The cutaneous anthrax occurred in bone-meal workers. The first patient developed a typical malignant pustule on the left side of his neck. He responded satisfactorily to penicillin V, 120 mg. five times daily for 15 days. The second patient developed a pustule just above his right loin. The constitutional upset was considerable. He had been given 1 mega unit of intramuscular crystalline penicillin just before admission. Thereafter he was treated with penicillin V, 250 mg. four times daily. His fever settled after three days, but, as is known to occur also with intramuscular penicillin (Banks, 1951), the sore continued to develop for five to six days after treatment started. The necrosis was extensive, but healing was complete after six weeks.

An adult male developed pyaemia from a sore on one finger. He was severely ill on admission, and had symptoms and signs suggestive of perinephric abscess. His response to penicillin V was rapid.

Comment

The advantages of the oral route are indisputable. The distress of children when subjected to injection is avoided, and the possibility of sepsis is reduced. The use of compressed tablets or, better still, sealed capsules obviates the occurrence among nursing staff of sensitization reactions. Penicillin can be given without precipitating paralysis by intramuscular injection in those with latent poliomyelitis infection. Also a great deal of time is saved; this is particularly important in small hospitals, such as this, where effective running depends very much on the quality of a small nucleus of trained staff and a large number of untrained orderlies. Finally, there is no significant difference in the cost between penicillin V and the various forms of penicillin G which are injected. Whilst the other oral forms of penicillin G are no more expensive, it must not be forgotten that it is recommended that these preparations should be given in doses four or five times greater than that required intramuscularly. This is not the case with oral penicillin V. Our use of the drug over an extended period has produced results no less satisfactory than those obtained when penicillin was previously given intramuscularly, and we have been able to enjoy all the considerable advantages of oral therapy.

Summary

In the twelve months ended October, 1956, 110 cases were treated with oral penicillin V. Of these, 100 were cases of pulmonary infections. Cases which were wholly untreated before admission are given in greater detail. Penicillin was regarded primarily as an oral drug like the tetracyclines and chloramphenicol, and the results appear to justify that policy.

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Over 50 members of the medical section of the Library Association attended a week-end conference in Edinburgh from June 28 to July 1. Members were the guests of the University at a dinner presided over by Professor J. H. GADDUM, F.R.S., after which they were shown some of the medical treasures of the library, including the Harvey tercentenary exhibit. Visits paid to the libraries of the Royal College of Physicians, Royal College of Surgeons, Royal Medical Society, and the Central Medical Library were a reminder that Edinburgh has one of the richest collections of medical literature in the Commonwealth. Other places visited included the National Library of Scotland and the Royal Society of Edinburgh, where the extensive collection of Slavonic and Oriental periodicals of medicine and science were of special interest.

A TRIAL OF PENICILLIN V

RESPONSE OF PENICILLIN-RESISTANT STAPHYLOCOCCAL INFECTIONS TO PENICILLIN

BY

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Many patients with staphylococcal sepsis are seen in a busy out-patient department. When the sepsis is serious enough to warrant treatment with an antibiotic, it has been the practice in this hospital to give penicillin by injection. Penicillin has not often been given by mouth because of doubts of its absorption from the alimentary tract, although the use of oral penicillin would save nurses' time, and would be preferred by the majority of patients. Penicillin V (phenoxymethylpenicillin) is more stable in an acid medium than penicillin G, and, probably because of this, blood levels reached after giving penicillin V by mouth are higher and better sustained than those from an equivalent oral dose of penicillin G (Rinsler and Cunliffe, 1956; *British Medical Journal*, 1956).

This paper records the results of a trial carried out in the casualty department of this hospital. The object of the trial was to determine the reliability of oral penicillin V in the treatment of staphylococcal sepsis by comparing its efficacy with that of penicillin by injection. During the trial observations were made on the response to treatment with penicillin of infections due to resistant (penicillinase-producing) staphylococci.

Methods

The trial involved 346 patients attending the casualty department with infections principally due to staphylococci. All except eight were seen by one of us (J. I. B.), and all had septic lesions which were thought to need treatment with penicillin. In general, except for boils on the face, which were always treated with chemotherapy, boils and other minor infections were not treated unless accompanied by appreciable lymphangitis or lymphadenitis. Patients with septic fingers were not included. The series also did not include patients attending other departments such as those of the ear, nose, and throat or the skin. So far as was possible swabs were taken from the patients when first seen, or when the lesion was incised.

