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SENSITIVITY TO REPOSITORY PENICILLINS*†

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Introduction

Some side-reactions to penicillin have been observed since the antibiotic first came into general use during the closing stages of the second world war.

Commonly, the reactions are of a sensitivity type ranging from severe (sometimes fatal) anaphylaxis, as reported by Bell (1954), Carlquist and Pontius (1954), Christenson, Hedrick, and Schugmann (1953), Idsøe (1954), Kern and Wimberley (1953), and Nemser (1954), to serum sickness-type reactions with angioneurotic oedema, pains in the muscles, fluid in the joints, and urticaria. Others consist of skin reactions ranging from erythema simplex and multiforme to frank dermatitis. Pre-existing fungal eruptions may occasionally flare and trichophytid lesions may arise. There is also a risk of dermatitis in those who handle the drug. Given orally, there is the added possibility of gastro-intestinal reactions with sore mouth, black tongue, occasionally indigestion, nausea and vomiting, enteritis, and rectal soreness and irritation. These effects may arise from partial sterilization of the bowel leading to inefficient synthesis of vitamin B, and from the overgrowth of other organisms, including fungi, in the bacterial vacuum so created.

Of other effects reported, Batchelor, Horne, and Rogerson (1951) had eight cases of maniacal attacks with feelings of impending death among 2,699 injections of aqueous procaine penicillin. These were considered to have arisen from the procaine rather than the penicillin moiety of the compound. McLachlan and Brown (1947) reported menstrual disturbances in 91·3 per cent. of non-pregnant women, and other disturbances were noted during pregnancy, the puerperium, and the menopause. These findings have not since been substantiated and may have resulted from the impurities in the earlier penicillins then in use rather than from penicillin itself.

With the increasing use of penicillin, one would expect to find an increasing incidence of reactions as more persons become sensitized each year. In the 9 years after its introduction, Kekwick (1956), quoting Kutscher, Lane, and Segall (1954), noted that only two deaths from penicillin had been recorded, while fifteen were reported (usually from anaphylaxis) during the next 2 years. Serious reactions are reported as occurring in about 3 per cent. of patients. Bell (1956) stated that about one patient a month who was sensitive to penicillin was encountered at a North of England plastic unit. He expressed the opinion that about one patient in seven will eventually become sensitive to penicillin after repeated courses of the drug.

The incidence of reactions seems to vary with the type of penicillin used. Lepper, Dowling, Robinson, Stone, Brickhouse, Caldwell, and Whelton (1949), in an analysis of 1,303 patients treated with penicillin, found 1·2 per cent. of allergic reactions with aqueous crystalline penicillin G, 2·7 per cent. with penicillin in oil-beeswax, and only 1·4 per cent. with procaine penicillin. The incidence of reactions in some patients receiving a high dosage of aqueous penicillin was as high as 7·8 per cent., but apart from this the figures were inconclusive as to any relation between the dose and the number of reactions.

It has been feared in some quarters that long-acting penicillins may provide an additional hazard because of the risk of the continued and prolonged sensitivity reactions which could theoretically follow a single dose. Satisfactory evidence for or against this hypothesis is so far lacking, but reactions which

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are delayed in their appearance or more than usually prolonged are certainly uncommon. Certainly one would expect them to be relatively frequently reported from venereal disease clinics where long-acting preparations have been in continued and widespread use for many years.

Thomas, Landy, and Cooper (1948) reported no serious reactions in over 10,000 patients treated with penicillin (usually penicillin in oil-beeswax which was the first repository penicillin preparation). Treatment had to be stopped in only two cases, both on account of severe urticaria. Schafer (1954) made a comprehensive analysis of penicillin reactions in American venereal disease clinics. In the years 1946–1950, some 185,577 patients were treated with penicillin in 36 clinics with only 578 reactions (3·11 per 1,000), including two deaths. Of 70,037 patients treated during 1950–1952, only 56 (0·8 per 1,000) had severe reactions, and there were no deaths. On this evidence the problem would not appear to be an increasing one.

