epidemiologically. Mr. Coleman probably acquired his infection at the college, which had a history of earlier cases of diarrhoea. In the case of Mr. Powell there is very strong support for the assumption that his infection was acquired at his home, where his brother fell ill on the same day, a few days after Mr. Powell returned to college.

Outbreak II

Twenty-three of the 30 cases from May to December due to type 3 have been found in a colony for mentally defective people at intervals over the whole period of this investigation. No other type has been isolated from this colony, and it is a fair assumption that all these infections have been acquired at the colony. By the nature of living conditions and habits of the mentally defective it will be very difficult to do more than confine the outbreak to the particular blocks affected.

Previous records showed that there had been a severe outbreak of Sonne dysentery at a babies' home, involving almost all the babies and staff. One strain of that outbreak had been kept, and was also found to belong to type 3.

Outbreak III

Type 3 was also responsible for an outbreak in the hospital which had suffered earlier in the year from type 81. On this occasion, however, a patient was admitted into the ward with infection due to this type, and the other three cases in this ward were close contacts and obviously infected by him. One other case in another ward had positive cultures of this type on admission.

So far 29 cases of type 3 have been accounted for; the remaining one was an isolated case in the city.

Conclusions

From the foregoing, although the number of strains typed is very small, some conclusions about the kind of information that Sonne phage-typing will yield may be drawn already. The types are very numerous and the isolation of seven different types in a town of moderate size like Bristol during seven months shows that the epidemiological unit is very much smaller than the town. It is indeed very small in space—family or institution—and also seems to be of short duration, unless the circumstances are exceptional, as amongst the mentally defective.

The multiplicity of types and the smallness of the epidemiological unit will make it possible to trace some of the strands in the tangle of the pathways of infection. We hope to obtain strains from outside Bristol and from other parts of the country, to follow in detail such phenomena as, for instance, the appearance of new types after the holidays.

Much remains to be done to establish the degree of stability of the types *in vivo* and *in vitro*. Many technical difficulties, which may occasionally upset the type determination, must have their importance assessed. The influence of the composition of the medium on the phage titre makes some difficulties in correlating results obtained in Bristol and in Sweden. The occurrence of phage-carrying and lysogenic strains may confuse the appearances unless care is taken to avoid these organisms for the propagation and standardization of the phages used. Many of these difficulties have been described by Hammarström in very clear detail, and it seems likely that they do not destroy the main epidemiological importance of type determination on most occasions. Whether examination over a longer period will give rise

to important exceptions to the belief that type identity is the result of recent close genetic relationship, or that type dissimilarity necessarily means lack of such relationship, has yet to be shown.

REFERENCES

- Cooper, K. E. (1950). *J. roy. sanit. Inst.*, **70**, 200.
 Davies, I. G., Cooper, K. E., and Fleming, D. S. (1942). *Lancet*, **1**, 129.
 Felix, A., and Pitt, R. M. (1934). *Ibid.*, **2**, 186.
 Green, C. A., and MacLeod, M. C. (1943). *British Medical Journal*, **2**, 259.
 Hammarström, E. (1947). *Lancet*, **1**, 102; Thesis, Stockholm, 1949.
 Hutchinson, R. Irene (1947). *British Medical Journal*, **1**, 134.
 Mayr-Harting, A. (1948). *J. gen. Microbiol.*, **2**, 31.
 — (1949). Thesis—"A Study of *Ps. pyocyanea*." Bristol, University.

AUREOMYCIN AND CHLORAMPHENICOL IN INFANTILE DIARRHOEA

BY

ROBERT A. SHANKS, M.D., M.R.C.P., F.R.F.P.S.

Lecturer in Child Health, University of Glasgow

The purpose of this communication is to describe briefly a preliminary trial of "aureomycin" and chloramphenicol in the treatment of infantile diarrhoea, or gastro-enteritis. Although diarrhoeal diseases of infancy have long been responsible for a considerable proportion of deaths in the first year of life, there is still no true understanding of their aetiology. Indeed, even definitions are difficult in the light of the diversity of views upon their pathogenesis. It is arguable whether diarrhoea of purely dietetic origin exists, and all cases which cannot unequivocally be assigned to other causes (such as coeliac disease or irritant poisons) should be regarded as infective even though the infective agent is as yet unknown. Nevertheless the acceptance of the infective nature of diarrhoea in infancy does not wholly solve the problem. It is usual to describe two groups: one in which the presumed infective agent is located in the alimentary tract (enteral infection) and for which there is very little direct pathological evidence, and the other in which it is located outside the alimentary tract (parenteral infection) and for which there is even less.

