Bull. Org. mond. Santé
Bull. Wld Hlth Org. } 1968, **38**, 159-188

Nature and Extent of Penicillin Side-reactions, with Particular Reference to Fatalities from Anaphylactic Shock

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An appraisal is made of toxic, microbiogenic and allergic side-reactions occurring in man as a result of the large amounts of penicillin increasingly used in medical and veterinary practice.

The allergic reactions constitute the most common and significant side-effects of penicillin. The major antigenic determinant in penicillin allergy, the penicilloyl group derived from the penicillanic acid nucleus, is common to all penicillins and explains, at least in part, the cross-reactivity of man to any penicillin derivative or preparation. Available data do not permit conclusions as to the true frequency of allergic reactions to penicillin which are reported to vary from 0.7 % to 10 % in different studies in different countries. Among the side-reactions, the anaphylactic type may occur in about 0.015 %–0.004 % with a fatality rate from shock of 0.0015 %–0.002 % among treated patients.

There is no convincing evidence that the frequency of allergic side-reactions to penicillin has increased in the last 10 years in relation to the increasing, world-wide use of penicillin. Persons in contact with penicillin may respond by producing antibodies, the presence of which can be determined by immunological procedures, and these are believed to be partly responsible for sudden penicillin side-reactions. Routine prospective skin testing prior to penicillin administration cannot, however, be generally advocated at present but, in special instances, it can be undertaken in co-operation with specialists and competent laboratories.

The present investigation includes a study of 151 anaphylactic fatalities reported to have followed penicillin administration. Of these persons, 14 % had evidence of previous allergies of some kind, 70 % had received penicillin previously and one-third of these had already experienced prior sudden allergic reactions. In most of these fatal cases, the symptoms leading to death occurred within 15 minutes. An Expert Committee of WHO has emphasized that most anaphylactic fatalities can be prevented by measures to reduce penicillin sensitization environmentally in the population on the one hand, and by the preparedness of doctors, on the other, that is, with prompt and proper treatment and management of reactions when they occur.

In previous studies we have endeavoured to assess international trends regarding the nature and extent of penicillin side-reactions after the introduction of this antibiotic and its widespread use (Guthe et al., 1958; Idsøe & Wong, 1958; Willcox, 1958). The increasing incidence of allergic and other side-reactions to penicillin reported some years ago focused the attention of health administrations and the general public as well as the medical profession on this matter. It would seem to be justified that the concern felt at that time should have been regarded seriously, although the actual frequency of serious allergic reactions, as judged by reports and articles

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TABLE 1
ANTIBIOTICS PRODUCTION [a] IN THE USA, 1951–65 [b]

5-year periods	Penicillin		All other antibiotics [c]		Total weight (thousands of pounds) [d]
	Weight (thousands of pounds) [d]	%	Weight (thousands of pounds) [d]	%	
1951–55	3 135	40.6	4 373	59.4	7 508
1956–60	3 164	29.4	7 559	70.6	10 723
1961–65	7 228	29.9	16 909	70.1	24 137
Total	13 527	–	28 841	–	42 368

[a] Excluding feed supplements.
[b] Source: Communication from the United States Food and Drug Administration to WHO, February 1967.
[c] "Other antibiotics" includes, *inter alia*, streptomycin, dihydrostreptomycin, neomycin, tetracyclines.
[d] 1 pound = 454 g.

in the medical literature, seems to have been low. The present study should be seen in the light of these developments and of the increasing attention requested by health administrations to adverse drug reactions in general. Considerable importance is attached to the systematic collection, evaluation and dissemination by WHO of relevant information on these effects in pursuance of resolutions of the 15th, 16th, 17th and 18th World Health Assemblies.

During the last 10 years, the use of penicillin in preventive and clinical human and veterinary medicine has continued widely, although relatively less so than before because of the steadily increasing application of newer broad-spectrum, and other, antibiotics, of which a wide choice is now available for therapy in many infections. Production data from the United States of America shown in Table 1 illustrate these aspects. Against this background we have thought it of interest to assess new knowledge and trends, avoiding as far as possible reiteration of findings and information contained in our previous studies of the subject.

TOXICITY

Modern penicillin preparations, i.e., benzylpenicillin and derivatives of 6-aminopenicillanic acid, are generally regarded as non-toxic to man and to most animals, although the guinea-pig is an exception (Stewart, 1964). Excessive doses given to rats and mice may cause convulsions and may be lethal (Boyd et al., 1960). Only isolated reports have been made of apparent haematological and hepatic toxicity, e.g., with oxacillin (Freedman, 1965), and of haematological toxicity with meticillin (McElfresh & Huang, 1962). Concentrations of benzylpenicillin of 50 mg per 100 ml in serum and tissues have caused no symptoms, which suggests that this drug is much less toxic than many "physiological" substances (Stewart, 1964). New-born babies have, on occasion, been given a daily dose of 2 g for several days without demonstrable ill-effects (Willcox, unpublished data). Although such large doses are not usually given, it should be remembered that the sodium salt, rather than the potassium salt, is to be preferred since potassium itself in large amounts may produce side-effects, particularly renal disturbances (Stewart, 1964).

Embolic toxic reactions arising from accidental intravenous injection of procaine penicillin have been described (Freedman, 1964; Popper, 1964), suggesting the procaine element as the major toxic factor; a blood-vessel may inadvertently be entered in the course of about 1 in 150 intramuscular injections (Popper, 1964). Embolic toxic reactions, sometimes with marked psychotic disturbances but with no evidence of circulatory dysfunction (anaphylactoid) have also been attributed to the presence of large particles of procaine penicillin (up to 100 μ in diameter) in some preparations (Batchelor et al., 1951). Non-typical neurological occurrences have also been reported after very large doses of procaine penicillin and antihistamine penicillin. These, as well as other rare types of reaction to penicillin, may

possibly be of an allergic, rather than a toxic, nature. Pure penicillin preparations are harmless to veins as well as to the lungs (aerosols) but local irritant effects have been reported to follow intrathecal injections of injudicious amounts of penicillin (Melin, 1964). Certain penicillins are considered by some to be locally toxic when they cause pain in the muscle at the site of injection; in some instances local necrosis has been reported after injection of benzathine penicillin (Marie et al., 1964). There is, however, no evidence of teratogenic effects after treatment with penicillin during pregnancy (Stahlsberg, 1967).

MICROBIOGENIC EFFECTS

Microbial resistance

Resistance of micro-organisms to penicillin may be natural or acquired; some strains of staphylococci were naturally resistant at the time when penicillin was first introduced. Acquired resistance is usually considered to develop in a stepwise manner from already partly resistant micro-organisms, or from strains which have grown in the presence of penicillin and have become selected for resistance, each generation more resistant than the last. In some cases, resistance may develop either by conjugation with resistant micro-organisms or by acquisition of cytoplasmic or nuclear agents (e.g., DNA, RNA) transferred from living or dead organisms (Barber, 1964; Watanabe, 1963). Almost all strains of resistant staphylococci appear to belong to similar bacteriophage types (Barber, 1964; Borowski et al., 1964). It has been suggested that naturally resistant organisms tend to be more virulent than those with acquired resistance (Barber, 1964). A main cause of resistance to penicillin has been found to be penicillinase, produced by resistant bacteria, which opens the β-lactam ring of the nucleus, required for antibiotic activity (Stewart, 1966). Some bacteria (e.g., coliforms) produce a penicillin acilase (also sometimes called penicillin-amidase) which may by de-acylation remove the side-chain and inactivate some penicillins, e.g., penicillin G, penicillin V and ampicillin (Stewart, 1965).

The most important benzylpenicillin-G-resistant bacteria are staphylococci, Gram-negative bacilli and coliforms, of which a high proportion of strains were naturally resistant at the time when penicillin was introduced; later, the emergence of widespread resistance was rapid. The gonococcus, on the other hand, was initially fully susceptible, with no naturally resistant strains. Resistance has increased slowly, induced by the greater use of penicillin, but even today the situation is not uniform; the resistance pattern is geographically quite uneven, as shown in investigations made by the International Gonococcus Centre, Copenhagen (WHO Expert Committee on Gonococcal Infections, 1963).

The practical therapeutic reaction to the difficulties caused by penicillin-G-resistant micro-organisms is to use other penicillins, which withstand the action of penicillinase, or antibiotics other than penicillin. To prevent the development of microbial resistance to antibiotics, their misuse must be limited and unnecessary mass use of antibiotics should be avoided. Furthermore, in individual cases, sufficiently large doses of a suitable penicillin preparation should be applied at the start of the treatment to ensure rapid control of the micro-organism, and in this way the continued use of repeated small doses over a long period is avoided.

So far, there is no experimental, clinical or other scientific evidence that *Treponema pallidum* is less susceptible to penicillin today than it was when penicillin was first used. A WHO study in 1962 showed that no true resistance of *T. pallidum* had been observed clinically or experimentally although it is pointed out that data on this point are lacking (Schamberg, 1963) because it is not possible to cultivate the organism *in vitro*, and because it is some years since the minimum curative doses of penicillin in rabbit syphilis were adequately assessed. Recent experimental and clinical findings (Collart et al., 1962) of " dormant " treponemes in lymph nodes and spinal fluid, despite previous antisyphilitic treatment, cannot be regarded as " resistance " since it has been shown to be related to duration of infection, inadequate treatment or to reinfection (Yobs et al., 1965).

Microbial overgrowth

Following administration of penicillin and other antibiotics, microbial overgrowth may occur by (1) superinfection from organisms already present which have natural or acquired resistance to the drug, or (2) invasion of such resistant organisms present elsewhere in the host, or (3) originating from another person (cross-infection or " hospital " infection). Overgrowth of resistant organisms is primarily a consequence of suppression during therapy of the normal susceptible bacterial flora in the organs involved (Stewart, 1965).

Staphylococci. Penicillin-resistant coagulase-positive, i.e., virulent, staphylococci (some of which are found to be resistant to numerous antibiotics) breed particularly in the nasopharynx of persons in hospitals, both staff and patients, either by superinfection in patients undergoing antibiotic treatment or by cross-infection. The organisms may be widely and rapidly spread either by carriers or by other means. Cases of staphylococcal pneumonia, urinary infections, skin infections, staphylococcal ophthalmia, staphylococcal enteritis and infections of the umbilical cord may then arise. Fortunately, however, many patients lose their staphylococci within a few weeks of leaving hospital.

Coliforms. Superinfection with coliforms occurs as frequently as staphylococcal superinfection but is less dangerous, except in debilitated individuals and in infants (Stewart, 1965).

The problem of superinfection is tackled through general hygiene and cleanliness and by the proper use of penicillins which are not destroyed by penicillinase. There is, however, evidence that some of the newer penicillins, e.g., meticillin, may be susceptible to destruction by penicillinase. Since the penicillinase-resistance of these newer compounds is unreliable, they should be used with discretion.

Monilia. Overgrowth with *Candida albicans*, encouraged by the suppression of penicillin-sensitive saprophytes, is more common after oral administration of tetracyclines than after penicillin, which is most frequently given parenterally. Such overgrowth may occur in the oral cavity, respiratory and intestinal tracts, genitalia and skin, where *C. albicans* is a common inhabitant in normal persons (Guthe et al., 1958). Although this overgrowth is usually of minor significance, severe complications may occur in diabetic patients who are particularly exposed to moniliasis (Leites, 1960). The rectal pruritus and soreness which sometimes follow treatment with oral tetracyclines is attributed to overgrowth by monilia where *Escherichia coli* has been eliminated or substantially reduced in number by the drug. As benzylpenicillin G is ineffective against *E. coli*, this phenomenon is not common with this preparation. But with the wider spectrum of ampicillin, which is active against *E. coli*, this complication needs to be considered, as is indicated by case reports (Daikos, 1964).

Microbial lysis

It has been thought that the Herxheimer reaction is caused by "endotoxins" released from killed treponemes following initial administration of the treponemicidal drugs, resulting in both systemic disturbances and local reactions of the syphilitic lesions (Stokes, 1944). This view is still considered valid (Willcox, 1964a; Skog & Gudjonsson, 1966), although some investigators believe that there are characteristics associated with the clinical picture and the histopathological changes of the syphilitic lesion which could explain the Herxheimer reaction as an allergic phenomenon induced by released treponemal substances (Sheldon & Heyman, 1949; Moore et al., 1948). Skog & Gudjonsson (1966) in a recent study of haematological and histological findings related to Herxheimer reactions in more than 300 patients, and after considering the results of sensitivity skin tests in these patients, could not find evidence of causative hypersensitivity.