As a result of the increase in reported cases of anaphylactoid reactions in the years 1953–1954, a significant proportion of which were fatal, physicians in charge of 24 American centres cooperated in a study to investigate penicillin reactions (Smith, Cutler, and Price, 1955). During a 4-month period, 16,345 patients were treated: 75 per cent. with procaine penicillin with aluminium monostearate, 24 per cent. with benzathine penicillin, and only 1 per cent. with other penicillins. Only 109 patients reported reactions (6·7 per 1,000).

With the introduction of benzathine penicillin, first reported by Szabo, Edwards, and Bruce (1951), and the even more prolonged serum penicillin levels obtained dose for dose as compared with the earlier penicillins, the possibility of protracted allergic reactions has constantly been kept in mind. Subsequent events have not so far shown any increased danger in this respect. Fletcher and Knappett (1953), in the course of trials with benzathine penicillin, referred to this possibility and suggested that theoretically the incidence of sensitivity may be high, in view of the long-continued exposure of the patient to low and at times intermittent penicillin levels. O'Brien and Smith (1952) reported 1,377 cases of gonorrhoea treated with single doses of benzathine penicillin and suggested that the incidence of significant penicillin reactions was not greater than 0·3 per cent. Further, in a study of four patients who developed urticarial manifestations within 10 days of the injection, the reaction lasted only 2 to 3 days and cleared up while assayable penicillin was still present in the blood. They concluded that no direct relationship could be shown between the duration of the reaction and the use of penicillin injections which are capable of producing prolonged serum levels.

Stollerman and Rusoff (1952) gave 1,753 injections of benzathine penicillin to 135 children and eight adults for the prophylaxis of rheumatic fever. Urticaria in two cases and pruritus in two cases were transient and did not recur with further therapy. The most extensive series was reported by Smith, Kamp, Olansky, and Price (1956); the incidence of reactions with benzathine penicillin (in 7,109 patients) was only 2·39 per 1,000, and with procaine penicillin with aluminium monostearate it was 7·96 per 1,000. It was considered possible that the greater number of recorded reactions with procaine penicillin with aluminium monostearate was occasioned by the need for more injections of this preparation compared with benzathine penicillin. No significant differences were noted between the two penicillin preparations when single injections were given. Anaphylaxis to injected benzathine penicillin has rarely been reported. Grekin and O'Brien (1954) reported two cases, but to our knowledge no fatal case has so far been recorded.

Present Investigation

In view of the increasing use of repository penicillins following the introduction of benzathine penicillin, and in view of the awakened interest in penicillin reactions, it was thought worth while to record a decade of experience of penicillin reactions encountered in a venereal diseases clinic in Britain. The records of a clinic near London were examined retrospectively. Penicillin was first used in 1946 in the form of penicillin-in-oil-beeswax. Procaine penicillin in oil with aluminium monostearate was introduced during 1949 and has been in use until the present time. Various batches of the "Penidural" brand of benzathine penicillin were used in the period 1954–1956, and benethamine penicillin ("Benapen") was given to some patients during 1954 and 1955. The time covered by the investigation extends from 1946 until the end of August, 1956, during which a total of 7,947·4 mega units of repository penicillin was given intramuscularly in 7,300 injections to 895 patients (451 male and 444 female).

The data are reviewed according to the types of penicillin reaction, sex, age, diagnosis, number of injections, total dosage, duration of treatment, type of penicillin preparation, and year of reaction.

In the consideration of penicillin reactions, only those believed to be due to penicillin sensitivity are included. Jarisch-Herxheimer reactions have been excluded, of which two were noteworthy: one was an exacerbation of syphilitic nerve deafness during penicillin therapy which was considered to be a probable Herxheimer effect; the other was the occurrence of a fatal stroke in a known hypertensive patient aged 68 years which

followed within 24 hours of the first penicillin injection and which was regarded as possibly the result of Jarisch-Herxheimer reaction.

