrated a sensitivity to penicillin. Care should be taken to avoid accidental intravenous administration, and resuscitative drugs such as epinephrine, antihistaminics, aminophylline, etc., should be readily available for emergency intravenous administration." (Welch et al., 1953.)

Although these latter events were rare, the picture as a whole justified the opinion that " penicillin sensitivity clearly deserves our respectful attention " (Kern & Wimberley, 1953) and that " penicillin can no longer be regarded as an innocuous drug " (*J. Allergy*, 1953).

By 1955, Hussar was able to report that over 200 deaths from antibiotics had been recorded in the literature up to that time. By 1957, taking into account non-venereal cases, it was estimated that 1000 deaths from anaphylaxis due to penicillin had occurred in the USA (Peters, Henderson & Prickman, 1957).

Similar reports soon came in from all over the world and there was an awakening concern about these problems. It is noticeable that only a small proportion concerned patients under treatment for syphilis. As many of the reported serious reactions followed the use of crystalline penicillin, it would appear that the chances of such reactions are reduced when the more slowly absorbed procaine penicillin preparation with aluminium monostearate is used.

The reported reactions in venereal disease patients have remained comparatively few in number. Smith, Cutler & Price (1955) reported that more than one million persons had been treated in the venereal diseases programme of the US Public Health Service. In the period 1946-50 only 3 patients per 1000 had severe reactions and there was only one death in 93 000 cases treated while, with the arsenic and bismuth schedules previously in use, there was one death in 8700 treated. In 1954, an intensive study of penicillin reactions was made at 24 centres in 13 States. Of 16 345 treated (75% with PAM) the reported reaction rate was 6.7 per 1000, the most frequent reaction being urticaria (5.5 per 1000). Only 4 anaphylactoid

reactions were reported—one in every 4000 patients treated—all of which occurred following the most used preparation, PAM.

Meanwhile, the results obtained with PAM in the treatment of syphilis and other treponematoses remained excellent and its use has increased in a spectacular fashion year by year. The relative scarcity of reactions to penicillin in venereal disease is also confirmed by an inquiry made by WHO among leading venereal disease clinics in various parts of the world (Willcox, 1958). Certainly the faith of its users in the value of the antibiotic has not been shaken. Pratt & Dufrenoy (1953) considered that " for all practical purposes penicillin may be considered to be devoid of toxicity for the average patient, especially when administered parenterally ". Drill (1954) wrote: " Penicillin is the queen of drugs. It is the most satisfactory therapeutic weapon known in that it does its particular task with utmost efficiency and negligible harm. Its edge is sharp but it can scarcely harm the user." Thomas in 1956 was likewise still of the opinion that " no other effective antisyphilitic agent has been as free from reactions as penicillin ". Siegal (1957) rightly considered that penicillin allergy of minor importance should not be permitted to frighten the medical profession into therapeutic paralysis when major indications, e.g., subacute bacterial endocarditis and syphilis, were present. Kalz (1958) indicated that penicillin can usually be given even to reactive patients if antihistaminic or steroid drugs are used. At the Royal Victoria Hospital, Montreal, Canada, there were 12% of reactions in 1200 syphilitic patients. It was always possible to complete treatment. Steroid therapy was necessary in only two cases. These matters will be considered in a later section of these studies.

More Recent Developments: Problems of Antibiotic Resistance

The most recent phase has been the development of new penicillin salts, such as benzathine penicillin by Szabo, Edwards & Bruce (1951) (which gives even more prolonged serum levels dose for dose than PAM), benethamine penicillin, penicillin V, penicillin O, etc. Some of these have advantages for certain uses: for instance, penicillin V (phenoxymethyl penicillin) for oral administration; Neo-Penil (the diethylaminoethyl ester hydriodide) for the production of high concentrations in the cerebrospinal fluid, etc.

None of these penicillins, except the particularly long-acting benzathine penicillin — and to a small extent benethamine penicillin — has, however, been widely used in the treatment of venereal diseases and treponematoses.

With many of these penicillins there have been initial reports of a lower incidence of reactions. Although these newer salts are free from procaine,

and the possibility of reactions to the procaine component rather than to penicillin is thereby eliminated, there is no doubt that they can all cause penicillin reactions in a sensitive person, even with the so-called hypo-allergic penicillins (allylmercaptomethyl penicillin, and *l*-ephanamine penicillin (6) (Krantz & Carr, 1954). Moreover, the mentioned pattern of a reduction in sensitivity reactions early after the introduction of new penicillin preparations is by now recognized as a transient one. It requires several years and the treatment of a large number of patients before a permanent trend can be decided (Hussar & Holley, 1954).

Within recent years, the more chronic problem of resistance of bacteria to penicillin has had greater prominence, and the possibility of the development of widespread resistance to penicillin, from previous experience with sulfonamides, has been of some concern from the beginning of the penicillin era. So far, there have been no authenticated reports of treponemes becoming resistant to penicillin. Neither has the gonococcus shown convincing signs of penicillin resistance in man.

From the beginning, instances were reported of superinfection of the antibiotic-treated patient and of cross-infection with penicillin-resistant staphylococci — causing septicaemia which was sometimes fatal — and with monilia when its natural bacteria inhibitants were removed by the antibiotic.

The problem of penicillin-resistant staphylococci is not so much a therapeutic one of individuals—although it can be—as at present an epidemiological problem of hospitals. Through the years a striking increase in the proportion of antibiotic-resistant staphylococci in hospitals in many parts of the world has been recognized. Certainly, antibiotic-resistant staphylococci are found much more frequently among in-patients than in out-patients. Instances of complete resistance of staphylococci to all antibiotics have been encountered. The resistance of staphylococci to antibiotics is directly related to the antibiotic in current favour. In hospitals, the resistant micro-organisms may be propagated by direct or indirect contact with other patients, or may be spread by a member of the staff who is a carrier. Alternatively, the resistant micro-organisms may cause superinfection in the original patient.

The full implications of the penicillin-resistance of the staphylococcus and subsequent superinfection and cross-infection have yet to be understood. Neither is it known to what extent similar problems will be met with other micro-organisms. It has been pointed out that many micro-organisms are less able than staphylococci to produce resistant strains. By 1955, no resistant form of Group A haemolytic streptococci, pneumococci, gonococci or spirochaetes had yet developed, although it has been indicated that penicillin was ineffective against otherwise sensitive haemolytic streptococci in the presence of a penicillinase-producing staphylococcus (Gray, 1956). Recent reports (Rantz & Rantz, 1956) suggest, however, that in the last

five years there has been an increase in the numbers of resistant strains of *Escherichia coli*, paracolon bacillus and *Proteus* as well as staphylococci. This may be suggestive for the future.

Objectives of the Present Study

From the foregoing, it can be appreciated that reactions to penicillin therapy constitute no static subject. The importance of such reactions and the relative emphasis to be put on the various facets of the problem have fluctuated as new penicillin preparations have been evolved over the years and as the antibiotic has enjoyed wider and wider use. The most serious problems clearly are (*a*) the anaphylactic sensitivity phenomena, which are sometimes fatal to the patient, (*b*) superinfection with penicillin-resistant organisms, which may also be fatal, and (*c*) cross-infection with the same organisms which — if occurring widely — might cause grievous harm to the community.

Syphilologists are still unanimous that penicillin is the most effective and safest therapeutic weapon ever available for the treatment of syphilis. All are likewise agreed on its great value in the treatment of yaws and pinta. The World Health Organization has consistently pressed for the widest possible use of penicillin in treponematoses programmes wherever there were individual or public health indications for its use. Reports in the literature concerning the ill effects of penicillin, albeit in only a very small proportion of people actually treated, might to some extent impede the full adoption of the antibiotic in some areas. For this reason it is considered that a survey of penicillin reactions is timely — a decade and a half after the introduction of the drug — so that these reactions may be considered in relation to the present world-wide use of the antibiotic and the vast campaigns against the treponematoses undertaken in many regions.

TOXICITY OF PENICILLIN

The action of a drug is determined by a set of interacting factors which modify the response induced in the host. Some of these factors are modified by the stimulus provided by the drug itself, while others influence the responding system. This is particularly the case when the host is infected by pathogenic micro-organisms, although the microbiogenic effects may further modify the balance of the interacting factors. Dose, route of administration and similar factors may vary widely while other factors, such as age and body-weight, may influence the metabolism of the drug to a limited extent only or not at all.

The major interacting factors influencing the response of the host to the drug are shown below:

I. Stimulus or drug

1. Chemical structure
2. Pharmacological properties
3. Dose and frequency of administration
4. Route of administration
5. Resorption and distribution of drug
6. Presence of other drugs (see also III 7 (*b*))
7. Other stimuli

II. Microbiogenic factors

1. Species and type of micro-organism
2. Virulence and infectivity
3. Mode and route of inoculation
4. Number of micro-organisms
5. Sensitivity and resistance to drugs
6. Microbial lysis
7. Other unknown factors

III. Responding system

1. Age, sex
2. Race, species, body-weight
3. Hereditary factors
4. Temperature
5. Presence or stage of pathological conditions
6. Tolerance and allergy
7. Fate of the drug:
   (*a*) metabolism, mode of action
   (*b*) competition, antagonism, accumulation
8. Other factors

While successful *drug action* presumes a certain reciprocal balance between these various conditioning factors, *drug reactions* may result from the upsetting of these relationships, as they are dependent on the same set of factors. Many investigators consider drug reactions to be synonymous with " by-effects ", "side-effects ", " side-reactions ", etc., by which is meant any type of untoward response following the use of drugs, regardless of the nature of the reactions — i.e., whether local or systemic, acute or delayed, or occurring on initial or repeated application — and independent of dose or route of administration.

For many years such undesirable drug effects were accepted by clinicians under the broad designation of " toxic reactions ". In contrast to this, the investigators of pharmacological properties of drugs tended to define toxicity in a more limited sense, namely, in terms of the pathological lesions and other changes resulting from poisoning by over-dosage and which *always affected everyone sufficiently exposed to the drug.* Such poisoning is a *quantitative* pharmacological effect, determined by the chemical properties of the drug concerned, expressing its nature, even when used in moderate dosages on internal or external application.

The tremendous advances in the chemistry of natural and synthetic products which have contributed to the isolation of the antibiotic substances have resulted in a reappraisal of this concept of toxicity and toxic reactions in recent years. It became possible to reduce the toxicity of drugs by chemical substitution of toxic radicals without affecting the basic effectiveness of the drugs concerned (Marti-Ibañez, 1955). This development contrasted with the previous belief that the effectiveness of drugs was always parallel to their toxicity. Systematic study of the new, well-defined drugs has shown that a very low degree of cellular and functional damage results from the use of effective dosages as compared with the gross pathology often observed

following the use of the crude drugs previously available. The type of untoward reaction occurring with modern drugs represents a *qualitative* rather than a quantitative pharmacological effect and *does not always occur in everyone exposed to the drug*; but when occurring, the pattern of reactions is usually the same, and sometimes represents little more than incidental annoyance.

As a consequence of these developments, untoward reactions following the use of modern drugs can no longer be considered "toxic" in the previous sense. This applies particularly to the allergic reactions which are based on sensitization phenomena with subsequent characteristic manifestations, including anaphylaxis, and which are evoked by an antigen-antibody mechanism. In the case of antimicrobial drugs, there are also a number of other side-effects which cannot be considered " toxic " in the above sense and which have definite, although sometimes little understood, mechanisms.

The overlooking of these developments has given rise to much confusion in the medical literature; this is particularly evident in the field of antibiotics. Contradictory observations are often encountered as shown in the following examples:

On the one hand, it is stated that: " One of the most remarkable features of penicillin is the relative *low toxicity*[1] to man " (Kolmer, 1947); or "*Penicillin is entirely free from toxic effects*[1] even when given in enormous doses over long periods " (Bate, 1954). Another example is:

" Bien qu'elles soient loin d'assumer à elles seules les effets seconds de la chimiothérapie antibactérienne les manifestations *allergiques et toxiques*[1] des antibiotiques présentent aujourd'hui un intérêt grandissant... " (Bickel, 1955)

On the other hand, many investigators maintain the previous, broad, inclusive definition of toxicity, and state that: " *The toxic reactions* . . . namely pain or irritation at the site of infection, the *cutaneous manifestations*[1]... are all easily recognized." (Herrell, 1945); or "Problems of drug toxicity demand attention increasingly, and most unpredictable of the forms of *drug toxicity is that due to allergy*." [1] (Siegal, 1955b).

The matter of an inclusive or exclusive definition of " toxic reactions " and " toxicity " is not a matter of semantics. It is the basis for a rational consideration and classification of untoward drug reactions as a whole.

Florey et al. (1949) stated that:

" The possible toxic effect of penicillin . . . to the various cells and tissues of the body . . . add up to very little. There remain three other groups of undesirable effects which are apparently of a somewhat different nature . . . gastro-intestinal disturbances . . . Herxheimer reaction . . . and reactions justifiable to consider as allergic of nature."

A similar distinction between penicillin reactions is also the basis for the present authors' concept of untoward drug reactions. They may be studied according to their pathogenesis: *toxic manifestations, microbiogenic*

[1] Our italics

sequelae, and *allergy*. It will be realized that it is inevitable that certain untoward manifestations following the use of penicillin may fall into more than one of these groups and also that some reactions can be classified only with uncertainty.

Toxic Manifestations

Fleming observed the low toxicity of crude penicillin for animals as early as 1929. Injections of crude filtrates were then found to be no more toxic than plain broth. Subsequently, several pure, chemically defined penicillins, salts and preparations have been developed, e.g., benzyl penicillin or penicillin G (or II),[1] A^2-pentenyl-penicillin or penicillin F (or I); *para*-hydroxybenzelpenicillin or penicillin X (or III); N-heptylpenicillin or penicillin K; allylmercaptomethyl penicillin or penicillin O; phenoxymethyl penicillin, or penicillin V; N-N-dibenzyl-ethylenediamine dipenicillin G or benthazine penicillin;[1] procaine benzyl penicillin G[1] and several others. They all have in common that their toxicity is extremely low as determined by a systematic study of their effect on the tissue cells of the respiratory, nervous, gastro-intestinal, cardiovascular, muscular, haematological, and other organic systems of animals. Although some difference in degree of toxicity is found between the different laboratory animals and routes of administration, the truly toxic doses far exceed those required to obtain therapeutic effect (Table 1).

TABLE 1. TOXICITY OF VARIOUS PENICILLIN SALTS IN ANIMALS*

Author	Salt	Animal	Minimum lethal dose per kilogram		Maximum tolerated dose per kilogram	
			g	units	g	units
Hobby, Mayer & Chaffee (1942)	Na	Mice	1.8			
"	NH_4	Mice	0.67			
Robinson (1943)	Na	Mice	1.0-2.0		0.5	
Hamre et al. (1943)	Na	Mice	1.0-1.5	90 000-139 000	0.7	69 700
"	Na	Guinea-pigs	0.59-0.83	53 000-75 000	0.35	31 300
"	Na	Rabbits	0.78	70 200	0.53	47 000
Welch et al. (1944b)	Na	Mice	1.68	200 000	1.48	175 000
"	Mg	Mice	0.16	35 000	0.14	30 000
"	NH_4	Mice	0.76	235 000	0.06	225 000

* Quoted from Kolmer (1947) by courtesy of Appleton-Century-Crofts, Inc., New York.

[1] Commonly used in the treatment of the treponematoses

Penicillin is more toxic for guinea-pigs than for mice (Hamre et al., 1943; Herrel, 1945; Eyssen, De Sommer & Dijck, 1957).[1] Guinea-pigs are the only animals in which toxicity can be regularly produced with relatively small doses: anorexia and death ensues in many cases (Stevens & Gray, 1953). In some instances the heart muscle of affected guinea-pigs has shown areas of necrosis, and likewise areas of necrosis have been found in the liver (Hamre et al., 1943). It has been suggested that the higher mortality in guinea-pigs is due to allergy rather than to toxicity, for the lungs of these animals have been shown to contain several penicillin-producing organisms (Ambrus et al., 1952) which might induce sensitivity in the animal. Others (e.g., Feinberg, Feinberg & Moran, 1953) do not subscribe to this explanation. Indeed it has been stated by Rolle & Mayer (1953) and by De Somer et al. (1955) that the intestinal tract of the guinea-pig normally contains lactobacilli but becomes overgrown by coliforms by the penicillin administration. Toxins from these coliforms prove lethal to the animal.

Acute toxicity from penicillin in animals has been shown to be due not to penicillin itself but to its cation (Welch et al. 1944a, 1945b). Sodium, lithium, ammonium, strontium, calcium, magnesium and potassium salts were shown to be toxic in ascending order. The more potent the penicillin (and therefore the less the impurities in it), the less the toxicity (Welch et al., 1944b). Certain esters of penicillin proved relatively more toxic (Mayer et al., 1944).

Toxicity in man is thus due to the chemical nature of the drug and the effect of these chemicals on cellular physiology. The severity is in proportion to dosage and the toxic complications may be local or systemic (Hussar & Holley, 1954).

Local toxic reactions

Local reactions consist of thrombophlebitis when the drug is given intravenously and pain and cellulitis when it is given intramuscularly or subcutaneously (Moore, 1946). Such local reactions were more often encountered with the early amorphous penicillins and relatively little pain was produced once crystalline penicillin G had been developed. The earlier penicillins, for example, were shown to have some selective toxicity for sarcoma cells (Cornman, 1944). It was noted that whereas the yellow sodium salt produced some damage to sarcoma cells the highly purified penicillin did not (Lewis, 1944). The little used ammonium salt, particularly, might cause severe pain (Putman, Welch & Olansky, 1945). Occasionally, severe local reactions with cold abscesses may result from allergy — the Arthus phenomenon (Kutscher et al., 1953).

[1] More recently, hamsters have also been shown to be relatively susceptible (Schneierson & Perlman, 1956).

The problem of local toxic reactions became minimal once crystalline penicillin G was isolated. During the era of penicillin in oil-beeswax (POB) local reactions in the buttock were common but these were usually due to a giant urticaria of an allergic nature. Irritative local reactions virtually ceased when procaine penicillin with aluminium monostearate (PAM) was introduced, although local urticaria is still occasionally encountered.

The problem of local toxicity was revived when the early batches of benzathine and benethamine penicillin became available. They proved far more painful to the patient than the usually painless PAM. Differences have been shown in the local deposits of benzathine penicillin and procaine penicillin; after an injection of benzathine penicillin the penicillin is deposited in crystalline heaps between fasciculi of the muscles. Following procaine penicillin degeneration and necrosis of muscle cells are noted at the point of injection. In both granulation tissue is ultimately produced, in one replacing necrotic tissue and in the other replacing serofibrinous exudate (Gallego, 1956). Since the appearance of better products, the problem of local pain from benzathine penicillin may, however, now be considered largely to have been overcome.

However, by and large, local toxicity from penicillin has been no appreciable problem.

