TWO CASES OF LISTERIAL MENINGITIS IN INFANTS

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No published case of human listeriosis has occurred in Britain since 1941, when *Listeria monocytogenes* was isolated from a case of infectious mononucleosis by Webb (1943). The last reported occurrence in this country of meningitis due to this organism was in 1938 (Wright and Macgregor, 1939). This indicates an extreme degree of rarity of human listeriosis which is borne out by most British and American authors—for example, Webb and Barber (1937), Kaplan (1945), and Finegold *et al.* (1954)—but not by German authors, as is pointed out by Murray (1955). In this survey, Murray shows that German writers—for example, Potel (1951), Erdmann and Potel (1953), and many others—list some 150 published cases throughout the world, many of them in Germany, since the organism was first isolated and studied in 1924 by Murray, Webb, and Swann (1926). Murray estimates that human listeriosis occurs in the following clinical categories: meningitis or encephalitis, 33% of cases; "granulomatosis," 29%; septicæmia, 21%; mononucleosis, 8%; and conjunctivitis, 6%. Hoeprich and Chernoff (1955) have also described one case of listerial subacute bacterial endocarditis.

The following two cases of listerial meningitis in infants occurred near Edinburgh, as did the previous case of Wright and Macgregor, mentioned above, and the case of Gibson (1935).

Case 1

Baby Ross, aged 3 months, was born in the Western General Hospital, Edinburgh. He was the first of identical male twins of a normal first pregnancy. Birth weight was 4 lb. 9 oz. (2,070 g.). The infant was well at birth, but became jaundiced on the second day. As the serum bilirubin level was 27 mg. per 100 ml. on the third day, he was given an exchange transfusion. Thereafter he did well and was discharged from hospital when 5 weeks old, with a weight of 6 lb. (2,720 g.). He continued to progress satisfactorily until two days before admission, when his mother noted that he had become irritable and whimpered, and that his eyes looked glazed and rolled about. He took his feeds and slept well, however. The following day he was slightly feverish, tired, and rather inactive. The doctor was called, and, although he could not find any cause for the infant's upset and pyrexia, considered that the child should be sent to hospital for observation.

On admission on April 6, 1956, the infant appeared well nourished, weighing 8 lb. 13 oz. (4,000 g.). He had been fed on national dried milk, and this was continued. He did not look really ill, but had rather a strained facies. Temperature was 103° F. (39.4° C.), pulse rate 160, and respiration rate 40 a minute. There was slight bulging of the anterior fontanelle, but Kernig's and Brudzinski's signs were negative. The eyes appeared normal. There were no petechial spots,

icterus, or cyanosis. The tongue was clean, with healthy mouth and throat. White-cell count was 12,000 per c.mm. (polymorphonuclear leucocytes 64%, lymphocytes 28%, monocytes 8%), haemoglobin 68% (Sahli). Lumbar puncture on admission revealed a slightly turbid cerebrospinal fluid under slight increase of pressure: cell count was 12,000 per c.mm. Examination of the heart, lungs, abdomen, and urine revealed no abnormality. No pathogenic organisms were cultured from a throat swab.

Following the initial examination meningitis of uncertain origin was diagnosed, and treatment was immediately started with one million units of penicillin intramuscularly, followed by 250,000 units six-hourly. Sulphadiazine, 0.5 g. six-hourly, and chloramphenicol, 125 mg. six-hourly, were also administered. An organism resembling *Listeria monocytogenes* was isolated that was fully sensitive to the drugs which were being given. The infant's temperature remained at a level of 102° F. (38.9° C.) for two days and fell to 98.6° F. (37° C.) by the fourth day. Over the next 17 days the temperature varied from 98.6 to 99.4° F. (37 to 37.4° C.), then remained normal until discharge on the 27th hospital day. Penicillin had been given for six days, sulphadiazine for 17 days, and chloramphenicol for 10 days. In view of the slightly fluctuating temperature, chlortetracycline, 15 mg. six-hourly, was given on the 16th day for six days.

The infant was never critically ill during his stay in hospital, and continued to feed well and gain weight. There was no vomiting or diarrhoea. Lumbar punctures on the 7th and 15th hospital days were sterile. On discharge the infant was well and thriving. No clinical abnormality could be found at that time nor when the child was recalled for assessment a month later.