Also omitted from consideration have been local reactions. These were negligible with penicillin-in-oil-beeswax and with procaine penicillin with aluminium monostearate, but were not inconsiderable, both in degree and frequency, with some of the earlier British brands of benzathine and benethamine penicillin tested. These difficulties have now been overcome.

Patients experiencing local pain sometimes developed painful lumps and local erythema. Fever also was not uncommon during the first 24 hours and was usually associated with local pain. The fever might be sufficient to resemble influenza and cause the patient to stay away from work; it might be accompanied by an oral herpes. Such systemic reactions have not been encountered with recent batches of benzathine penicillin, and it is considered that they were due to local tissue irritation rather than to sensitivity to penicillin, for in most subjects further injections of benzathine or other repository penicillins were given without trouble. In the present series, such occurrences in patients who were allowed to continue penicillin treatment without antihistaminic drugs and who experienced no further trouble are not included as allergic reactions. They have been included, however, in those cases where no more penicillin was used, either because the reaction caused anxiety sufficient to justify withholding it, or because it was not medically necessary, or where antihistamines were given with subsequent injections.

TABLE I
REACTIONS TO PENICILLIN

	Type of Reaction	Male	Female	Total
Probable	Dermatitis	3	—	3
	Dermatitis, Urticaria, Oedema	—	1	1
	Urticaria (general)	8	4	12
	Urticaria (local)	1	3	4
	Urticaria, Oedema	3	—	3
	Asthma, Rash, Oedema	—	1	1
	Oedema	1	1	2
	Total	16	10	26
Possible	Dermatitis	—	3	3
	Rash	1	3	4
	Oedema	—	1	1
	Irritation	1	1	2
	Dyspnoea, Tetany	1	—	1
	Faintness	1	2	3
	Dizziness, Diarrhoea	—	1	1
	Nausea, Vomiting	—	2	2
	Total	4	13	17
Combined Total		20	23	43

Reactions Noted

A total of 43 patients (twenty males and 23 females) reported some reaction. In sixteen of the males the reactions were considered to be probably due to penicillin sensitivity and in four the association was "possible". The association was "probable" in ten of the females and "possible" in thirteen. The reactions are summarized in Table I.

"Probable" Reactions.—Four patients, three of whom were male, had frank dermatitis and in one the condition was preceded by urticaria and oedema. The fourth patient was an old lady aged 68, with a leg ulcer of 10 years' duration, who received ten injections of penicillin-in-oil-beeswax and developed urticaria 2½ months from the onset of treatment. Dermatitis supervened and became generalized, and admission to hospital proved necessary. She died of pneumonia while still in hospital 5½ months from the beginning of treatment. None of the three male cases with dermatitis, two of whom had leg ulcers, received more penicillin. Apart from the foregoing, twelve males and seven females (nineteen cases) had urticaria, which was local in four and generalized in fifteen. In three of these it was accompanied by oedema. In nine cases, seven of whom were male, it was possible to continue penicillin treatment combined with antihistamine drugs, which were administered once for every two injections; in the remainder, this course was not attempted. One male and one female showed oedema without other signs, and one female had oedema, a rash, and asthma. None of these had further penicillin.

"Possible" Reactions.—There were three cases of dermatitis in females, and in one the dermatitis was generalized. No more penicillin was given to this third patient, but the dermatologist, who was consulted afterwards, gave the opinion that the condition was that of nummular eczema and was probably not associated with the penicillin and bismuth she had received. In both the other cases penicillin was given later, at first with Benadryl and later without, and no further exacerbations of the dermatitis were noted.

There were four cases of rash, three of them in females. One, returning after a lapse from treatment, stated that she had had "measles" and was given no more penicillin. In two others, further penicillin treatment was not attempted, but in one female case further penicillin was given without antihistamines and without any trouble. There were two cases of irritation, one in each sex. The female case received more penicillin without antihistamines, with no ill-effects. There was also one female patient with swollen fingers who received more penicillin with Benadryl but with no further trouble.