Systemic toxic effects

During the early years of penicillin therapy, mild systemic toxic reactions were observed (Mahoney et al., 1944). These were largely due, however, to impurities in the drug. Some pyrogenic reactions were noted in the very first cases treated (Smith & Walker, 1951), and secondary fever was encountered in approximately 2% of syphilitics five or more days after commencement of treatment (Moore, 1946). Later, reactions were sometimes observed due to the salt with which penicillin was combined, the toxicity of which was often greater than that of penicillin itself (Welch et al., 1944b). General systemic manifestations with nausea, chills, dizziness and headaches were met with, but rarely. Characteristically, the intensity of the symptoms increased with larger doses of the drug. The fatalities encountered during the early period of penicillin therapy (1941-45) were apparently extremely few (Thomas, 1949). With the introduction of pure preparations, particularly crystalline penicillin G, and subsequently of several other penicillin salts and combinations, toxic reactions from penicillin became rarer in spite of its increasing use.

Indeed, with the highly purified products of sodium penicillin commercially available by 1946 it was calculated that the 50% lethal single dose (LD_{50}) for humans would be 150 626 000 units (154.2 g) for a 70-kg man —a dose far in excess of what it would be practical to give. Even with

potassium penicillin, the LD_{50} for a single dose was calculated to be 25-30 millions units (Moore, 1946).

Severe and even fatal complications of the central nervous system have rarely been reported following intramuscular injection of penicillin (Huber, 1954), although the nature of the reaction is uncertain (allergic?). Peripheral neuritis has also been noted. Not only have these cases arisen from the injection of a nerve with penicillin (Broadbent, Odom & Woodhall, 1949), but brachial neuritis has also been observed following gluteal injections (Kolb & Gray, 1946). Similarly unclear from the point of view of pathogenesis are rare reports of transient psychoses following intramuscular injections of penicillin (Kline & Highsmith, 1948; Corcoran, 1950), although when such psychoses have followed the use of procaine penicillin the possibility that they might be due to the procaine moiety has been considered (Batchelor, Horne & Rogerson, 1951; Björnberg & Selstam, 1957). Such reports led one investigator (Huber, 1954) to advocate that a small dosage of penicillin should be used in treatment of neurosyphilis. This view is, however, not generally accepted because of the obscurity of the nature of these reactions and their extremely rare occurrence.

Penicillin may also show local toxicity when given intrathecally (Wilson, Rupp & Wilson, 1949; Erickson, Matson & Suckle, 1946; Edwards & Kellsey, 1950). Convulsions have been produced in animals by direct application of penicillin to the cerebral cortex (Walker, Johnson & Kollross, 1945) and in human beings by penicillin injected into the ventricles (Johnson & Walker, 1945; Walker et al., 1946). Abnormalities in the cerebrospinal fluid were also found, these being related to the dose of penicillin given rather than to the concentration (Morginson, 1946). Intrathecal administration of crystalline penicillin causes meningeal irritation (Hussar & Holley, 1954). Headache, nausea, vomiting, listlessness, respiratory difficulty, cyanosis, vascular collapse, muscle twitchings, convulsions, flaccid paralysis and sensory disturbances — with a rise of protein and cell count in the cerebrospinal fluid — have all been reported (Morginson, 1946; Talbot, 1948; Wilson, Rupp & Wilson, 1949, Erickson, Matson & Suckle, 1946 and Edwards & Kellsey, 1950). Fatality within a few hours after such use has also been described (*J. Amer. med. Ass.*, 1955b).

Such reactions may be due to chemical meningitis with subsequent adhesive spinal arachnoiditis resulting in subarachnoid block, transverse myelitis, radiculitis or at times cerebral cortical damage. Although it was doubtful whether these symptoms were due to penicillin itself or to impurities, Hussar & Holley (1954) considered that the weight of the evidence pointed to the antibiotic itself being responsible, although the impurities present in the earlier penicillins may have aggravated these symptoms. Today, however, intrathecal penicillin is very seldom used, and the past is of academic rather than of practical significance.

There is also isolated mention in the literature of cardiac complications, infarctions, and electrocardiographic and histological changes associated with hypersensitivity following penicillin therapy (Kline & Highsmith, 1948; Felder & Felder, 1950; Binder et al., 1950; Glotzer, 1954; von Oettingen, 1955; Winton & Nora, 1955) Severe renal complications are normally rare, although azotaemia (nausea, vomiting, albuminuria and rising blood urea) has been reported (Herrell, 1945; Moore, 1946; Brown, 1948 and Spring, 1951), subsiding on cessation of the drug. Renal complications have also been noted in cases of exfoliative dermatitis due to penicillin (Harlem, 1955; Langdon, 1950).

Blood dyscrasias were among the most common toxic reactions in the sulfonamide era. Such complications may also follow the use of antibiotics (e.g., chloramphenicol), but no unequivocal cases have been observed following penicillin therapy. Penicillin is toxic to leucocytes but the concentrations required are much higher than those obtained during penicillin therapy (Abraham et al., 1941; Welch et al., 1945a). With penicillin, no damage is caused to the bone marrow or haemopoietic system and the antibiotic may be safely given in severe anaemia (Kolmer, 1947), although Spain & Clark (1946) did record an isolated fatal example of agranulocytosis in a penicillin-treated patient.

Examples of increased bleeding-time and increased capillary fragility under penicillin treatment have also been reported (Davis & Goar, 1949). Purpura is not rare (Graves, Carpenter & Unangst, 1944; Anderson, 1947; Criep & Cohen, 1951; Harkavy, 1952; Liebgott, 1955; and Kekwick, 1956a). Purpuric manifestations are of a non-thrombocytopenic type often with a positive Rumpel-Leede tourniquet test which returns to normal when the purpura subsides. These findings indicate a vascular rather than a haemopoietic origin (Criep & Cohen, 1951). The nature of these reactions is not yet clear. They are not necessarily toxic but may be of allergic origin.

A case of acrodermatitis atrophicans due to penicillin was reported by Burkhardt (1956), and eosinophilia and pulmonary infiltration (Löffler's syndrome) have also been noted following penicillin therapy (Falk & Newcomer, 1949; Reichlin, Loveless & Kane, 1953).

Penicillin is not normally toxic to the liver although liver damage without jaundice has been noted in patients with penicillin urticaria (Felder & Felder, 1950). Hepatitis with diffuse arteritis has also been noted (Waugh, 1952). The 47 cases of hepatitis reported by Howells & Kerr (1946) were syringe-transmitted virus hepatitis due not to penicillin but to improper sterilization of syringes. This was a common condition in many venereal disease clinics towards the close of the arsenical era when many intravenous injections were given; but is a very rare and avoidable complication at the present time and it is less common following intramuscular than intravenous injection.

Penicillin has no effect upon spermatozoa (Seneca & Ides, 1953). Earlier penicillins were stated to affect the female menstrual rhythm although this is seldom reported today. McLachlan & Brown (1947) noted menstrual disturbances in 91.3% of 216 non-pregnant women treated with penicillin, and there were other disturbances noted during pregnancy, the puerperium and menopause. Threatened abortion due to penicillin or impurities was also recorded (Leavitt, 1945). It has been considered that these findings also arose from impurities rather than from penicillin (Willcox, 1953).

In summary it may truly be said that the toxic effects of penicillin in man are, in the broad run of events, negligible. They certainly have detracted little from the use and usefulness of penicillin in clinical practice and public health programmes.

MICROBIOGENIC SEQUELAE OF PENICILLIN THERAPY

During treatment with antibiotics, certain undesirable reactions may occur from interference with the metabolism of the microbial flora. Such microbiogenic sequelae may result from:

(*a*) *development of microbial resistance* to the antibiotic;

(*b*) *overgrowth by micro-organisms* not affected or less affected by the antibiotic than others, resulting in *superinfection* and *cross-infection*—problems closely related to (*a*);

(*c*) *microbial lysis* with liberation of noxious products; and

(*d*) other manifestations.

Microbial Resistance

Microbial resistance is by definition the phenomenon whereby a micro-organism requires more antibiotics than most other strains of the same species to prevent its growth. This may be a natural or an acquired characteristic.

Natural resistance may arise through penicillinase formation—a penicillin-destroying enzyme produced by several cocci, bacteria and fungi, e.g., staphylococci and *Esch. coli*. Acquired resistance is produced in a series of steps. Each microbial generation will possess greater resistance to the antibiotic than the previous one through the selective breeding of relatively more resistant mutants. Antibiotic-resistant variants are pre-formed mutants grown out selectively in the presence of antibiotics (Eagle & Saz, 1955). Many factors are involved, including increased penicillinase production and the ability to synthesize amino-acids within the microbial cell (Böe & Vogelsang, 1951). The exact mechanism of resistance is not yet

fully understood. The matter is undoubtedly complex and is not yet amenable to precise genetic analysis (Bryson, 1956).

From the beginning, there have been naturally penicillin-resistant organisms (*Esch. coli*, etc.) and quite early it was noted that staphylococci might readily acquire resistance. The possibility of an increasing problem of microbial resistance to penicillin has always been in the minds of venereologists since their experience with the gonococcus in relation to the sulfonamides.

The clinical and public health importance of microbial resistance to penicillin is—for the time being, at least—principally concerned with staphylococcal infections and with the increased distribution of penicillin-resistant staphylococci. This increase has, however, been overemphasized by the results obtained in selected hospital populations. Infections with *Streptococcus pyogenes*, *Str. pneumoniae* and *Gonococcus* have shown little well-authenticated evidence of adaptation to penicillin, and in the case of spirochaetes there is no evidence that *Treponema pallidum* becomes less susceptible under treatment *in vivo*. Some patients with syphilis have been considered " penicillin failures " on the grounds of clinical remanifestation of the disease or because of " sero-resistance " (Deneuve, 1954). Among the former group of patients, treatment might have failed (*a*) because of the use of sub-therapeutic doses of penicillin (often non-repository or inadequate penicillin preparations with insufficient blood-level duration), (*b*) because of abnormal penicillin metabolism of the host, inadequate absorption or unusually quick renal elimination, or (*c*) from rapid reinfection following effective treatment of the early disease. In " sero-resistant " cases of syphilis it is now recognized that older infections may remain seropositive for life following adequate treatment by whatever method.

Microbial resistance as a complication of therapy is probably avoided by applying initially sufficiently large doses of suitable penicillin preparations to ensure rapid death of the prevailing micro-organisms, thereby obviating the need of using repeated small doses over a longer period of time—the latter mechanism being perhaps the most likely one to stimulate the development of microbial resistance. It is not likely that the use of other types of penicillin than the one that has failed and has created microbial resistance will effect recovery, although in the laboratory some micro-organisms may show sensitivity variations to different penicillins. The use of other effective drugs is the obvious alternative.

Overgrowth by Insusceptible Organisms: Superinfection and Cross-infection

It is its low toxicity and profound selectivity of action as between micro-organisms and the host which makes penicillin the " queen of drugs " (Drill, 1954). But this selectivity may also give rise to undesirable sequelae.

Secondary microbial invasion or " superinfection " following administration of an antibiotic effective against a particular micro-organism may result from (*a*) overgrowth of organisms which acquire resistance during the administration of the antibiotic; (*b*) invasion by organisms which are already resistant and originate from another person (cross-infection); (*c*) overgrowth in the same person of organisms that are inherently resistant to the antibiotic and which find encouragement to grow when sensitive strains are eliminated; and (*d*) invasion by organisms insusceptible to the antibiotic. These matters are all inseparable from the problems of microbial resistance.

While penicillin resistance of the treponeme itself has offered no problems in the treatment of the treponematoses, microbial resistance as a whole provides a long-term problem of some potential magnitude for there is the increasing risk of the spread of antibiotic-resistant diseases in the community caused by patients treated with antibiotics for antibiotic-sensitive conditions which themselves have been satisfactorily subdued.

Observers have commented on the fact that many organisms, previously practically non-pathogenic, sometimes cause fatal infections (Clarke, 1956). The two organisms most commonly involved are staphylococci and moniliae.

Staphylococcus

Wide variations to sensitivity to penicillin are noted with staphylococci (Finland, Wilcox & Frank, 1950) and such variations extend to the other antibiotics.

Micrococcus pyogenes contains two types of penicillin mutants: penicillin decomposing (natural) due to penicillinase production, and penicillin non-decomposing (artificial). The latter is an example of acquired resistance, which is obtained in a series of steps (Demerec, 1945). The " artificial " " acquired ", or " transient " resistance is easily attenuated *in vitro* (Szybalski, 1953).

In primitive populations there may be only a few strains of penicillin-resistant staphylococci. Rountree (1956) found that 23 of 100 persons in New Guinea were nasal carriers of *Staphylococcus aureus* but in none were the organisms antibiotic-resistant. In a " normal " population it has been calculated that there may be 25%-50% of carriers of coagulase-positive staphylococci with a fairly rapid turnover of resistant strains (Lepper, Jackson & Dowling, 1955), but the staphylococci in the general population are predominantly sensitive (Vogelsang, 1951; Dowling, Lepper & Jackson, 1953; Saint-Martin et al., 1954). There is little doubt that the human nasopharynx is the primary reservoir of coagulase-positive staphylococci (Hare & Mackenzie, 1946; Saint-Martin, 1954; Hinton & Orr, 1957).

Gradually, during the last decade or so, there has been noted in hospitals throughout the world a general increase in the prevalence of antibiotic-resistant staphylococci in in-patients, 50%-70% of whom may on occasion be demonstrated to carry such organisms (Barber & Rozwadosma-Dowzenko, 1948; Ødegaard, 1948; von Berger, 1949; Rountree & Thomson, 1949; Biegelman & Rantz, 1950; *New Engl. J. Med.*, 1950; Böe & Vogelsang, 1951, Reiss et al., 1952; Wilson & Cockroft, 1952; Kirby & Ahern, 1953; Needham & Nichols, 1953; Welch, 1953; Fairbrother, 1956; Rantz & Rantz, 1956; *Antibiot. ann. 1956-57*). About three-quarters may be resistant to penicillin (Finland & Haight, 1953). The resistance is not confined to penicillin and, indeed, cases of complete resistance to all antibiotics are met (Spink, 1951; Clarke, Dalgeish & Gillepsie, 1952; Koch & Bourgeois, 1952; Miyahara, Cariker & Clapper, 1953; Hussar & Holley, 1954).

Although resistance in micro-organisms has been increasing there are some indications that the increase may ultimately slow down (Weil & Stempel, 1955).

The resistant organisms appear in the wards of hospitals following the use of antibiotics (Böe & Vogelsang, 1951; Lepper et al., 1954). The carrier rate increases in treated patients (Böe & Vogelsang, 1951; Knight & Holzer, 1954). (See Table 2.).

TABLE 2. PREVALENCE OF PENICILLIN RESISTANT STRAINS OF POTENTIALLY PATHOGENIC STAPHYLOCOCCI IN HEALTHY AND HOSPITAL POPULATIONS *

Type of population		Strains isolated (%)		
		sensitive	marked resistance	relative resistance
Healthy individuals		94.6	3.9	1.5
Hospital patients	before penicillin treatment	64.0	15.5	68.1
	after penicillin treatment	22.6	20.3	9.7

* Based on figures given by Böe & Vogelsang (1951).

Indeed, the resistance of the staphylococci is related to the antibiotic in current favour (Hinton & Orr, 1957; Finland, 1955; Wise, Cranny & Spink, 1956).

Once present in the ward, the staphylococcus can become a danger in two ways: (*a*) by *superinfection* of the patient already treated for some other condition by antibiotics; and (*b*) by *cross-infection* of others in the

ward who may or may not have been treated with antibiotics. It is not always possible to determine which has occurred.

Increasing numbers of non-fatal and fatal staphylococcal infections have been reported in hospitals. Staphylococcal pneumonias and urinary and wound infections have become of serious concern in medical, paediatric, surgical and gynaecological wards (Finland, 1951; Welch, 1953, Prissick, 1953; Hussar & Holley, 1954; Grund & Humke, 1956; Shooter et al., 1957). Staphylococcal pneumonia in infants has been reported by Disney, Wolff & Wood (1956) and by Beaven & Burry (1956), who stated that minor staphylococcal infections in nurseries must no longer be taken lightly. Nasal staphylococcal carriers may cause outbreaks of pemphigus neonatorum in maternity hospitals (Gillespie, Pope & Simpson, 1957). In Ilford, England, an increase in the incidence of staphylococcal ophthalmia neonatorum has been noted—even in babies delivered at home (Gordon, 1957). That staphylococcal infection of the lower respiratory tract may produce a severe and often fatal illness during an influenza epidemic was indicated by Evans & Evans (1956).

Staphylococcal enteritis as a complication of antibiotic therapy more commonly occurs following orally administered antibiotics (of which the tetracyclines are the most commonly used) than with penicillin (Robinson, Hirsh & Dowling, 1948). The organisms overgrow in the " bacterial vacuum " created by the partial sterilization of the bowel. Fatalities have been reported (Cuningham & Beaven, 1955; Dearing, 1956). A review of the literature up to 1955 showed that 56 fatal cases had been published (Thaysen et al., 1955). This complication can occur, also with fatal results, following penicillin or streptomycin given parenterally, as a result of superinfection of the bowel from antibiotic-resistant organisms in the mouth and throat (Fairlie & Kendall, 1953; Terplan et al., 1953; Hussar & Holley, 1954). Six fatal cases of acute staphylococcal enteritis were reported from Switzerland by von Leemann & Fehr (1956) and 31 cases from Great Britain (all but two of which followed penicillin therapy, with 14 fatalities) by Cook et al. (1957). Many strains of staphylococci may be sensitive to other drugs, however, and acute staphylococcal bacteraemia may be successfully treated by a combination of antibiotics (Norland & Craig, 1956). On the other hand, fatal cases of staphylococcal septicaemia complicating exfoliative dermatitis due to penicillin in spite of the use of other antibiotics and cortisone have been reported (Phillips, Romansky & Nasou, 1955).

Clinical staphylococcal infections in hospitals may become widespread. Of 1172 in-patients examined in a spot-survey by Finland & Jones (1956), 181 had staphylococcal infections, of whom 113 (16 serious or potentially so) had acquired their infections in hospital. On account of the resistance of the staphylococcus to a number of antibiotics, such infections are becoming exceedingly difficult to treat. Although at the present time new anti-

biotics are being discovered each year, there is the danger that the pool of available drugs may be exhausted faster than new ones can be discovered (Hussar & Holley, 1954). On the other hand, once established in hospitals, cyclical variations of the incidence of penicillin-resistant staphylococci appear to occur, the cause of which is not known (Altemeier, 1957).

The dust derived from clothing and from bed-clothes of carriers is also important in the transfer of these organisms (Duguid & Wallace, 1948; Colebrook, 1955). Organisms present on the skin are of importance both in the pathogenesis of skin lesions by superinfection and by direct cross-infection (Devenish & Miles, 1939; Hinton & Orr, 1957). The umbilical cord may be a reservoir of staphylococcal infection in neonatal units (Jellard, 1957). Furthermore it has been shown that the air in hospitals contains more antibiotic-resistant staphylococci (and other organisms) than does air from non-hospital and outdoor areas (Engley & Bass, 1957).