In determining how the patients should be allocated to the two treatment groups it was not thought practicable to adopt any method which involved frequent alteration in the routine, and accordingly patients were treated in alternate periods of six weeks by injection or penicillin V by mouth, any local treatment being the same in both groups. There was clearly no question of withholding the nature of the treatment from the patient or the person assessing the results. In common with others we have not thought it justifiable to treat a comparable series of patients without chemotherapy, and there is therefore no control group against which to judge the efficacy of either form of penicillin. We can only compare them with each other.

Patients treated by injection received a single daily dose of 1 ml. of " abbocillin 800 M," which contained 600,000 units of procaine penicillin and 200,000 units of crystalline penicillin G. Those given penicillin V were instructed to

swallow two capsules, each containing 125 mg. of the drug, before each of the three main meals of the day. So far as we could tell, the patients complied with these instructions. Taking both series of patients together, 218 were treated for five days, 10 for more than five days, and 82 for less than five days. Of the latter group, 68 were patients whose lesions healed in two to six days. Except for Sundays, all the patients were seen by one of us daily for the first three days. After that, patients receiving penicillin by injection were seen daily until their course was complete. They were then seen at one- or two-day intervals until discharged. Patients receiving oral penicillin differed only in that some were not seen on the fourth and fifth days.

Laboratory Methods—Cultures were made on blood-agar plates from which two cups had been cut with a cork-borer. After inoculation these cups were filled with penicillin (10 units/ml.) and tetracycline (50 μg./ml.). The sensitivity of the organism isolated was thus determined in primary culture, penicillinase production being noted by the method described by Waterworth (1948). Staphylococci which coagulated plasma in a tube were called *Staphylococcus pyogenes*.

TABLE I.—*Comparison Between the Two Treatment Groups and Between Cases with Sensitive and Resistant Staphylococci*

	Total	Treatment		*Staph. pyogenes* Infections	
		Intramuscular Penicillin	Oral Penicillin	Sensitive	Resistant
Total No.	346	179	167	173	66
Course not completed	28	16	12	7	5
Transferred to oxytetracycline	8	3	5	4	2
No. available for analysis	310	160	150	162	59
Male	237	117	120	126	45
Female	73	43	30	36	14
Age range	6–74	6–74	8–71	6–73	9–63
Age mean	*35·8*	*36·0*	*35·5*	*36·0*	*32·9*
History of symptoms (days):					
Range	1–14	1–14	1–14	1–14	1–13
Median	*3*	*3*	*3*	*4*	*3*
Temperature 99° F. (37·2° C.) or more	130	59	71	74	28
Diagnosis:					
Boil	106	56	50	60	24
Abscess	63	32	31	37	14
Carbuncle	80	33	47	55	19
Infected wound	27	16	11	8	2
Primary cellulitis	23	15	8		
Other[1]	11	8	3	2	—
Complications[2]:					
Cellulitis	35	21	14	22	7
Lymphangitis	38	18	20	20	3
Lymphadenitis	185	83	102	111	34
None	94	61	33	31	19
Size of lesion[3]:					
Less than 5 sq. cm.	107	46	61	53	22
5 sq. cm.	97	52	45	52	21
10 ,,	51	26	25	34	8
20 ,,	22	14	8	11	4
30 ,,	33	22	11	12	4
Median	*6*	*7*	*6*	*7*	*5*
Incised	78	51	27	43	21
Not incised	232	109	123	119	38
Bacteriology[4]:					
Staph. pyogenes—sensitive	167	73	94	Penicillin	
,, ,, —resistant	60	31	29	Inj. 71	31
Other organism	13	7	6	Oral 91	28
Sterile	19	12	7		
No swab	57	39	18		

[1] Erysipeloid, 8; pustule, 3.
[2] More than one complication may be recorded for each patient.
[3] The length multiplied by the breadth of the area of induration.
[4] Including 6 cases where another organism was found in association with a staphylococcus.

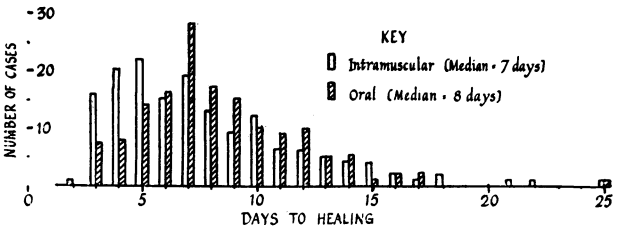
Results

Twenty-eight patients did not complete treatment, and eight others failed to respond to penicillin and were treated with oxytetracycline. These patients were well balanced between the two treatment groups and there is no reason to suppose that their exclusion from the subsequent analysis is likely to have biased the results. As shown in Table I, within broad limits, the two series were comparable in respect to the characteristics which were recorded. It should be noted that the size of the lesion has been calculated by taking the area of induration and multiplying the "length" by the "breadth." In view of the fact that size has been recorded for comparison, it was not thought worth considering a more mathematically exact method.