One male patient exhibited an odd reaction after the second injection of benzathine penicillin; he developed dyspnoea which continued until he called

in his doctor on account of tetanic cramps. It is likely that there was considerable psychological overlay in this case, but the risk of a further injection was not taken as his medical condition did not warrant it.

Three patients (two female) fainted the same evening after single injections of benzathine penicillin. One felt sufficiently ill to return to the casualty department after clinic hours. The fainting did not occur in anyone in the clinic or in the environs of the hospital and none received further penicillin. This group offers the nearest to anaphylactoid reactions encountered in the entire series. In addition, one female had nausea 1½ hours after treatment and another felt dizzy and had diarrhoea for 3 days, both after single injections of benzathine penicillin. It is unlikely that either of these two cases would have been noted had reactions to this brand of penicillin not been intensively studied at this time; it is doubtful, therefore, whether the reactions were significant. There was, however, no necessity to treat them further to test this hypothesis. Another female, who was pregnant, experienced vomiting after two injections of procaine penicillin with aluminium monostearate, but was able to tolerate further injections of aqueous procaine penicillin and of benethamine penicillin without any ill-effects. It is likely that the sickness in this case was functional. It is probable that many of these cases did not represent penicillin allergy at all, but were merely the results to be expected after any injection in psychologically-sensitive persons.

TABLE II

REACTIONS RELATED TO SEX, AGE, DIAGNOSIS, NUMBER OF INJECTIONS, TOTAL DOSAGE, DURATION OF THERAPY, PREVIOUS PENICILLIN ADMINISTRATION, AND TYPE OF PENICILLIN (BY PATIENTS)

No. of Patients Treated			No. of Reactions		Reactions (per cent.)	
			Probable	Total	Probable	Total
Sex	Male	451	16	20	3·6	4·4
	Female	444	10	23	2·3	5·2
	Total	895	26	43	2·9	4·8
Age (yrs)	0–20	156	0	1	0	0·6
	21–30	370	11	14	3·0	3·8
	31–50	263	8	17	3·0	6·5
	Over 50	106	7	11	6·6	10·4
	Total	895	26	43	2·9	4·8
Diagnosis	Syphilis	366	24	33	6·6	9·1
	Gonorrhoea	207	0	0	0	0
	Other Conditions	322	2	10	0·6	3·0
	Total	895	26	43	2·9	4·8
No. of Injections	One Only	383	2	6	0·5	1·6
	2–4	128	3	6	2·3	4·7
	5–9	127	10	12	7·9	9·5
	10–19	143	7	12	4·9	8·4
	20 and Over	114	4	7	3·5	6·1
	Total	895	26	43	2·9	4·8
Dosage (mega units)	1	331	0	0	0	0
	1·0–5·9	246	13	20	5·3	8·1
	6·0–11·9	106	6	10	5·7	9·4
	12·0–19·9	90	6	9	6·7	10·0
	20 or More	122	1	4	0·8	3·3
	Total	895	26	43	2·9	4·8
Duration of Therapy (yrs)	<1	725	19	30	2·6	4·1
	1–2	74	2	4	2·7	5·4
	2 and Over	96	5	9	5·2	9·4
	Total	895	26	43	2·9	4·8
Previous Penicillin Therapy	Yes	111	4	6	3·6	5·4
	No	784	22	37	2·8	4·7
	Total	895	26	43	2·9	4·8
Type of Penicillin	POB	320	9	11	2·8	3·4
	PAM	520	16	27	3·1	5·2
	Benzathine	225	4	14	1·8	6·2
	Benethamine	52	0	3	0	5·8

TABLE III

REACTIONS RELATED TO SEX, TYPE OF PENICILLIN, AND YEAR OF OCCURRENCE (BY INJECTIONS)