Of perhaps greater significance is the accumulation of nasal and skin carriers which occurs in the hospital staff (Knight & Holzer, 1954; Rountree & Thomson, 1949). It has been demonstrated that the nasal role of carriers of penicillin-resistant organisms in student nurses entering hospital may increase from approximately 5%-8% to 50% within one month (Goldberg & Masterson, 1957). Resistant organisms may be passed from one patient to another by means of hospital personnel who acquire resistant strains from penicillin-treated patients (Biegelman & Rantz, 1950; *New Engl. J. Med.*, 1950; Summers, 1952; and Koch & Bourgeois, 1952). In the hospital survey reported by Finland & Jones (1956), 18 members of the house staff were reported to have large furuncles, many in unexposed places. In the Swiss series recorded by von Leemann & Fehr (1956), an epidemic of furunculosis involved 86 patients and staff.

Fortunately, on leaving hospital, a considerable proportion of patients lose their staphylococci within a few weeks, but in some cases they may be transferred by the patient to a household contact and then to another person (Dowling, Lepper & Jackson, 1953). A cause of real anxiety is the possibility that antibiotic-resistant infections in the general community may provide a new source of hospital epidemics when such organisms are admitted with the patient (*Lancet*, 1956a). It is evident that the incidence of antibiotic-resistant staphylococci in the general population is a figure which must be closely watched.

Oswald et al. (1954) found no change of staphylococcal resistance in the general population over a period of 10 years. Certainly there has been no great increase in the incidence of such organisms in out-patients (Voureka & Hughes, 1949; Böe & Vogelsang, 1951). In out-patients, the increase has been much less noticeable than in in-patients and in the former there is no relationship between resistant strains and previous antibiotic administration (Hussar & Holley, 1954). Until recently, therefore, notwithstanding the potential danger, the evidence has been that outside hospitals the natural

loss of resistance and the dilution of existing resistant strains in the general population have resulted in resistant staphylococci presenting no actual problem. However, recent papers such as that of Rountree & Rheuben (1956), who reported twice as high an incidence of nasal carriers of staphylococci among Australian blood donors in 1955 as in 1954, warn that this may not always be the case.

The problem of staphylococcal resistance is an insidious one. It cannot be directly appreciated when the physician is treating diseases, such as yaws and syphilis, due to other organisms. A gradual increase of staphylococcal resistance is probably not preventable (Hussar & Holley, 1954), but it may be retarded in hospitals by asepsis, isolation of staphylococcal cases and carriers, and by the treatment of the noses of hospital staff with other antibiotics (Gould & Allan, 1954; Rountree et al., 1956).

Almost all authors agree that to reduce the problem of microbial resistance antibiotics must not be used indiscriminately (e.g., Alleman & Roost, 1951; *J. Pediat.*, 1953; Watkins, 1955; Tibbetts, 1956; Clarke, 1956), although some (e.g., Leyton, 1956) believe that resistant strains are spread only in closed communities and that their diffusion among the general public is not excessive. It may well be that a relatively minor reduction in the amount of antibiotics used—still within the demands of sound and legitimate curative and prophylactic use—may achieve a major reduction in the number of carriers of resistant strains (Hinton & Orr, 1957). In order to deal with the problem, Lepper (1955) has suggested the following measures, which apply not only to penicillin but to antibiotic therapy as a whole:

(1) Combination of antibiotics. This is often done at present (Welch, 1957). In individual patients, such combination may delay the occurrence of resistance but has not eliminated it (Lepper et al., 1957).

(2) Introduction of new drugs.

(3) Diminution of use of resistance producers.

(4) Reduction in use of all antibiotics to a minimum. This implies the use of antibiotics only when there is convincing evidence of indication for therapeutic or prophylactic needs. Their routine prophylactic use in surgery has been deplored by many writers. Sulfonamides are preferred (Cook et al., 1957; *Antibiot. ann. 1956-57*). The routine prophylactic use of all antibiotics, except for such conditions as rheumatic fever and venereal disease in which their usefulness has been proved, must be seriously questioned (Boger, 1957).

(5) Use of drugs of a limited spectrum in minimal effective dose (a view endorsed by von Leemann & Fehr (1956), Swift (1957) and many others and in direct contradiction to the first measure listed). This is particularly necessary in the case of children in whom there is immaturity of the defence mechanism (Swift, 1957).

(6) Bacterial study before treatment of patients with chronic or mixed infections.

(7) Treatment for evidence of infection and not for mere presence of bacteria.

(8) Correction of possible underlying anatomical, immunological, pathological or metabolic defects.

(9) Precaution against hospital cross-infection.

The strict limitation of the use of anti-staphylococcal antibiotics such as erythromycin, novobiocin and spiramycin, reserving their use so that they will be effective in an emergency, is recommended by von Leemann & Fehr (1956) and by Hinton & Orr (1957). The New Zealand Government, perplexed by the problem of staphylococcal resistance, have decreed that the anti-staphylococcal weapon—erythromycin—should not be blunted by general use (Fowler, 1956). When resistant staphylococci are endemic in the ward only antibiotics effective against these organisms should be used (Binns, 1956).

Precautions against hospital cross-infection include measures of isolation, barrier nursing, wearing of masks by staff, etc. One can visualize a future when a small furuncle appearing in a ward might well cause the same administrative upset as diphtheria, scarlet fever, gonococcal vulvovaginitis, or one of the many serious infective diseases which antibiotics have helped to overcome.

Monilia

Overgrowth with *Candida albicans* is more common after the orally administered tetracycline antibiotics than following parenteral penicillin, but cases of moniliasis, commonly in the mouth, have been reported regardless of the route of administration (Woods, Manning & Patterson, 1951; Reichlin, Loveless & Kane, 1953).

It has been noted that penicillin, like chlortetracycline, might enhance the growth of *C. albicans* (Foley & Winter, 1949). The presence of coliforms suppresses the growth of monilia (Paine 1952), which doubtless explains the lower incidence of rectal soreness and pruritus (believed to be due to an overgrowth with monilia) following the use of orally administered penicillin than following the tetracycline antibiotics.

Clinical cases of monilial overgrowth following antibiotic therapy have been reported to occur in the oral cavity, respiratory and intestinal tracts (Balex, 1954), genitalia (Bjøro, 1956) and skin, where *C. albicans* is a common inhabitant in normal persons. The frequency of *C. albicans* may increase in the sputum following antibiotic therapy (Carpenter, 1955) and in throat or rectal swabs from patients receiving antibiotics—including penicillin (Stewart, 1956). When symptoms occur they usually subside after

discontinuation of the drug, but they may sometimes add to the discomfort of elderly, weak patients (Kekwick, 1956a). Infections of distant organs have also been demonstrated, such as endocarditis, urinary tract infection and disseminated moniliasis (Hussar & Holley, 1954). Fatalities have occurred (Brown et al., 1953; Taylor & Rundle, 1952; Wolff, 1952; Davis et al., 1956) but usually following the tetracycline antibiotics or chloramphenicol.

Outbreaks of napkin eruptions due to thrush, in which association with antibiotics gievn to the mother have been considered, have also been noted (Bound, 1956). *C. albicans* may give rise to an infective eczema in penicillin-treated persons (Peterkin, 1956). It was observed early on that penicillin might cause an existing fungus eruption to flare up (Feinberg, 1944; Lamb, 1944; Kolodny & Denhoff, 1945).

Aspergillosis fumigatus infection and geotrichosis of the lungs have also been reported following antibiotic therapy (Hussar & Holley, 1954; Muratore, 1954).

Other organisms

The relative " toxicity " of penicillin in guinea-pigs has been attributed to the toxins produced by bacterial overgrowth of *Esch. coli* following suppression of the normal lacto-bacilli present in the alimentary tract (Rolle & Mayer, 1953; De Somer et al., 1955).

Finland (1955) pointed out that the greatest human clinical problems arising from resistance were concerned with tuberculosis and staphylococcal infections. He and others (e.g., Terrial & Chabbert, 1955) noted that there were no resistant forms of Group A haemolytic streptococci, pneumococci, gonococci, or spirochaetes. In addition to staphylococci, however, there was a general increase of resistance of *Esch. coli*, paracolon bacillus and proteus bacilli in hospitals (Rantz & Rantz, 1956). *Proteus*, *Pseudomonas* and allied infections may arise during repeated antibiotic therapy and give rise to pulmonary infections (Applebaume & Lett, 1948; Sommer & Favour, 1949), empyema, meningitis (Weinstein, 1947), peritonitis, arthritis and urinary infections (Hussar & Holley, 1954). *Proteus* may overgrow in the intestinal tract (Ruiz Sánchez and colleagues, 1956). Certainly at the present time antibiotic-resistant organisms causing chronic urinary infections have a high nuisance value in urological wards where the rate of cross-infection is high. Hospital cross-infection has been blamed (Kirby, Corpron & Tanner, 1956; Dutton & Ralston, 1957). Resistance has also been described with pneumococci, streptococci, meningococci and actinomyces but these are of little clinical significance so far (Hussar & Holley, 1954). That penicillin may fail against a sensitive haemolytic streptococcus in the presence of a penicillinase-producing staphylococcus has also been noted (Gray, 1956).

The combined use of penicillin with other antibiotics—as sometimes employed by practitioners—may thus increase the risk of all forms of superinfection, and this " broad spectrum " approach should be avoided if no real indication exists (Bickel & Rentchnick, 1954; Bacaj & Pitzura, 1955; Nasou & Romansky, 1956; von Zinzius, 1956).

Although it may be said that the resistance factor is not too serious a problem at the present time " one shudders to contemplate its clinical significance in another decade " (Smith & Walker, 1951).

Microbial Lysis: Therapeutic Shock and Therapeutic Paradox

Signs and symptoms of certain infections sometimes undergo exacerbation by treatment with powerful antimicrobial drugs. Traditionally this exacerbation is ascribed to the release of noxious substances, particularly in spirochaetes killed by the drug. Such *therapeutic shock* is striking in the treatment of syphilis with penicillin, although the " Jarisch-Herxheimer reaction " (therapeutic shock) was classically recognized in the era of the arsenicals (Blom-Ides, Poland & Hevremann, 1955). Similar reactions have also been encountered in the treatment of *gonorrhoea* (Suchet, 1944; Cohn and co-authors, 1944; Frumkin & Ruark, 1946; Siedlecky, 1946), *asthmatic conditions* (Hampton et al., 1945), *certain dermatoses* (Carpenter, Nicholls & Dyke, 1947; Florey, 1952) and in *Vincent's angina* (Sweeney et al., 1945).

Only in syphilis, however, is the Herxheimer type of reaction of practical importance, although it is usually of limited consequence in the early form of the disease. In early acquired syphilis it occurs in as much as 80%-90% of the patients, as indicated by elevation of temperature (and sometimes by an intensification of a rash), but in most instances discontinuation of therapy is not required (Mahoney, Arnold & Harris, 1943; Leifer, 1944; Stokes et al., 1944; Moore et al., 1944; Romansky & Rein, 1946; Farmer, 1948; Putkonen & Rehtijarvi, 1950). Febrile reactions are also noted in early congenital syphilis (Heyman & Yampolsky, 1946; Bowen et al., 1948; Pardo & Tucker, 1949; Putkonen, 1950). The reaction may apparently prove fatal in weakly debilitated syphilitic babies (Platou et al., 1945; Ehrengot, 1950; Stenger, 1950; Debré et al., 1951; Seelig & Sudhoff, 1952; Küster & Bechmann, 1952; Holzel, 1956), although some authors (e.g., Oehme, 1951) consider the seriousness of the reaction to be overrated. Deaths from Herxheimer reaction have also occurred in late *neurosyphilis* (Barksdale, Frost & Nolan, 1948; Shaffer & Shenkin, 1949), particularly general paresis (Tucker & Farmer, 1947; Bush, 1950; Putkonen & Rehtijarvi, 1951), in *cardiovascular syphilis* (Moore, 1946; Dolkart & Schwemlein, 1946; Callaway et al., 1946; Diefenbach, 1949; Scott, Maxwell & Skinner, 1949; Whorton & Denham, 1951; Butterly & Fishman, 1952), and in *gummatous syphilis* (Scott, Maxwell & Skinner,

1949). In late neurosyphilis, convulsions (Stokes et al., 1945), rapid paretic deterioration (Rose et al., 1945), exacerbated psychosis (Callaway et al., 1946) and quickly deteriorating optic atrophy (Moore, 1946) may occur.

There is no indication that large doses are more apt than small ones to produce therapeutic shock, which appears to be an " all or none " phenomenon, although many physicians commence treatment with penicillin in late syphilis with small doses. For a full review of this particular subject the reader is referred to the excellent work of Florey (1952).

As a possible consequence of therapy and microbial lysis *therapeutic paradox* may take place. This could be in spite of, or because of, too rapid healing of lesions and the patient might get worse from the effects of the resultant scarring process. Possible examples are ascites and liver failure occurring after too rapid shrinkage of a gummatous liver; rapid mental deterioration in paresis in spite of the assumption of a normal spinal fluid; occurrence of or increase of regurgitation in syphilitic aortitis. Therapeutic paradox was described during the arsenical area. Although a number of possible examples have been reported in patients treated also with penicillin, few are unequivocal. Thus aortic insufficiency appearing months after the penicillin treatment of latent syphilis has been recorded (Reynolds, 1948; Mohr & Hahn, 1952). This could have been due either to therapeutic paradox or to treatment insufficiency.

A more recently described example of therapeutic paradox in a condition other than syphilis is that of antibiotic deafness reported from the Union of South Africa (Popper, 1957). When large doses of antibiotics are given for middle ear disease, the inflammation is rapidly averted and the retained fluid in the middle ear becomes sterile but the capillaries are not stimulated to dilate and absorb this fluid. Deafness may ensue and drainage is required.

Other Manifestations

Penicillin also shares with other antibiotics the responsibility for sometimes causing clinical deficiency syndromes arising from disturbance of the vitamin B complex and vitamin K metabolisms in the gastro-intestinal tract. The black tongue (Barford, 1951; Tomaszewski, 1953; Kutscher et al., 1953; Cross, 1949; Wolfson, 1949)—a complication not infrequently seen following penicillin or the broad spectrum antibiotics given orally—has also been reported among workers in a penicillin factory presumably following inhalation of the antibiotic (Bartalini & Parmeggiani, 1956), and has been connected with nicotinamide deficiency but not with convincing evidence (Hussar & Holley, 1954). It begins within 2-4 days and disappears 5-14 days after therapy. Furthermore, mucosal surfaces may become damaged or sensitized by direct contact with the drug (Kutscher et al., 1953).

The oral lesions, the gastro-intestinal phenomena and the mechanism of avitaminosis are not completely understood, even if overgrowth by a " foreign " potentially pathogenic flora can be established. The microbial " invasion " might conceivably be a harmless overgrowth without clinical significance in the causation of the lesions or symptoms (Merliss & Hoffman, 1951). Most authors believe, however, that an overgrowth is not unlikely in such cases, for tissues damaged by chemical irritation, allergic reaction or avitaminosis may prepare the soil for invasion by moniliae or other potential pathogens, the lesions and symptoms themselves being produced by the combination of these factors.

For the sake of completeness, mention is made of untoward reactions of a more general nature, arising from erroneous injection of other organisms and from erroneous intramuscular technique by accidental intravascular or intraneural injection of antibiotics (e.g., foot-drop from intravascular injection—Matson, 1950), although such sequelae can hardly be said to be of " microbiogenic " origin. Howells & Kerr (1946) reported 47 cases of syringe-transmitted hepatitis following injections of penicillin and Mitchell, Pordy & Wallach (1946) recorded a case of gas gangrene arising at the site of injection. The provocation of the clinical manifestations of poliomyelitis by the traumatic effect of an intramuscular injection of penicillin into persons *incubating* this infection must also be considered. The necessary coinciding circumstances for this to happen would, however, be present only exceptionally. But in a rural area of epidemic poliomyelitis in a Pacific island, where systematic injections of penicillin were being given in the course of a mass campaign against yaws, a number of cases of clinical poliomyelitis occurred in injected children (Tross—personal communication, 1956). This is unusual, for generally speaking there is little likelihood in treponematoses campaigns of encountering populations in underdeveloped areas not infected with poliovirus at a very early age.

ALLERGIC SKIN REACTIONS

Although it is considered that allergy is a broader term than " hypersensitivity ", for reasons of convenience the two are sometimes used synonymously and an antigen-antibody mechanism is assumed to be the basis of untoward allergic reactions. It has already been stated that drug allergy is responsible for a clinical and pathological pattern different from that arising from toxicity. While toxic manifestations occur as a result of normal pharmacological action on a quantitative basis in every person exposed to the drug, allergic reactions arising from a qualitative hypersensitivity evoke abnormal humoral and cellular reactions not inherent in the pharmacological nature of the allergen. The altered reactivity of the individual towards a specific substance usually results from previous experience with

the same or a related substance (Carpenter, 1956). Such reactions may follow even minute dosages and, although they occur in only a few individuals, reactions following re-exposure to penicillin have created an increasing problem. During the early years of penicillin therapy, such reactions generally concerned the skin, with symptoms of eczema, urticaria and oedema. In later years, however, more serious reactions have been observed, sometimes with anaphylactic response and occasionally followed by death from shock. Unfortunately, it is not possible accurately to compare the frequency of penicillin reactions in the early period and in later years. Among the reasons for this are (*a*) that little attention was paid to the nature and extent of the untoward reactions in the early period, and accurate information is therefore not available, and (*b*) that data usually relate to hospital patients or to selected occupational or other groups, which would tend to overemphasize the magnitude of the problem.

Penicillin may cause different allergic responses, i.e., skin reactions and anaphylactic reactions, as is the case for other allergens. Much of their mechanism remains to be understood. Clinical and experimental evidence suggests that at least two antibodies are produced: a skin-sensitizing antibody and an antibody involving the Schwartzman phenomenon and anaphylaxis (McClosky & Smith, 1944; Cormia, Lewis & Hopper, 1947; Tompsett, Schultz & McDermott, 1947; Feinberg, Feinberg & Moran, 1953; Hansel, 1953; Winton & Nora, 1955; Feinberg & Feinberg, 1956; Nair, 1956). Depending then on the preponderance of one or the other, skin reactions or anaphylactic reactions may emerge. It is also suggested that there exists a certain affinity of antibodies to selected " shock organs ", for example the skin, internal organs, etc. This may account for the different types of allergic reaction. Heredity and other individual factors are also considered to be of importance.

In a recent survey undertaken by Welch et al. (1957), of 3419 case-histories relating to antibiotic reactions in 827 hospitals in the USA, 1070 reactions (31.3%) were classified as life-threatening. These included 809 cases of anaphylactic shock, 107 superinfections, 70 severe skin reactions, 46 blood dyscrasias and 38 cases of angioneurotic oedema with cerebral or respiratory involvement. Penicillin was responsible for 793 of the anaphylactic reactions, 47 of the severe skin reactions and 37 of the cases of angio-oedema — but for none of the blood dyscrasias and for few of the superinfections.