The highest incidence of the Herxheimer reaction is in primary seronegative and seropositive syphilis, where it occurs in more than half of the cases treated either with penicillin or arseno–heavy-metals (Hochleitner, 1965), even up to 95% in primary seropositive cases (Putkonen et al., 1966). There is no important difference in the course of the reaction whatever therapeutic agent may be used (Knudsen & Aastrup, 1965). The first symptom is usually a steep rise in temperature, which may take place within 1 to 11 hours after the injection, accompanied by exacerbations of local manifestations (Knudsen & Aastrup, 1965; Willcox, 1964a). Experience has shown that treatment in early syphilis can continue without other complications (Sablan & Best, 1964), and there is consequently no reason for preventive pre-treatment, either with small doses of penicillin or with bismuth (Willcox, 1964a).

Acute, local inflammation due to a Herxheimer reaction has been particularly feared in late symptomatic syphilis, especially in cardiovascular syphilis, gumma of the larynx and primary optic atrophy. For safety reasons some physicians feel, therefore, that penicillin-treatment of late syphilis should be initiated routinely by heavy metals or with small penicillin doses (Huriez & Vanoverschelde, 1965). However, during the 25 years which have elapsed since penicillin therapy was introduced, in a few cases only has a probable causative connexion been reported (Willcox, 1964b) between penicillin treatment of late syphilis and complications by a Herxheimer reaction. It may certainly be difficult sometimes to decide whether symptoms, presumably of a Herxheimer-type reaction, may rather be an incidental exacerbation of the syphilitic disease. Fatal cases have been seen in debilitated individuals, frequently

new-born babies, with such extensive syphilitic organic changes that specific treatment probably could not have saved them from an inevitable exitus (Wattiez, 1954). Experimental investigations indicate that the Herxheimer reaction follows an " all or nothing " law (Willcox, 1961); the reaction will then occur whether treatment is initiated with bismuth or with small penicillin doses (Heyman et al., 1952). The majority of clinicians have therefore reached the conclusion that late syphilis should usually be initiated with normal penicillin dosages (Willcox, 1964a); only in cases in which the potential risk of increased local damage is more serious than usual (syphilitic optic atrophy or nerve deafness) is initial treatment with very small doses, or with steroid cover, thought to be justified (Huriez et Vanoverschelde, 1965; Huriez & Agache, 1958). Due to the suppressive effect of the corticosteroids on inflammatory tissue reactions, these drugs have been used occasionally—initially or concomitantly with penicillin—in late syphilis, in order to weaken a Herxheimer reaction in the particular cases mentioned above (Huriez & Vanoverschelde, 1965; Durel & Borel, 1957).

The phenomenon of therapeutic paradox, i.e., clinical progression in spite of biological cure, due to rapid replacement of organic tissue by fibrotic scar-tissue, was much discussed during the period when arseno–heavy-metal treatment was in use; some occurrences then of the paradox may have been caused by the toxicity of the metals (Stokes, 1944; Wile, 1922). Few instances of therapeutic paradox have, however, been reported following penicillin treatment of late syphilis (Mohr & Hahn, 1952; Reynolds, 1948). In some of these cases that were reported, the worsened condition may have been due to inadequate treatment (Mohr & Hahn, 1952). Most syphilologists consider a therapeutic paradox following penicillin-treatment to be an insignificant risk needing no particular precautions.

NATURE AND CLASSIFICATION OF ALLERGIC REACTIONS

Allergic reactions are assumed to be the result of an antigen–antibody or antigen–" sensitized cell " interaction. The altered reactivity of an individual towards a specific antigen, e.g., penicillin, results from previous contact with the same or a related substance, or it may develop during subsequent exposure to the antigenic agent (Guthe et al., 1958; Bendixen, 1966). Allergic penicillin reactions fall into several main groups, each of which has a different immunological pattern; they are as follows.

Sudden or "immediate" reactions and "accelerated" reactions, including anaphylactic reactions

These have a sudden onset, occurring within seconds or up to an hour after penicillin administration (Weingartner, 1964), and are followed by recovery or death; the symptoms resemble those of anaphylactic shock in animals. There may sometimes be weak symptoms only, e.g., palpitation, vertigo, dizziness, perspiration, tingling of the tongue, ill-defined malaise, etc., which may either subside or develop into severe vasomotor collapse. They may sometimes be followed by signs of cerebral damage (Cohen, 1963; Fox, 1965). The so-called " accelerated " urticarial reactions occurring from a few minutes up to 1–2 days after administration of penicillin are now usually classified with sudden or immediate reactions (Westerman et al., 1966). The character of the immediate reaction indicates that antibodies must already be present in the patient as the result of previous exposure to penicillin (Bendixen, 1966). Such exposure may have occurred a decade or more previously (Schümmelfeder et al., 1965).

Late allergic reactions

These reactions include: (1) Cutaneous manifestations of various types: generalized urticaria erythemas and morbilliform exanthemas, erythrovesicular eruptions (" id-reactions "), and some rarer types, e.g., erythema nodosum, purpura, erythema multiforme, fixed drug eruptions (Verma, 1959), acute necrotic epidermolysis (Coricciari & Friggeri, 1962) and periarteritis nodosa. Exfoliative dermatitis, which may be fatal, may occur (Weingartner, 1964). (2) Serum-sickness-like reactions, usually with urticaria, skin lesions, fever, polyadenopathy, joint-swelling and pain, sometimes angioneurotic oedema (Westerman et al., 1966); the latter often occurs separately, but is usually also part of the immediate reaction. Erythematous and urticarial reactions are most frequent, the latter accounting for more than half of the total penicillin reactions (Calman, 1964). In late reactions there may have been no previous exposure to penicillin and the reaction occurs only after some days (usually 5–14) after the commencement of a series of penicillin administrations (Westerman et al., 1966; Matner & Leonhardi, 1966), during which time the anti-penicillin antibodies have been formed. The term " late " or " delayed " reaction merely refers to the delay elapsing between the administration of penicillin and the occurrence of the clinical symptoms; it does not imply that such

symptoms are due to a " delayed-type " hypersensitivity, i.e., to an immunological mechanism involving, presumably, sensitized lymphocytes instead of classical circulating antibodies.

Contact dermatitis

This results from local application of, or exposure to, penicillin. It is seldom accompanied by allergy to penicillin of the immediate type, although systemic sensitization may result (Mahoney et al., 1944). It is usually observed among nurses and physicians handling penicillin preparations (Hussar & Holley, 1954), and among workers in the pharmaceutical industry exposed to penicillin during its manufacture (Maffer & Napolitano, 1955). Also it occurs frequently in patients exposed to prolonged local penicillin treatment, the risk of sensitization being particularly high when the drug is applied to damaged skin because of the close contact with the epidermis (Goldman et al., 1946; Epstein, 1966; Voronina, 1965).

Other rare, possibly allergic, or possibly toxic types of reactions

Such reactions to penicillin have been described, for example, acute psychotic syndromes (" anaphylactoid reactions ") (Bjornberg & Selstam, 1960), pachymeningitis, (Willcox, 1966), gangrene (Fang, 1958) and intestinal haemorrhage (Willcox, 1966), temporary or permanent renal damage (Beidelman, 1962), liver necrosis (Murphy & Mireles, 1962), myocardial damage (Haden & Langsjoen, 1961) and acute pericarditis and eosinophilia (Schoenwetter & Siber, 1965). In certain individuals large doses of penicillin appear to induce haemolytic anaemia by an immunological mechanism (Dawson & Segal, 1966; Swanson et al., 1966; Petz & Fudenberg, 1966).[1] It has been suggested that symptoms like nausea, vomiting, anorexia, convulsions, diarrhoea, glucosuria, anuria, myocarditis, etc., may possibly be toxic side-effects of penicillin rather than effects of previous sensitization (Swanson et al., 1966; see also pp. 160-161).

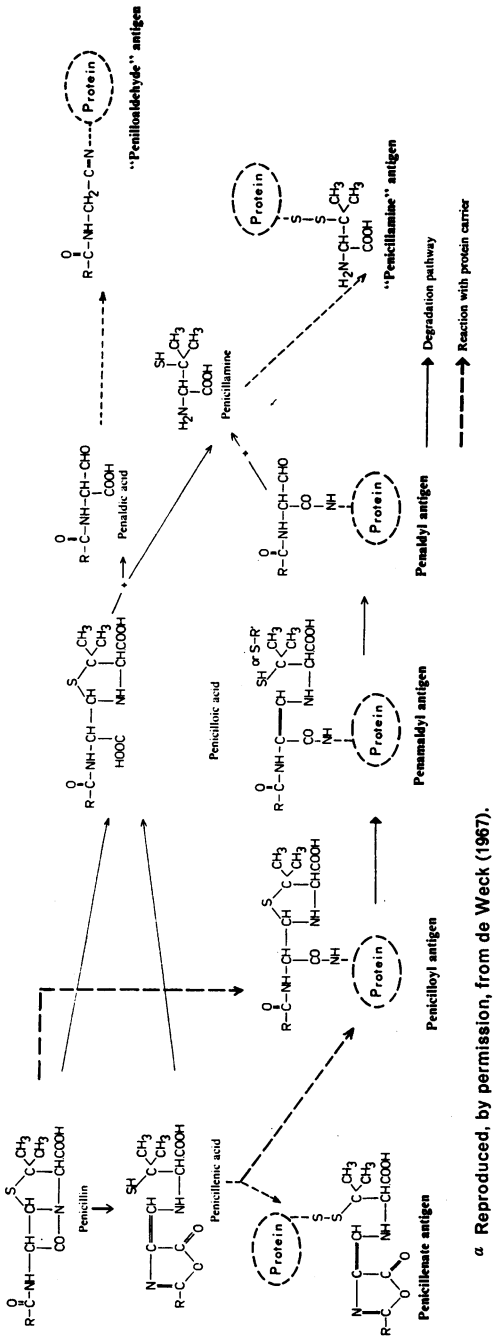
IMMUNOLOGICAL ASPECTS OF ALLERGIC REACTIONS

Antigens (Fig. 1–3)

Allergies are clinical manifestations or immunological reactions based on antigen–antibody or antigen–" sensitized-cell " interactions in human

[1] Also Levine, B. B. & Redmond, A. (1966) *Information Exchange Group No. 5*, Memo No. 168.

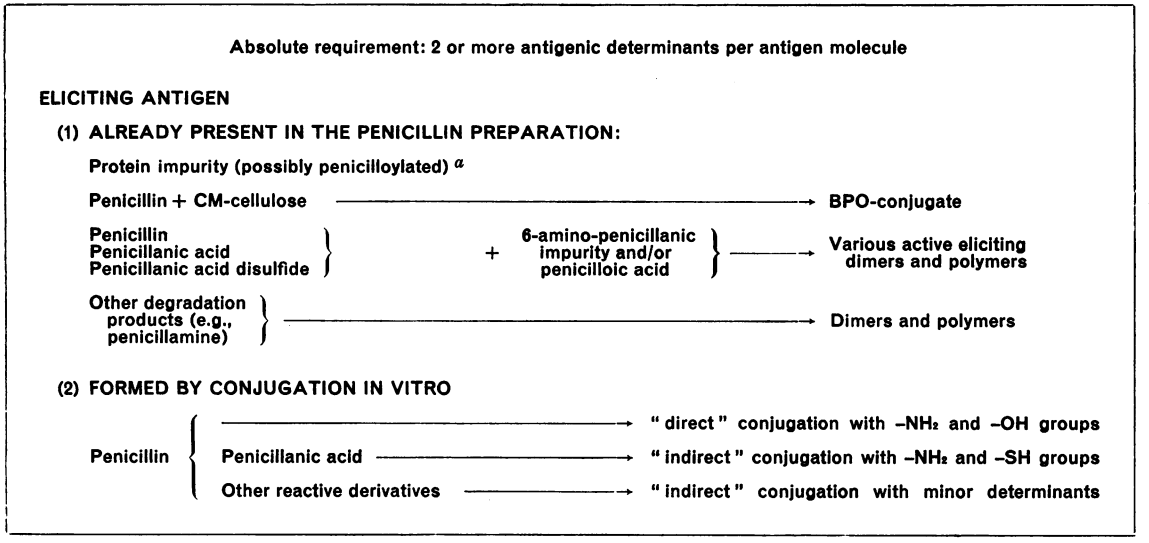
FIG. 1. FORMATION OF COMPLETE ANTIGENS FROM PENICILLIN, AND STRUCTURE OF SOME OF THE ANTIGENIC DETERMINANTS INVOLVED IN PENICILLIN ALLERGY[a]



[a] Reproduced, by permission, from de Weck (1967).