		No. of Injections	No. of Reactions		Reactions (per cent.)	
			Probable	Total	Probable	Total
Sex	Male	3,606	16	20	0·4	0·6
	Female	3,694	10	23	0·3	0·6
	Total	7,300	26	43	0·4	0·6
Type of Penicillin	POB	2,044	9	11	0·4	0·5
	PAM	4,343	16	27	0·4	0·6
	Benzathine	797	4	14	0·5	1·8
	Benethamine	116	0	3	0	2·6
Year of Occurrence	1946	43	—	—	—	—
	1947	637	—	—	—	—
	1948	835	5	5	0·6	0·6
	1949	658	2	2	0·3	0·3
	1950	897	3	7	0·3	0·8
	1951	608	1	3	0·2	0·5
	1952	640	2	3	0·3	0·5
	1953	655	2	2	0·3	0·3
	1954	860	5	7	0·6	0·8
	1955	718	3	6	0·4	0·8
	1956	749	3	8	0·4	1·1
	Total	7,300	26	43	0·4	0·6

Analysis of Data

The reaction rate in the whole series lay between 2·9 and 4·8 per cent. of patients (Table II, previous page) and between 0·4 and 0·6 per hundred injections (Table III).

The reaction rate in males was between 3·6 and 4·4 per cent. of patients, and in females it was between 2·3 and 5·2 per cent. (Fig. 1). In other reported series, *e.g.*, Smith, Cutler, and Price (1944–55), a greater incidence of reactions has been reported in females than in males. Our own data are inconclusive in this respect.

Penicillin sensitivity must be related to the number of exposures to the drug. The number of injections of repository penicillin given varied widely. Many received only a single injection and the majority of these were not observed for long periods of time, 3 months being the usual maximum. The largest number given to any one patient was 117 over a 9-year period. The incidence of reactions was low after single injections (1·6 per cent. total reactions; 0·5 per cent. "probable"), but increased with the number of injections up to nine (Table II; Fig 2).

The incidence apparently declined a little at twenty injections or over.

Similar trends were naturally noted in respect of dosage (Fig. 3, overleaf). No reactions were noted with a dosage of less than one mega unit, the bulk being found in the 1·0–19·9 mega units range, with a marked fall thereafter, by which time most of the sensitivity likely to occur had probably declared itself. The greatest quantity of penicillin received by any one patient was 160·4 mega units.

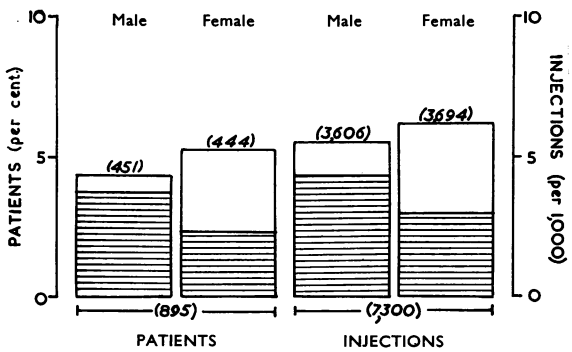

FIG. 1.—Relation of penicillin reactions to sex.

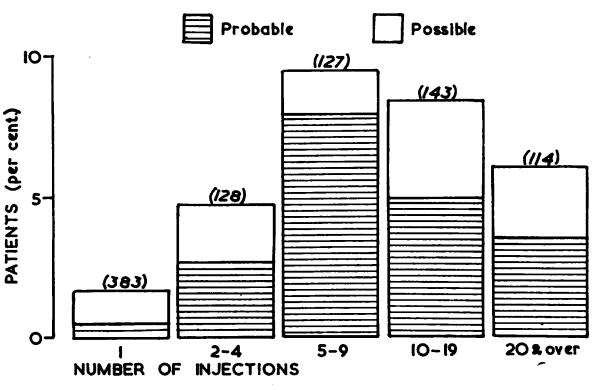

FIG. 2.—Relation of penicillin reactions to number of injections (in 895 patients).