Eczematous Reactions

Contact dermatitis

Contact dermatitis caused by local skin sensitization following penicillin application, usually as ointment or in solution, is the most common type of eczema. It occurs also after direct contact with the drug by doctors

and nurses who handle it (Pyle & Rattner, 1944; Friedlander, Watrous & Feinberg, 1946; Berke & Obermayer, 1948; Marsh & New, 1948; Siegal & Peck, 1948; Barton, 1949; Peck & Feldman, 1949; Hitschman, Leider & Baer, 1950; Kile, 1950; Curtis et al., 1951; Roberts, 1953; Hussar & Holley, 1954), and particularly in workers in the pharmaceutical industry (Maffei & Napolitano, 1955). Penicillin patch tests are positive in 30%-50% of individuals with contact dermatitis (Binkley & Brockmole, 1944; Graves, Carpenter & Unangst, 1944; Hanson, 1944; Bedford, 1946; Friedlander, Watrous & Feinberg, 1946; Hopkins & Lawrence, 1947; Templeton, Lunsford & Allington, 1947). Among workers in the penicillin industry, skin tests may almost always be positive (Siegal, 1955b) and systematic testing should be carried out for the detection of latent cases so that potential victims can be diverted to other employment (Maffei & Napolitano, 1955). It is of general interest that the injection of serum from sensitized persons into the skin of normal individuals results in passive immunization of the infiltrated skin area (Templeton, Lunsford & Allington, 1947).

The eczematous manifestations may come as early as 1-2 weeks (Graves, Carpenter & Unangst, 1944; *J. Allergy*, 1953) or as late as 12 months (Silvers, 1944; Barker, 1945) following the repeated use of penicillin ointment. Generalized sensitization of the skin to penicillin may develop (Mahoney et al., 1944). Systemic sensitization may also result, with generalized immediate reactions including pruritus, erythema, urticaria and anaphylactic shock on subsequent penicillin administration. Cohen (1951) reported a case of atopic dermatitis in a two-year-old child who had been given penicillin orally.

Contact dermatitis has been estimated to occur in about 4% of patients exposed to prolonged local penicillin treatment (Cohen & Pfaff, 1945) or in those who regularly handle the drug (Bate, 1954), although more recent figures of 5%-10% have been given (Sloane, 1956). Obviously, when the drug is applied to macerated skin the risk of sensitization is particularly high because of the close contact with the epidermis. In skin complaints, reactions frequently follow the use of local penicillin (Cohen & Pfaff, 1945; Vickers, 1946; Barton, 1949). Goldman and his colleagues (1946) noted 16 eczematous reactions in 350 cases of various skin disorders treated. Such reactions appeared frequently on the face.

As a rule, avoidance of contact with penicillin is obviously necessary in the case of sufferers from contact dermatitis of other etiology. If such contact is virtually unavoidable (as, for instance, in doctors and nurses) desensitization can sometimes be undertaken (Morris-Owen, 1956). In any case, it is considered that penicillin preparations should be used only exceptionally for surface skin infections and its application should in any circumstances be limited to 3-5 days (Pyle & Rattner, 1944; Barker, 1945; Bedford, 1946; Morginson, 1946; O'Donovan & Klorfain, 1946; Vickers, 1946; MacInnis, 1947; Meara, 1948).

Trichophytid-like reactions

These are eczematous manifestations which may result from the administration of penicillin by the parenteral or inhalation routes to persons with latent sensitivity. They are characteristically localized to the groins, the interdigital spaces, and the palms and soles (pompholyx). They are of an erythemato-vesicular type, resembling the " id " eruptions of epidermophytosis—hence their name (Graves, Carpenter & Unangst, 1944; Leifer, 1944; Mahoney et al., 1944; Brown, 1948; Peck et al., 1948; Haunz & Grinnel, 1949; *J. Allergy*, 1953; Siegal, 1955b).

Such reactions may occur in individuals who have apparently not previously received penicillin. It has been suggested that a previous *fungus* infection may result in a cross-sensitivity to penicillin (Graves, Carpenter & Unangst, 1944; Goldman, Friend & Mason, 1946; Pyle & Rattner, 1946; Hopkins & Lawrence, 1947; Peck et al., 1948; Haunz & Grinnel, 1949; Reyer, 1952; Siegal, 1955b; Nasou & Romansky, 1956), since the common fungi contain both specific and non-specific antigens, including penicillin-like substances (Peck & Hewitt, 1945; Cormia, Lewis & Hopper, 1947; Jadassohn, Schaff & Wohler, 1947; Sulzberger & Baer, 1947; Huber, 1949; Hensler, Wurl & Gillespie, 1952). Certainly, the reverse is often the case, for fungus eruptions may flare into activity during penicillin administration (Feinberg, 1944; Lamb, 1945; Kolodny & Denhoff, 1945; Huber, 1949). A *latent* stage of penicillin sensitivity induced by a previous fungal infection characterized by a positive trichophytin test, and also frequently associated with a positive penicillin skin test of the delayed type (scratch or intradermal test) (Welch & Rostenberg, 1945) may eventually develop into an *active* trichophytid-like eruption as a result of a subsequent penicillin administration (Peck et al., 1948; Siegal, 1955b). During the *active* stage of trichophytid-like penicillin reactions, the delayed scratch or intradermal penicillin skin tests will be positive in the majority of cases, while the patch test commonly is negative (Peck et al., 1948).

In the USA a positive penicillin skin test of the delayed type is found in about 5% of adult persons who are not known to have received penicillin therapy (*J. Allergy*, 1953; Siegal, 1955b). Caution in the administration of penicillin to patients with presumed latent penicillin sensitivity (indicated by a positive delayed penicillin skin test) has been recommended (Haunz & Grinnel, 1949).

It is also claimed that trichophytid-like penicillin eruptions occur more frequently in men than in women (Hensler, Wurl & Gillespie, 1952; Hussar & Holley, 1954) and that they are rarely encountered in children (Peck et al., 1948; Siegal, 1955b). Such observations suggest exposure to a previous fungus infection as a possible cause for the sensitization. However, so many persons show positive skin tests to trichophytin (about 40% of the adult population in countries in Europe and North America) that this

test cannot be accepted as a criterion for or against penicillin sensitization. In addition, epidermophytosis (particularly " athlete's foot ") is so widespread in all regions of the world that the possibility of sensivity to penicillin induced by a previous fungus infection (regardless of the route) must await further clarification.

Generalized dermatitis

In eczematous penicillin reactions, both the contact dermatitis and the " id " reaction have a good prognosis after discontinuation of penicillin treatment. The symptoms will usually vanish after some days or a few weeks with appropriate treatment. In prolonged cases, hydrocortisone applied topically has proved to be of value (Siegal, 1955b). Generalized eruptions or exfoliative dermatitis develop rarely and are frequently of a mild type (Haswell & Wilkinson, 1946; Farrington & Tamura, 1947; Hopkins & Lawrence, 1947; Rabinovitch & Smitkoff, 1948; Hansel, 1953) although serious complications (e.g., anuria) have been reported (Harlem, 1955). Severe and fatal cases of pneumonia (Willcox & Fryers, 1957) and staphylococcal septicaemia (Phillips, Romansky & Nasou, 1955), both of which may be due to antibiotic-resistant organisms, have been reported (Barksdale, Frost & Nolan, 1948; Rabinovitch & Smitkoff, 1948; Langdon, 1950). Photosensitivity occurs occasionally (Canizares, 1945). Bullous forms may be met (Berne, 1950). Occasionally, the exfoliative dermatitis may become haemorrhagic and gangrenous (Derzavis & Beinstein, 1948). Petechiae may appear when penicillin is given following a previous penicillin dermatitis (Graves, Carpenter & Unangst, 1944).

The hypersensitivity of the skin to penicillin is frequently transient. It may decline spontaneously within 6-12 months but rarely in less than six weeks. Accordingly, a positive patch test, or a positive delayed scratch or intradermal test, may in time become negative (*J. Allergy*, 1953). However re-treatment with penicillin in patients who have a past history of eczematous penicillin reactions should be considered with caution — even if the skin test is negative — since the possibility of re-occurrence of the symptoms cannot be excluded, and also since the possibility of systemic rather than skin sensitization must be kept in mind (Siegal, 1955b). Artificial desensitization has been successfully achieved in some cases (Peck & Siegal, 1947).

Urticaria, Angio-oedema and Serum-sickness-like Penicillin Reactions

Urticaria may appear within 30 minutes to several weeks after the administration of penicillin. Giant urticaria and angio-oedema may occur. Laryngeal oedema may be frightening or even fatal (Anderson, 1951; Hussar & Holley, 1954).

Although urticarial eruption is usually the dominant element and often occurs alone, it is now generally accepted that urticaria following administration of penicillin is not always an isolated phenomenon, but a part of a syndrome which also includes erythema, anorexia (Mendell & Prose, 1946; Kendig & Toone, 1947), malaise, pruritus, arthralgia and fever, and sometimes also angio-oedema, especially of the face (Peck et al., 1948; von Oettingen, 1955; Siegal, 1955b; Carpenter, 1956), pain and swelling of muscles and joints (Eisenstadt, 1946; Gordon, 1946; Strakosch, 1946; Strazza, 1946; Criep, 1949; Hussar & Holley, 1954; Winton & Nora, 1955) and lymphadenopathy (Watson, 1948; Feldman, 1949). The blood sedimentation rate is often accelerated (Rådmark, 1956) and eosinophilia may be present (Riley, 1952). The symptoms are often delayed (Gordon, 1946). Sometimes the skin eruption is scarlatiniform and resembles erythema multiforme (Davis, 1953; Rådmark, 1956) or erythema nodosum (Kern & Wimberley, 1953). Mixed patterns are not uncommon. Fixed drug eruptions are reported to be rare following penicillin administration, but they may be intense. Drug fever is encountered only occasionally (Hussar & Holley, 1954; Herrell, 1955). The symptoms closely resemble those seen in serum-sickness following the injection of sera. Also the pathogenesis and the mechanism seem to be similar. It is therefore convenient to consider all these reactions collectively (for many treat them as one entity). The term " serum-sickness-like penicillin reaction " is therefore considered justified by many authors and covers the urticarial response to penicillin administration, whether this symptom appears alone or in association with other serum-sickness symptoms (Urbach & Gottlieb, 1946; Hansel, 1953; Hussar & Holley, 1954; von Oettingen, 1955; Siegal, 1955b; Carpenter, 1956).

The incidence of periarteritis nodosum increased threefold after the introduction of the sulfonamides in 1935. More recently the occasional case of penicillin reaction has resulted in necrotizing arterial damage sometimes with fatal outcome (Surdakowski, 1954). Harkavy (1952) reported two fatalities in persons with purpuric lesions and in whom extensive visceral lesions due to penicillin reaction were encountered. Kern & Wimberley (1953) reported two similar cases.

Even the LE phenomenon has been linked with penicillin sensitivity. Gold (1951) reported eight cases of systemic lupus erythematosus in which penicillin sensitivity was blamed, but the evidence was equivocal. LE cells have been found in patients with severe serum-sickness-like reaction (Walsh & Zimmerman, 1953; Paull, 1955).

Urticaria was observed as early as 1943, when Keefer and his colleagues estimated an incidence of 2%-3% among patients treated with penicillin. Stokes reported similar figures in 1944. Following the introduction of long-acting penicillin in oil and beeswax (POB) in 1944 an increase in the frequency of urticaria took place. This has been attributed to the beeswax component of the preparation (Kolmer, 1947; Haunz & Grinnel, 1949;

Kern & Wimberley, 1953; Hussar & Holley, 1954). Since procaine penicillin G in aqueous suspension and in oil with 2% aluminium monostearate (PAM) came into general use in 1949, the urticarial reactions have probably become less frequent and the incidence of such reactions has been estimated at 1%-2% of all patients receiving penicillin treatment (Hussar & Holley, 1954). As the incidence of urticarial reactions is apparently the same with crystalline penicillin G as with procaine penicillin G (*J. Allergy*, 1952), the procaine component does not seem to give rise to appreciable sensitization. As to benzathine penicillin, it is possible that it is followed by less urticaria than when other preparations are used, but, on the other hand, it has often been noted that the incidence of reactions tends to fall with the introduction of new preparations only to rise again as increasing numbers become sensitized to them (Hussar & Holley, 1954).

The serum-sickness-like penicillin reactions frequently occur—as in genuine serum-sickness—following the first exposure to the allergen, penicillin. The appearance of the symptoms is, however, delayed for some days, during which sensitivity develops and antibodies are produced (Rådmark, 1956). These sensitizing antibodies react with the remainder of the antigen (Hansel, 1953; Urbach & Gottlieb, 1946; Carpenter, 1956). The intensity of the symptoms depends to a certain degree on the amount of antibodies and available antigen. In this delayed type of serum-sickness-like penicillin reaction the incubation period may vary from 5 to 14 days (Keefer et al., 1943; Hansel, 1953; Siegal, 1955b; Carpenter, 1956), although urticaria has recurred as late as 5 weeks after completion of penicillin treatment (Truitt, 1946; Shawyer, 1948).

Following a second or subsequent penicillin administration an accelerated type of serum-sickness-like penicillin reaction may sometimes occur within 3-5 days, indicating that the patient was already sensitized by an earlier administration, with antibodies still being present, although in relatively small amounts (Urbach & Gottlieb, 1946; Friedlander, Watrous & Feinberg, 1946; Hansel, 1953; Siegal, 1955b; Feinberg & Feinberg, 1956; Idsöe & Wang, 1958). These antibodies will react with further allergen now introduced by the provoking administration. The symptoms of accelerated reactions are usually of moderate intensity, with a slight urticarial rash. However, in highly sensitized individuals with abundant antibodies, subsequent penicillin administration may provoke stronger reactions, i.e., an explosive urticaria. This is sometimes associated with other marked symptoms of the serum-sickness-like syndrome, particularly angio-oedema and fever (Winton & Nora, 1955; Idsöe & Wang, 1958). Such reactions can occur very shortly after the provoking penicillin dose, but they have also been recorded as late as 1-2 weeks after it (Winton & Nora, 1955). Exceptionally, cardiovascular collapse may occur (Siegal, 1955b; Feinberg & Feinberg, 1956; Idsöe & Wang, 1958) with a resulting picture resembling that of an anaphylactic shock (Siegal, 1955b). The immunological relation-

ship between the typical anaphylactic response to penicillin and such aggravated serum-sickness-like penicillin reactions is not clear, particularly since the latter rarely seem to precede the anaphylactic reaction. Individual factors may perhaps influence the emphasis of either one or the other of the skin-sensitizing or the anaphylactic antibodies, or the possible association of sensitivity to different shock organs may explain the difference in the clinical and immunological pattern encountered.

Obviously, skin testing before the administration of penicillin is of no value in excluding patients who would react with delayed serum-sickness-like symptoms, since such persons, not having been exposed to penicillin previously, are not actually sensitized at the time of administration and no antibodies are present (Sullens, 1945). These develop only during the " incubation " period, before the occurrence of the delayed symptoms. A negative test before a first administration of penicillin can therefore be followed by reactions of this type. On the other hand, the *delayed* penicillin skin test may become positive (after the onset of the symptoms) as soon as the amount of antibodies has reached a reactive level (Siegal, 1955b): such positive skin tests have been reported in up to 40% of the cases (Peck et al., 1948). Consequently, a positive delayed test before an administration of penicillin would indicate existing penicillin sensitivity, which might result in an *accelerated* serum-sickness-like reaction (Mosko, Nejedly & Rostenberg, 1955). The significance of immediate skin tests and immediate penicillin reactions will be discussed later, but it is stressed at this point that sensitivity reactions to penicillin may occur despite a negative outcome of any skin test (Rådmark, 1956; *J. Allergy*, 1953).

Most investigators agree that children are less prone to develop the serum-sickness-like penicillin reactions than are adults and that the symptoms are generally less marked in children (Siegal, 1955b; Collins-Williams & Vincent, 1954). As between the sexes, little difference has been noted except for a slight preponderance of females (Smith, Cutler & Price, 1955; Idsöe & Wang, 1958).

The penicillin sensitivity which may result in an urticarial serum-sickness-like syndrome is usually temporary (Peck et al., 1948; Siegal, 1955b). Sensitivity may decrease over a period of 6-12 months, the interval seldom being less than 6 weeks. Therefore, a recurrence of reactions on subsequent penicillin administration is not constant. (Indeed, urticaria occurring with benzathine penicillin may sometimes disappear despite the fact that penicillin is still demonstrated in the blood.) Nor are recurrences necessarily of an increased severity (Siegal, 1955b), although giant urticaria and oedema of the glottis have been observed (Sullens, 1945). With the fading of the sensitivity, a positive delayed skin test may revert to negative (Hussar & Holley, 1954), a phenomenon which might give some basis for considering the re-administration of penicillin (Siegal, 1955b). On the other hand, a negative test does not necessarily mean expired sensitivity, and the risk of

immediate severe reactions should always be kept in mind when considering re-treatment of a patient who has experienced a serum-sickness-like penicillin reaction (*J. Allergy*, 1953; Hinman, Warner & Li, 1956). It is interesting to note that the majority of cases of serum-sickness-like reactions which have been reported have not revealed a past history of other allergic manifestations, such as asthma or hay fever (Hansel, 1953; Haunz & Grinnel, 1949; Peck et al., 1948).

The urticarial syndrome usually subsides within days or a few weeks (Anderson, 1954) if penicillin treatment is discontinued. A prolongation of the symptoms, however, lasting up to 15 months, is not too infrequent, as pointed out by Siegal (1955b), who himself observed six cases persisting for 3 to 12 months.

Weak reactions usually do not require any particular treatment, but in severe or prolonged cases antihistamines (Curtis & Owens, 1945; Willcox, 1946; Friedlander, 1946; Davis, 1947; Dean, 1947; Pillsbury, Steiger & Gibson, 1947; Brown, 1948; *J. Allergy*, 1953), epinephrine and cortisone (Hensler, Wurl & Gillespie, 1952; Davis, 1953; *J. Allergy*, 1953; Siegal, 1955b) have proved to be effective. ACTH and cortisone may be life-saving (Rådmark, 1956). In prolonged cases, refractory to ordinary treatment procedures, penicillin desensitization has occasionally been found to be successful (Siegal, 1955b). On the other hand, orally or parenterally administered antihistamine preparations given prophylactically are considered to be of no value in preventing the reactions, and have not been recommended as a worth-while routine precaution (*Brit. med. J.*, 1955; Mathews et al., 1955, 1956).

A recent development is the use of penicillinase (Neutrapen). Single injections of 5000 units of this penicillin-destroying enzyme have been shown to inactivate 100 000 units of crystalline penicillin G. With the object of inactivating circulating penicillin, penicillinase has been successfully used in cases of chronic urticaria and angio-oedema which have proved resistant to other methods, including steroids (Becker, 1956, 1958; Chen, Bard & Balsito, 1958; Zimmerman, 1958). A dose of 800 000 units intramuscularly is given as soon as possible after symptoms of penicillin reaction appear. If necessary, the dose may be repeated at 3-day or 4-day intervals. A further recent development is the introduction of an antihistamine-penicillin salt (1-p-chlorbenzyl-2-pyrrolidylmethyl-benzimidazol-penicillin-G). This preparation is designed to obviate the allergic reactions in persons sensitive to penicillin, at the same time retaining the antimicrobial effect of the antibiotic (Ahnefeld, 1954; Fenner, 1956; Walther, 1957).