FIG. 2

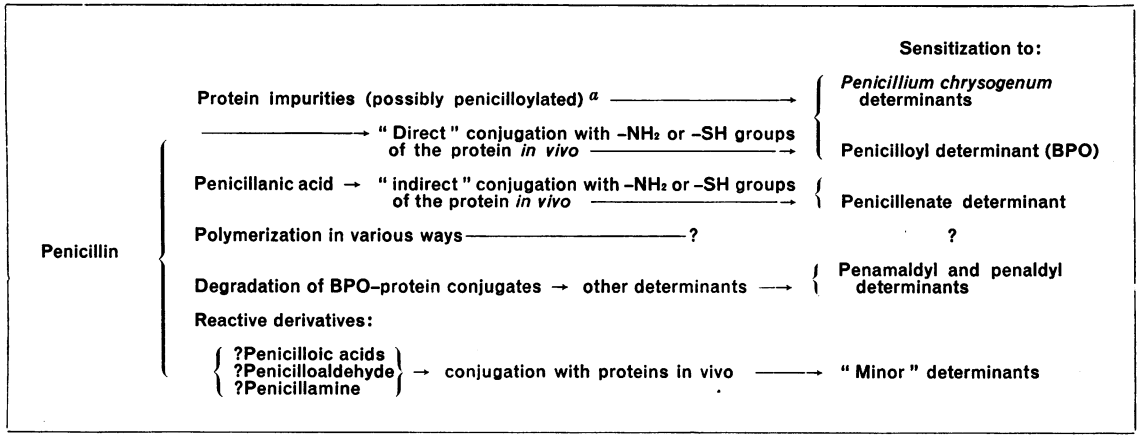
ANTIGENS RESPONSIBLE FOR THE ELICITATION OF IMMEDIATE-TYPE ALLERGIC REACTIONS IN PATIENTS SENSITIZED TO PENICILLIN



a Role in sensitization not yet established.

FIG. 3

PATHWAYS TO SENSITIZATION BY PENICILLIN



a Role in sensitization not yet established.

tissues. To induce antibody synthesis, simple chemicals of low molecular weight are believed first to combine irreversibly with protein to form antigenic hapten–protein conjugates (Landsteiner, 1945). Although structural characteristics of many drugs indicate their incapacity to combine irreversibly with proteins, they can nevertheless cause allergies through their intermediate metabolic or degradation products which form the required immunogenic hapten–protein-conjugates inducing the antibody response. In penicillin allergy, the haptenic system and the nature of drug sensitivity are now becoming

known and this is leading also to possibilities for the better understanding of allergic conditions in general. Thus, investigations have shown that benzylpenicillin gives rise to a main antigenic determinant—the penicilloyl group—formed by conjugation of protein lysine residues with the degradation product benzyl-penicillenic acid (de Weck & Eisen, 1960; Levine & Ovary, 1961; Parker, 1964), or with benzylpenicillin directly (Schneider & de Weck, 1965) (Fig. 1). Since conjugated protein (i.e., penicilloyl–human-serum-albumin) are potent immunogens,[1] i.e., inducers of antibody formation, there would be a substantial risk of sensitization of normal individuals if a penicilloyl-protein conjugate were used for skin-testing in humans. The reaction of penicillins or penicillenic acids with a polymerized lysine carrier (polylysine) yields penicilloyl–polylysine (PPL) (Parker et al., 1962a; Levine, 1964a, 1964b). Since maximally substituted PPL appears to be non-antigenic (Levine, 1964c; Parker et al., 1965; de Weck & Schneider, 1967; de Weck & Blum, 1965), it can be used safely as a skin-testing antigen. The test is reproducible and the antigen in test doses has been reported as non-sensitizing in man (de Weck & Blum, 1965; Rytel et al., 1963; Parker & Thiel, 1963). Apparently, PPL in appropriate dosage is less capable than penicillin of inducing systemic reactions in animals and humans on skin-testing (Parker et al., 1962; Brown et al., 1964). Some observations indicate that this cannot be absolutely excluded (Resnik & Shelley, 1966; Ettinger & Kaye, 1964) and systemic reactions by overdosage in highly sensitive patients may in principle occur, as with any other complete antigen used in allergy skin tests. However, by choosing an appropriate test schedule beginning with a preliminary scratch test and then using progressive PPL concentrations (de Weck & Blum, 1966), it is possible to avoid almost entirely (Parker et al., 1962b; Brown et al., 1964) such systemic reactions in practice. On the other hand, skin tests with penicillin as such appear to be somewhat more dangerous, because the conjugate required for elicitation of the local test reaction has to form *in situ* with a large excess of penicillin. This excess of free penicillin may diffuse rapidly out of the test site, elicit reactions at distant sites, and therefore facilitate systemic reactions. With penicillin, a relative overdosage is almost impossible to prevent.

As illustrated in Fig. 1, penicilloyl-conjugated antigen arises directly from the penicillin molecule or from penicillanic acid and is considered a *major* antigenic determinant (de Weck, 1963a; de Weck & Blum, 1966). Other derivatives of the penicillin molecule may form different haptenic conjugates; the structure of some is not yet definitely established (Levine & Price, 1964). Penicillin allergies induced by these so-called minor antigenic determinants (Levine & Price, 1964) may possibly be detected by use of benzylpenicillin as antigen in skin-testing (Voss et al., 1966). Finally, there may exist additional —yet unknown—pathways, leading to the formation of other antigen determinants from the penicillin G molecule (Voss et al., 1966). All these considerations point to the complexity of the immunological mechanism in penicillin sensitivity.

Recent experiments (Batchelor et al., 1967; Stewart, 1967) showed that a high-molecular-weight protein isolated by fractionation of the sodium salt of 6-amino-penicillanic acid (6-APA) gave strong passive cutaneous anaphylactic reactions in guinea-pigs. A similar reactive proteinic impurity was found in commercially available benzylpenicillin. Other active substances may develop during storage of benzylpenicillin; possibly they may be derived from the penicillin molecule by polymerization. Results of skin tests in man also suggested (Knudsen et al., 1967) that such a " purified " penicillin was less antigenic than commercial penicillin. The findings, however, do not preclude the formation from purified penicillin of penicilloyl conjugates with tissue protein or by subsequent polymerization (Stewart, 1967). Furthermore, low-molecular-weight substances derived from the penicillin molecule itself are certainly also responsible for penicillin allergy. Further research is needed on the antigenic role of protein impurities, and of dimers and polymers of penicillin, in conditions similar to those in clinical practice. It remains uncertain whether these impurities are present in sufficient amounts in actual therapeutic doses to be responsible for the majority of allergic reactions to penicillin. The implications of the presence of impurities in relation to the safety of oral preparations (Knudsen et al., 1967; *Lancet*, 1967) are not yet known.

All penicillins with the 6-aminopenicillanic acid nucleus will show some immunological cross-reactivity due possibly to the conjugation of protein with the respective intermediate benzylpenicillenic

[1] The term " immunogens " and " immunogenicity " have been preferred by the authors to define the property of sensitizing and of inducing antibody formation. The terms " antigens " and " antigenicity " refer to the capacity to react with antibody and to elicit reactions in already-sensitized individuals.

TABLE 2
CHARACTERISTICS OF " ANTI-PENICILLIN " ANTIBODIES

Characteristics	Immunoglobulin M (IgM)	Immunoglobulin G (IgG)	Skin sensitizing antibodies, " reagins " " anaphylactic antibody " (SSA)
Sedimentation coefficient	19S	7S	–
Electrophoretic mobility	$\gamma 1-\beta$	$\gamma 2$	$\gamma 1-\beta$
Thermostability	+	+++	–
Sensitivity to 2-mercaptoethanol	+++	–	+++
Agglutination of penicillin-incubated erythrocytes			
(1) in saline	+++	+	(+)
(2) in serum diluent	+++	+++	?
Haemolysis of penicillin-incubated erythrocytes	–	–	–
Passive transfer in humans (Prausnitz-Kustner)	–	–	+++
Passive cutaneous anaphylaxis in guinea-pigs	–	++	–
Specificity	Penicilloyl; Other minor determinants?	Penicilloyl; Other minor determinants?	Penicilloyl; Penicillin; Other determinants
Pathological role	Some exanthemas?	Blocking antibodies. Haemolytic	Anaphylaxis, urticaria

acid (Batchelor et al., 1965) but more likely due to the direct reaction of the β-lactam ring with amino groups (de Weck, 1962a; Schneider & de Weck, 1966). Cross-reactions have also been found between cepfalotin (derived from 7-aminocephalosporanic acid) and benzylpenicillin G, indicating that the former may form structures related to the benzylpenicilloyl group (Thoburn et al., 1966; Brandriss et al., 1964; Kabins et al., 1965).

Antibodies and immunological tests

Persons in contact with penicillin may thus respond immunologically by the formation of antibodies, among which skin-sensitizing and haemagglutinating antibodies have so far been identified. Their properties, as far as characterized up to now, are shown in Table 2.

Skin-sensitizing antibodies (SSA). These substances have been reported to be 7S gamma-globulin (Josephson et al., 1962) and to possess at least 2 different specificities: those that can be demonstrated by the penicilloyl–polylysine (PPL) antigen and those that can be demonstrated only by benzylpenicillin. The existence of skin-sensitizing antibody (or groups of antibodies) of other specificities has been suspected from skin-test and passive transfer results but the specific antigenic determinants have not yet been identified (Parker, 1964; Levine, 1964b; Voss et al., 1966). Skin-sensitizing antibodies specific for the major penicilloyl antigenic determinant are mostly associated with immediate and early urticarial reactions (" accelerated reactions ") which arise within the first 48 hours after penicillin administration. PPL skin-testing frequently suggests the presence of these antibodies (Table 3) and appears somewhat more reliable than passive transfer (Prausnitz–Küstner). Skin-sensitizing antibodies specific for the minor penicillin G antigenic determinants are thought by some authors to be associated with " sudden " anaphylactic reactions and can be detected through skin testing with penicillin G (Siegel & Levine, 1964). For such authors, positive skin tests with penicillin G are more indicative of potential anaphylactic reactions than a positive

TABLE 3
RESULTS OF SKIN TESTS WITH PENICILLOYL-POLYLYSINE (PPL) IN PERSONS WITH AND WITHOUT HISTORY OF PENICILLIN ALLERGY

Year	Investigators	History of penicillin allergy		History of no penicillin allergy	
		Persons tested	Percentage of skin reactors	Persons tested	Percentage of skin reactors
1961	Parker et al. (1962a)	59	76	1 191	3.7
1962	Shapiro [a]	137	86	3 530	4.6
1962	Simpson (1963)	330	36	2 837	6.1
1963	Rytel et al. (1963)	43	35	825	6.8
1963	Edwards [a]	70	24	1 161	5.4
1963	VanArsdel et al. (1963b)	43	32	—	—
1964	Levine & Price (1964)	41	27	30	3.3
1964	Brown et al. (1964)	1 003	39.5	13 489	6.5
1964	Budd et al. (1964)	22 [b]	91	40	2
1964	Budd et al. (1964)	27	26	—	—
1965	Finke et al. (1965)	53 [c]	62	59	10
1965	Finke et al. (1965)	67	17	—	—
1962-65	de Weck et Blum (1965) (correlated) [d] (see Table 4)	329	58	228	10.5
1966	Levine et al. (1966) [e]	68	43	103	8.7
		49	59	—	—
1966	Matner et Leonhardi (1966)	46 [f]	42	22	—
1967	Gayet [g]	40	62	50	4
1967	Nilzen et al.	32	69	—	—
Total patients		2 332	—	22 462	—

[a] Personal communication.
[b] Alleged reaction less than 3 months old.
[c] Alleged reaction less than 3 years old.
[d] And unpublished cases.
[e] Information Exchange Group No. 5, Memo No. 249.
[f] Maculo-papular exanthemas excluded.
[g] Unpublished thesis.

skin test with the PPL antigen (Levine, 1964a). However, there seems to be little doubt that one may also observe anaphylactic reactions due mainly or entirely to penicilloyl-specific skin-sensitizing antibodies (Levine, 1964b). Reports of such cases have also been published recently by the group holding, rather, the minor determinants to be responsible for anaphylactic reactions (Fellner et al., 1967a). It is the opinion of one of us (A. de W.) that both major (penicilloyl) and minor determinants may be involved in anaphylactic reactions to penicillin. Skin-testing with crystalline penicillin G is therefore of supplementary value to skin-testing with PPL. Together they serve to detect both minor and major determinants (Siegel & Levine, 1964; Finke et al., 1965).