When one considers that the parenteral infection which is supposed to cause diarrhoea must apparently resolve itself into one of the upper respiratory tract, and that infections of the meninges and bones are not associated with diarrhoea, and even primary pneumonia and infections of the urinary tract by no means consistently so, it would appear that this distinction begs too many questions to be of real value. In all, there seems little justification for any more precise term than that of infantile diarrhoea, which is used here to indicate the non-specific diarrhoea of infancy. In this connexion it may be stated that only such established specific organisms as the *Shigella* and some *Salmonella* are excluded by this definition, and neither *Proteus vulgaris* nor the more recently incriminated varieties of *Bact. coli* are regarded as specific for the purposes of this communication.

Where a disease cannot be precisely defined it is particularly difficult to establish criteria of cure. Assessment of the result of any series of cases will inevitably depend to some extent upon largely subjective factors, such as the degree of severity and the presence or absence of parenteral infection, as well as upon factors that are administrative or social, such as the type of case admitted and the nature of the population from which the cases

are drawn. In the light of these considerations comparison between published series becomes extremely difficult. It seems not unlikely, moreover, that the difference between the series may be due as much to social and administrative factors as to the nature of the treatment of each, or perhaps even more. It is probable that real progress in the therapeutics of this condition must await a more precise understanding of the aetiological factors involved. Nevertheless, so serious a threat to the infant population must be met, and at the moment only empirical measures are possible.

Substances Used in Treatment

It is obvious that antibacterial substances had to be tried in infantile diarrhoea not only because the infective agent might have proved susceptible but also in order to deal with a parenteral infection, real or assumed. Sulphonamides were introduced early, and although opinion is divided (Campbell and Cunningham, 1941; Henderson, 1943; Hinden, 1948) it is usually conceded that they are of value in dealing with concomitant infections, while the use of compounds designed to have a local action on the bowel has on the whole been disappointing. The use of penicillin can be justified on the same grounds, and in particular when a concomitant infection, whether or not it is regarded as a cause of the diarrhoea, may well retard or jeopardize recovery. It is safe to say that neither the sulphonamides nor penicillin can be regarded as in any way specifically effective in the treatment of infantile diarrhoea.

The use of other antibiotics with a wider range of action offers an obvious advantage. On the accepted principle that concomitant infections should be dealt with, an antibacterial substance which combines the range of the sulphonamides with that of penicillin and which, moreover, can be administered by mouth is an obvious choice. In addition there is the not unreasonable hope that the infective agent itself might prove sensitive to one of the newer antibiotics. That rickettsiae and even some viruses have been shown to be susceptible lends countenance to this view (Long *et al.*, 1950).

Streptomycin was an early choice, and James, Kramer, and Armitage (1948) reported strikingly favourable results in the treatment of 30 cases of infantile gastroenteritis with oral streptomycin. *Proteus vulgaris* was isolated on stool culture in most of these cases, but improvement was not confined to these. Both streptomycin and "polymyxin" were submitted to trial at this hospital and in various centres in Scotland under the aegis of the Scientific Advisory Committee of the Department of Health for Scotland. One may not anticipate the report of this trial, but our own experience was unremarkable.

Aureomycin would seem at first sight to have all the necessary qualifications as a wide-range antibiotic. It is effective against both staphylococci and coliform organisms, and has the obvious merit of obviating parenteral therapy. Moreover, the reported response of primary atypical pneumonia and ornithosis encouraged the hope that, even though the presumed infective agent in infantile diarrhoea should be a virus, for which there is already some evidence (Sabin, 1951), it might nevertheless respond to aureomycin. Its successful use in the treatment of infantile diarrhoea and vomiting has been reported from Stockholm (Magnusson *et al.*, 1950).

Chloramphenicol has many of the same advantages as aureomycin without, however, the same effectiveness

against Gram-positive organisms (Long *et al.*, 1950). As these organisms are presumably not so likely to be implicated in infantile diarrhoea (although the concept of parenteral diarrhoea may not always permit this assumption, particularly in view of the prevalence of staphylococci in upper respiratory infections), and as chloramphenicol is more readily available in this country, it is to this antibiotic that most attention has been paid (Smellie, 1950; Cerruti and Scarzella, 1950). Smellie records 27 cases of infantile diarrhoea in which 75 mg. of chloramphenicol per lb. (0.45 kg.) of body weight was given, this being continued for 10 to 12 days. All were seriously ill, and each patient except the one who died showed marked clinical improvement in two days. Cerruti and Scarzella also report encouraging results, using only 50 mg. per kg. body weight. In particular the incrimination of newly recognized varieties of *Bact. coli* in infantile diarrhoea has lent point to the use of chloramphenicol, to which they are sensitive.