Serum-sickness-like penicillin reactions usually follow injections of the antibiotic, but may also occur after other forms of administration: application of penicillin ointment on the skin, tablets, inhalations, and instillations of penicillin preparations to the conjunctival mucosa, the sinuses, and the nasal and oral mucosa. The oral, nasal or conjunctival mucosa may be

sensitized and react to penicillin application. Thus, rhinitis and stomatitis have been reported to occur in 5%-15% in patients treated locally (Kleinfeld, 1946; McGregor, 1947; Hansel, 1953; Kutcher et al., 1953). Penicillin reactions of the vaginal and rectal mucosa following local application are extremely rare. The local reactions can be annoying to the patient, and therefore *per se* usually contra-indicate re-applications of the remedy. Of greater importance is the mucosa as port of entry for the antigen, causing generalized allergization (Everett, 1951; Weiss, 1953; Dubberley, 1955).

Only an occasional patient with urticaria alone later develops anaphylaxis on receipt of more penicillin: anaphylaxis is more common following the other symptoms of serum sickness (*J. Allergy*, 1953).

ANAPHYLACTIC REACTIONS

Eczematous and urticarial serum-sickness-like reactions rarely constitute a serious threat to life. The anaphylactic type of allergic penicillin reaction, on the other hand, may prove fatal, and a considerable number of cases have been reported in the medical literature during the last ten years. Reactions in such cases have a sudden onset with vasomotor collapse, immediately or soon after penicillin administration, which is followed by quick recovery or death. The symptoms closely resemble those of anaphylactic shock in animals, induced by repeated injections of antigen, and for which the terms " anaphylactic ", " anaphylactoid " or " shock-like " reactions have been used. They have also been called " severe immediate allergic reactions associated with some degree of shock-like symptoms " (Weiss, 1953).

Penicillin anaphylactic reactions apparently occur only in individuals with sensitivity induced by previous use of the antibiotic, and not following an initial administration. Most available evidence suggests that during anaphylactic shock some histamine-like substance is released from the cells upon which an antibody reaction takes place, and that this substance is transplanted in the circulating blood to muscles and other tissues (Carpenter, 1956). In the majority of cases of penicillin sensitivity, the antibodies are cellular, but in severe anaphylactic forms of sensitivity they are humoral, as shown by the immediate reaction and by the Prausnitz-Küstner type of passive transfer (Kern & Wimberley, 1953). There is wide agreement that circulating antibodies exist in severe penicillin sensitivity (Templeton, Lunsford & Allington, 1947; Simon, 1950; Siegal, 1951; Mayer et al., 1953).

Reported Cases of Anaphylaxis

It was shown quite early that anaphylactic sensitization could be induced by injections of amorphous penicillin into guinea-pigs (McClosky & Smith, 1944). Anaphylaxis due to penicillin was first reported in humans in 1945 (Cormia, Jacobsen & Smith, 1945).

The first fatality from penicillin treatment—an elderly man given penicillin following gastrectomy, who developed vomiting, fever and rash, and who died after three days—was reported by Wilensky in 1946. The second fatality, recorded in 1949 by Walbott, occurred in a patient who died within three hours of receiving the antibiotic. It was stated later, however, that only two deaths from penicillin sensitivity had been recorded in the first nine years of use of the antibiotic (Kern & Wimberley, 1953). The picture changed during the next 18 months, when 15 more deaths occurred (Kern & Wimberley, 1953); and by 1954 no less than 48 had been noted, of which 39 in the years 1952-53 (Hussar & Holley, 1954).

There is general agreement that only a small proportion of the fatalities which do occur are recorded in the literature (Brown, 1948; *J. Allergy*, 1953). In some cases, coronary thrombosis may be unfairly blamed; in others the practitioner may be unwilling to place an unfortunate mishap on record (Rajam & Rangiah, 1956). Welch and his colleagues (1953) reported an investigation into penicillin reactions at 95 hospitals with 51 000 beds and found a further 59 cases of severe reactions (19 deaths) which had not been recorded: in addition, the existence of a further 25 cases with 5 deaths was reported by one pharmaceutical firm. Corr & Wellman (1956) reviewed the English and North American literature up to June 1954 and found 250 cases of severe reactions to penicillin, of which 74 had proved fatal. By November 1955, some 561 anaphylactic reactions had been recorded in the world's literature, of which 81 were fatal (Rajam & Rangiah, 1956). In 1957, Welch et al. described a further survey of penicillin reactions in the USA, covering 827 hospitals (198 332 beds) during the period 1954-56. A total of 3419 case-histories relating to antibiotic reactions was studied, of which 422 were discarded. As has been mentioned earlier, a total of 1070 life-threatening reactions was uncovered, which included 809 cases of anaphylactic shock, 107 superinfections, 70 severe skin reactions, 46 blood dyscrasias and 38 cases of angioneurotic oedema with cerebral or respiratory involvement. No less than 793 of the anaphylactoid reactions, including all of 72 deaths, followed penicillin. The majority of these anaphylactoid reactions followed the most used penicillin: 90.1% following procaine penicillin G, 5.6% following benzathine penicillin G, 2.9% following potassium penicillin G, 1.1% following phenoxymethyl penicillin (V), and 0.3% following penicillin O (Roberts, E. F.—personal communication, 1958). It is obvious that as the number of reactions occurring in a given country increases, the likelihood of practitioners to describe, or of journals to publish, individual cases will decrease, as their occurrence is inevitably less " newsworthy ". Peters and co-authors (1957), as has been mentioned earlier, estimated that 1000 deaths from anaphylaxis due to penicillin had occurred in the USA.

It is apparent that the majority of fatalities has been reported in the USA, which has the greatest penicillin consumption in the world (Barksdale,

Frost & Nolan, 1948; Burleson, 1950; Berne, 1950; Irving et al., 1951; Everett, 1951; Higgins & Rothchild, 1952; *J. Allergy*, 1952; Stroud, 1952; Curphey, 1953; Christenson, Hedrich & Schugman, 1953; Feinberg, Feinberg & Moran, 1953; Mayer et al. 1953; Siegal, Steinhardt & Gerber, 1953; Kern & Wimberley, 1953; Rosenthal, 1954; Nudelman, 1956). Indeed, during the period 1954-56, no fewer than 900 tons of penicillin were produced in the USA—600 tons if human medicine alone was considered, or 2000 million doses of 300 000 units (Welch et al., 1957). Against this staggering total, the incidence of severe reactions must be considered very small. The country next in the number of cases reported is the *United Kingdom of Great Britain and Northern Ireland* (O'Donovan & Klorfain, 1946; Batchelor, Horn & Rogerson, 1951; Humphreys, 1951; Thomson, 1952; Wylie-Smith, 1952; Yuval, 1952; Altounyan, 1953; Beauchamp, 1953; Pick & Patterson, 1953; Bell, 1954; Swift, 1954; *Brit. med. J.*, 1955; Calvert & Smith, 1955; Campbell, 1955; Dubberley, 1955; Tidswell, 1955; *Lancet*, 1956b; Rajam & Rangiah, 1956). There is thus no doubt that the highest numbers of reported cases have occurred in those countries in which penicillin has been much used for the longest periods of time. However, reports have also come from other countries where penicillin has been in ever-increasing use since the middle of the 1940's. Since 1952, some anaphylactic cases, including several fatalities, have been observed: in *France* (Léchelle & Chapuis, 1950; Calas & Jaubert, 1955; Graciansky & Delaporte, 1956), in *Belgium* (Corajod, Fournel & Chatillon, 1951), in *Germany* (Beickert & Noetzel, 1952; von Zinzius, 1956), in *Switzerland* (von Leemann & Fehr, 1956), in *Italy* (Caldana & Bottoli, 1953) and in *Greece* (Isakidis, 1951). A few anaphylactic cases have also been reported in Scandinavia (Wagner et al., 1957): in *Norway* (Harlem, 1955; Myhre, 1956), in *Sweden* (M. Tottie—personal communication, 1955) and in *Denmark*, including three deaths (Hofman-Bang, 1955; Rud, 1955; Andersen, 1955, 1956), Cases have been published in other countries with high medical standards, including *Canada* (Mignault & Mitchell, 1953; Collins-Williams & Vincent, 1954) and the *Union of South Africa*, where at least 3 deaths after penicillin administration have been observed (Smith, 1955; Blumberg, 1955; Eales, 1955).

In *Japan*, where penicillin is undoubtedly in wide use, deaths occurring immediately after the administration of the antibiotic have alarmed both the medical profession and the general public, as also in Taiwan (Idsöe & Wang, 1958). In other countries where the use of penicillin has reached only a limited segment of the population, only a few cases have been reported, notably in *India* (Panja & Banerjee, 1951; Rajam & Rangiah, 1956), in the *Philippines* (Icasiana, 1953), in *Morocco* (Bickel, 1954), in *Puerto Rico* (Cruz Hernandez & Rosa-Febles, 1955) and in *Argentina* (Dumm, Raimondi & Moreno-Ramirez, 1955). It is noticeable that these cases occurred almost exclusively in urban areas, where penicillin is fairly easily obtainable. In

Thailand, there were only 21 cases of anaphylaxis in 938 299 patients with yaws and 196 482 with syphilis treated with penicillin during the years 1950-55 (Suvarnasara & Panikabutra, 1956).

Many countries, particularly in the Caribbean, South American, African, Middle Eastern, South-East Asian and the Western Pacific areas have, with WHO assistance, undertaken mass campaigns against the treponematoses based on the use of long-acting penicillin without anaphylactic reactions having been reported, although several million people have received penicillin injections. Such mass campaigns have been carried out predominantly in rural areas, among populations previously not exposed to penicillin. In Taiwan, where serious and fatal reactions have occurred (Idsöe & Wang, 1958), the population has had a fairly high penicillin consumption, comparable to that of many European and North American countries where a majority of the people have been in contact with the drug.

Symptoms of Anaphylaxis

Although most investigators emphasize syncope as the dominating entity of the anaphylactic reactions, other phenomena may be associated with them, either as the sole representatives or in combination. Among the symptoms most frequently encountered are the following: tingling of the tongue or of the hands (Eisenstadter & Hussar, 1954; Peters, Henderson & Prickman, 1955), dry taste in the month (Siegal, Steinhardt & Gerber, 1953; Peters, Henderson and Prickman, 1955), feeling of weakness, perspiration (Eisenstadter & Hussar, 1954), palpitations, vertigo, dizziness, as well as feelings of oppression which may initiate the attack. Frequently, there are complaints of " tightness in the chest " (Siegal, Steinhardt & Gerber, 1953; Peters, Henderson & Prickman, 1955), precordial pain (Pick & Patterson, 1953), and a feeling of inability to breathe. Facial flush changing to pallor is often apparent. Occasionally, epigastric pain or nausea and vomiting, or both, also initiate or are associated with the reaction (Humphreys, 1951; Smith, 1955). Sometimes nervous symptoms, such as visual disturbances and convulsions (Calas & Jaubert, 1955), may dominate, as is shown from the following tabulation of symptoms:

Frequent symptoms	*Occasional symptoms*
Tingling of tongue	Epigastric pain
Dry taste in mouth	Nausea
Weakness	Vomiting
Perspiration	Visual disturbances
Palpitation	Convulsions
Vertigo	Defaecation
Dizziness	Incontinence
Oppression	Oedema of eyelids
Tightness in chest	Urticaria
Pallor-flush	

Urge to defaecate, frequent stools or incontinence of urine are not infrequent (Siegal, Steinhardt & Gerber, 1953; Eisenstadter & Hussar, 1954; Calvert & Smith, 1955). Coughing from bronchial irritation, also oedema of the eyelids or of the pharynx (Humphreys, 1951; Long, 1954; Peters, Henderson & Prickman, 1955) and urticaria are also seen, either as single symptoms or associated with the syncope or mingled with some of the other symptoms (Humphreys, 1951; Etter & Merryman, 1954; Peters, Henderson & Prickman, 1955). Haemorraghic bullous dermatitis involving the mucous membrane of the mouth and skin and resembling pemphigus vulgaris has been described (Winton & Nora, 1955). Fever and joint pains are rare.

All these symptoms generally precede the vasomotor collapse with cyanosis, dyspnoea, laboured respiration, rapid, weak or imperceptible pulse, unconsciousness and sometimes death (Thomson, 1952; Yuval, 1952; Siegal, Steinhardt & Gerber, 1953; Fisher, 1954; Hussar & Holley, 1954; Dumm, Raimondi & Moreno-Ramirez, 1955; Lang & Clagett, 1955; Peters, Henderson & Prickman, 1955; Winton & Nora, 1955). Usually these events take place very rapidly.

Apart from general observations, for obvious reasons few exact detailed clinical examinations can be performed during the attack. In a few instances blood-pressure readings have been recorded. The blood-pressure drops alarmingly, to less than 50/30 mm of mercury and becomes immeasurable (Lang & Clagett, 1955; Carter & Cope, 1954; Peters, Henderson & Prickman, 1955). Electrocardiograms have exceptionally been taken during the acute attack. Transient and abnormal T-waves have been observed (Siegal, Steinhardt & Gerber, 1953; Farber, Ross & Stephens, 1954; Glotzer, 1954). A few blood studies of anaphylactic reactors have been undertaken but no significant findings having been made (Siegal, Steinhardt & Gerber, 1953).

Previous Sensitization to Penicillin

Pre-established allergy has been accepted to date by most observers as a *sine qua non* of anaphylactic shock reactions. In the case of anaphylaxis to penicillin, sensitization is thought always to have been induced by previous administration of the antibiotic, even if the latter in some cases is not definitely known, has been overlooked, or has been forgotten by the patient (Urbach & Gottlieb, 1946; Hansel, 1953; Kern & Wimberley, 1953; Long, 1954). A negative history of previous penicillin administration may be misleading. Injections are usually remembered but this is not always the case for penicillin-containing creams, ointments, tulle gras, eye or ear drops, lozenges, inhalations, etc. (Bell, 1956). In the very few cases in which a foregoing penicillin administration has not been realized, circumstances will usually point to the likelihood of such exposure in the majority of the cases (Idsöe & Wang, 1958).

Anaphylactic reactions are believed to be extremely rare in infants (Levin & Moss, 1951; Yodar & Lysander, 1952; Collins-Williams & Vincent, 1954; Hensler, Wurl & Gillespie, 1952; *J. Amer. med. Ass.*, 1957) although some authors—e.g., Matheson & Elegant (1955)—have suggested they are more frequent than is supposed and may produce symptoms which are difficult to interpret. While pre-existing sensitivity may not be traced back to previous penicillin treatment, the possibility of intra-uterine sensitization of the foetus by penicillin administration to the mother, or of sensitization resulting from penicillin in the milk of the mother, has been considered by some authors (Urbach & Gottlieb, 1946; Hussar & Holley, 1954).

It has been suggested that superficial fungus infections (Huber, 1949; Hensler, Wurl & Gillespie, 1952; Hansel, 1953), or generalized penicillinosis (Simons, 1954), may account for sensitization in those rare cases in which a past history of penicillin administration has not been obtained, or even that penicillin moulds, which are among the most common contaminants and which are nearly always present in the air and often in the food (cheese), may be inhaled or digested and thus act as antigen causing sensitization (*J. Allergy*, 1950; Sanchez-Cuenca, 1950; Gollman, 1951; Kern & Wimberley, 1953; Hussar & Holley, 1954). The same objections, however, as have been raised earlier in this study to fungi as a potential source of sensitization, preceding trichophytid-like penicillin reactions, are also considered to pertain in respect of anaphylactic reactions (Feinberg, Feinberg & Moran, 1953; Mosko, Nejedly & Rostenberg, 1955). Furthermore, a past or present history of superficial fungus infection has rarely been observed in anaphylactic patients (Haunz & Grinnel, 1949; Weiss, 1953; Everett, 1951; Rosenthal, 1954), and a generalized penicillinosis is only an isolated medical occurrence (Simons, 1954).

In some of the reported fatalities there had been evidence of reaction to previous penicillin administration (Anderson, 1955; Thomson, 1952). It has been said that to give more penicillin in such cases is to court disaster (Kern & Wimberley, 1953).

Evidence of symptomatic previous allergy to penicillin is not infrequently obtained (Siegal, Steinhardt & Gerber, 1953; Criep & Ribeiro, 1953). Indeed a considerable number of fatal cases have occurred in asthmatics (Walbott, 1949; Curphey, 1953; Feinberg, Feinberg & Moran, 1953; Kern & Wimberley, 1953; Pick & Patterson, 1953; Sterling, 1953; Anderson, 1955). It has been calculated that in the USA one person in seven will therefore eventually become sensitized to repeated penicillin treatment (Kern & Wimberley, 1953; Bell, 1956).

A further study of the reported cases shows that in the majority intramuscular injections had been the method of introduction of the sensitizing agent. This does not necessarily mean, however, that the parenteral route is more likely than the oral or other routes to induce sensitivity. Taking

into account the fact that medical practitioners usually administer penicillin by intramuscular injection, it is only natural that this method is associated with a higher number of sensitized individuals than are other, less frequently used methods.

Anaphylactic reactions, including serious and even fatal ones, have been repeatedly reported in patients who, before the causative penicillin administration, had been exposed to penicillin tablets (Weiss, 1953; Surdakowski, 1954; Lang & Clagett, 1955; Peters, Henderson & Prickman, 1955), spray (O'Donovan & Klorfain, 1946), lozenges (Hussar & Holley, 1954), antral instillations (Everett, 1951; Weiss, 1953) and ointment (Dubberley, 1955). It is likely that the amount and concentration of penicillin contained in the preparations used for these applications were relatively very small. Furthermore, anaphylactic reactions have been observed in individuals whose previous contact with penicillin has been limited to prolonged professional handling of penicillin, even in very low concentrations (Coleman & Siegel, 1955). These authors showed that although boiling of penicillin induces a rapid fall in antibiotic potency, traces of penicillin could still be detected after 16 hours of boiling. Amounts greater than found capable of producing antigenic effects have been found in syringes thus contaminated. Obviously then, under certain circumstances (e.g., in the presence of macerated skin or following prolonged application of penicillin) the mucous membranes and the skin may facilitate the entry of penicillin as a sensitizing agent. At least, it would seem that no method of administration can safely ensure that subsequent sensitization will be avoided (Hussar & Holley, 1954; *J. Indian med. Ass.*, 1955; Winton & Nora, 1955; Feinberg & Feinberg, 1956).

Concerning *amounts and preparations* of penicillin previously received by potential reactors, or the time period over which penicillin has been administered, the reports available are very incomplete. Often the antibiotic has been given by others than the doctor in charge at the time, and the memory of the patients or their relatives often enough is failing. Total doses of more than 60 million units of procaine penicillin given over a 10-week period almost immediately preceding the causative administration are known (Myhre, 1956) as well as repeated administration during the preceding year (Curphey, 1953), or repeatedly over a two- or three-year period (Siegal, Steinhardt & Gerber, 1953). In the reports from Taiwan (Idsöe & Wang, 1958) total amounts of 0.6-4.8 mega-units were those most frequently given in previous administrations.