The above considerations relate to early ("accelerated") urticarial reactions and to "immediate" anaphylactic manifestations. The so-called "late" allergic penicillin reactions, including "serum-sickness"-like reactions, begin days or weeks after penicillin therapy and are perhaps not all associated with skin-sensitizing antibodies (Levine, 1964). This is especially true for late morbilliform exanthemas (Levine et al., 1966b). In serum-sickness-like cases, on the other hand, the association with skin-sensitizing antibodies of penicilloyl specificity detected by PPL skin test is very frequent (de Weck &

TABLE 4
RESULTS OF COMPARATIVE SKIN TESTING WITH PENICILLIN AND PENICILLOYL-POLYLYSINE (PPL) IN PERSONS WITH HISTORY OF PENICILLIN ALLERGY

Year	Investigators	No. of persons tested	Percentage PPL-reactive	Percentage penicillin-reactive
1963	VanArsdel et al. (1963b)	31	48	19
1964	Levine & Price (1964)	39	35	8
1964	Budd et al. (1964)	49	55	6
1965	Finke et al. (1965)	120	37	15
1962-65	de Weck et Blum (1965) [a]	90	61	25
1966	Levine et al. (1966) [b]	49	59	67
1967	Nilzen et al. (1968)	32	69	53

[a] And unpublished cases.
[b] Information Exchange Group No. 5, Memo No. 249.

Blum, 1965) (Table 4). Sensitization may, of course, arise during the course of penicillin therapy in previously non-sensitized individuals. Initially negative skin tests do not, therefore, exclude the possibility that such late penicillin reactions (Voss et al., 1966) may occur. The relatively high percentage of patients without history of allergic reactions to penicillin found positive in PPL skin-testing (Table 3) does not detract from the value of the PPL skin test, as such patients, according to several authors (Parker et al., 1962a; de Weck & Blum, 1965; Brown et al., 1964) possess in fact a latent penicillin allergy. Arguments supporting this statement are beyond the scope of this paper.

Haemagglutinating antibodies. These substances may be 7S or 19S immunoglobulins (Schwartz & Vaughan, 1963). They frequently occur together with skin-sensitizing antibodies in sudden (immediate) anaphylactic, early urticarial reactions and serum-sickness-like reactions (de Weck & Blum, 1966; Voss et al., 1966) (Table 5). High titres of haemagglutinating antibodies are observed when penicillins and 6-amino-penicillanic acid are injected into rabbits (Chisholm et al., 1961; de Weck, 1962a; Wagelie et al., 1963; de Weck, 1963b). These antibodies have usually been found to be specific for the penicilloyl determinant. Significantly higher titres of haemagglutinating antibodies are found in patients with a history of penicillin hypersensitivity than in those without such a history or who have never received penicillin previously (de Weck & Blum, 1965; de Weck, 1964; McGovern, 1964; VanArsdel, 1963a).[1] It appears that such antibodies are merely an indicator of the immunological response and not the cause of penicillin allergy (de Weck & Blum, 1965; VanArsdel, 1963a).

Most investigators have found no direct correlation between the amount of haemagglutinating antibodies and the results of skin-testing (VanArsdel et al., 1963a; Rudgski et al., 1965; Harris & Vaughan, 1961). Haemagglutinating antibodies may be found also in patients without clinical allergy to penicillin (de Weck, 1964; Watson et al., 1960); they are usually specific for the penicilloyl determinant but also for other antigenic determinants (Thiel et al., 1964). With an especially sensitive haemagglutination technique, it has been claimed that anti-penicilloyl antibodies are found in 97%–100% of the population of New York (Levine et al., 1966b);[1] it must be noted, however, that the titres found in more than 60% of normal people investigated are rather low (Levine et al., 1966a). As haemagglutination is observed in such cases only with the help of a high colloidal diluent (dextra-serum mixture) which may favour non-specific haemagglutination (Hummel, 1966), the conclusion that nearly 100% of the people possess "natural" anti-penicilloyl antibodies requires confirmation by some other technique.

Some authors have found that in some individuals with PPL-positive skin tests who do not develop immediate anaphylactic reactions, high titres of

[1] Also Levine et al. (1966) *Information Exchange Group No. 5*, Memo No. 249.

TABLE 5

RESULTS OF PENICILLOYL-POLYLYSINE (PPL) SKIN-TESTING AND HAEMAGGLUTINATION ACCORDING TO SYMPTOMS OF PENICILLIN ALLERGY IN 329 PERSONS 1962-65 [a]

Reactions	Reactions less than 2 months old			Reactions more than 2 months old		
	Examined	PPL skin reactors (%)	Haemagglutination positives (%)	Examined	PPL skin reactors (%)	Haemagglutination positives (%)
Immediate types of reaction						
Accelerated urticaria	28	71	50	29	62	10
Serum-sickness-like disease	26	69	58	27	85	22
Asthma	3	66	33	6	66	0
Angioneurotic oedema	3	66	66	11	64	9
Late urticaria	24	50	42	37	38	5
Anaphylactic shock	20	45	30	24	41	8
Total	104	60	46 [b]	134	64	10 [c]
Other types of reaction						
Localized reactions	5	60	60	9	33	11
Exanthemas	24	34	25	17	18	0
Varia	11	45	27	25	48	8
Total	14	40	30	51	33	6

[a] From de Weck & Blum (1965).

[b] Among the patients with the immediate type of reactions and who had positive PPL skin tests, 76 % had positive haemagglutination tests in the group with reactions *less* than 2 months old.

[c] Among the patients with immediate type of reactions and who had positive PPL skin tests, 16 % had positive haemagglutination tests in the group with reactions *more* than 2 months old.

haemagglutinating antibodies are found. It has therefore been suggested that the haemagglutinating antibodies may act as " blocking antibodies ", competing for antigen with the skin-sensitizing anti-penicilloyl antibodies, preventing or slowing the reactions due to tissue-fixed skin sensitizing antibodies (SSA). On the contrary, a low haemagglutinating titre associated with a positive skin test to PPL would favour an immediate anaphylactic reaction at the time of a subsequent administration of penicillin, due to the lack of " blocking " antibodies. A high haemagglutination titre and a positive PPL reaction would then render unlikely the occurrence of an immediate anaphylactic reaction on subsequent penicillin injection, but would be compatible with an accelerated urticarial reaction (Levine et al., 1966b).

Clinical observations support the experimental results and empirical conclusions in regard to the immunological and immunochemical mechanisms outlined above. It has also been shown that patients with a past history of penicillin allergy but negative skin tests to both major and minor determinant reagents experienced no immediate anaphylactic or accelerated urticarial reactions on subsequent penicillin treatment, suggesting that their antibodies had disappeared (Voss et al., 1966). It cannot be excluded, however, that some of these patients had never been sensitive in the first place. Patients with positive PPL skin tests treated with penicillin may fail to develop anaphylactic reactions (Parker et al., 1962b), an observation also made by other investigators (Brown et al., 1964), although the frequency of severe accelerated urticarial reactions was 10%–12% *versus* less than 0.5% in patients with negative PPL skin tests. In some series (Parker et al., 1962b), the frequency of severe generalized reactions in PPL positive patients under treatment with penicillin was so high (42%) that this type of experiment had to be discontinued. The fact that a majority of patients with penicilloyl-specific SSA do, nevertheless, tolerate penicillin injection may, aside from

the presence of blocking antibodies mentioned above, also be explained by the quantitative balance (varying with time and from patient to patient) between the amount of SSA present, the amount of eliciting plurivalent conjugate formed *in vivo* from penicillin, and the amount of unreacted penicillin reacting with SSA as a free inhibiting hapten ("in-built inhibition") (de Weck & Blum, 1965; de Weck, 1965).

Positive skin-reactivity to PPL or benzylpenicillin or both may be evanescent and disappear with time (de Weck & Blum, 1965). Thus, in patients who had allergic reactions 2–2½ months prior to testing, the PPL skin test was positive in 90%, while in patients who had had allergic reactions 5–10 years previously, the positivity was 25%–35% (Budd et al.. 1964). A similar transient pattern is seen after skin tests with benzylpenicillin G antigen (Finke et al., 1965; Levine et al., 1966b). The evanescence of the skin-reactivity to the two antigens need not be parallel. However, it is probable that the evanescence of skin-reactivity is associated with decrease or disappearance of clinical sensitivity to penicillin. Voss et al. (1966) found that none of 69 patients with a past history of penicillin allergy and with negative skin tests developed immediate or accelerated urticarial reactions on subsequent penicillin administration; the above-mentioned phenomenon of inbuilt inhibition might also be responsible for the fact that clinical allergic reactions to penicillin often follow a rather unpredictable course.

Other immunological tests. In addition to the immunological tests discussed above, there is also available the *in vitro* indirect basophil degranulation test introduced by Shelley (1963); degranulation of rabbit's basophils may be observed in the presence of penicillin and serum from the patient. Peritoneal mast cells of rats can be used instead of rabbit basophils; since the mast cells keep longer than the basophils, this modified test is more convenient and easier to perform (Schwartz et al., 1965). Some investigators have found the test promising (Katz et al., 1964; Schwartz et al., 1965), although it appears not to be technically satisfactory yet and may have an incomplete theoretical and experimental basis (Keller, 1966). Human skin-sensitizing antibodies responsible for most of the immediate clinical allergic reactions do not appear to bind to rat or rabbit tissues and do not cause passive cutaneous anaphylaxis in these species. A rabbit test in which the serum under examination for penicillin antibodies is injected into the denuded abdominal skin was reported by Cortes & Hernandez (1963a, 1963b). An intravenous injection of penicillin and 1% Evans blue is then made. The degree of positivity is assessed according to the degree of extravasation and intensity of coloration at the site of the injected serum.

Antibodies against penicillin have also been demonstrated by passive cutaneous anaphylaxis in the albino rat (Sonntag & Marcus, 1963) and in the guinea-pig (Josephson et al., 1962), but these antibodies appear to be blocking 7S IgG, not related to the skin-sensitizing antibodies responsible for the allergic reactions. Recently a test was introduced (Shelley & Comaish, 1965) based on fluorimetric assay for histamine release in blood from rabbits passively sensitized with fresh human sera. As in all tests mentioned above, it seems that systems involving the mixing of cells and immunoglobulins of heterologous species do not reveal the presence of human skin-sensitizing antibodies but only that of other immunoglobulin species, unrelated to the allergic manifestations. On the other hand, human skin-sensitizing antibodies may be passively transferred to monkey tissues (skin, ileum) and demonstrated by passive cutaneous anaphylaxis or a Schulz–Dale type of experiment (Kuntz et al., 1967; Girard et al., 1967). Lymphocytes of penicillin-sensitive patients may show increased blast formation and mitotic activity when cultured in a penicillin-containing medium, although the relationship between the results of lymphocyte cultures and clinical penicillin allergy appears irregular (Fellner et al., 1967b; Sarkany, 1967). The tests mentioned above are still under investigation and have for the time being not gained practical application.

In the foregoing discussion we have been concerned with immediate anaphylactic or accelerated urticaria penicillin reactions or both and with intradermal skin testing. The scratch test is considered to be less sensitive than the intradermal test, and can be used when a high degree of hypersensitivity is thought to exist (Siegal, 1955) since severe systemic reactions may follow the amounts of penicillin used in intradermal skin-testing procedures in susceptible subjects (as will be discussed later), although this seems to be quite rare. No anaphylactic reactions to skin tests with PPL on more than 14 000 patients were reported (Brown et al., 1964). Untoward reactions to the scratch test were not noted during an 8-year period in which 1527 penicillin skin tests and 2169 penicillin injections were administered (Yeager & Kvinge, 1965). On the other

hand, the intradermal test is generally preferred because small and graduated concentrations of test solutions can be exactly applied by this method.

When dealing with the problem of prospective skin tests, it seems illogical to advise against it on the ground that they are potentially dangerous. If prospective testing is not performed, the patient may receive a much larger dose of allergen, the only safeguard being the prior history-taking by the physician, but this is potentially a more dangerous procedure than a skin test. Mostly for practical reasons, however, routine skin tests with penicillin or PPL or both prior to penicillin administrations cannot be generally advocated, although they might be justified in special situations. Such tests should be undertaken, if possible, by specialists trained and experienced in allergy skin testing, in co-operation with a competent laboratory (*Canad. med. Ass. J.*, 1967). With this reservation, it can be concluded that some prevention of immediate, serious penicillin reactions would be achieved if skin tests (and, whenever possible, other immunological tests) were performed on patients who presented a possible allergy to penicillin in an endeavour to obtain an objective diagnosis and to furnish the patient with a permanent record (" allergy warning card "), but the tests should be made within 1–3 months of a reaction.