One point that calls for comment is the increased frequency with which lesions in patients receiving penicillin by injection were incised as compared with the lesions in the oral group (51 or 32%, as compared with 27 or 18%). Lesions were incised only when it was thought necessary, and during the trial there was no conscious selection of patients for incision in the two groups. We can only account for the increased frequency of incision by relating it to the fact, already mentioned, that probably more of the patients receiving injections were seen on the fourth and fifth days of treatment.

Comparison of Results of Treatment in the Two Groups

The main criterion used in judging the response to treatment was the time taken from the beginning of treatment until the lesion healed. Table II shows that, to begin with, the injection group did better, 36.8% being healed by the fifth day, as compared with 19% of the oral group. This difference can be shown to be significant, but in view of the possible sources of bias, including the fact that the patients in the oral group may have been seen less often, it is doubtful if much reliance can be placed on such a finding. Probably of more importance is the finding (see Chart) that the difference in healing-time is soon evened out, 79% of the injected group being recorded as healed by the tenth day as compared with 77% of the oral group. Even if this represents the natural healing rate uninfluenced by



Comparison of healing-time between the two treatment groups.

TABLE II.—*Time of Healing for Two Treatment Groups and for Sensitive and Resistant Staphylococci*

	Total	Days to Healing																	Median
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16–20	21–25	
Intramuscular penicillin:																			
Incised	51	—	—	1	1	5	5	5	3	3	5	4	4	3	3	4	3	2	*10*
Not incised	109	—	1	15	19	17	10	14	10	6	7	2	2	2	1	—	2	1	*6*
Total	160	—	1	16	20	22	15	19	13	9	12	6	6	5	4	4	5	3	*7*
Oral penicillin:																			
Incised	27	—	—	—	—	—	3	4	6	1	3	1	2	3	2	—	1	1	*9*
Not incised	123	—	—	7	8	14	13	24	11	14	7	8	8	2	3	1	3	—	*7*
Total	150	—	—	7	8	14	16	28	17	15	10	9	10	5	5	1	4	1	*8*
Sensitive staphylococci	162	—	—	2	8	12	22	27	19	19	9	11	9	5	6	3	8	2	*8*
Resistant ,,	59	—	—	—	3	11	4	12	5	3	8	—	5	3	2	1	—	2	*7*

chemotherapy, it does suggest that patients treated with oral penicillin V are not more likely to have prolonged healing-times than those treated by injection. The comparison between the two methods of treatment still holds good if separate types of lesions or lesions of different sizes are analysed separately.

The figures given in Table II for the time to healing of the incised cases show, as might be expected, that these cases are slower to heal. Only 7 out of the 78 cases in the two groups were healed in five days. The slightly better results attributed to the injection method in the first days of treatment cannot therefore be due to the fact that these cases were more often incised.

Results of Treating Infections Due to Penicillin-resistant Staphylococci with Penicillin

Table I shows that the trial included 66 patients infected with penicillin-resistant strains of *Staph. pyogenes*, who were included because, once the decision to treat a patient with penicillin had been made, it was adhered to despite laboratory reports of resistance. They were distributed evenly between the two treatment groups and can hardly have influenced the results already discussed. For comparison with previous findings in this casualty department, after subtracting numbers of the staff, of 218 patients with staphylococci, 55 or 25% were infected with penicillin-resistant strains of *Staph. pyogenes*.

In the last two columns of Table I these patients are contrasted with 173 infected with penicillin-sensitive staphylococci. The resistant group can be seen to have a slight excess of patients failing to complete treatment, of patients transferred to oxytetracycline, of cases treated by injection, and of short-history uncomplicated cases. The numbers involved are small, but, although all these factors might be associated with a good response to treatment, we do not consider that the disparity is sufficient to account for the results obtained (Table II). In whatever manner these figures are analysed, there is no great difference in the healing-time between infections due to penicillin-resistant staphylococci and those due to sensitive staphylococci.