It is remarkable to note the small amounts of penicillin which seem capable of producing sensitivity. In the cases referred to above in which tablets, lozenges, instillations, and ointment have apparently induced the sensitivity, the actual amount of penicillin was, as noted, probably very low. Coleman & Siegel (1955) reported a most interesting case in which intense sensitivity to penicillin in a hospital maid was apparently induced

by washing syringes which had contained penicillin. In the Taiwan material (Idsöe & Wang, 1958), a previous dose as low as 0.05 mega-unit apparently produced sensitivity which one year later resulted in a fatal reaction upon re-exposure to the drug. The fact that this small dose was given orally in a tablet adds to the complexity of unknown factors which may make penicillin an allergic drug.

The same complexity pertains in regard to the *type of penicillin previously given.* Any of the commonly used types may be found to have been given in the cases reported in the literature, although procaine penicillin in aqueous solution or in oil with 2% monostearate (Myhre, 1956) had been given previously in the majority of cases of penicillin reactors, as would be expected on account of the widespread use of procaine penicillin in recent years. These preparations were given either alone or in combinations, and included crystalline penicillin G in water (Humphreys, 1951; Campbell, 1955) crystalline penicillin G + streptomycin (Dumm, Raimondi & Moreno-Ramirez, 1955), penicillin O (Mosko, Nejedly & Rostenberg, 1955) and the various penicillin preparations used in ointments, inhalations, tablets, instillations, etc.

Of considerable interest are questions of the *time interval* between the last previous administration of penicillin and the exposure which caused an anaphylactic reaction. In other words, how quickly can sensitivity develop, and once established how long will it persist? Rather few relevant data are recorded in the reports. Generally speaking, the reported intervals between the two penicillin administrations range from ten days to eight years. More precisely some reporters have registered three and four weeks (Idsöe & Wang, 1958), two months (Myhre, 1956), three months (Idsöe & Wang, 1958), four months (Carter & Cope, 1954), six to nine months (Idsöe & Wang, 1958) and seven to eight years (Idsöe & Wang, 1958; Dubberley, 1955).

In these cases no relationship has been found between the intervals and the amount or preparation of penicillin previously given, or between these factors and the severity of the reactions following the subsequent administration. Thus in one patient with severe reaction 2 mega-units of procaine penicillin had been given intramuscularly two months previously, in another " one injection some months previously " (Myhre, 1956). In one case, one tablet of 50 000 units apparently produced allergy which caused a fatal reaction on re-exposure 12 months later (Idsöe & Wang, 1958). In two cases, occurring after periods of seven and eight years following the previous administration, the drug had been given in the form of ointment and lozenges respectively (Dubberley, 1955; Calvert & Smith, 1955). Apparently, allergy to penicillin, resulting in anaphylactic reactions on subsequent re-exposure to the drug, can be produced within a few weeks and may be maintained for years, even after small amounts. The suggestion that the shorter the interval between the foregoing administration of penicillin and

that causing the reaction, the greater the likelihood of severe reactions seems to have only limited value. In this respect, also, it is likely that unknown individual factors are involved in the mechanism of sensitization.

More accurate information as to the minimum period of time needed to produce sensitivity in individuals exposed to penicillin (incubation period) may be derived from the very few cases reported in which reactions have occurred suddenly during continuous treatment courses. Myhre (1956) reports one case of severe anaphylactic shock following an injection of 0.6 mega-unit of procaine penicillin in a patient who had had three weeks' continuous daily injections of the said dosage, and who had finished a similar seven-week treatment course 14 days earlier; he also reports on two patients who, after four weeks' continuous daily treatment of 1 mega-unit suddenly collapsed following an injection. In the Taiwan material (Idsöe & Wang, 1958) three reactions, including two fatal ones, occurred following penicillin injections 10-14 days after the initiation of a treatment course of 0.6 mega-unit every other day. Other observations (Kern & Wimberley, 1953) also seem to indicate that 5-10 days is the absolute minimum time period required for the production of sensitivity. Obviously, it is the first administration of penicillin following a previous administration which may cause an immediate anaphylactic reaction (Hussar & Holley, 1954). If the first injection does not bring about a reaction, subsequent administrations in the same series will probably be harmless providing the interval between the doses is not longer than four days (Kern & Wimberley, 1953). This assumption may indicate that in treatment courses rather high single dosages, with but short intervals between administrations, should be given so that total dosages can be reached in a very short period, and that frequent courses with small dosages should be avoided (*J. Amer. med. Ass.*, 1955a).

On the other hand, it is worth keeping in mind that prolonged courses with penicillin can be continued with regular intervals for several years. Such treatment has been recorded for at least six years without the patients involved showing any untoward reactions (*J. Amer. med. Ass.*, 1955a). It is also striking that so few anaphylactic reactions, and indeed so few allergic reactions as a whole, are reported to have occurred among prostitutes, who are obviously more exposed to the risk of penicillin sensitization than other population groups. In many parts of the world, many of these women are under practically continuous prophylactic and curative penicillin treatment, sometimes for many years (Idsöe & Wang, 1958; Goodman, 1955; Fabrega, 1955; Guthe, 1955; Samamé, 1951; Thomson, G. M.—personal communication, 1957; Ram, L. M.—personal communication, 1958).

The Penicillin Administration Causing Reaction

Not only may sensitivity to penicillin be produced by all types of penicillin preparations but also almost all preparations have been reported

as capable of provoking anaphylactic reactions (Hussar & Holley, 1954; Kern & Wimberley, 1953; Alexander, 1955). In view of the overwhelming use of procaine penicillin in aqueous solution or in oil, and eventually in venereal diseases clinics with 2% aluminium monostearate (PAM), it is evident that procaine penicillin preparations apparently cause more reactions than those less frequently employed (Siegal, Steinhardt & Gerber, 1953; Peters, Henderson & Prickman, 1955). Also, fatal outcome has in the majority of cases followed the administration of procaine penicillin (Humphreys, 1951; Yuval, 1952; Beauchamp, 1953; Campbell, 1955; Bell, 1956).

It is remarkable, however, to note the many fatalities which have occurred subsequent to injections of crystalline penicillin G in water (Thomson, 1952; Burleson, 1950). This might indicate first that the penicillin as such and not the procaine component is responsible for the antigenic effect of the preparations, and secondly that the rapid resorption of crystalline penicillin G in water, resulting in a sudden influx of antigen and a high initial penicillin concentration in blood and tissues, may intensify the severity of the reaction. Many authors have stated that procaine is unlikely to induce sensitivity (Mayer et al., 1953; Siegal, Steinhardt & Gerber, 1953; Hussar & Holley, 1954). Although positive skin tests to both procaine and penicillin may be encountered in sensitive subjects (Fernström, 1956), in two of the reported cases in which sensitivity to the procaine component was suspected aqueous penicillin was given and the patient died (Thomson, 1952; Fisher, 1954).

Anaphylactic reactions have been recorded following penicillin 0 (Mosko, Nejedly & Rostenberg, 1955), compenamine (Krantz & Carr, 1954) oral penicillin V (Martin, Nichols & Heilman, 1955; Welch, 1956) and following oral benzathine penicillin (Welch et al., 1953; Bell, 1956) but such cases to date have been comparatively rare (doubtless owing to less use of these preparations) with relatively few fatalities. Several deaths, however, followed the use of penethamate hydriodide (Stormont, 1953; Welch et al., 1953).

The overwhelming majority of penicillin preparations causing reactions were administered by intramuscular injection, as this is the most common method used. It is probable, however, that intravenous injections of even small amounts of penicillin will result in a more rapid contact of penicillin with the shock tissues than occurs with other routes of administration (Urbach & Gottlieb, 1946; Hussar & Holley, 1954; Alexander, 1955). In Taiwan (Idsöe & Wang, 1958) fatality is reported following an intravenous injection of only 10 000 units of crystalline penicillin G in water.

The possibility of pulmonary embolism resulting from the accidental discharge of penicillin-in-oil preparations into a vein is controversial. As the results of some experiments suggest that pulmonary embolism may play an important part in the causation of reactions in animals (Bell, Rannie & Wynn, 1954), it has been deduced that intravenous injections

may be the cause of some of the severe and fatal reactions in man (Walbott, 1949). Other experimental studies, however, have indicated strongly that such a risk is negligible and that the theory that many severe reactions are explained by intravenous injections is not well founded (Siegal, 1955b).

Anaphylactic reactions usually occur after the first administration following a previous exposure. The causative doses commonly found in the reports are in the range 0.3-1.8 mega-units, 0.3 and 0.6 mega-unit probably being the most frequent (Siegal, Steinhardt & Gerber, 1953; Siegal, 1955b; Myhre, 1956). It ought to be emphasized, however, that smaller dosages have often provoked reactions. Indeed, it seems to be rather characteristic of many severe and fatal reactions that they may be caused by low dosages—a fact which may indicate a very high degree of allergy in the individuals concerned. Thus, a large number of the reports of fatal cases reviewed indicated causative doses of between 0.1 and 0.3 mega-unit (Humphrey, 1951; Thomson, 1952; Yuval, 1952; Beauchamp, 1953; Siegal, Steinhardt & Gerber, 1953; Bell, 1954; Fisher, 1954; Siegal, 1955b).

Severe anaphylactic reactions have been reported after instillations of penicillin in sinuses (Everett, 1951; Weiss, 1953), after penicillin aerosols (Feinberg, Feinberg & Moran, 1953), after ophthalmic ointments (Carter & Cope, 1954), and after troches and lozenges (Higgins & Rothchild, 1952; Mayer et al., 1953; Madalin, 1954). Severe reactions following the use of penicillin tablets have been commonly reported (Brown, 1948; Blanton & Blanton, 1953; Eisenstadter & Hussar, 1954; Surdakowski, 1954; Calvert & Smith, 1955; Peters, Henderson & Prickman, 1955; Siegal, 1955b). As few as 10 units may evoke a reaction: certainly one tablet of 1000 units has done so (Calvert & Smith, 1955) and a fatality has been reported after administration of only one tablet (Siegal, 1955b; Calvert & Smith, 1955). There are remarkable records of severe reactions immediately following intracutaneous skin tests (O'Donovan & Klorfain, 1946; Siegal, 1955b); these have been observed even after 0.02 ml of a concentration of 1000 units per ml (Berger & Eisen, 1955) and after 15 000 and 30 000 units of crystalline penicillin (Idsöe & Wang, 1958). Also a patch test of highly diluted penicillin 0 has responded with an anaphylactic reaction (Blanton & Blanton, 1953). Some individuals may possess such a high level of allergy to penicillin that generalized reactions have occurred after washing syringes which contained traces of penicillin (Coleman & Siegel, 1955), or from merely being in a room where penicillin powder has been handled (Blanton & Blanton, 1953).

Anaphylactic reactions have quite frequently followed the administration of *combined types of antibiotics*, particularly combinations of crystalline penicillin G and streptomycin (Idsöe & Wang, 1958; Dumm, Raimondi & Moreno-Ramirez, 1955). It may sometimes not be clear whether such reactions are caused by the penicillin or by the streptomycin component. A history of previous streptomycin or penicillin-streptomycin administra-

tions should raise the suspicion that streptomycin may be the causative allergen, a presumption which would be greatly strengthened by a negative penicillin skin test and a positive streptomicyn test. Similar considerations would naturally also apply to any other type of antibiotic combined with penicillin which might cause reactions. It is also conceivable that a combination of antibiotics might tend to strengthen the allergenic effect, thus increasing the danger of sensitization and the severity of reactions (Hussar & Holley, 1954; Nair, 1956).

The problem of *cross-sensitivity* in the same individual to different types of penicillin preparation is also of considerable potential interest for the interpretation of the allergic penicillin reactions as well as for the practitioner in his handling of allergic cases. It seems to be generally accepted from skin test studies (Risman & Boger, 1950; Peters, Henderson & Prickman, 1955; Mosko, Nejedly & Rostenberg, 1955) that the common penicillin preparations are immunologically equivalent, which view is also supported by clinical experience (Siegal, Steinhardt & Gerber, 1953; Siegal, 1955b). Consequently, a change of penicillin preparations in order to avoid reactions which have already occurred in an individual is not generally advocated (Siegal, 1955; Winton & Nora, 1955; *J. Amer. med. Ass.*, 1956a; Nair, 1956). Very severe responses may be experienced as a result of such attempts (Everett, 1951; Siegal, 1955b). On the other hand, there are some indications that penicillin preparations which have been in use for some time will provoke more and severer reactions than newer preparations. Any definite claims of low antigenity of future preparations should be withheld until supported by the experience of repeated use in the same individual (Kern & Kimberley, 1953). In urgent cases it has been said that a change to one of the latter could occasionally be justifiable (*J. Amer. med. Ass.*, 1956a), but the authors are of the opinion that it would be safer to use an alternative antibiotic.

As a whole, it seems likely that once allergy to penicillin has been established in an individual, the type of preparation, the dosage and the mode and site of administration play rather minor roles in provoking the reactions, and that it is probably the level of sensitivity and individual personal factors are more decisive elements.

Influence of Personal Factors on Anaphylactic Reactions

Allergic diathesis

Our knowledge of individual factors which might contribute to the occurrence of anaphylactic penicillin reactions or influence their course is still very incomplete. However, there is clear evidence that penicillin-sensitized patients with a present or past allergic diathesis may react more easily and more severely on subsequent penicillin administrations than do normal individuals (Siegal, Steinhardt & Gerber, 1953; Hussar & Holley,

1954; Lowell, 1955; Peters, Henderson & Prickman, 1955; Siegal, 1955b; Kekwick, 1956b; Nasou & Romansky, 1956; von Zinzius, 1956; *J. Amer. med. Ass.*, 1956a). It has been suggested that the incidence of reactions is twice as high in those with polyvalent allergy as in others (Collins-Williams & Vincent, 1954).

Bronchial asthma particularly has been frequently reported to be present in the anamnesis of the patients (Walbott, 1949; Everett, 1951; Curphey, 1953; Feinberg, Feinberg & Moran, 1953; Pick & Patterson, 1953; Kern & Wimberley, 1953; Siegal, Steinhardt & Gerber, 1953; Sterling, 1953; Rosenthal, 1954; Anderson, 1955; *J. Amer. med. Ass.*, 1955a; Siegal, 1955b). A fatal outcome of the reactions has occurred remarkably often in asthmatics (Walbott, 1949; Curphey, 1953; Siegal, Steinhardt & Gerber, 1953; Siegal, 1955b; Anderson, 1955). It is also noticeable that exacerbation of existing asthma associated with the occurrence of the shock symptoms is not infrequently seen. Apparently, the presence of bronchial asthma in an individual who has previously had penicillin treatment will considerably increase the risk of serious anaphylactic reactions on re-exposure to the antibiotic, and should therefore call for great care if re-treatment of the patient is indicated (Siegal, 1955b; Kekwick, 1956b) and all possible precautions should be taken before administering penicillin. Other allergies such as hay fever, rhinitis and pollen allergy are occasionally revealed on questioning reactors (Siegal, Steinhardt & Gerber, 1953; Dumm, Raimondi & Moreno-Ramirez, 1955), and such disclosures should also call for similar attention before penicillin treatment is initiated. Furthermore, a considerably higher incidence of allergic penicillin reactions occurs in allergic than in non-allergic children (Collins-Williams & Vincent, 1954), although this point has been denied (Levin & Moss, 1951).

As a rule, eczematous reactions of the " id " types, and delayed serum-sickness-like urticarial reactions due to previously administered penicillin do not seem to be forerunners of anaphylactic reactions in the same individuals on subsequent penicillin treatment (*J. Allergy*, 1953; Hussar & Holley, 1954; Siegal, 1955b). On the other hand, contact dermatitis has been observed in the past history of anaphylactic reactors (O'Donovan & Klorfain, 1946; Mosko, Nejedly & Rostenberg, 1955) and obviously should be regarded as a warning to avoid penicillin treatment. Also penicillin sensitized patients with severe allergic dermatitis may develop a fatal anaphylactic reaction if given further penicillin treatment (Winton & Nora, 1955). Several patients suffering from penicillin anaphylaxis have experienced previous penicillin reactions of the " immediate " type, including acute urticaria (Hussar & Holley, 1954; Collins-Williams & Vincent, 1954), indicating an immunological connexion between immediate penicillin reactions of all types.

The preceding reactions need not necessarily include syncope; even mild symptoms such as itching, a tingling feeling of the tongue or fingers,

a peculiar taste in the mouth, a flushing of the face, dizziness, increase in asthma, slight fever, etc., would indicate the presence of anaphylactic sensitivity which might persist and later result in explosive shock reactions, occasionally leading to fatalities on re-exposure of the patients to penicillin (Brown, 1948; Everett, 1951; Thomson, 1952; Beauchamp, 1953; Blanton & Blanton, 1953; Mayer et al., 1953; Hussar & Holley, 1954; Rosenthal, 1954; Ruskin, 1954; Campbell, 1955; Siegal, 1955b). Obviously, even such vague side-effects of previous penicillin administration should serve as a serious warning, a red light, precluding re-exposure to any type or amount of preparation, and by any route or site of administration (Siegal, 1955b). Even skin tests may under such circumstances provoke serious reactions, and should be undertaken only very carefully as scratch tests with high initial dilutions (Berger & Eisen, 1955; Siegal, Steinhardt & Gerber, 1953).

In this connexion it has been suggested that the small content of penicillin in the Salk polio vaccine could be a hazard to those who are already allergic to penicillin, and such vaccine should therefore be withheld in persons, including children, who actually have had reactions (Siegal, 1955b; *Brit. med. J.*, 1956). Until now, however, no severe sensitivity reactions due to penicillin in Salk vaccine have been recorded (*Brit. med. J.*, 1956). Passive transfer experiments have shown that the penicillin content of polio vaccine is negligible (Siegal, 1955a). Turner (1957) states that only a trace of active penicillin originally added to the culture, and insufficient to evoke reactions even in penicillin-sensitive children, remains in the vaccine. He considers that dangers of penicillin sensitivity from polio vaccine have been grossly exaggerated in the Union of South Africa. In any event even minor reactions from polio vaccine have been very small. Of 231 902 children receiving one or more injections of poliomyelitis vaccine or of control—both containing small quantities of penicillin—there were 1694 minor reactions (0.7%) and seven major reactions (0.003%), not necessarily due to penicillin (Poliomyelitis Vaccine Evaluation Center, 1957).

On the other hand, there is no proof that once established, a sensitivity of the anaphylactic type will persist for the rest of the patient's life. There is some evidence that this allergy also may be transient. Thus Myhre (1956) reports a patient who, two months subsequent to a very serious anaphylactic penicillin shock, received 1 mega-unit daily for three days without any ill effects. But it must also be underlined that the fact that a patient had received penicillin without having reacted is no guarantee that anaphylaxis will not occur if he is re-exposed to the drug (Nemser, 1954).

Time factors

A characteristic feature of the anaphylactic penicillin reactions is the sudden onset of the symptoms. Usually the onset is described as "immedi-

ately " or " within seconds " or after " a few minutes " (Everett, 1951; Andersen, 1955; Siegal, Steinhardt & Gerber, 1953; Siegal, 1955b; Myhre, 1956). Infrequently, the symptoms start after some hours (Idsöe & Wang, 1958) and extremely rarely after 24 hours, although a prolonged interval of five days between oral administration of a penicillin tablet and development of anaphylactic reactions has been reported (Weiss, 1953).