In contact dermatitis of suspected penicillin origin patch tests with the penicillin preparation concerned are sometimes of value. False negative results of such tests, due to insufficient skin penetration of the test substance, as well as false positive results due to local skin irritation, may occur. Therefore, factors pertaining to the test technique and influencing the test response should be considered, i.e., the vehicle, the preservatives, the adhesive tape, etc. (Calnan, 1964; Magnussen & Hessle, 1966). Patch tests with penicillenic acid can be more regularly positive than patch tests with penicillin (de Weck, 1962b), but this is not always so (Caron, 1963).

Sensitizing and eliciting penicillin preparations

Experience has shown that sensitivity can be induced, and anaphylactic reactions provoked, by any type of penicillin preparation administered in any kind of commonly used vehicle, and by any method of application.

Thus, severe immediate reactions have been reported after instillation of penicillin in sinuses (Weiss, 1963), after penicillin aerosols (Feinberg et al., 1953), after use of ophthalmic ointments (Carter & Cope, 1954), after troches and lozenges (Higgins & Rothchild, 1952; Aphentoules & Isopoulos, 1961), after intranasal application (Rabinovitch, 1963), after rectal and vaginal penicillin suppositories (Héraud & Stoft, 1964; Grasreiner, 1954), and after application of penicillin paste used as dental depot (Hurley, 1963). In most of these cases, crystalline benzylpenicillin G has been involved. Allergic reactions after the use of oral tablets are of particular interest since this mode of application is much preferred by physicians for reasons of convenience, and since many of the new penicillins are suitable for oral use. By 1957, Welch et al. (1957) had counted 49 anaphylactic reactions from oral penicillins out of a total of 793 such reactions reported from all preparations of penicillin. While at that time penicillin V was mostly employed in oral medication, recent reports show that severe anaphylactic reactions, some of them fatal, appeared also after the introduction of the new acid-fast oral penicillins (Fox, 1965; Martin & Wellman, 1963; Marks & Williams, 1966; Levine et al., 1960; Krapin, 1960; Miller, 1960), a phenomenon due to the cross-sensitivity of all penicillins derived from 6-amino-penicillanic acid (Stewart, 1962). Since these oral penicillins do not contain procaine, the latter is unlikely to be the causative antigenic factor in anaphylaxis, or in most of the other allergic reactions, encountered after administration of procaine penicillin, as has been suggested (Fernström, 1960).

Small amounts of penicillin seem to be capable of producing sensitivity and of provoking reactions, as is evident from the use of tablets, lozenges, etc. (Miller, 1960). Even minute concentrations may provoke anaphylactic reactions, such as have sometimes been experienced in connexion with skin tests (Siegal, 1955; Cortes, 1960; Wang, 1957), and after intradermal injection of 0.02 ml of a concentration of 1000 IU penicillin per ml (Berger & Eisen, 1955). In fact, an incidental scratch with a needle contaminated with only traces of penicillin has been reported as provoking anaphylactic shock (Wirth, 1963).

Hidden penicillin contacts

Therapeutic and prophylactic administration of penicillin constitute sources of penicillin sensitization and also a common way of provoking reactions in sensitized individuals. Furthermore, penicillin-sensitization is an occupational hazard to persons who handle drugs, i.e., drug-plant workers, doctors, nurses, etc. Previous contact with penicillin may be

known in individual cases, but there are a great many possibilities for sensitization to have occurred without the knowledge of the patient. Thus, " hidden penicillin " as a source of sensitization and cause for later reactions is very real (Woné, 1966; Siegel, 1959). Important among the hidden contacts with penicillin are the following.

Milk and milk-products. These may be contaminated with penicillin during treatment of cows for mastitis, etc., and other foods may be treated with penicillin as a preservative. A total of 6% of samples of milk in the USA and from 5% to 45% of samples in England and Wales have been shown to contain penicillin (*Lancet*, 1960). In France, in 1966 appreciable quantities of penicillin and other antibiotics were found in milk, and attention was focused on the hazard of using antibiotics in order to preserve animal foods (Woné, 1966). Cheeses appear to have been cleared in this respect: far from containing penicillin, they have been reported to have a penicillin-inactivating substance (Ledford & Kosikowski, 1965). However, degradation products may also be present in cheese.

Penicillin-contaminated air. Penicillin particles, demonstrated to be present in the air in hospital rooms, have given rise to severe anaphylactic reactions in sensitized persons (Gould, 1958; WHO, Expert Committee on Venereal Infections and Treponematoses, 1960) as also has skin-contact with penicillin-contaminated dust, e.g., from hospital floors (WHO Expert Committee on Venereal Infections and Treponematoses, 1960).

Contaminated sterilizer water. Water from boiled syringes may contain small amounts of penicillin degradation products capable of provoking reactions in sensitized individuals (Coleman & Siegel, 1955). Even boiling for 16 hours does not appear to destroy the antigenic properties of penicillin solutions, at least for some patients (WHO Expert Committee on Venereal Infections and Treponematoses, 1960). These observations call attention to current procedures of syringe sterilization, and, on the other hand, to the safety in using " throw-away " types of syringes and needles, which are now produced in practical designs for penicillin injections.

Vaccines. Penicillin or other antibiotics are not added to modern smallpox vaccine (WHO Expert Group on Requirements for Biological Substances, 1966). However, in accordance with requirements of the World Health Organization (WHO Expert Group on Requirements for Biological Substances, 1966), inactivated poliomyelitis vaccine may not contain more than 0.05 International Unit of penicillin per human dose, and oral poliomyelitis vaccine may have antibiotic or other preservatives and stabilizers " . . . provided they have been shown . . . not to impair the safety and effectiveness of the vaccine ". Also, the label shall state " the nature and amount of antibiotics used in the preparation of vaccine ". There is, thus, a potential risk of penicillin reactions after vaccinations against poliomyelitis, and anaphylactic reactions have actually been reported from Denmark, England, the USA (WHO Expert Committee on Venereal Infections and Treponematoses, 1960) and Switzerland (de Weck, personal communication). Also, the possibility of actual induction of penicillin-sensitivity by the poliomyelitis vaccines cannot be ignored.

Mycotic infections. Saprophytic, and numerous pathogenic, fungi produce small amounts of penicillins and penicillin-like substances which may therefore represent a " hidden " contact with penicillin. A frequent, but not obligatory, relationship between mycotic infections of the skin and penicillin hypersensitivity has been documented (Schuppli, 1962; Blum & de Weck, 1966).

Influence of personal factors

Our knowledge of individual factors which might contribute to the occurrence of anaphylactic penicillin reactions or influence their course is still very incomplete. There is, however, clear evidence that patients with a present or past allergic diathesis may react more easily and more severely to repeated penicillin administration than do normal individuals. This is particularly so in cases of bronchial asthma (*J. Amer. med. Ass.*, 1955), but also other allergies, e.g., hay-fever and pollen allergy, are occasionally revealed during the questioning of penicillin-reactors (Siegel et al., 1953). Allergic children have been found to show a greater frequency of penicillin reactions than do non-allergic children (Collins-Williams & Vincent, 1954). Anaphylactic penicillin-reactors, like penicillin-reactors of other types, have been found most commonly among adults between 20 and 49 years old, with a decreasing frequency in older age-groups (Feinberg & Feinberg, 1956). They are rare among children under 12 years old, although severe anaphylactic reactions have been observed even in infancy (Matheson & Elegant, 1955; Green, 1959). The age-distribution may be due to variations in the penicillin intake at different age-periods, and also, the less frequent reactions in

older age-groups may be due partly to evanescence of sensitivity with the passing of time.

Generally, allergic penicillin reactions are observed to be approximately evenly distributed among males and females (Siegal, 1955), paralleling the sex distribution in the population at large (Steenfeldt-Foss, 1965).

Frequency of allergic penicillin reactions

During the early years of penicillin therapy, when amorphous penicillin was used, allergic reactions to the drug generally affected the skin, i.e., late allergic reactions with symptoms of urticaria, angioneurotic oedema and dermatitis. As early as 1943, urticaria was observed in 2%–3% of patients treated with penicillin (Keefer, 1943). An increase in the frequency of urticaria was reported after 1944, with an estimated frequency of 6%–8% (von Dettingen, 1955), possibly due to the vehicle component in the penicillin-in-oil and the beeswax preparations which were introduced at that time (Kolmer, 1947). Following the introduction of crystalline penicillin in 1947, and aqueous procaine penicillin as well as procaine benzylpenicillin in oil with aluminium monostearate (PAM) about a year later, the frequency of urticarial reactions did not seem to increase. On the contrary, about 1953–54 they were estimated to occur only in 1%–2% of all patients receiving penicillin (Hussar & Holley, 1954), whatever preparation was used (*J. Allergy*, 1952). As to benzathine penicillin, introduced in 1952, it apparently caused no notable change in the frequency of urticarial reactions reported. Contact dermatitis also was observed as early as 1943, being estimated to occur in approximately 3% of patients exposed to prolonged local penicillin treatment (Long, 1954). By 1956, values of 5%–10% were given (Sloane, 1956). The chances of sensitization were then considered too high and local application of penicillin was largely avoided, the more so since other antibiotics were becoming available. As a whole, it may be said that in the early years of penicillin treatment, skin symptoms, predominantly of late types, dominated the allergic reactions caused by this antibiotic.

It was claimed in 1944 that anaphylactic sensitization could be induced in guinea-pigs by injections of amorphous penicillin (McClosky & Smith, 1944) and anaphylaxis due to penicillin was first reported in man in 1945 (Cormia et al., 1945). Only 2 deaths were reported from penicillin-sensitivity in the first 9 years of use of the antibiotic (Kern & Wimberley, 1953). Subsequently, increasing numbers of anaphylactic shock reactions following immediately the administration of penicillin—occasionally leading to the death of the patient—were reported from countries where penicillin had been widely used. In the years 1952–53, 39 fatalities were recorded (Hussar & Holley, 1954). In an investigation in 1953 of penicillin reactions at 95 hospitals with a total of 51 000 beds in the USA, Welch et al. (1953) found 59 cases of severe anaphylactic reaction, including 19 deaths, which had not been published. In another similar nation-wide survey in 1957 covering 827 hospitals with nearly 200 000 beds, a total of 809 anaphylactic reactions were found to have occurred during the year. No less than 793 of these anaphylactic reactions, including all the 72 deaths (9%), followed the use of penicillin. From 1953 to 1956 there was a increase in reported cases of fatal penicillin anaphylaxis from 24 to 301 (Welch et al., 1957). Obviously, all fatalities with this cause have not been reported in the literature, and the actual number of such deaths up to 1957 was estimated to be about 1000 (Peters et al., 1957).

Total allergic penicillin reactions, including anaphylaxis, since 1957, are illustrated by the following data. In a survey in Australia in 1959 among 6832 patients treated in general practice, 88 (1.3% of the total) developed reactions and 8% had anaphylaxis (Anderson, 1959). Of 1800 patients treated in general practice in an American city in 1959, 3.2% had reactions, but no cases of anaphylaxis were seen (Moore & Woody, 1960). In the USSR in 1959 among 6200 patients, 1% showed allergic reactions after treatment with penicillin (Askarov, 1959). In Mexico, in 1960, reactions were estimated at between 4.2% and 8.0% (Cortes, 1960). In 1963, among 2000 Finnish soldiers, penicillin hypersensitivity was found in 2.6% (Peltonen et al., 1963). In Switzerland, 1071 patients treated in 1965 for a variety of diseases showed a 1.6% frequency of penicillin allergy (Schuppli, 1963), and among 10 483 patients in a university city hospital in Switzerland in the same year, 59 patients (0.56%) had been hospitalized because of allergic reactions to penicillin (de Weck, unpublished data). In 1966 among US army recruits, 1% had allergic reactions following penicillin treatment (Rytel et al., 1963), and 7.8% of 408 patients in a US hospital also had allergic reactions (6.2% anaphylaxis, 60% urticaria, 21% serum-sickness-like reactions, and the remainder, other mixed reactions) (Smith et al., 1966). In Czechoslovakia, 0.66% of penicillin-treated patients showed such reactions (Ciercierski & Suchanek,

1966). All these surveys, although widespread geographically and from countries with developed medical services, refer to rather small and selected patient-groups and the data are not referable to the populations from which they were drawn. There can therefore be little doubt that there is a lack of information concerning the real frequency of penicillin reactions, in developed—as well as in developing—countries, and that studies on time prevalence and incidence should be encouraged, to obtain a clear picture of a possibly changing situation. A preliminary study along these lines has been made by one of us (A. de W.) in Switzerland (1967), where in an area with a population of 200 000 people, all the 211 physicians in the area were interviewed. A total of 53 severe, non-fatal anaphylactic shocks, 30 cases with shock-like manifestations, and 4 deaths following penicillin injections were reported, corresponding to a rate of 0.04% anaphylactic reactions and a fatality of 0.002%.