In view of the controversial nature of this finding, we examined the possibility that a difference between the sensitive and resistant group might emerge, using a different criterion—time to relief of complications. Table III shows

TABLE III.—*Time to Relief of Complications for Cases with Sensitive and Resistant Staphylococci*

Staphylococci	Total	Days to Relief of Complications*										Not Known
		1	2	3	4	5	6	7	8	9	Median	
Sensitive ..	136	10	23	36	23	13	5	2	1	—	*3*	23
Resistant ..	43	—	6	7	12	2	—	4	1	1	*4*	10

* Time to absence of tenderness for lymphadenitis and disappearance of redness for lymphangitis and cellulitis.
Note.—This table is based on all cases (including some "defaulters") for whom complications were recorded.

a slight advantage for the sensitive group, a median of three days compared with four days. Although it is difficult to interpret these results in view of the number of cases where the information was not recorded and the difficulty of deciding when complications were relieved, there is certainly no evidence of any marked difference between the two groups. A similar analysis of the two treatment groups showed no appreciable difference between them.

Discussion

Our results suggest that patients with staphylococcal sepsis treated with oral penicillin V respond almost as well as those treated with penicillin by injection, and that it makes very little difference if the infecting staphylococcus is a penicillinase-former—that is, a conventional resistant staphylococcus—or not. Before accepting these conclusions the reservation must be made that, as has been said, the trial contains no proper control series of patients untreated with an antibiotic. It is our firm impression that cases of infection thought serious enough to be treated with penicillin, and therefore included in this series, undoubtedly do improve faster with penicillin than when left untreated, and that complications occur less often. But we have no proof.

If the validity of these results is accepted, the finding that for practical purposes penicillin V by mouth is as effective as injection of a mixture of procaine and crystalline penicillin is not surprising in view of the reliable way in which penicillin V is absorbed. In severe illness the prescription of penicillin by injection means that the patient receives the drug with certainty: injection, however, takes time, and the cost of washing and replacing syringes is appreciable. For conditions usually treated in the out-patient department it would seem that penicillin V can be relied on to work as efficiently, with a saving of time and money.

Unless the conditions treated would have got better as quickly if left alone, it is difficult to avoid the conclusion that infections of the skin and subcutaneous tissue due to penicillin-resistant staphylococci respond as well to penicillin as those due to penicillin-sensitive staphylococci.

We may have been misled by the small size of the groups, and several factors in favour of the resistant group have been mentioned. That the finding is a real one is suggested by experience in the past with individual patients and by the results in Table II, particularly the absence of patients with long-delayed healing.

If true, the response of other forms of resistant staphylococcal infection to penicillin will presumably depend on the way in which penicillin is able to act on resistant organisms. Staphylococci are normally thought to be resistant because they form penicillinase, an enzyme which destroys penicillin, and it might be argued that the present findings are the result of treating resistant staphylococci which made penicillinase feebly and slowly. There is no easy or rapid method of assessing the rate of penicillinase formation, but our experience with 400 strains of staphylococci in the past (Birnstingl, Shooter, and Hunt, 1952; Rees, Shooter, and Shawe, 1955) has shown that penicillin-resistant staphylococci isolated from out-patients include staphylococci with a wide range of *in vitro* resistance to penicillin, and, incidentally, has confirmed the value of Waterworth's (1948) method of detecting penicillinase formation in primary culture.

In the test-tube many resistant staphylococci can thrive in the presence of high concentrations of penicillin. What is observed in the laboratory is of course bacterial growth, and it is conceivable that although penicillin-resistant staphylococci can grow in the presence of penicillin they are unable to form essential toxins. An explanation of this sort would explain the effect of penicillin on resistant staphylococci in the body. A more probable answer may be that, in most soft-tissue infections of the kind we have been treating, the centre of the lesion is in any case uninfluenced by penicillin. If in this type of infection the action of penicillin is confined to eradicating staphylococci at the edge of the infection, the relatively low amounts of penicillin in the blood may be able to deal with the small number of resistant staphylococci in this situation.

Much has been made in recent years of the increase of penicillin-resistant staphylococci. If others confirm our findings, it would appear that penicillin is still adequate for the treatment of most staphylococcal sepsis. Other antibiotics are indicated only if the clinical condition merits their use, and should not be solely dependent upon a laboratory report of an *in vitro* penicillin-resistant organism.

Summary

Penicillin V by mouth has been found to be almost as satisfactory as penicillin by injection in the treatment of staphylococcal sepsis. Infections due to penicillin-resistant staphylococci have apparently responded as well

to treatment with penicillin as infections due to sensitive staphylococci. If these observations are confirmed, it suggests that penicillin is still adequate for the treatment of most forms of staphylococcal sepsis seen in out-patients.

We are indebted to Eli Lilly and Company Limited for the supply of penicillin V.