Also, the interval between onset and recovery or death is usually very short, most commonly reported to be within 15-30 minutes. In reported cases many fatalities have happened quickly: " a few seconds ", 1-5 minutes or 10 minutes after the beginning of the symptoms (Curphey, 1953; Siegal, Steinhardt & Gerber, 1953; Bell, 1954; Fisher, 1954; Andersen, 1955). There is some evidence that the more serious the reactions, the quicker the onset and development of symptoms (Kern & Wimberley, 1953; Siegal, 1955b; Feinberg & Feinberg, 1956; Kekwick, 1956b) but this is not constant. In Taiwan (Idsöe & Wang, 1958), reactions which appeared almost immediately ended fatally two days later; while Campbell (1955) reports on a patient who reacted more than one hour after receiving a penicillin injection and died a few minutes later. The majority of the very quickly occurring serious reactions, including deaths, have taken place after parenteral administrations of penicillin (Kekwick, 1956b), but symptoms may also sometimes develop quickly when oral and other routes are used (Everett, 1951; Peters, Henderson & Prickman, 1955).

Age and sex distribution

Anaphylactic penicillin reactors, like penicillin reactors of other types, have been found most commonly among adults between 20 and 49 years old, and considerably less frequently in older age-groups, with a decreasing frequency according to increasing age (Feinberg & Feinberg, 1953; Smith, Cutler & Price, 1955; Siegal, 1955b). They have rarely, although occasionally, been found among children under 12 years old (Feinberg & Feinberg, 1953; Hussar & Holley, 1954; Collins-Williams & Vincent, 1954). In children, extremely few fatalities (among these a child with asthma) have been reported (Matheson & Elegant, 1955).

The predominance of reactions encountered in the middle years of life may be due to a higher consumption of penicillin at that period, with consequently wider possibilities of sensitization and re-exposure. But it might also demonstrate that persons in the prime of their biological life-cycles possess no more resistance towards allergization and reactions to penicillin than do growing and aging individuals. Penicillin skin tests performed among large groups of children show very few positive responses, even in those previously exposed to penicillin (Collins-Williams & Vincent, 1954; Matheson & Elegant, 1955)—a fact which might suggest less capability for penicillin sensitization in children than in adults. As for the older age-groups, apart from a presumably lower consumption of penicillin,

could it be that desensitization in the course of time is partly accountable for the rarer occurrence of penicillin reactions at that period of life?

Generally, the anaphylactic reactions are reported to be approximately evenly distributed among males and females (Siegal, 1955b). In the Taiwan material (Idsöe & Wang, 1958), there is a slight preponderance of women, which could be due to a corresponding preponderance of women in the population, and to a considerably higher attendance at hospitals and clinics by women than by men.

Autopsy reports

Individual factors, not merely the penicillin preparation, the dosage, or the mode of administration, seem to influence the acuteness of the reaction. Apart, however, from the frequent history of an allergic diathesis and of reactions to previous penicillin administration, nothing is so far known which indicates the nature of such individual factors.

Diseases or anomalies of the patients concerned which could help to explain the particular individual course of the reactions have rarely been reported (von Oettingen, 1955). The overwhelming majority of the patients who suffered from anaphylactic reactions were apparently treated for diseases which did not substantially weaken their constitution or biological resistance. This has also been confirmed by the autopsies which have been performed on some of the patients who died in the course of the reaction. Apart from general findings, for example, related to occasional associated asthmatic disorders, little has been revealed by the autopsies except for suggestive evidence of anaphylactic shock, such as oedema of the brain, small vascular haemorrhages of the brain, and sometimes oedema and petechial haemorrhages of the lungs, myocardium and epiglottic folds, and cloudy swelling of liver and kidneys (Bell, 1954; Fisher, 1954; Andersen, 1955; Campbell, 1955; Winton & Nora, 1955; Cheng & Chiang, 1956). Generally, the findings of autopsies have been briefly described as " death due to anaphylactic shock " (Bell, 1954; Andersen, 1955).

PREVENTION OF PENICILLIN-REACTION FATALITIES

Fatalities due to *sensitivity* reactions are the main concern in this section. The treatment of the less serious sensitivity reactions has been considered previously. The prevention of undesirable *microbiogenic sequelae* can best be achieved by restricting the unnecessary use of the antibiotic.

Treatment of Anaphylactic Reactions

The treatment of anaphylactic reactions follows that of the routine therapy of shock conditions (Hussar & Holley, 1954). Subcutaneous injections of adrenaline (epinephrine) are recommended as soon as symptoms

appear (Alexander, 1953); if the patient fails to respond, the intravenous route may be used, or even injections directly into the heart. The dosages usually given are 0.5-1 ml of a concentration of 1:1000. Further injections should be given according to the condition of the patient. In cases of prolonged depressed blood-pressure continuous infusion drip of plasma (Alexander, 1953) or of *l*-arterenol (levophed-noradrenaline) have been recommended (Winton & Nora, 1955). Nicotinamide has also been suggested (Thomson, 1952; Nair, 1956). Antihistamines might be of some effect (Humphreys, 1951), and should always be given. Benadryl or Pyribenzamine (25-50 mg) or 10-20 mg of Chlor-trimeton may be given, using only material labelled for intravenous use (Tiegland, 1957). They have been considered life-saving (Burleson, 1950). Aminophyllin has also been recommended when there is respiratory distress (Farber, Ross & Stephens, 1954; Nair, 1956). The said preparations should be given parenterally at the acute onset, and can thereafter be continued orally for some time. Cortisone (50-100 mg) by intramuscular or ACTH by intravenous injection should be applied in protracted cases (*J. Allergy*, 1953; Winton & Nora, 1955; Nair, 1956).

The first requisite is to be prepared for the emergency. This includes having available a tourniquet, sterile syringes, epinephrine, diphenhydramine hydrochloride (Benadryl) or tripelennamine (Pyribenzamine) for parenteral use, other indicated drugs and oxygen (Hoagland, 1952). The tourniquet should be applied at once if the injection has been given in the arm; and for this reason some authors (Alexander, 1953) suggest that this site should be preferred. It is not, however, either a good or a convenient one for repeated injections of repository preparations in venereal disease clinics, where it is still the general practice to use the buttock. Prickman & Lofgren (1956) have listed the contents of an emergency set which they consider should be kept in any clinic in which penicillin is used.[1] It has also been suggested that persons who are sensitive to penicillin should carry a disc or card recording the fact (Bell, 1956).

It is advisable to initiate the complete anti-shock treatment before collapse occurs, as this usually happens in a matter of seconds. Thus the administration of oxygen (preferably under positive pressure — Farber, Ross & Stephens, 1954), artificial respiration and intravenous transfusions may be life-saving. Obviously, such measures can best be performed at hospitals, to which seriously affected patients should be referred as emergency cases, after having been given initial parenteral injections of epinephrine and other remedies which are commonly available to the practitioner (Beauchamp, 1953; Siegal, Steinhardt & Gerber, 1953; Collins-Williams & Vincent, 1954; Cruz Hernandez & Rosa-Febles, 1955; Peters, Henderson

[1] This contains two 1-ml ampoules of 1:1000 adrenaline, two 2-ml syringes, two hypodermic needles, two needles 1 inch and 4 inches (2.5 cm and 10 cm) long, two ampoules of aminophyllin (0.24 g each), one 1000-ml bottle of 5% dextrose in distilled water, one intravenous set, one 10-ml ampoule of diphenhydramine hydrochloride (Benadryl) (10 mg per ml), one bottle of hydrocortisone (dilution to 2 ml gives 50 mg per ml), one ampoule of distilled water, one scalpel, one haemostat, one ampoule of absorbable catgut with needle, alcohol, gauze sponges, swab tongue blade and one 20-ml syringe. Oxygen should also be to hand.

& Prickman, 1955; Ribeiro, 1955; Siegal, 1955b; Tidswell, 1955; Kekwick, 1956a).

In an attempt to avoid anaphylactic reactions, some consideration has been given to prophylactic treatment with antihistamines administered either mixed with the penicillin preparation or concomitantly, orally or parenterally. This procedure has not won support (Simon, 1950; Kalz & Prichard, 1952). Clinical experience (Mathews et al., 1955; Winton & Nora, 1955) and studies of contra-lateral passive transfer in penicillin-sensitive individuals (Coleman & Siegel, 1956) have shown the very limited effect of prophylactic antihistamines. Procaine amide (Pronestyl) has also been used with moderate success (Jennings & Olansky, 1954). Similarly, pre-treatment with ACTH or cortisone has been suggested (E. L. Keeney, quoted by Kern & Wimberly, 1953) but there are inevitably few data on which to judge the success of such a measure in preventing anaphylaxis, as the dangers of such an event in an individual in whom it is anticipated are far too great to justify its use — and there are usually some alternatives to treatment with penicillin in such cases. It has been suggested that if a severe anaphylactic reaction emerges from penicillin administration, only enormous quantities of antihistamines would be able to neutralize the excess of antibodies present in the blood and tissue of the patient concerned. Moreover, the suppression of weak reactions not threatening life would deprive both patients and doctors of the warning of such reactions, and thus a subsequent administration of penicillin to the same patient might be fatal (Brown, 1948; *Brit. med. J.*, 1955; Mathews et al., 1955; Peters, Henderson & Prickman, 1955; Siegal, 1955b; Feinberg & Feinberg, 1956).

Desensitization of penicillin-sensitive individuals is possible but takes a long time (O'Driscoll, 1955). As anaphylaxis has occurred in sensitive persons from a mere skin-test dose of penicillin (*J. Allergy*, 1953), desensitization procedures are too risky in patients who have experienced anaphylaxis to be of practical value. Generally it is better to substitute the tetracycline antibiotics (*J. Amer. med. Ass.*, 1956b).

It may be that penicillinase, which was reported on by Becker (1956, 1958), by Zimmerman (1958) and by Chen and his colleagues (1958), in three papers presented at the Fifth Annual Symposium on Antibiotics in Washington, D.C., will prove of value. Penicillinase, an enzyme that hydrolyses and inactivates penicillin, has been shown to clear the circulating antibiotic from the blood. Given simultaneously, 5000 units of penicillinase will completely inactivate 100 000 units of crystalline penicillin (Chen, Bard & Balsito, 1958). In anaphylaxis, a dose of 800 000 units intravenously followed by 800 000 units intramuscularly is generally recommended. It has been suggested that just as adrenaline is on hand in every doctor's office and hospital where penicillin is used to prevent tragic anaphylactic accidents, so should penicillinase be kept for this purpose (Becker, 1958).

Use of Skin Tests [1]

A much more dominant question is whether existing penicillin anaphylactic allergy in an individual can always be demonstrated by means of skin tests, so that skin testing could serve as reliable screening procedure before administration of penicillin. Preliminary skin testing in allergic persons has been urged by a number of authors (Walbott, 1949; Pick & Patterson, 1953).

The basis for a positive penicillin skin reaction is the presence of humoral antibodies (reagins) in the skin which react with the penicillin antigen applied. The response depends on the amount of antibodies present and the concentration of the antigen, as well as on the manner in which these substances are brought together. Circulating antibodies in individuals with anaphylactic reactions to penicillin have repeatedly been demonstrated by positive passive transfer of the Prausnitz-Küstner type (Criep, 1949; *J. Allergy*, 1953; Mayer et al., 1953; Coleman, 1955; Siegal, 1955b), by contra-lateral passive transfer reaction, by positive precipitin reactions and also by immediate, wealing skin reactions following application of penicillin to the skin of sensitized individuals (Templeton, Lunsford & Allington, 1947; *J. Allergy*, 1953; Kern & Wimberley, 1953; Mayer et al., 1953; Weiss, 1953). Also to be considered is the existence of skin-sensitizing antibodies (Winton & Nora, 1955) and the relative amount of these substances in the epidermis. Questions are posed whether antibodies in a sensitized individual need always be present in the skin, or whether the presence of antibodies in the epidermis necessarily implies the existence of allergy (Mosko, Nejedly & Rostenberg, 1955).

The clinical features of anaphylactic reactions could depend primarily on the presence of antibodies in the particular *shock-tissues* (Hansel, 1953), but there may not necessarily be any correlation between the skin as a shock organ and the internal shock organs (Mosko, Nejedly & Rostenberg, 1955). This would partly explain the negative response to skin testing

[1] Three types of skin test are discussed, the results of which are designated as " positive " or " negative ": (1) patch tests, in which a piece of linen moistened with penicillin solution is placed on the skin and the reaction, if any, is read after 48 hours; (2) scratch tests, in which the penicillin solution is scratched into the epidermis in a manner similar to that used in the Von Pirquet tuberculin technique; and (3) the intradermal test. The scratch test and the intradermal test are read after 10-20 minutes (the " immediate " test) and after 48 hours (the " delayed " test). (In order to avoid confusion the terms " immediate test " and " delayed test " are used to distinguish the test readings from " immediate reactions " and " delayed reactions " — terms applied in this review solely to the untoward clinical manifestations following the administration of penicillin.) Inhalation tests with penicillin aerosols, as described by Lowell & Schiller (1948) and Schiller & Lowell (1952) have not gained general favour and are regarded as potentially dangerous (*J. Allergy*, 1953). In scratch tests a drop of a solution containing 10 000 units of crystalline penicillin G is used, or some crystalline penicillin G powder is applied and mixed *in situ* with a drop of saline solution (Peters, Henderson & Prickman, 1955). In intradermal tests, 0.02 ml of the saline solution is usually injected, starting with a concentration of 500 units per ml. If the response is negative the concentration is increased to 5000 units per ml and eventually to 50 000 units per ml (*J. Allergy*, 1953; Siegal, Steinhardt & Gerber, 1953; Myhre, 1956). Some investigators consider that a concentration of 10 000 units per ml is usually satisfactory (Siegal, Steinhard & Gerber, 1953; Berger & Eisen, 1955; Mosko, Nejedly & Rostenberg, 1955; Peters, Henderson & Prickman, 1955; Tuft, Gregory & Gregory, 1955). The tests should not be read before 20 minutes have elapsed. A control test with the solution material or vehicle should be made at the same time. The lack of stability of penicillin G solutions has probably been exaggerated. Diluted testing solutions keep for several weeks at room temperature. It is probably advisable, however, to test the patient with the same preparation as that intended for administration. This procedure has proved of particular value in treatment with combined preparations (Dumm, Raimondi & Moreno-Ramirez, 1955).

found in some individuals who later reacted with anaphylactic shock following further penicillin administration. It would also explain why some individuals who have had some symptoms of anaphylaxis following a previous penicillin administration do not exhibit substantially more positive readings to skin tests than do those who have had no reactions following previous penicillin treatment (Collins-Williams & Vincent, 1954; Berger & Eisen, 1955; Tuft, Gregory & Gregory, 1955). Furthermore, even if the epidermis lacks antibodies, in view of the relatively low concentrations of penicillin antigen usually applied for testing, it would require some level of sensitivity to provoke a positive test (Coleman, 1955; Siegal, 1955b). On one hand, therefore, positive skin tests may be encountered only after increased concentration of the penicillin antigen (Siegal, 1955b); on the other hand, in highly sensitized individuals minute concentrations of antigen may give positive responses and sometimes even serious generalized reactions (Idsöe & Wang, 1958; O'Donovan & Klorfain, 1946; Mayer et al., 1953).

The value of the published reports on skin testing is certainly reduced by a lack of uniformity in the study material, as well as in regard to the preparation and concentration of the penicillin antigen and the methods employed (Tuft, Gregory & Gregory, 1955). It has particularly to be emphasized that the *delayed*, tuberculin-like test has no value as indicator of penicillin allergy of the immediate-reaction type to which anaphylactic reactions belong (Hussar & Holley, 1954; Tuft, Gregory & Gregory, 1955). It is the *immediate* skin test which might respond if an anaphylactic level of sensitivity was reached (Siegal, 1955b). Certainly, patch tests appear to be of little value in penicillin sensitivity—except in contact dermatitis (Tuft, Gregory & Gregory, 1955). The immediate intradermal test, however, is usually positive in cases of anaphylaxis (*J. Allergy*, 1953; Hussar & Holley, 1954).

A positive immediate skin-test reading may be evanescent and disappear within 2-3 months even in penicillin reactors, either in parallel to the systemic sensitivity or as an isolated phenomenon with persistence of sensitivity of internal shock organs (Tuft, Gregory & Gregory, 1955). Penicillin with its amino-acid-like structure is a poor antigen (McClosky & Smith, 1944). Therefore, tests performed shortly after the occurrence of reactions have a greater likelihood of positivity than those performed at a later stage.

In view of these facts, many diverse views on the subject of skin tests and penicillin sensitivity have been ventilated in the literature (Peck, Siegal & Bergamini, 1947; Brown, 1948; Burleson, 1950; *J. Allergy*, 1953; Weiss, 1953; Collins-Williams & Vincent, 1954; Berger & Eisen, 1955; Coleman, 1955; Matheson & Elegant, 1955; Mosko, Nejedly & Rostenberg, 1955; Siegal, 1955b; Siegel et al., 1955; Tuft, Gregory & Gregory, 1955; Feinberg & Feinberg, 1956; Fernström, 1956; Myhre, 1956; Nilzén, 1956; Rajam

& Rangiah, 1956). These range from the view that skin testing is of no, or of very limited, value in predicting anaphylactic sensitivity to a rather reserved support of the usefulness of such testing. They have certainly been regarded as useless in mass campaigns (Suvarnasara & Panikabutra, 1956).

As a whole, however, the present situation may be summarized as follows: a positive immediate penicillin skin test signals likely anaphylactic allergy to penicillin. The use of penicillin is then contra-indicated. False positive tests rarely occur (Peters, Henderson & Prickman, 1955). On the other hand, a negative skin test does not exclude penicillin allergy and a severe reaction to subsequent penicillin administration may occur. Despite this limitation, the use of skin testing is at present the only available objective practical diagnostic procedure for revealing penicillin sensitivity. Properly performed and evaluated, it may be a useful aid to the physician in individual cases. Passive serum transfer procedures are too complicated to be of practical use. Recent studies of new serological techniques for the detection of very small amounts of antibodies, therefore, are of great potential interest.

It is generally agreed that intradermal tests are more sensitive than scratch tests. The latter are said to be safer, since severe constitutional anaphylactic reactions (even almost fatal ones) following intradermal tests of rather smaller doses have been reported (O'Donovan & Klorfain, 1946; Mayer et al., 1953; Siegal, Steinhardt & Gerber, 1953; Siegal, 1955b; Idsöe & Wang, 1958). The scratch test might therefore be useful as a screening test. If negative, intradermal tests with increasing concentrations of penicillin antigen can then be performed (Siegal, 1955b).

Because of the sometimes equivocal results of penicillin skin tests, they cannot be relied on alone but should be considered one of the precautions which can be taken for reducing the incidence of penicillin reactions. Much is still lacking in our knowledge of the nature of allergic reactions and their immunobiological mechanism.