The father and mother were well and had had no recent illness. No evidence was obtained of cases of glandular fever or adenitis in the neighbourhood. There was no history of contact with any ill human being, and the twin was healthy and remained well. The father was an office worker with the National Coal Board and had no contact with rats or other animals. No animals were kept in the home. No dog came into the house. There were two cats next door, and one of these was said to have had contact with the baby's milk five days previous to the onset of the child's illness. The cats appeared healthy. There were no mice, rats, guinea-pigs, rabbits, fowl, cattle, sheep, goats, or other animals in contact with the infant. The family owned their house, which was in a small mining town about 10 miles south of Edinburgh.

Case 2

Baby Fraser was born at home, 20 miles west of Edinburgh, on April 29, 1956, the third child of healthy parents. His brothers were aged 1 year 7 months, and 11 months respectively. The pregnancy, which had apparently been normal in every way, was of 39 weeks' duration and terminated with a normal vertex delivery. The infant appeared quite normal at birth, and he weighed 6 lb. (2,720 g.). His mother had failed to feed her two previous children at the breast, so he was started on a national dried milk formula, which he took slowly. On the second day of life a "foul-smelling" nasal discharge appeared; this persisted till the time of admission, when it was no longer in evidence.

On the afternoon of the 10th day of life the infant choked during a feed, becoming cyanosed. He remained a poor colour and was admitted to the Royal Hospital for Sick Children, Edinburgh, the same day, May 9, 1956.

On admission he was slightly dehydrated, but otherwise no abnormal physical signs could be elicited. He weighed 4 lb. 8 oz. (2,040 g.). His temperature was 97.8° F. (36.6° C.). No nasal or other discharge could be found. A specimen of urine contained a trace of albumin but no pus cells. His haemoglobin was 88% (Sahli), white-cell count 15,600 per c.mm. (polymorphonuclear leucocytes 70%, lymphocytes 24%, monocytes 6%). He took his feeds well the next day and seemed to be improving slightly. Thirty-six hours

after admission he had a generalized convulsion lasting several minutes. Immediately afterwards no abnormality could be discovered on physical examination and the anterior fontanelle was normotensive. However, a lumbar puncture was carried out and a cloudy fluid under normal pressure was obtained. A film of this fluid showed many polymorphonuclear leucocytes and many bacilli which were presumed to be *E. coli*. He was accordingly treated with streptomycin, 50 mg. twice a day intramuscularly, and sulphadiazine, 0.5 g. followed by 0.25 g. six-hourly by mouth. Later the same day one of us (P. N. E.) reported the organism to be *Listeria monocytogenes*. It was decided, in view of the first case here reported, to replace the streptomycin with chloramphenicol, in a dosage of 125 mg. six-hourly for 12 days. The biochemistry of the cerebrospinal fluid was: protein, 900 mg.; glucose, 12 mg.; chlorides, 600 mg. per 100 ml.

For the next week the baby remained listless, feeding poorly and twitching occasionally. He was therefore given phenobarbitone, $\frac{1}{2}$ gr. (8 mg.) twice a day by mouth. Although the convulsions became less frequent, he had them occasionally until the 33rd hospital day, but none thereafter. Because he fed so slowly, he was tube-fed from the 5th to the 19th day after admission. After that date he sucked well and gained weight. All treatment was stopped on the 35th day, and he was discharged home on June 16, well in every way, weighing 5 lb. 13 oz. (2,635 g.).

When seen on September 17 he weighed 9 lb. 11 oz. (4,395 g.), was feeding well, had had no further convulsions, and no abnormal signs could be elicited.

The father was a miner. There was no history of recent illness in either parent. The condition of the child on admission indicated an unhygienic background. The family kept an apparently healthy dog but no other pets. There was no contact with any livestock, although there were mice and beetles in the house.

Bacteriological Investigations

A Gram film of the turbid cerebrospinal fluid taken from Baby Ross by lumbar puncture on admission showed numerous leucocytes, about 70% of which were polymorphonuclear. A few Gram-positive bacilli, medium-sized with rounded ends and occurring singly and in side-to-side pairs, were seen, both intracellularly and extracellularly placed. Culture on digest human blood agar, incubated aerobically at 37° C. overnight, gave a moderate growth of *Listeria monocytogenes*.