Similarly, the incidence of reactions was also noted to increase with the duration of therapy, 2·6 per cent. having "probable" reactions with periods of treatment of less than 1 year, increasing to 5·2 per cent. of patients with periods exceeding 2 years (Fig 4).

Information was incomplete, especially during the earlier years, concerning penicillin administered to patients before their arrival at the venereal diseases clinic, except in respect of previous venereal diseases. The incidence of "probable" reactions in those previously known to have had penicillin was 3·6 per cent. of patients, compared with 2·8 per cent. of those not known to have had penicillin (Fig. 5, opposite). However, 170 patients were given treatment, often intermittently, over periods of a year or more, and those of this group, who had in fact received previous treatment, showed a much higher rate of reaction than those treated for less than one year.

When the reactions were related to diagnosis, none was noted in 207 patients with gonorrhoea who usually received only a single injection, but in 366 patients with syphilis there were 6·6 per cent. of "probable" reactions (Fig. 6, opposite). Those treated for other conditions, a greater number of whom frequently had more than one injection compared with the gonorrhoea patients, occupied an intermediate position with 0·6 per cent. of "probable" reactions. Syphilitics, by the nature of their disease, received more injections and more courses of injections over much longer periods of time than those of the other two groups.

Particularly striking was the tendency of patients with leg ulcers to show reactions; this was doubtless occasioned in many cases by sensitivity induced by topical applications, including penicillin. In males, four of the "probable" reactions and one "possible" reaction occurred in patients with leg ulcers, four of them syphilitics. Two female syphilitics with "probable" reactions also had leg ulcers, and one with a "possible" reaction, who was also a diabetic, had an open lesion from cellulitis. In addition, another female with a "possible" reaction had lesions of the calf resembling erythema induratum. Thus, no less than nine of the 43 patients showing some reaction had ulceration of the legs (20·9 per cent.). Six (25 per cent.) of the 24 "probable" reactions in syphilitics were in persons with leg ulcers, a proportion far in excess of the proportion of leg ulcers in the syphilitic patients as a whole. Indeed, there were few patients with ulceration of the legs who escaped penicillin sensitivity.

When the incidence of reactions was related to age, it was found that there were no reactions in patients under the age of 20, and that from 21–50 years, the incidence remained at 3 per cent.; over the age of 50, it rose to 6·6 per cent. (Fig. 7, opposite).

Patients in the last group, however, were usually late or latent syphilitics who had had many injections, often in repeated courses. There were, therefore, very few instances of single injections, as for the gonorrhoea patients.

As the years go by, more and more persons in a given population will have received penicillin and increasing numbers are likely to have become sensitized. In the present series of 7,300 injections of repository penicillin, 6,515 (89·2 per cent.) were given to patients who had previously had penicillin. The percentage was lowest in 1946 (30·2 per cent.), which was the first year of its use in the clinic. In 1947 it was 81·6 per cent. and thereafter ranged between 88·1 and 94·3 per cent. When related to the year of occurrence, the incidence of "probable" reactions, which was zero until the third year of

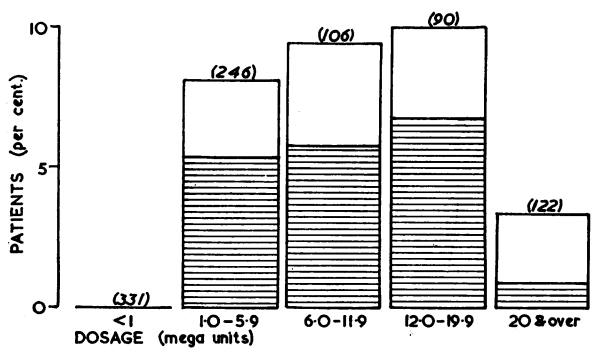

FIG. 3.—Relation of penicillin reactions to dosage (in 895 patients).