It is believed that syphilis and gonorrhoea patients might represent a group particularly suitable for assessing the frequency of allergic reactions, and for a study of factors related to the occurrence of such reactions, since their treatment is usually protracted. Nevertheless, these patients do represent a selected group, although the period of follow-up observation would be long. Thus, in Norway (Oslo) in 1960, among 5231 patients treated with penicillin for venereal diseases, just under 1% showed reactions of all types. None had anaphylaxis and there were no fatalities (Gjessing, 1960). In France, in 1964, of 7526 ambulatory patients treated for syphilis, it was found that 0.3% showed allergic reactions to penicillin; only 3 (0.04%) had severe shock and none died (Thiers et al., 1964). Of about 30 000 patients in the USA treated with penicillin for venereal diseases, Brown (1956) estimated in 1956 that 0.72% total allergic reactions, mostly urticaria, occurred; only 1 per 10 000 patients suffered anaphylactic reactions, and none died. In the USA, in a continued comparative clinical study throughout the country at Public Health Service venereal disease clinics, it was found (United States of America, Public Health Service, 1965) that the annual incidence of reactions was 0.97% in 1959 and 0.69% in 1965. Moderate to severe anaphylaxis occurred in 0.035% of cases in 1959 and in 0.015% in 1965, indicating a decline since 1959–60. In reviewing reports to WHO from several countries, Willcox (1962, 1964) estimated in 1962–64 that among about 74 000 patients treated with injections of penicillin for venereal diseases, less than 1% had allergic reactions of all types, and he found 11 fatalities among some 800 000 individuals (0.0014%) treated with penicillin for venereal diseases. This compares with the fatality rate of 0.002% found among the population at large in the Swiss study referred to above. So far as syphilis is concerned, these frequency indications should be compared with the very much higher death rate (0.01%–0.03%) when metal-therapy was in use. Willcox found, in one series of 1635 venereal disease patients treated with penicillin, a total of 4.2% of allergic reactions of all types; however, among those who received 1 injection of penicillin, the percentage of reactions was only 0.73 increasing to 5.69 when the number of injections increased to 20 or more. Up to 3.58% had previously experienced allergic reactions to penicillin, or other forms of allergy, i.e., bronchial asthma. They were therefore not given penicillin treatment but received drugs other than penicillin. Consequently, penicillin treatment was used in about 97% of the patients and this resulted in the limited number of reactions mentioned above. It appears, therefore, that there is a minor risk of fatal allergic reaction to penicillin treatment of venereal diseases. Allergic reactions as a whole can be reduced when individuals who have suffered previous allergic reactions to penicillin, or other allergic reactions, are excluded from such treatment by a careful anamnestic inquiry. Apparently, this applies particularly to immediate (anaphylactic) reactions, since in these cases the individuals concerned have been sensitized by a previous penicillin administration and are therefore potential reactors at the very beginning of a new course of treatment. Late reactions are frequently induced and provoked during the treatment with penicillin, and, consequently, protracted multiple treatment schedules would increase the possibilities for such reactions to occur.

Anaphylactic reactions to penicillin have so far caused little concern in the vast mass campaigns against treponematoses (yaws, pinta and endemic syphilis) assisted by WHO in which more than 45 million people over the last 15 years have been treated with penicillin in 45 countries. An estimated 60 million injections of long-acting penicillin (PAM) have been given in these campaigns. Relatively few reactions to penicillin are believed to have occurred and only a few deaths from anaphylaxis are known. This is thought to be due to the fact that it is predominantly children from rural developing tropical

areas who are concerned in these campaigns, and these children have had little or no previous penicillin medication. It is also possible that the recording and classification of side-effects were not systematically carried out.

The world production of penicillin has continued to increase. Thus in the USA it rose from 324 million IU in 1951 to 1351 million IU in 1965. Assuming injections of doses of 0.6 megaunit this corresponds to more than 540 million injections in 1951 and more than 2000 million injections in 1965. Estimating that possibly 300 persons have died annually of penicillin anaphylaxis in the USA since around the 1950s, it is tempting to project that if 1 fatality occurred per 1.8 million penicillin injections in 1951, 1 fatality per 7.5 million injections occurred in 1965. This estimate of 300 deaths a year is, however, based on non-verifiable data. Furthermore, the absolute increase in penicillin consumption is certainly related in part to increase in its non-medical use. In the United Kingdom an over-all downward trend has been suggested: 8 deaths following penicillin administration were reported in 1957 and 7 deaths in 1963; the number fell to 1 in 1964. The number of deaths in England and Wales resulting from the use of chloramphenicol was reported (England & Wales, Registrar-General, 1967) to be 6 in 1963 and 3 in 1964. There is really at present no way to know whether the mortality from penicillin anaphylaxis has increased, decreased or remained stable, but, as a whole, penicillin allergy is the most frequent of all drug allergies (Maha, 1961; Feinberg, 1961) and the danger of severe and sometimes fatal reactions must not be disregarded.

All these surveys and investigations from countries with developed medical services indicate the frequency of total allergic penicillin reactions to be within a wide range of 0.7%–10%, depending on methods of observation, criteria for recording, and nature and composition of the treated group, including the number of injections given (Willcox, 1964b). It seems that anaphylactic reactions may occur in about 0.015%–0.04% of patients treated with penicillin, with a fatality of 0.0015%–0.002%. Longitudinal community studies and epidemiological research on these phenomena are needed to illustrate their true frequency.

ANALYSIS OF 151 FATALITIES FROM ANAPHYLACTIC PENICILLIN REACTIONS

With a view to exploring factors related to penicillin anaphylaxis, we have undertaken a study of 151 deaths following penicillin administration, based on available medical literature during the period 1951–65 (Tables 6–11).

Table 6 shows that more than half of the fatalities occurred in the 25–64-years age-groups, the remainder being evenly distributed below the age of 25 and in those of 65 years and above; 10 of the deceased were below 5 years of age and 6 of these were 2 years old or less, including 2 who were only 3 months old. In total, the deaths occurred evenly among males and females; there were no significant sex differences in the different age-groups.

About 44% of the patients were actually treated for infections of the respiratory tract; half of these had bronchitis or pneumonia. Somewhat more than one-quarter were treated for various infections, e.g., balanitis, gingivitis, paronychia, skin infections, furunculosis. In 5 cases the treatment had been initiated on vital indications, e.g., pericarditis, endocarditis, meningitis, phlegmone manum. One child aged 3 months received an injection of penicillin by mistake; of the other children below the age of 2 years, 1 had erythrodermia, 2 had infections of the respiratory tract, and no information is available for the 2 others.

In 3 cases the indication for treatment was syphilis (e.g., a man with primary syphilis, a woman with late syphilis who died following a " test " dose of 0.01 IU of penicillin intravenously, and a man with general paralysis). In 2 patients the treatment was for gonorrhoea. Penicillin was applied for prophylactic purposes in 12% of the cases, ranging from tooth extraction (2 cases) to intra-abdominal surgery. In 10.6% of the treatments, the diagnosis was not given or was uncertain.

Table 7 shows constitutional allergies in the 151 patients. In 28% allergic diathesis was definitely stated. Bronchial asthma occurred in 14% and hay-fever-type allergies and skin eruptions, including drug allergies, in 3.3%. Of other and unspecified types, 10.0% was noted, while in more than 50% no information was available. In 18.5% no allergy was revealed. The information published concerning the allergic constitutions of the patients who died from penicillin anaphylaxis is thus very incomplete. However, among 20 fatalities reported in the Scandinavian countries, and where anamnestic information was accessible, 65% had allergies (Bertelsen & Dalgaard, 1965); one-quarter of them had bronchial asthma.

Table 8 shows that 38 of the 151 fatalities (25%) had experienced reactions following previous peni-

TABLE 6

AGE AND SEX DISTRIBUTION AND TREATMENT INDICATION IN 151 PATIENTS WHO DIED OF ANAPHYLACTIC SHOCK FOLLOWING PENICILLIN TREATMENT

Indication for penicillin treatment	0-14 years		15-24 years		25-44 years		45-64 years		≥65 years		Unknown		Total		Grand total [a]
	M	F	M	F	M	F	M	F	M	F	M	F	M	F	
Various infections (unspecified)	1	1	4	4	4	6	8	5	4	2			21	18	39 (26.0)
Upper respiratory infections (including nasopharynx)	3	1	1	4	4	10	4	3	—	3	1	—	13	21	34 (22.5)
Lower respiratory infections (including bronchitis and pneumonia)	1	2	—	—	2	4	10	4	2	7	—	—	15	17	32 (21.2)
Genitourinary infections (including venereal diseases)	—	—	—	1	5	3	2	1	—	—	—	—	7	5	12 (8.0)
Prophylaxis in surgery and other fields	1	—	1	—	1	5	5	2	2	1	—	—	10	8	18 (12.0)
Uncertain or unknown	1	2	—	—	5	4	1	2	1	—	—	—	8	8	16 (10.6)
Total	7	6	6	9	21	32	30	17	9	13	1	—	74	77	151 (100)
Grand total [a]	13 (8.6)		15 (10)		53 (35.1)		47 (31.1)		22 (14.6)		1		—		—

[a] Percentages in parentheses.

cillin administration. However, of the 104 (69%) patients known to have received penicillin previously, 36.5% suffered reactions. Immediate-type reactions accounted for more than half of the known reactors; only one patient had a late-type reaction. The previous reactions were caused by all commonly used penicillin preparations, although with a slight preponderance of short-acting varieties. In about 30% of the total, nothing is known of previous penicillin administration, and in more than 50% no information on previous reactions was available. In 37 cases information is given on the time interval between

TABLE 7

CONSTITUTIONAL ALLERGIES AND PREVIOUS PENICILLIN REACTIONS IN 151 PATIENTS WHO DIED FROM ANAPHYLAXIS FOLLOWING SUBSEQUENT PENICILLIN ADMINISTRATION

Constitutional allergies	Immediate-type reaction	Late-type reaction	Unspecified reaction	Unknown	No reaction	Total [a]
Bronchial asthma	2	—	3	8	8	21 (14.0)
Rhinitis (hay-fever type)	—	—	—	—	1	1 (0.7)
Skin eruption type and drug allergy	1	—	1	—	3	5 (3.3)
Others or unspecified types	—	—	6	6	3	15 (10.0)
Unknown	11	1	8	59	2	81 (53.6)
No constitutional allergy	2	—	3	12	11	28 (18.5)
Total [a]	16 (10.6)	1 (0.7)	21 (14.0)	85 (56.0)	28 (18.5)	151 (100)

[a] Percentages in parentheses.

TABLE 8

PREVIOUS PENICILLIN REACTIONS IN RELATION TO TYPE OF PENICILLIN PREPARATION IN 151 PATIENTS WHO DIED FROM ANAPHYLAXIS ON SUBSEQUENT PENICILLIN ADMINISTRATION

Previous penicillin reactions	Oral preparation	Long-acting preparation [a]	Intermediate-acting preparation [b]	Short-acting preparation [c]	Unspecified preparation	Unknown preparation	Total [d]
Immediate-type reaction	1	1	1	3	10	–	16 (10.6)
Late-type reaction	–	–	–	–	1	–	1 (0.7)
Unspecified reaction	–	–	1	2	17	1	21 (14.0)
No reactions	2	3	1	2	28	3	39 (25.8)
Unknown	1	1	1	3	25	43	74 (49.0)
Total [d]	4 (2.6)	5 (3.3)	4 (2.6)	10 (6.6)	81 (53.6)	47 (31.1)	151 (100)

[a] Long-acting intramuscular preparation: procaine penicillin G in oil with 2% aluminium monostearate (PAM).
[b] Intermediate-acting intramuscular preparation: procaine penicillin G in water.
[c] Short-acting intramuscular preparation: benzylpenicillin (crystalline penicillin G).
[d] Percentages in parentheses.

previous penicillin administration and the administration causing death. The intervals ranged from 10 days (1 case) to 6–7 years (2 cases), the majority (20 cases) being within a 1–12-month period.