The cerebrospinal fluid taken from Baby Fraser on admission was turbid and showed a similar predominantly polymorphonuclear picture. Numerous Gram-positive bacilli were seen, both intracellularly and extracellularly placed. Culture yielded a heavy growth of *Listeria monocytogenes*. Blood cultured from this case on admission, as well as urine and a rectal swab taken the day after, yielded a growth of this organism.

All the five cultures from these two cases gave smooth grey semi-opaque colonies approximately 2 mm. in diameter after 24 hours at 37° C. on digest human blood agar. Slight haemolysis was present, confirmed by soluble haemolysin test (see Webb and Barber, 1937). Films of the cultures showed Gram-positive bacilli of the same morphology as in the cerebrospinal fluid films, and included many end-to-end V-shaped pairs as well as packets of parallel bacilli. The arrangement of the bacilli was similar to that seen in the case of diphtheroid bacilli, but the individual organisms were more smoothly symmetrical than diphtheroids and lacked the tendency to clubbing often seen in the latter. Overnight broth cultures showed rather scanty motile forms, with end-over-end motion, amongst numerous apparently non-motile bacilli. Later cultures in glucose broth incubated at 25° C. gave much more marked motility. Good growth, but with smaller colonies, occurred on nutrient agar, and very small colonies grew on McConkey's medium after 24 hours at 37° C. Growth also occurred in 6.5% saline broth at 37° C., and slow growth took place in the refriger-

ator on blood agar. Murray's (1955) statement that *Listeria monocytogenes* survives heating at 80° C. for five minutes could not be confirmed for any of the cultures, and the type 4 strain of the organism obtained from the National Collection of Type Cultures (N.C.T.C.5214) also failed to survive in this test. All the cultures, however, resisted heating at 56° C. for five minutes.

Biochemical Reactions

The following sugars were rapidly fermented with acid but no gas: glucose, maltose, mannose,* rhamnose, salicin, dextrin. Late fermentation (first observed between the 3rd and 17th days of incubation) occurred with lactose, sucrose, sorbitol, and glycerol.* No fermentation had occurred by the 17th day in dulcitol, mannitol, inositol, xylose, raffinose, galactose, and arabinose.

No indole was produced, the methyl-red test was positive, and the Voges-Proskauer test very faintly positive after incubation of the reagents for 24 hours (the last three tests were done with the techniques of Wilson, 1935). Urea was not split on Christensen's medium. Neither coagulated serum nor gelatin was liquefied after three weeks' incubation at 37° C. Haemagglutination tests carried out by Dr. J. P. Duguid, Edinburgh University, with 24- and 48-hour 37° C. blood-agar cultures, and the deposits from 48-hour 37° C. digest broth cultures, were uniformly negative against human, horse, sheep, ox, and guinea-pig red cells, both in the cold and at room temperature.

Animal Pathogenicity

Ross Strain.—Two rabbits inoculated intravenously with 0.5 ml. of plate-culture suspension of Brown's opacity 3, and 0.5 ml. of 24-hour broth culture respectively, became ill after 24 hours and were dead within 40 hours. Post-mortem examination showed the usual features of experimental listeriosis, the main feature being the mottled liver consisting of a mass of minute necrotic foci. The organism was recovered in large numbers from the liver and other tissues.

Production of Monocytosis in Rabbits.—Three rabbits were given doses of culture intravenously, which were calculated, as described by Webb and Barber (1937), to be around the minimum lethal level. Differential white cell counts were performed before and after the inoculations, and the results are shown in Table I. In the rabbit receiv-

TABLE I.—Production of Monocytosis in Rabbits

Dose of Culture		Leucocyte Count per c.mm.			
		Ross Strain		Fraser (C.S.F.) Strain	
		Total	Absolute Monocyte Count	Total	Absolute Monocyte Count
0.002 mg./kg.	Pre-injection	9,600	336	9,400	282
	3rd day ..	9,000	1,350	14,200	3,190
	5th " ..	21,600	3,880	23,000	5,290
	7th " ..	19,000	3,230	15,800	2,210
0.008 mg./kg.	Pre-injection	8,200	246	12,600	441
	3rd day ..	14,400	1,730	13,800	2,350
	5th " ..	28,800	10,510	16,200	2,590
	7th " ..	23,000	3,800	11,800	1,300
0.02 "	Pre-injection	9,600	336	Not done	
	Died within three days				

ing the intermediate dose, the absolute monocyte count rose from the pre-injection level of 246 to 10,510 per c.mm. The rabbit which was given 0.02 mg./kg. died before the third day. A marked monocytosis was therefore produced by sublethal doses of the organism.