Present Series

It was decided, therefore, to use first aureomycin and then chloramphenicol in the treatment of infantile diarrhoea as already defined. They were given in every second case admitted to one medical unit of the Royal Hospital for Sick Children, the others serving as controls. It should be made clear that of the cases of infantile diarrhoea seen at this hospital only those are admitted whose condition is so severe that out-patient treatment is considered quite unsuitable. Normally, therefore, only the more severe cases are admitted, and the average severity will be higher than that of the aggregate number seen. This is naturally reflected in the overall mortality. It was nevertheless convenient to classify all cases as mild, moderate, or severe. It will be remembered that these are relative terms.

Aureomycin was used from March to June inclusive, and chloramphenicol from July to October inclusive. Although the trial of chloramphenicol continues as part of an investigation into the distribution of the sub-varieties of *Bact. coli*, it was felt that the clinical results were already conclusive enough as regards the major issue involved. It should be conceded that a really effective method of treatment does not require a very large series for its proof. What the physician who has charge of infants wants to know is whether the condition which he knows by the name of infantile gastroenteritis is cured by aureomycin or chloramphenicol. To this question a relatively small series may well provide the answer.

Method

All cases were given the routine starvation regimen in use in this unit. On admission a clinical assessment of the child's condition and a note of any obvious parenteral infection were made. All feeds were withheld for at least twelve and usually twenty-four hours. During this time the child was given a mixture of molar sodium lactate and half-strength physiological saline in the proportion of 1 in 80. In children aged less than 4 weeks this solution is diluted with an equal amount of water. More concentrated solutions readily produce oedema in very young infants. If the condition of the child permitted, an attempt was made to rehydrate him by mouth before resorting to parenteral therapy. After a brief resuscitation in a warm cot the infant was offered this lactate-saline.

If, as often happened, the child was sick his stomach was gently washed out and 3-4 oz. (85-114 ml.) of lactate-saline was left in the stomach. Only if this failed was parenteral fluid given, and it is noteworthy that a large number of children who had all the appearances of severe dehydration, and who with less patient nursing would undoubtedly have required parenteral fluid, responded dramatically to these measures. Gastric lavage has been found a most effective measure against persistent vomiting. If parenteral fluid was required the intravenous route was used exclusively. The fluids chosen were human plasma followed by half-strength physiological saline containing molar sodium lactate in the proportion of 1 in 40 together with 5% glucose. In infants aged less than 4 weeks quarter-strength instead of half-strength physiological saline was used. The re-introduction of feeds was accomplished gradually with $\frac{1}{2}$ -oz. (14-ml.) feeds of half-cream National dried milk four-hourly (six times a day) for the first day and increasing by $\frac{1}{2}$ oz. (14 ml.) a day. When the diarrhoea has ceased, sugar was added and the feeds were then adjusted to the child's requirements, including the changing over to full-cream National dried milk and the addition of mixed feeding if appropriate.

For the first four months of the trial every second case was given aureomycin in doses of 25 mg. per kg. of body weight in three or four divided doses (six- or eight-hourly) for seven days. The aureomycin was dispensed in 25-mg. powders and administered orally in small amounts of glycerin or honey. In addition, and probably unnecessarily, each child was given a 4-gr. (0.26-g.) tablet of Philip's yeast together with 50 mg. of ascorbic acid lest serious interference with bacterial synthesis of vitamins should lead to some deficiency. For the second four months of the trial chloramphenicol was used, again in every second case, in doses of 150 mg. per kg. of body weight a day in six divided doses (four-hourly) for seven to ten days. The drug was dispensed in 50-mg. powders and administered in the same way as aureomycin. A loading dose of 300 mg. per kg. of body weight was used.

The controls were given, in addition to the routine treatment outlined above, a sulphonamide and/or penicillin as indicated by their clinical condition. The absence of unequivocal evidence of a parenteral infection in a seriously ill child was not regarded as a bar to its receiving this treatment.

Results

Aureomycin.—During the period March to June inclusive, 34 cases (17 aureomycin, 17 controls) were treated, with an overall mortality of 14.7%. There were two deaths in the aureomycin-treated cases and three in the controls. The figures are given in Tables I-IV and show an analysis of the cases according to severity, age, percentage of expected weight, and average duration of stay in hospital. The last-named figure may be of more significance than the mortality, as the actual number of deaths in any one group is small. Of the two fatal cases treated with aureomycin, one is worthy of note in that, although the two stool cultures taken before death yielded no growth on the usual media, the diarrhoea persisted. Aureomycin had apparently dealt effectively with the intestinal bacteria without, however, benefiting the child. Of the three controls, one died within three hours and another within forty-eight hours of admission.