Restriction of Unnecessary Use of Penicillin

The best method of prophylaxis of allergic reactions in general is to reduce the chances of inducing sensitivity in the population at large. Rajam & Rangiah (1956) comment that " no other potent medicinal agent has been so consistently, thoughtlessly and repeatedly misused as penicillin ". Penicillin should thus only be used on sound clinical and epidemiological indications (Alleman & Roost, 1951; Watkins, 1955). The fear expressed by Falk as far back as 1945 that penicillin was liable to be used indiscriminately and that the sensitivity reactions which had already appeared would increase, together with the added risk that strains might become resistant,

would appear to have been fully justified. Its use should be avoided in banal diseases such as common colds, eczemas, impetigo, pharyngitis, bronchitis, etc. (Gilman 1950; Hussar & Holley, 1954; Peters, Henderson & Prickman, 1955; Siegal, 1955b; Winton & Nora, 1955; Bell, 1956; Feinberg & Feinberg, 1956; Ferreira de Mello & Mendes, 1956; Kekwick, 1956a; Myhre, 1956; Nair, 1956; Nasou & Romansky, 1956; Tibbetts, 1956). Its topical use should be abandoned. The inclusion of penicillin in tooth-paste, chewing gum and similar substances is indefensible. Reports of fatal shock cases indicate that about half of the patients died following unnecessary treatment with the drug (Hussar, 1955). In one fatal case recorded, the condition treated was gynecomastia—not even an infection (Higgins & Rothchild, 1952). In another, a common cold was treated with penicillin by an unqualified person (Feinberg, Feinberg & Moran, 1953). Exact information is available as to the bacterial reaction of penicillin and of the infections which respond satisfactorily to penicillin therapy. The period has passed when practitioners might " try " the wonder drug in cases of suspicious bacterial etiology. It should be possible in doubtful cases to arrange for bacteriological examinations.

It has been suggested by some that routine use of preventive penicillin before surgical operations, as is sometimes employed, is not medically founded and should be abandoned (Gilman, 1950; Battezatti & Tagliaferro, 1956). A survey, including 1000 patients in five hospitals in the USA, showed that 32% had received antibiotic treatment after admission (Hussar, 1955), obviously a hint that curative and prophylactic treatment has been stressed beyond medical indications.

Stern warnings seem necessary against self-medication with antibiotics so frequently used by pharmacists, nurses and doctors. First-aid " do it yourself " antibiotic kits are to be deplored. A number of serious reactions have followed such practice (Siegal, Steinhardt & Gerber, 1953), and it has even been estimated that 10% of all fatal cases have resulted from self-medication. The keeping of a national register of antibiotic deaths has been urged in the USA (Hussar, 1955). Antibiotics have a wide potential non-medical use in agriculture and in the preservation of meat and fish (Hussar & Holley, 1954; Ingram, Barnes & Schewan, 1956). The possible danger of inducing penicillin sensitivity in consumers must be considered.

Management of Patient Receiving Penicillin

Prior to penicillin administration a careful past history should be taken, with particular stress on whether the patient has had penicillin before, whether any reactions have occurred, and whether there is a personal or family history of allergy. Details concerning the preparation, dosage and route of administration of any previous penicillin and whether it was given

in prolonged or frequent courses (*J. Amer. med. Ass.*, 1955a) or in a short course with a massive dosage in a manner which might give less possibility of sensitization are helpful. Any side-reactions experienced should be noted, not forgetting pruritus, tingling sensations, or slight cardiovascular sensations. Especially important is the time factor in previous reactions. Sensations or reactions noted immediately or soon after penicillin was given should be regarded as more serious than when the reaction occurred after some days. In asthmatics not only should the patient be questioned concerning previous attacks, but a physical examination should also be made to disclose present status. In cases of doubt the physician would be wise to choose another drug (Rajam & Rangiah, 1956).

For instances where it is known that the patient has been previously treated with penicillin and has not had any reaction, skin testing has been recommended by numerous authors (Feinberg & Feinberg, 1956; *Lancet*, 1956c; Mathews et al., 1956; Myhre, 1956; Thomas, 1956). If the results are positive, treatment should be abandoned. If any reactions had followed the previous administration, or if the patient has a history of asthma, further treatment with penicillin should usually be forsaken, regardless of the outcome of skin testing (Berger & Eisen, 1955; Tuft, Gregory & Gregory, 1955; Feinberg & Feinberg. 1956). In most cases sulfonamides, the tetracycline antibiotics, or yet other antibiotics can be given instead of penicillin. If treatment with penicillin is still considered important, as in bacterial endocarditis, a negative skin test might permit the administration, although it would be worth trying a penicillin preparation other than that which previously produced a reaction (Myhre, 1956; Idsöe & Wang, 1958). Giving penicillin during an acute attack of asthma should be avoided, regardless of the outcome of the skin tests (Siegal, Steinhardt & Gerber, 1953). Routine skin testing of all patients, whether previously treated or not, before the administration of penicillin, as has been suggested (Ferreira de Mello & Mendes, 1956), is not considered a practical procedure in view of the limited value of the tests, which give an insufficient margin of safety in relation to the effort required. The systematic use of skin tests before treatment of persons who routinely handle penicillin, such as workers in penicillin factories, doctors and nurses, should however be considered (Maffei & Napolitano, 1955).

Technique of Injection

The injection should be carefully performed. The penicillin must be deposited deep in the muscle and intravenous injections should be avoided. It has been suggested (Berger & Eisen, 1955; Mathews et al., 1955; Ribeiro, 1955; Ferreira de Mello & Mendes, 1956) that intramuscular injections should be given in one of the upper arms, in order that, should

reaction occur, a further inflow of penicillin into the " shock " organs might be delayed by the tightening of a tourniquet around the arm—a procedure not possible in the case of the buttock. This procedure is thought to be somewhat unrealistic as the possibility of holding back for long a substantial amount of the antigen would be small.

During the injection, which should be given slowly, the patient should be watched so that the slightest reaction can be noticed, in which case the injection should immediately be discontinued and antishock treatment initiated (Peters, Henderson & Prickman, 1955; Siegal, 1955b). If possible, patients should be allowed to remain in the consulting room for about 15 minutes after treatment. Materials for the immediate treatment of reactions should be ready to hand for the doctor or nurse who performs the injection.

It has been suggested that the injection of penicillin might be split and that a small dose should first be given and the outcome awaited for a few minutes before completing with the total amount (Walbott, 1949; Siegal, Steinhardt & Gerber, 1953). This procedure seems reasonable and is worth undertaking in doubtful cases.

Coleman & Siegel (1955) have shown that penicillin may not be completely destroyed by boiling and that the minute amounts present as a contaminant in syringes can evoke an immediate allergic reaction in a sensitive patient.

This means that not only are penicillin-sensitive patients in some jeopardy when receiving an injection from a syringe which has recently contained penicillin, or which has been sterilized in a container used for the sterilization of such syringes, but that other non-sensitive persons on whom such syringes are used for other purposes than the administration of penicillin could become sensitized to the antibiotic.

If this view is accepted, it is logical to reserve certain syringes, needles and sterilizing equipment solely for the use of penicillin, and to ensure that such apparatus used for other purposes does not become contaminated. So far little attention has been paid to this matter, but it is one which deserves further consideration under present circumstances.

Health Education concerning Penicillin Reactions

The education and information of the general public, and of nurses and auxiliaries, on the proper use of penicillin, as well as on the risk of sensitization and reactions is necessary. It has to be admitted that the belief of the public in penicillin as a panacea has been partly induced by too optimistic popular medical information. It might now be advisable to brake this tendency.

* * *

Although it is again stressed that allergic anaphylactic reactions may occur in patients who have never had any reactions following previous administrations of penicillin, who are free from allergic disorders and who show negative skin tests, the precautions outlined can be of considerable value in their prevention. Experience in Taiwan (Idsöe & Wang, 1958) indicates clearly that the occurrence of severe reactions is less likely in clinics in which the precautions outlined are observed than in private clinics where they are not.

DISCUSSION

With increasing use of penicillin, wider segments of the population will be exposed to the sensitizing effects of the drug and allergic reactions are likely to be encountered in increasing numbers. The incidence of delayed urticarial serum-sickness-like reactions, where the inducement of sensitivity and the occurrence of the reactions follow the first administration of penicillin, will probably remain relatively constant. On the other hand, as more people will receive penicillin in repeated dosages, it is not unlikely that the *absolute* number of immediate anaphylactic shock reactions will increase. As this type of reaction causes fatalities, it necessarily attracts the widest attention. But, however serious this problem appears, it should not overshadow a realistic consideration of the rate of reactions related to the total consumption of penicillin. At the present time, little exact information concerning this matter is available, although some presumptive data are at hand.

In Denmark, a country where the medical services and the machinery for the compilation of vital statistics are well developed, three fatal anaphylactic reactions following penicillin administration have been reported as occurring during the four years preceding 1956 (Andersen, 1955). Approximately 4 million penicillin injections have been given annually to a population of about 4.5 million. Thus, some 0.3 fatalities per million injections have occurred. Supposing that in the USA the same number of anaphylactic deaths occurs relative to the population as in Denmark, about 50 such deaths would be expected in the population of 160 million. This correlates fairly well with other estimates (Peters, Henderson & Prickman, 1955; Hussar, 1955). An annual consumption of about 300 tons would suffice for 150 million courses of treatments of 3 million units each (Feinberg & Feinberg, 1955), which would give about 0.1 deaths per million injections, assuming an average of three injections per course.

Following the same pattern of calculation, a total yearly world consumption of 500 tons of penicillin (Hussar, 1955) would result in about 75 anaphylactic deaths each year. Consideration must be given to the presumption that there is a concentration of treatment in the age-groups of 19-50 years, and further to the fact that many persons receive repeated

courses. The incidence of 0.1-0.3 fatalities per million injections could thus probably be multiplied by about four.

The incidence of non-fatal reactions is thought to be several times that of fatal reactions (Peters, Henderson & Prickman, 1955). Thus, a study in the USA of over 16 000 patients in venereal disease clinics showed that 0.2% had anaphylactic reactions following penicillin administration, while none of these patients died (Smith, Cutler & Price, 1955). On the other hand, a survey of patients in 95 hospitals with a capacity of 51 000 beds, conducted during two years revealed that 59 penicillin anaphylactic reactions and 19 fatalities had occurred (Welch et al., 1953). It seems, however, that such studies are to some extent based on selected material. It is not clear whether the patients in the last-mentioned survey, for example, included those who had been admitted to the hospitals as emergency cases for anaphylactic shock, nor is there information as to the capacities of the beds during the said period.

In a further survey of 827 hospitals (198 332 beds) for the years 1954-56 a total of 2500 penicillin reactions was disclosed, of which 793 were life-threatening (Welch et al., 1957). As one-third of the hospitals in the USA were covered in this three-year survey, this implies over 700 life-threatening reactions a year for the whole country. An average of 300 tons of penicillin was provided annually in the USA during this period, of which 200 tons were used in human medicine.

In Thailand, during 1950-55 only 21 cases of anaphylaxis (1 fatal) were reported from no less than 938 299 patients treated for yaws and 196 482 treated for syphilis (Suvarnasara & Panikabutra, 1956). A large proportion of these patients were probably treated with single injections, which are less likely to evoke reactions than repeated courses. In Taiwan, during the two-year period 1953-55 a total of 15 574 patients were treated with penicillin for venereal diseases, and 21 (0.12%) experienced anaphylactic reactions. (None of these, who were treated by doctors trained by the health administration, died.) During the same period 7332 persons were penicillin-tested for sensitivity and 1%-2% reacted positively. Thus, only about one-tenth of the presumed penicillin-sensitized individuals had anaphylactic reactions upon re-exposure to penicillin. Even taking into consideration the occurrence of false negative sensitivity tests, it is justified to consider penicillin a poor antigen (Weiss, 1953), and the risk of occurrence of immediate reactions on re-exposure seems to be minor in relation to the enormous use of the drug.

The warnings against indiscriminate use of penicillin will no doubt be heeded by doctors and patients. It is likely that more care will be paid to the handling of this drug, which maintains its status as the superior germ killer. Clear and sound individual or public health indications for administration, and reasonable regulations concerning prescription and sale, are obvious means of reducing the abuse of penicillin and of avoiding unneces-

sary exposure of the population to sensitization. Although it might be feared that in occasional cases life-saving administration might be withheld because of excessive caution, it is not likely that health activities depending upon penicillin administration will be harmed in countries with well-developed health services, and with good educational standards of both medical personnel and the public at large.

However, many countries with urgent problems are at present making great efforts to attack communicable diseases on a mass campaign basis. The WHO-assisted anti-treponematosis campaigns have, practically speaking, been made possible only by the wide use of penicillin treatment. Many populations have had their first experience of penicillin through these campaigns, and sensitization and reaction on subsequent administration of the antibiotic have not so far emerged as practical problems. But, it is to be expected that also in these countries with rising economic standards and improving distribution and sales organizations penicillin preparations will reach the general public in increasing amounts. One may also foresee an abuse of the drug such as has occurred in more developed countries and which has resulted in sensitization of wide segments of the population. Should cases of anaphylactic shock appear during re-treatment surveys in mass campaigns, a fear and lack of confidence in the activity might result.

In a way, the situation may be compared with that of the control of insect-borne diseases where a different problem—that of resistance to insecticides—is of present concern to those who conduct mass campaigns against such diseases. The agreed solution in this situation has—as is known—been to use existing methods selectively and to intensify the work so that the full value of available insecticides may be exploited before resistance has occurred in all areas.

In mass campaigns against the treponematoses, the problem—this time of antibiotic sensitivity and to some extent of resistance in non-treponemal micro-organisms—so great or immediate a menace to the successful management of mass campaigns, attracts great prominence because its cost is expressed directly in human life. The remedy, however, is the same: to exploit the existing successful methods to the full before, or merely in case, the problems of sensitivity or microbial resistance render them less successful in the future. Thus, if an adverse situation did develop, at least the great potential of penicillin would have been exploited. It is desirable, therefore, not to wait for such developments, but to anticipate them by carrying through mass campaigns as soon as possible, using shortened treatment schedules, preferably in one single injection, in order to minimize as much as possible the risk of sensitization by repeated dosages.

RÉSUMÉ

Cette étude consacrée aux réactions secondaires provoquées par la pénicilline est fondée sur la littérature parue sur le sujet, sur les réponses au questionnaire adressé par l'OMS à des membres du Tableau consultatif d'experts des Maladies vénériennes et des Tréponématoses, ainsi que sur les observations faites à Taïwan publiées dans un prédédent numéro du Bulletin de l'OMS.

Jusqu'en 1949, deux décès seulement, attribuables à la pénicillinothérapie ont été déclarés. Ce nombre augmenta dans les années qui suivirent, si bien qu'en 1955 le nombre total de réactions anaphylactiques signalées s'élevait à 561 (avec 81 décès). En 1957, on évaluait à 1000 environ le nombre total des décès par anaphylaxie survenus aux Etats-Unis. Il faut noter, en regard de ces chiffres, que la consommation de pénicilline avait atteint 500 tonnes en 1955 — soit la valeur de 250 000 millions de traitements à 3 millions d'unités chacun.

L'innocuité apparente de la pénicilline a encouragé son emploi et sa vente au public sans prescription médicale. Or le danger de substances telles que la pénicilline réside dans le fait que, tout en étant peu toxiques, elles peuvent agir comme antigènes. La sensibilisation à la pénicilline peut conduire à des réactions allergiques plus ou moins graves et au choc anaphylactique mortel. La pénicilline peut en outre perturber l'équilibre de la flore microbienne de l'organisme, susciter la formation de souches bactériennes résistantes, et troubler le métabolisme des vitamines B et de la vitamine K.

Les anticorps suscités par la pénicilline semblent appartenir à deux grands groupes: les uns provoquent une sensibilisation cutanée (eczéma, urticaire), les autres l'anaphylaxie. Des dermatites surviennent chez 4-6% des personnes ayant reçu des applications locales d'antibiotique. L'administration parentérale ou l'inhalation de pénicilline peut aussi produire des réactions eczémato-vésiculaires.

Des réactions analogues à celles qui caractérisent la « maladie du sérum », comprennent des manifestations allergiques, telles que l'urticaire, l'œdème angioneurotique, les douleurs articulaires, l'inflammation ganglionnaire, la fièvre. Elles peuvent être immédiates ou différées, survenir 30 minutes ou plusieurs semaines après l'injection. 1-2% des personnes traitées à la pénicilline-retard (PAM) présentent de telles réactions, bénignes en général. Toutefois des complications graves s'observent (œdème du larynx, périartérite noueuse par exemple). Les réactions bénignes ou de moyenne gravité disparaissent en général spontanément. On a préconisé récemment comme traitement les antihistaminiques et la pénicillinase. Il faut éviter de traiter par la pénicilline les malades ayant eu des symptomes cutanés, car la sensibilisation pourrait s'étendre non seulement à la peau, mais à l'organisme entier.

La plupart des décès ont été causés par des réactions anaphylactiques. Les données numériques à ce sujet proviennent surtout des Etats-Unis. Sur 2500 réactions signalées de 1954 à 1956, dans un tiers des hôpitaux de ce pays, environ 700 mettaient en danger la vie du malade. Au Danemark on estime à 3 le nombre des décès par 10 millions d'injections, d'après les chiffres réunis au cours des quatre années précédant 1956.

Qu'une sensibilisation soit à l'origine de ces réactions est corroboré par le fait suivant : lors des campagnes de masse contre les tréponématoses effectuées dans des populations n'ayant pas eu de contact préalable avec la pénicilline, des millions de personnes ont été traitées sans présenter de réaction anaphylactique.

En revanche, à Taïwan, dont la population est sensibilisée par une consommation intense de pénicilline on a constaté 74 réactions, avec 12 décès, de 1951 à 1955. Il suffit d'une dose minime pour sensibiliser des personnes prédisposées: il est arrivé qu'un comprimé de 50 000 unités absorbé une année auparavant ait déclenché une réaction lors de l'ingestion d'une seconde dose. L'intervalle entre l'absorption de la dose sensibilisante et celle de la dose déclenchant la réaction a varié, dans les cas observés, de 10 jours à 8 ans. Des traitements de brève durée avec de fortes doses sont préférables à des longs traitements avec de faibles doses.

Le type de préparation pénicillinique ne paraît guère importer. Il semble que ce sont plutôt des facteurs individuels peu connus qui déterminent la réactivité d'un sujet. La sensibilité paraît moindre chez les enfants et après 50 ans; elle est accentuée chez les allergiques.

En modifiant la flore bactérienne normale de l'organisme, la pénicilline peut, en supprimant la compétition, favoriser le développement de certains germes. Si *E. coli*, par exemple, est naturellement résistant à la pénicilline, d'autres germes le sont devenus, en particulier les staphylocoques, qui, dans les hôpitaux, ont provoqué des pneumonies, des infections rénales ou vésicales ou l'infection des plaies. Le danger d'apparition de la résistance peut être évité en réservant la pénicilline pour des traitements où elle est indispensable, et en donnant d'emblée des doses assez fortes.

Dans le traitement de la syphilis, des réactions de type Herxheimer peuvent survenir, dues à la mise en liberté de substances toxiques lors de la destruction massive des spirochètes.

Les auteurs indiquent les précautions à prendre en effectuant les injections, les mesures à envisager pour surveiller les malades et intervenir immédiatement en cas de complications subites.

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