Rabbit Conjunctival Test.—This test was described by Anton (1934) and its specificity for *Listeria monocytogenes* was confirmed by Julianelle (1941). A young broth culture was inoculated on to the conjunctiva by instillation, swabbing, and scarification plus swabbing, respectively, in each of three rabbits. In all three marked kerato-conjunctivitis

*Only the Ross strain was tested for fermentation of this sugar.

developed after 24 hours; this cleared up completely in four weeks without treatment.

Guinea-pig Inoculation.—Four guinea-pigs were inoculated, three intraperitoneally and one subcutaneously, with amounts of culture varying from 0.5 ml. of 24-hour broth culture to 1 ml. of very dense suspension from a blood agar plate. All died in three to four days, and post-mortem examination of each showed multiple small necrotic foci in the liver. *Listeria monocytogenes* was isolated in large numbers from liver and heart blood in every case.

Fraser Strain.—Rabbit conjunctival tests were positive for the cultures from cerebrospinal fluid, blood, urine, and rectal swab, but some tests had to be repeated before a typical reaction occurred. Monocytosis was produced in rabbits by the cerebrospinal fluid strain (see Table I). One guinea-pig inoculated intraperitoneally gave a typical result, with multiple necrotic foci in the liver. Four other guinea-pigs, one inoculated subcutaneously, the remainder intraperitoneally, survived unharmed. The Fraser organism therefore appeared to be of lower virulence for guinea-pigs and rabbits than the Ross strain.

Serology: Materials and Methods

National Collection strains of Paterson's (1940) four serological types were obtained. These were N.C.T.C.4886 (type 1), N.C.T.C.5348 (type 2), N.C.T.C.5105 (type 3), and N.C.T.C.5214 (type 4).

Techniques for preparation of antigens and sera, and of carrying out absorption and agglutination tests, were as described by Paterson (1939, 1940) with the following exceptions:

(1) H antigens for absorption tests were prepared as follows. A single smooth colony from a blood-agar plate culture was inoculated into a tube of digest broth and incubated overnight at 37° C. This was then subcultured at 25° C., when maximum motility was present. Six Roux bottles of nutrient 0.8% agar (Davis), containing 1% glucose, were liberally inoculated with this culture. After 24 hours' incubation at 25° C. the growth was harvested, tested for motility and purity, and 0.25% formalin added. The suspension was then centrifuged and the deposit resuspended in 6 ml. of saline containing 0.25% formalin.

(2) For absorption, 3-ml. suspension (either H or Paterson's O antigen adjusted to a similar density) was added to 2 ml. of serum. After absorption and centrifugation, the supernatant was decanted on to the centrifuged deposit from a further 3-ml. suspension, and the absorption repeated.

(3) It was found that a suitable dilution of the absorbing H antigen was adequate for use in agglutination tests.

H agglutinating antisera were prepared in rabbits for types 1, 2, and 4, and O antisera for types 1, 3, and 4, as well as the Ross strain. The antigenic constitution of these types is shown in Table II. Specific antisera for the antigenic factors I, IV, V, A, D, and C were prepared by absorption as indicated by Seeliger (1955).

TABLE II.—*Antigenic Constitution of Listeria monocytogenes According to Paterson (1940)*

Type	O Factors	H Factors
1	I, II, III	AB
2	I, II, III	BD
3	II, III, IV	AB
4	III, V	ABC

Results of Serological Tests

(1) **Typing of Ross and Fraser Strains.**—Table III shows that the Ross strain included factors V, A, and probably also C. The presence of the common O factor III was indicated by the cross-agglutination which occurred with O sera to types 1, 3, and 4, and the presence of the common H factor B, by agglutination with H sera 1, 2, and 4. Strain Ross therefore has the antigenic formula O=III, V; H=AB(C)—that is, it is type 4. This agrees with the information kindly supplied by Dr. Heinz Seeliger, of Bonn, to whom the Ross and Fraser strains were sent before the present work was completed. Seeliger (1955) described types 4a and 4b as subtypes of 4. It was found by him that