The type of penicillin preparation and dose causing fatal anaphylaxis is known in, respectively, 80% and 70% of the 151 cases, as seen in Table 9. Most fatalities were caused by intermediate-acting and short-acting preparations (37.7% and 32.5%, respectively), while long-acting preparations accounted for 7.0% and oral preparations for 2%. This distribution is reasonable, considering the assumed proportion of the consumption of these preparations in medical practice. The majority of known death-causing doses were within the ranges of 0.1 to 0.5 megaunit (45.7%), and 0.6 to 2.4 megaunits (20.5%), which are the doses commonly applied. It is noteworthy, however, that a 41-year-old female died a few minutes after an intradermal test of 4000 IU of penicillin G in water. She suffered from drug allergy, and had experienced an immediate reaction following administration of short-acting penicillin about 2 months previously. Also, reference is again made to the patient suffering from syphilis who

TABLE 9

TYPE OF PENICILLIN PREPARATION AND DOSE THAT CAUSED FATAL ANAPHYLAXIS IN 151 PATIENTS

Preparation	Dose in megaunits					
	< 0.1	0.1–0.5	0.6–2.4	> 2.4	Unknown	Total [a]
Oral preparation	–	1	1	–	1	3 (2.0)
Long-acting intramuscular preparation	–	3	3	–	4	10 (7)
Intermediate-acting intramuscular preparation	2	27	17	2	9	57 (37.7)
Short-acting intramuscular preparation	1	26	6	–	16	49 (32.5)
Unknown	2	12	4	–	14	32 (21.2)
Total [a]	5 (3.3)	69 (45.7)	31 (20.5)	2 (1.3)	44 (29.1)	151 (100)

[a] Percentages in parentheses.

TABLE 10
FATAL ANAPHYLAXIS IN 151 PATIENTS IN RELATION TO INITIAL AND SUBSEQUENT ADMINISTRATION OF PENICILLIN PREPARATIONS

Penicillin preparation	Order of administration			
	First administration	Subsequent administrations	Unknown	Total [a]
Oral preparation	3	–	–	3 (2.0)
Long-acting intramuscular preparation	6	2	2	10 (7)
Intermediate-acting intramuscular preparation	46	2	9	57 (37.7)
Short-acting intramuscular preparation	41	1	7	49 (32.5)
Unknown	27	1	4	32 (21.2)
Total [a]	123 (81.5)	6 (4.0)	22 (14.6)	151 (100)

[a] Percentages in parentheses.

died after an intravenous test dose of 0.01 IU of penicillin. She had had penicillin treatment (unspecified preparation) more than a year before, but nothing is known of subsequent reaction or of allergic constitution.

As shown in Table 10, 123 patients (81.5%) died following the first administration of penicillin, and 6 patients (4%) after the second administration. In 14.6% of the cases, no information was available. The great majority of known penicillin preparations that caused death after the first administration were of intermediate- and short-acting types (48.0% and 42.2%, respectively), which is expected considering the extent to which these preparations are prescribed. The 3 deaths following the use of penicillin tablets occurred after the first oral medication (see also " Toxicity ", pp. 160-161).

The intervals between administration of penicillin and manifestations of symptoms and death are known in about 96% and 97% of cases, respectively, as shown in Table 11. In almost 85% of the cases the symptoms appeared within 15 minutes of penicillin administration, half of them " immediately "; in about 11%, after an interval of about 1 hour; the

TABLE 11
INTERVAL BETWEEN ADMINISTRATION OF PENICILLIN, MANIFESTATIONS OF ANAPHYLACTIC SYMPTOMS AND DEATH IN 151 PATIENTS

Interval between manifestation and death	Interval between administration of penicillin and manifestation of symptoms				
	Immediate	Less than 15 min	1 hour or more	Unknown	Total [a]
0–14 min	59	23	–	–	82 (54.3)
15–59 min	9	21	2	1	33 (22.0)
1–23 hours	4	5	6	2	17 (11.2)
⩾ 24 hours	2	3	9	1	15 (10.0)
Unknown	–	2	–	2	4 (2.6)
Total [a]	74 (49.0)	54 (35.8)	17 (11.3)	6 (3.9)	151 (100)

[a] Percentages in parentheses.

remainder with intervals of up to 1 day. More than 50% of deaths occurred within 15 minutes of the fatal administration of penicillin; of the remainder, 22% took place between 15 and 60 minutes after the administration, 11.2% between 1 and 24 hours, and 10% after more than 24 hours. In almost half the cases, symptoms appeared and death occurred within 15 minutes. One group of authors described such a situation as follows: "The drama lasted 3 minutes maximum" (Vidal et al., 1960).

In 70 cases of the total 151, resuscitation procedures are reported to have been applied after the onset of symptoms. In order of frequency, the procedures were: cardiovascular stimulants, artificial respiration, oxygen application, cardiac massage, corticosteroids. In 40 cases more than one method was applied.

Discussion on analysis of fatalities

The statistical value of the tabulated data is limited by the high percentage of unknown or uncertain information given. This applies particularly to constitutional allergies and previous penicillin treatment and subsequent reactions. There are obvious reasons for these shortcomings. When anaphylactic reactions, including deaths, were reported from 1946 onwards, the immunological nature and mechanisms were only vaguely recognized, and therefore information related to immunological factors was only infrequently sought. Also, owing to the dramatic circumstances involved, incomplete anamnesis could, and can, only be filled-in by information from relatives or others who may have little knowledge of the deceased patient. Despite these failings, the following conclusions are believed to be warranted from the data presented.

(1) A large number of the 151 patients who died from penicillin anaphylaxis suffered from some kind of allergy; this fact supports the general experience of an association between penicillin anaphylaxis and constitutional allergy. This view is reinforced when considering the selected Scandinavian group of 20 anaphylactic deaths, of which about 65% had allergic complaints. Also, the particular role of bronchial asthma in the immunological pattern of penicillin anaphylaxis is emphasized by the evidence that in this group asthma constituted more than half of the known allergies. It stresses the need, before penicillin treatment is initiated, for a thorough inquiry on allergic constitution, with particular emphasis on bronchial asthma and hay fever, to be made; furthermore, it confirms that constitutional allergies as a whole should be considered as restricting the indications for penicillin treatment to cases not manageable by other antibiotics.

(2) Almost 70% of the fatal cases had received previous penicillin treatment, and nearly one-third had had subsequent reactions. (In the Scandinavian group, 90% had had previous penicillin treatment and one-third of those had had reactions.) This supports the general experience of the particular risk of anaphylactic reactions in patients who have been exposed to penicillin previously and who have had subsequent reactions. Since almost 100% of the known previous reactors in our group were of the immediate type it seems that particular attention should be given to this aspect of the anamnestic information before the initiation of penicillin treatment. The questioning should be precise (skin reactions, urticaria, etc.) and not too vaguely formulated.

The probability has already been discussed that rather few patients would be able to recall previous treatments with penicillin treatment, and almost certainly not the type of penicillin used. However, out of 98 patients in the group considered here, where the order of penicillin administration causing death is known, 91 (93%) reacted directly following the first administration and the remainder following the second administration, some 2 days later.

The present views on immunological mechanisms imply that in these patients antibodies due to previous exposure to penicillin were present in the blood and tissues at the time of the administration, i.e., "ready-made" for antibody–antigen reaction. In such cases, even a minute dose may cause a reaction: the quantity and quality of antibodies present will determine the extent or magnitude of the immunological reaction. It is possible that under these circumstances rapidly absorbed, short-acting preparations may facilitate an "explosive" antigen–antibody reaction more than would long-acting depot preparations.

(3) The effect of exposure to penicillin presumably accumulates in adult age-groups, which show the highest frequency of fatal anaphylactic reactors. However, following the present widespread use of penicillin, there is a serious risk of sensitization in children also, for example, through the use of atomizers with penicillin added to the contents, by oral medication, or from penicillin ointment. This study reveals 2 deaths, caused by penicillin, of 3-

month-old babies. Although immunological maturity is, in part, already reached at that age, younger infants may still carry antibodies from birth, passively transferred during intra-uterine life, from a mother previously exposed to penicillin. Inquiry into the "penicillin anamnesis" of the mother should be obligatory, therefore, before treatment of babies with penicillin.

(4) Almost half the 151 anaphylactic reactions were explosive and appeared immediately after penicillin administration, and in another 36% reactions occurred within 15 minutes. This dramatizes a rare situation in present-day medical practice; it is understandable that medical personnel may become confused over means and procedures for resuscitation. Obviously, very valuable time may be wasted if essential remedies for shock-treatment are not immediately available; this has been seen by one of us (T. G.) to happen in a hospital with a high reputation. The lack of information on procedures for resuscitation in more than half the cases in the study may, to some extent, be due to failures in this respect.

In this study it is shown that there is a direct relationship between the delay of symptoms and the delay of death, i.e., the sooner symptoms appear the sooner death occurs. This may be of prognostic importance, and further indicates the urgent intervention needed at the slightest appearance of symptoms.

(5) Short-acting penicillin preparations as well as oral preparations, both of which are free from the procaine component, cause fatal anaphylaxis. This supports the concept that the causative antigen is penicillin itself or derivatives of the penicillin nucleus, as has been discussed already.

PREVENTION AND TREATMENT OF PENICILLIN REACTIONS

An Expert Committee of the World Health Organization recommended in 1959 that individual and public health measures should be taken to prevent or treat penicillin reactions (WHO Expert Committee on Venereal Infections and Treponematoses, 1960); particular reference was made to anaphylactic reactions. These measures for prevention and treatment are still valid, and are summarized below with appropriate modifications according to recent experience and knowledge (Guthe et al., 1958; Epstein, 1966; Brandriss et al., 1964; Calnan, 1964; Danbolt, 1960; King & Nicol, 1964; American Public Health Association, 1960; A. Perdrup, personal communication).

Prevention of penicillin reactions at the patient level

(1) Always have emergency kit for treatment of allergic reactions readily available.

(2) Always have an exact past history of the patient's previous contact with penicillin, previous penicillin reactions, and allergic diathesis. In infants less than 3 months old, inquire about penicillin allergy in the mother.

(3) No penicillin treatment should be given to patients with a previous history of reactions; indications for administration of penicillin are severely restricted in patients with an allergic diathesis (e.g., bronchial asthma).

(4) If possible, refer patients with suspected penicillin allergy (preferably within 3 months of the alleged reaction) to a specialist trained in modern immunological techniques (skin-testing with penicillin and penicillin derivatives; serological tests) in order to provide the patient with an objective diagnosis and a permanent record.

(5) Always tell the patient that he is going to receive penicillin treatment.

(6) No penicillin should be employed for external treatment or on mucous membranes, particularly not on macerated or eczematized skin, especially likely to cause sensitization. Other antibiotics, not likely to be given systemically later, can be employed for local treatment (e.g., neomycin, bacitracin, gramicidin). Due to cross-sensitivity of the semisynthetic penicillins (all have the 6-aminopenicillanic acid nucleus in common) there will be no security in changing to one of these. Cross-reactions, although less frequent, may also be expected to occur eventually with cephalosporin.

(7) Avoid the use of penicillinase-resistant penicillins (meticillin, cloxacillin, nafcillin, ancillin and quinacillin) which should be reserved for infections caused by penicillinase-producing staphylococci.

(8) Ensure the thorough washing and adequate sterilization of all-purpose syringes which have been used in penicillin treatments, when using them to inject other drugs. If possible, use disposable syringes and needles.

(9) If possible, retain all patients for half-an-hour in the clinic after an injection of penicillin (most anaphylactic reactions occur shortly after injection).

Prevention of penicillin reactions at the public health level

(1) The use of penicillin in agricultural and veterinary products, particularly milk and dairy products, and in food-preservation should be regulated or prohibited. The possibilities for other hidden contamination (e.g., of syringes or virus vaccines) should be reduced to the lowest possible level.

(2) The distribution of penicillin should be regulated and it should be sold only on a doctor's prescription.

(3) The medical profession should be warned about the danger and should be asked to limit the use of penicillin to clinical and public health indications.

(4) Public health measures should be taken to protect employees and workers in the drug industry, and also professional people who handle penicillin regularly, from contamination with penicillin dust and other residues.

(5) Health programmes which depend on penicillin therapy, such as those for syphilis control and yaws eradication, should be fully and rapidly implemented using adequate dosages and simple injection techniques.