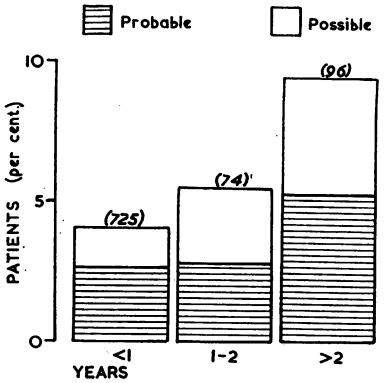

FIG. 4.—Relation of penicillin reactions to duration of therapy (in 895 patients).

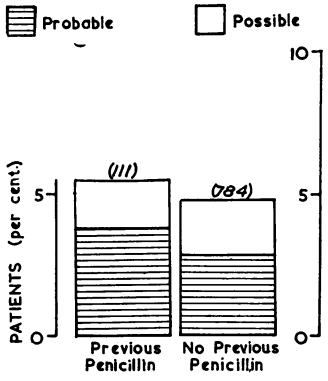

FIG. 5.—Reactions to penicillin related to previous penicillin administration (in 895 patients).

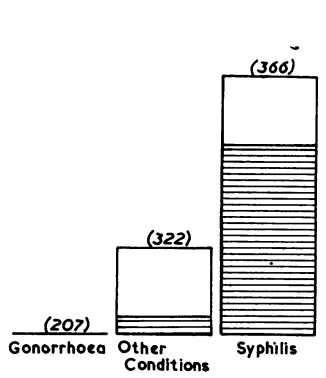

FIG. 6.—Relation of penicillin reactions to diagnosis (in 895 patients).

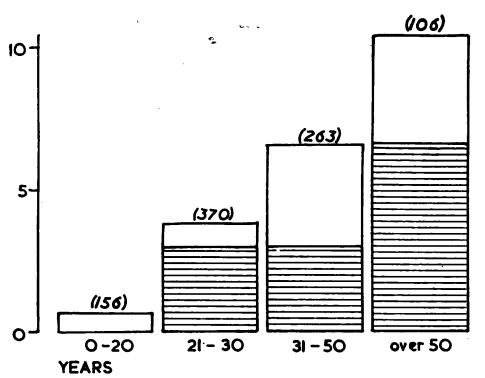

FIG. 7.—Relation of penicillin reactions to age (in 895 patients).

penicillin usage, has not substantially increased since (Table III; Fig. 8). If the "possible" reactions are considered, there was a tendency for these to become more frequent in the years 1954–1956, but there has been an increasing awareness of the possibility of penicillin sensitivity and, therefore, more conscientiousness in noting "possible" reactions during these years, especially as alternative antibiotics have been available for use should the occasion arise. Even so, the highest figure of "possible" reactions in 1956 was only 1·07 per cent. of injections.

An attempt has also been made to relate the incidence of reactions to the type of penicillin used (Table III). During the period 1946–1950, some 1,146·9 mega units penicillin-in-oil-beeswax were given in 2,044 injections to 320 patients. In the period 1946–1956 a larger total of 5,686·5 mega units procaine penicillin with aluminium monostearate was given in 4,343 injections to 520 patients. Penidural was given to 225 patients in 797 injections, to a total of 962·7 mega units during the years 1954–1956. Benethamine penicillin was used to a limited extent during 1954–1955 in 116 injections to 52 patients, to a total of 151·3 mega units. The reactions have been related to the type of penicillin by injections (Table III) and by patients (Table II; Fig. 9). As a number of patients received one or more different penicillins, all are counted for each preparation rather than attempting to decide which were actually sensitized. When the "probable" reactions alone are considered, there is little to choose between the incidence of sensitivity with the four preparations tested (a range of 0·4–0·5 per cent. of injections). Differences when the "probable" and "possible" reactions are combined are likely to have arisen from the more intensive study of the problem in recent years.