Ross was in fact 4b. The difference between this strain and the National Collection type 4 strain (N.C.T.C.5214) is seen in the different titres when the two strains react with factor V serum (see Table III). This difference was confirmed by cross-absorption tests between Ross (O) antiserum and N.C.T.C.5214 (O) serum, using O antigens for absorption and agglutination. Thus:

Ross serum, unabsorbed	Agglutinates Ross	1/2560
absorbed with N.C.T.C.5214	"	N.C.T.C.5214 1/<20
Ross serum absorbed with N.C.T.C.5214	"	Ross 1/320
N.C.T.C.5214 serum, unabsorbed	"	N.C.T.C.5214 1/2560
absorbed with Ross	"	Ross 1/<20
N.C.T.C.5214 serum, absorbed with Ross	"	N.C.T.C.5214 1/320

N.C.T.C.5214, hitherto known as type 4, can now therefore be called type 4a.

Table III also shows that the Fraser (C.S.F.) strain includes in its antigenic constitution H factor D and O factor I. The presence of the common factors III and B

TABLE III.—*Results of Agglutination Tests with Absorbed Sera*

Serum Factor:	O Reaction			H Reaction		
	I	IV	V	A	D	C
Type 1	1,280 *	<20	80	640	<40	<10
" 2	1,280	<20	20	<40	2,560	<10
Fraser C.S.F.	1,280	<20	20	<40	1,280	<10
Type 3	40	160	80	1,280	<40	<10
" 4	40	20	1,280	1,280	<40	20
Ross	<40	<20	320	1,280	<40	10

* Titres are expressed as the reciprocal of the final serum dilution at the end-point.

was shown by the same method as with the Ross strain. No attempt was made to demonstrate factor II, as this cannot be done with any certainty in the presence of factor I, and, in any case, the antigenic factors already determined place this strain definitely in type 2. Identification of the remaining Fraser cultures isolated from blood, rectal swab, and urine was carried out by slide agglutination with the factor-specific sera. They were all type 2.

(2) **Agglutination Tests with Patient's Sera.**—As only limited amounts of sera were available, tests had to be restricted to the reactions with the homologous organisms. Sera from Ross on the 1st and 13th hospital days were negative at 1/20 for Ross H and O antigens, and on the 25th day for Ross H. Sera from Fraser on the 1st, 12th, and 19th days were negative at 1/20 for Fraser H and O antigens.

(3) **Paul-Bunnell Test.**—This was negative in both cases.

Tests Done on Specimens from Contacts of Baby Fraser.—A vaginal swab taken from the mother one month after the baby's admission to hospital failed to yield listeria or any other organisms of significance. Serum taken the same day failed to agglutinate any of *Listeria* types 1-4 (H and O antigens). No listeria organisms could be isolated from a specimen of faeces taken at this time from the family dog. No specimen could be obtained from the family of Baby Ross.

Antibiotic Sensitivity Tests.—These were carried out on the Ross and Fraser strains using the disk technique of Gould and Bowie (1952). All the cultures were fully sensitive to chloramphenicol, tetracycline, penicillin, and streptomycin. A disk containing 100 µg. of "soluthiazole" (a soluble derivative of sulphathiazole), used with a saponin-lysed blood-agar plate, gave a zone of inhibition which was wider with these strains than with the Oxford Standard *Staphylococcus*.

Discussion

The behaviour of the Ross and Fraser organisms was in agreement at almost every point with the descriptions given of *Listeria monocytogenes* by Webb and Barber (1937) and Wilson and Miles (1955). From a bacteriological point of view, the nearest relations of this organism are the diphtheroid group and the genus *Erysipelothrix*, from which *Listeria monocytogenes* is readily distinguished by its

motility, antigenic characters, ability to grow at refrigerator temperature, tolerance of 6% sodium chloride, and other less important properties (see Murray, 1955).