(6) Health education programmes should be undertaken to inform the public of the danger resulting from the misuse of antibiotics.

Treatment of penicillin reactions

Emergency kit. The kit should contain the following items:

(1) A 1:1000 solution of adrenaline hydrochloride (epinephrine) ready to use;

(2) Two 2-ml syringes and hypodermic needles (disposable-type syringes and needles are preferable); and also if possible:

(3) Portable oxygen;

(4) A hydrocortisone preparation suitable for intravenous injection;

(5) Aminophylline, up to 0.5 g for intravenous injection;

(6) Penicillinase.

Procedure. The following procedure should be carried out as quickly as possible:

(1) Immediately on appearance of signs of reaction, make the patient lie down (head down, feet up).

(2) Inject 0.5–1.0 ml of adrenaline subcutaneously in the upper arm.

(3) If immediate response is not obtained, repeat the adrenaline treatment or give an injection of cortisone (25 mg–100 mg hydrocortisone intravenously).

(4) In angioneurotic oedema, urticaria or conjunctivitis, give antihistamines intramuscularly or intravenously.

(5) Where there is coughing, dyspnoea, respiratory distress or substantial discomfort, a slow intravenous injection of 0.25 g–0.5 g aminophylline can be used. Artificial respiration has also been successfully used (Heyworth, 1958).

These measures have been increasingly adopted in recent years and their use reduces the fatality rate in anaphylaxis from about 50% to about 9% (Westerman et al., 1966; Welch et al., 1958).

Most investigators hold the view that antihistamines have an insignificant effect both in the prophylaxis and in the treatment of immediate reactions (Calnan, 1964; Scipel et al., 1959) as also is the case with *prophylactic* ephedrine and theophylline (Herkheimer & Streseman, 1960). They are, on the other hand, recommended in late penicillin reactions (Willcox, 1964). The " anti-inflammatory " effect of corticosteroids, however, should be used also in the treatment of penicillin anaphylaxis after the emergency drugs have been administered (Calnan, 1964; Willcox, 1964). However, corticosteroids should not be trusted for prophylactic purposes except in cases where penicillin treatment is absolutely indicated despite the potential risk of the patient being penicillin-sensitive (Calnan, 1964).

Penicillinase has been found to be rapidly effective in breaking down circulating benzylpenicillin, at least as measured by the circulating blood level (Greaves, 1961), but its effect on already formed antibody–antigen complexes is not known (Westerman et al., 1966) and is likely to be minimal. Experience has shown, though, that it may be of some use in treatment of anaphylactic reactions if given very soon after symptoms have been observed (Westerman et al., 1966; Greaves, 1961; Trinca & Keen, 1960; Becker, 1960). In late reactions, particularly, the breaking-down effect on circulating

penicillin and tissue penicillin may prevent further protein-binding and formation of antigenic conjugates. However, penicillinase itself has in turn been reported to induce anti-penicillinase-antibodies (Weiss & Grepea, 1959) and to provoke sensitivity reactions (Becker, 1960), mostly of minor significance but also in some few cases of anaphylactic character (Caputi, 1959; Hyman, 1959; Reisch, 1959; Thomas, 1959), a fact which calls for caution (Becker, 1960).

Desensitization can be achieved by the use of graded doses (Reiseman et al., 1962) but the procedure is not without considerable danger and should be reserved for patients who are seriously ill and when there is no effective alternative antibiotic (Vallery-Radot et al., 1960).

RÉSUMÉ

Il y a dix ans, les auteurs du présent article évaluaient l'état des connaissances sur la nature et l'importance des réactions secondaires à la pénicilline. Depuis lors, la pénicilline a continué d'être très largement utilisée en médecine humaine et vétérinaire, bien que relativement moins qu'avant 1955 en raison de l'emploi accru des antibiotiques très divers à spectre plus ou moins large dont on dispose actuellement. La présente étude passe en revue les connaissances acquises depuis lors dans les domaines de la résistance microbienne, de la pullulation, de la lyse, etc., notamment pour ce qui est des gonocoques et des tréponèmes, étant donné l'emploi considérable de la pénicilline en vénéréologie, en médecine tropicale et dans d'autres spécialités. Les réactions allergiques sont étudiées en raison de leur importance particulière parmi les réactions secondaires à la pénicilline et des notions récentes concernant leur nature immunologique sont exposées. Les résultats d'une étude portant sur 151 décès dus à la pénicilline sont présentés. Enfin, la prévention et le traitement des réactions à la pénicilline sont discutés.

Toxicité

Les préparations modernes de pénicilline, c'est-à-dire les dérivés de l'acide amino-6 pénicillanique, ne sont toxiques ni pour l'homme ni pour la plupart des animaux. Des doses de benzyl-pénicilline largement supérieures aux doses utilisées en thérapeutique n'ont pas provoqué d'effets nocifs manifestes et seuls quelques rapports isolés font état d'une toxicité hématologique et hépatique de l'oxacilline et de la méticilline.

Des réactions toxiques d'embolie après injection intraveineuse accidentelle de pénicilline procaïne, parfois accompagnées de troubles psychotiques considérables, ont été décrites. Elles ont été attribuées au composant procaïne ou à la présence, dans certaines préparations, de grands cristaux de pénicilline. L'injection intramusculaire de benzathine pénicilline aqueuse est parfois douloureuse et peut entraîner une nécrose locale.

Effets microbiogènes

La résistance des microbes à la pénicilline peut être naturelle ou acquise; les micro-organismes qui présentent une résistance naturelle sont généralement plus virulents que ceux dont la résistance est acquise. La pénicillinase est une des causes principales de résistance à la pénicilline qui peut également être induite, dans certains cas, par la pénicillinacilase produite par des micro-organismes résistants. Les principaux micro-organismes résistants à la benzyl-pénicilline sont les staphylocoques, les bacilles ne prenant pas le Gram et les coliformes dont bien des souches présentaient une résistance naturelle au début de l'ère de la pénicilline, alors que la sensibilité du gonocoque était, à l'origine, totale. La résistance de ce dernier est apparue progressivement au fur et à mesure que l'emploi de la pénicilline devenait plus courant; la répartition géographique des souches résistantes est irrégulière. On ne connaît pas jusqu'ici de résistance de *Treponema pallidum* à la benzyl-pénicilline. Des pénicillines qui résistent aux actions de la pénicillinase et de la pénicillinacilase ou d'autres antibiotiques permettent de traiter les infections qui résistent à la benzyl-pénicilline.

La pullulation, c'est-à-dire la surinfection par des micro-organismes résistants, est essentiellement due à la suppression, pendant le traitement, de la flore bactérienne sensible normalement présente dans les organes atteints (infections hospitalières, « porteurs »).

La réaction de Herxheimer est généralement attribuée à la libération d'endotoxines au niveau des tréponèmes tués après le premier traitement médicamenteux. Jusqu'ici, rien ne permet de la rattacher à une hypersensibilité à des substances libérées par les tréponèmes. Cette réaction est surtout fréquente au cours de la syphilis primaire séropositive où elle est observée dans près de 95% des cas traités soit par la pénicilline soit par l'association arsenic/métaux lourds. Le risque de paradoxe thérapeutique, après traitement de la syphilis par la pénicilline, est insignifiant.

Réactions allergiques

Elles constituent de loin les effets secondaires les plus fréquents et les plus importants du traitement par la pénicilline. Elles sont dues à des réactions antigène-anticorps ou antigène-cellules sensibilisées. On les classe généralement en *a*) réactions allergiques subites ou « immédiates » (comprenant les réactions urticariennes accélérées). Dans ce cas, le malade possède déjà des anticorps par suite d'une exposition antérieure, connue ou non, à la pénicilline; *b*) réactions allergiques tardives,

qui comprennent des manifestations cutanées dont les plus fréquentes sont l'urticaire et des réactions du type de la maladie du sérum. Ici l'exposition antérieure à la pénicilline peut manquer et la réaction n'apparaît que quelques jours après le début du traitement, temps nécessaire à la formation d'anticorps; *c*) dermite de contact, due à l'application locale de pénicilline ou à une exposition localisée, et *d*) autres réactions, rares, peut-être allergiques, peut-être toxiques.

Un des déterminants antigéniques majeurs de l'allergie à la pénicilline est le groupe pénicilloyle dérivé du noyau de l'acide pénicillanique, commun à toutes les pénicillines, soit à partir d'un produit de dégradation, l'acide pénicillénique, soit directement à partir de la pénicilline. Ceci explique en partie l'existence d'une réactivité croisée à différentes pénicillines. La pénicilloyl-polylysine (PPL) est formée lors de la conjugaison de la pénicilline ou de l'acide pénicillénique avec une lysine polymérisée, la polylysine. La pénicilloyl-polylysine substituée au maximum n'a pas de propriétés immunogéniques et peut servir à des tests cutanés (tests cutanés PPL) qui décèlent les anticorps dermosensibilisants responsables de certaines réactions anaphylactiques, des réactions urticariennes précoces et de la plupart des réactions du type de la maladie du sérum. Seuls des tests cutanés à la pénicilline cristallisée permettent de déceler certains des anticorps dermosensibilisants qui provoquent les réactions (anaphylactiques) immédiates. Des hémagglutinines apparaissent souvent en même temps que les anticorps dermosensibilisants. Certains auteurs ont émis l'opinion que les hémagglutinines pourraient agir comme anticorps « bloquants » affaiblissant l'action des anticorps dermosensibilisants. Il existe d'autres épreuves immunologiques: le test indirect de dégranulation des basophiles, le test de libération de l'histamine, le transfert passif sur l'iléon de singe et le test de culture de lymphocytes, mais seuls des laboratoires et des spécialistes bien au courant des techniques peuvent se charger de les effectuer et de les interpréter. Des impuretés protéiniques de poids moléculaire élevé, de même que des dimères et polymères, tous fortement antigéniques, ont été isolées récemment de préparations de benzyl-pénicilline. La mise au point de préparations de pénicilline « purifiées » non antigéniques ou moins antigéniques aurait un grand intérêt pratique mais, en cette matière, de nouvelles recherches sont de toute évidence nécessaires.

L'analyse par les auteurs de 151 décès par réactions anaphylactiques après administration de pénicilline a montré qu'un quart environ des sujets présentaient une constitution allergique révélée le plus souvent par l'existence d'un asthme bronchique (14%). Dans un groupe de 20 cas mortels enregistrés dans des pays où les dossiers médicaux sont assez complets, deux tiers des sujets avaient présenté auparavant des phénomènes d'allergie, dont un quart était représenté par l'asthme bronchique. Ces faits confirment l'opinion générale selon laquelle il existe un rapport immunologique entre l'anaphylaxie à la pénicilline et l'allergie constitutionnelle. Dans près de 70% des cas mortels étudiés, les malades avaient déjà été traités par la pénicilline et près d'un tiers d'entre eux avait déjà présenté des réactions allergiques de type immédiat. Les nourrissons de moins de trois mois sont immunologiquement immatures mais ils peuvent présenter des réactions immédiates par suite du transfert passif à l'enfant d'anticorps anti-pénicilline provenant d'une mère traitée auparavant par cet antibiotique. L'étude a montré que les préparations de pénicilline de tous types sont capables d'induire une sensibilité et de provoquer des réactions. Plus de 90% des malades avaient présenté une réaction anaphylactique lors de l'administration initiale de pénicilline à l'occasion d'une nouvelle série (70% de ces malades avaient déjà reçu de la pénicilline auparavant) et dans près de 90% des cas mortels, les symptômes précédant la mort étaient apparus dans les 15 minutes.

Prévention et traitement

La prévention et le traitement des réactions allergiques à la pénicilline exigent une anamnèse aussi exacte que possible, portant sur la constitution allergique, les traitements antérieurs par la pénicilline, la possibilité d'une exposition dans d'autres conditions et les réactions que ces contacts ont pu entraîner. Lorsqu'il s'agit de nourrissons, les mères doivent être interrogées. Si des réactions antérieures sont signalées, le traitement par la pénicilline doit être abandonné. Une trousse d'urgence et des moyens de réanimation doivent toujours se trouver à portée de main et le malade doit être surveillé pendant au moins 30 minutes après l'administration de pénicilline. Les recommandations faites par un Comité d'experts de l'Organisation mondiale de la Santé concernant la prévention et le traitement des réactions à la pénicilline, tant sur le plan individuel qu'à l'échelon des administrations sanitaires, sont revisées en tenant compte des connaissances et expériences récentes.

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