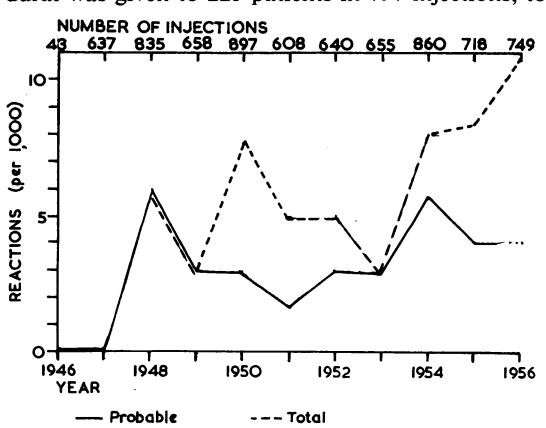

FIG. 8.—Rates per thousand injections of penicillin reactions by year of occurrence.

Summary and Conclusions

(1) A retrospective study has been made of the side-effects observed after the administration of 7,300 injections of four repository penicillins: penicillin-in-oil-beeswax, procaine penicillin with aluminium monostearate, benzathine penicillin

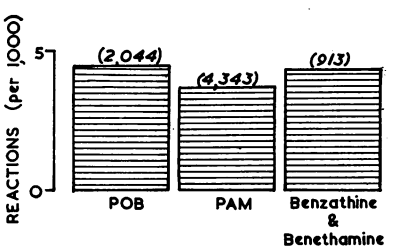

FIG. 9.—Probable reactions to penicillin related to type of penicillin (7,300 injections).

("Penidural"), and benethamine penicillin, given to 895 patients during an 11-year period in a venereal diseases clinic near London. The over-all incidence of "probable" reactions was 2·9 per cent. of patients and 0·4 per cent, of injections. If all "possible" reactions are included, the figures are 4·8 and 0·6 per cent. respectively.

(2) The incidence of reactions was directly related to the number of injections and also to the dosage of penicillin. The incidence of reactions was low after single injections but increased with the number of injections up to nine, after which there was an apparent fall. Similar trends were noted as regards dosage, there being no reactions with a dosage of less than one mega unit and a marked fall after twenty injections had been given.

(3) The incidence was also noted to increase with the duration of therapy (and therefore with the number of injections) and to be related to previous penicillin administration.

(4) In a venereal diseases clinic the reactions also tend to be related to diagnosis. Patients with syphilis who receive many injections of penicillin have more reactions than gonorrhoea patients who usually have but one injection. Similarly, there is an apparent relationship with age, for gonorrhoea patients who have only one injection (and therefore experience few reactions) are young, whereas many of the older patients have many injections (and therefore a greater incidence of reactions) for late and latent syphilis, which is relatively less common in the young.

(5) Particularly prone to sensitivity were patients with leg ulceration, with their greater opportunity for sensitization from topical application of penicillin.

(6) One might have expected an increased incidence of reactions with the years, but this has not been the case in this series, if only the "probable" reactions are considered.

(7) Similarly, there has been no significant difference in the incidence of "probable" reactions between penicillin-in-oil-beeswax, procaine penicillin with aluminium monostearate, benzathine penicillin (Penidural), and benethamine penicillin. Certainly no evidence has so far been forthcoming of unusually prolonged or delayed reactions after the use of long-acting penicillins.

(8) One fatality was noted in the series. This was due to bronchopneumonia complicating dermatitis after penicillin-in-oil-beeswax. No unequivocal cases of anaphylactoid reaction were observed.

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ANNOUNCEMENT

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The notes and photographic material referring to 100 of the cases presented at the Congress are to be published in book form as an extra supplement to *Acta Dermato-Venereologica*, not included in the ordinary subscription rate. Prof. Marion B. Sulzberger, M.D., and Prof. Sven Hellerström, M.D., have consented to write forewords to the book, which is expected to be ready in January, 1958.

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