So far as geographical distribution is concerned, there appears to be no localization of any particular serotype of *Listeria*, with the possible exception of type 2. Seeliger (1956, personal communication), who has typed almost 500 strains from various parts of the world, found only two other type 2 strains besides the Fraser organism. One of these was a human strain from East Germany isolated in 1953, the other was the Gibson strain, which was isolated in Edinburgh. This last strain was obtained by Gibson (1935) from a fatal human case of meningitis which occurred some 20 miles south-west of Edinburgh. It is now known under its N.C.T.C. number 5348, and was until now the only type 2 strain in the collection. So far as is known, no type 2 strain has yet been isolated from animals. This fact may possibly be connected with the considerably lower virulence for rabbits and guinea-pigs of the Fraser strain as compared with the Ross and other strains. The Gibson strain also showed low virulence at the time of isolation when inoculated by the subcutaneous route in guinea-pigs (Gibson, 1935).

Type 4 is widespread among many different animal species, but the incidence of type 4b—that is, the Ross strain type—as distinct from 4a, does not seem to have been investigated so far.

The epidemiology of human listerial infection remains obscure except in occasional instances where a particular animal species has been suspected. In the present cases the only history of contact with animals was that a cat had perhaps licked the Ross baby's feeding-bottle, that a dog was kept by the Fraser family, and that there were mice in the Fraser house. No record exists, so far as we can discover, of cats being naturally infected with *Listeria monocytogenes*. Murray (1955) states that the organism has been isolated from the dog as well as at least 25 other species of animal, including the mouse, but not the cat. The fact that type 2 strains have so far not been isolated from animals weighs against the probability of infection of Baby Fraser from the dog, though it does not of course rule it out.

The possibility of human-to-human infection is suggested by Line and Cherry (1952), who reported the cases of two babies born in the same delivery-room within two days of each other, who were in the same nursery for 24 hours, and whose mothers shared a common bath; these babies became ill with listerial meningitis within two days of each other. Burn (1934) reported a similar incident involving two successive cases of this disease in babies. In the present instance, however, any possible relation between the two cases is ruled out by the serological difference between the strains of *Listeria* concerned.

The question of healthy carriers was investigated by Stanley (1950), when 3,558 nose and throat swabs yielded only two cultures of organisms which resembled *Listeria monocytogenes* in some respects only. As regards the avenue of infection in humans little evidence is available, but the nose and throat were suggested as portals of entry by Pons and Julianelle (1939).

The possibility of congenital infection is suggested in the case of the Fraser baby by the short period elapsing between birth and the onset of symptoms. That such infections can occur is shown by the considerable numbers of cases reported in Germany of "granulomatosis infantiseptica" in which miscarriage or stillbirth due to listeriosis of the foetus has been accompanied in some instances by bacteriological or serological evidence of maternal infection with *Listeria monocytogenes*. It was disappointing, therefore, in the present instance that specimens from the mother could not be obtained until a month had elapsed from the onset of the child's illness. The negative results obtained from the culture of the vaginal swab must be given little weight under the circumstances. Had the mother suffered from a sub-clinical infection with listeria at or before the birth, it is

possible that agglutinins for this organism might have been present one month later. The importance of the negative result obtained at that time must, however, be discounted, since antibody is known to fade rapidly in humans following listerial infection (Murray, 1955).

Summary

Two cases of meningitis due to *Listeria monocytogenes*, one with septicaemic spread, are described in babies from the vicinity of Edinburgh.

Typing sera were prepared for the identification of the four main serotypes and two subtypes of this organism.

One strain (Ross) was found to be type 4b, the other (Fraser) was type 2.

We acknowledge with thanks the co-operation of Dr. H. Seeliger, of Bonn, and of Dr. J. P. Duguid, Edinburgh University, also the technical assistance given by Mr. J. C. Ferguson and other members of the laboratory staff.

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PENICILLIN V—A CLINICAL ASSESSMENT AFTER ONE YEAR

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Because of the instability of benzylpenicillin (penicillin G) in gastric juice its oral administration has never been universally accepted by clinicians. As there is achlorhydria in infants under 6 months, and a definite diminution of hydrochloric acid in gastric juice has been observed in adult cases of pneumonia, oral penicillin G was expected to be reliable in such cases. This has been reported by Buchanan (1946) and by Anderson and Landsman (1947). Other preparations, such as benzathine penicillin and a combination of penicillin G and probenecid, have been used orally, but there are conflicting reports of the reliability of absorption. There is, however, much evidence to suggest that phenoxymethylpenicillin (penicillin V), which is stable in gastric juice, can be relied on to produce therapeutic blood levels.

Therefore, in October, 1955, when penicillin V became available to this hospital, it was decided to use it in all