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INFLUENCE OF CORTISONE ON TERATOGENIC EFFECTS OF HYPERVITAMINOSIS-A

BY

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The important part which environmental factors may play in influencing the occurrence of congenital malformations is becoming recognized as a result of animal experiments in which the dams have been subjected during pregnancy to the effects of a wide variety of teratogenic agents. Amongst the substances whose teratogenic importance is now well established is vitamin A: both hypovitaminosis-A and hypervitaminosis-A in the mother have been shown to result in the birth of young with anomalies of the brain and its coverings. Congenital hydrocephalus has been reported in the offspring of animals fed on a vitamin-A-deficient diet (rabbits—Millen, Woollam, and Lamming, 1954; rats—Rokkones, 1955). In rats, maternal hypervitaminosis-A is known to produce anencephaly, exencephaly, and hydrocephalus in the young (Cohlan, 1953; Giroud and Martinet, 1954).

The investigation reported in the present communication was undertaken to explore the effect of cortisone, administered during pregnancy, upon the incidence of deformities of the brain and calvaria produced by hypervitaminosis-A.

Material and Methods

Female white rats of the Wistar strain were used in the experiments. Each of these rats had previously given birth to a normal litter. At the beginning of the experiment the rats were given 2,000 I.U. of vitamin D and 50 mg. of vitamin E by mouth to ensure that they had an adequate supply of these vitamins.

Daily vaginal smears were taken at 9 a.m. and conception was determined by the presence of spermatozoa. The day on which spermatozoa were found was regarded as Day 1 of the pregnancy. The pregnant rats were divided into three groups, each group consisting of 12 animals.

Group 1 received 60,000 I.U. of vitamin A acetate daily from the 8th to the 13th day, inclusive, of pregnancy.

Group 2 received 20 mg. of cortisone acetate daily from the 9th to the 12th day, inclusive, of pregnancy.

Group 3 received 60,000 I.U. of vitamin A acetate daily from the 8th to the 13th day, inclusive, and 20 mg. of cortisone acetate from the 9th to the 12th day, inclusive, of pregnancy.

Vitamin A was given by intubation. A rubber No. 8 French catheter was passed into the stomach and the dose of vitamin A dissolved in 1 ml. of arachis oil was introduced. The procedure was repeated on the appropriate days. Cortisone acetate was given by subcutanous injection.

The rats were killed on the 20th day of pregnancy and the young removed from the uterus. The foetuses were inspected for abnormalities and preserved in 10% formalin for further examination. Various deformities were encountered in the young, but only those affecting the brain and the calvaria are considered in this communication.

Findings

The results of the experiments are shown in the Table. It will be noted from this that the number of young in group 3 is much smaller than in the other two groups.

Incidence of Deformities of the Brain and Calvaria Found in the Young

Group	No. of Rats	Total No. of Young	No. of Young with Deformity of Brain and Calvaria	Percentage of Young with Deformity of Brain and Calvaria
1	12	77	6	7·8
2	12	73	0	0
3	12	41	15	36·6

This was due to the resorption of all the young in three animals, and of many of the young of another four animals. Total resorption also occurred in two of the rats in group 2.

Varying degrees of malformation were encountered and are shown in the illustration. In some animals the deformity was in the nature of a small meningocele associated with a marked acrocephaly, whilst in others there appeared to be a complete extroversion of the cerebral hemispheres, so that the chorioid plexuses were exposed on the surface of the brain. In the latter animals the amniotic fluid was invariably tinged with blood pigment.

The various degrees of deformity of the brain and calvaria (actual size).

Discussion

The most significant finding which emerges from this experiment is that cortisone given to hypervitaminotic rats on the 9th to 12th days produces a great increase in the number of young, surviving on the 20th day, which show malformations of the brain and calvaria (36.6%).

It is well known that hypervitaminosis-A in rats results in malformations of the brain and calvaria in their young. As has been stated earlier, anencephaly and exencephaly have been reported by Cohlan (1953) and by Giroud and Martinet (1954). Cohlan (1954) obtained young with a congenital cranial anomaly in 48.7% of the foetuses by giving 35,000 I.U. of vitamin A daily from the 2nd or 4th day to the 16th day of pregnancy. Giroud and Martinet (1956) observed a 6% incidence in the young of rats which had received 20,000 I.U. of vitamin A daily for 12 days from the 2nd or 4th day of pregnancy. The incidence of 7.8% young with gross deformities of the brain and skull obtained in group 1 of the present experiment (rats which received 60,000 I.U. of vitamin A daily from the 8th to the 13th day) is in complete agreement with these earlier reports.

Cortisone alone has not been shown to have a teratogenic action. The animals which received 20 mg. of cortisone daily from the 9th to the 12th day (group 2 of the experi-