TABLE I.—*Classification According to Severity (Deaths in Parentheses)*

	Mild	Moderate	Severe	Total
Aureomycin	6 (—)	8 (1)	3 (1)	17 (2)
Controls	8 (—)	5 (—)	4 (3)	17 (3)
Total	14 (—)	13 (1)	7 (4)	34 (5)
Chloramphenicol	12 (—)	12 (2)	6 (2)	30 (4)
Controls	12 (—)	9 (—)	7 (3)	28 (3)
Total	24 (—)	21 (2)	13 (5)	58 (7)

TABLE II.—*Age Distribution (Deaths in Parentheses)*

	Under 4 Weeks	4-8 Weeks	Over 8 Weeks
Aureomycin	2 (—)	6 (1)	9 (1)
Controls	6 (2)	1 (—)	10 (1)
Total	8 (2)	7 (1)	19 (2)
Chloramphenicol	5 (—)	6 (2)	19 (2)
Controls	2 (1)	5 (—)	21 (2)
Total	7 (1)	11 (2)	40 (4)

TABLE III.—*Percentage Expected Weight on Admission (Deaths in Parentheses)*

	Less than 60%	60-75%	Over 75%	Over 100%
Aureomycin	3 (2)	4 (—)	10 (—)	
Controls	2 (—)	3 (1)	11 (1)	
Total	5 (2)	7 (1)	21 (1)	
Chloramphenicol	1 (—)	8 (—)	18 (4)	3 (—)
Controls	3 (1)	6 (—)	13 (—)	4 (—)
Total	4 (1)	14 (—)	31 (4)	7 (—)

Three patients who were critically ill on admission, and were not therefore weighed, are omitted from this table.

TABLE IV.—*Average Stay in Hospital of Non-Fatal Cases*

Aureomycin	12.1 days	Chloramphenicol	13.8 days
Controls	11.1 "	Controls	12.2 "

Chloramphenicol.—During July to September inclusive there were 58 cases, of which 30 received chloramphenicol, the rest being controls. The overall mortality was 12.1%. Four deaths occurred among the chloramphenicol-treated cases and three among the controls. Tables I to IV again give the relevant figures. Of the four fatal cases in the treated series one had a congenital malformation of the heart (complete transposition of the great vessels) and another had congenital syphilis. This latter case had been under treatment with penicillin for some weeks, and at necropsy there was little beyond some scarring of the liver to indicate the syphilitic infection.

Discussion

In each series there was a reasonable similarity between the treated cases and the controls. The proportion of severe cases, neonates, and marasmic babies, all factors influencing the outcome of infections, was much the same in each series. Indeed, the most striking feature of each set of figures is its similarity to the others. The mortality and average duration of stay in hospital show no significant difference between the three methods of treatment. So far as the mortality is concerned it is perhaps worth noting that of the 12 deaths three occurred within twenty-four hours of admission and a further two within sixty hours of admission.

The failure to demonstrate any striking difference between the results of the aureomycin and chloramphenicol groups and of the controls does not, of course, indicate that there are no virtues in the use of aureo-

mycin and chloramphenicol for the treatment of infantile diarrhoea, but merely that there is no evidence that they add anything to that already obtainable with a combination of a sulphonamide and penicillin. This in itself is sufficient to warrant the use of a single antibiotic instead of a combination of drugs. The choice between aureomycin and chloramphenicol would appear to depend as much upon the importance of staphylococci in this condition, and for which aureomycin would be necessary, as upon the coliform organisms which are sensitive to both. In this connexion one may mention that the use of sulphonamides and penicillin in infantile diarrhoea has caused a striking fall in the incidence of middle-ear infections found *post mortem*.

It seems unlikely that these results would be radically altered by merely increasing the number of cases, and it remains to consider the possible effect of the selection of cases. By definition, infantile diarrhoea in this series has been taken to include all cases of diarrhoea in the first year of life which were of non-specific origin. (In practice this excluded only dysentery and coeliac disease.) This wide definition was considered necessary in view of the difficulties of interpretation if any more precise distinctions were attempted. This is true whether the attempted distinctions are clinical, such as the separation of parenteral diarrhoea from enteral diarrhoea, or bacteriological, as in the differentiation of varieties of *Bact. coli*. Whatever the ultimate judgment upon these issues it is worth while to restate the fundamental difficulty in assessing the treatment of infantile diarrhoea. While the aetiology remains in doubt it is unlikely that a specific treatment will be found. Nevertheless it seems legitimate to conclude that the relative ineffectiveness of a wide range of antibacterial substances is strongly suggestive of a non-bacterial causation.

Summary

Aureomycin or chloramphenicol was used in alternate cases of a series of 92 consecutive infants admitted with infantile diarrhoea during a period of eight months. The controls were given penicillin and/or sulphonamides as indicated.

No significant difference was noted between either of the treated series and the controls. It is suggested that any wide-range antibacterial substance is likely to have a definite but limited value in the treatment of infantile diarrhoea. So far, however, it seems that no available antibiotic has a specific curative effect upon this disease. This may be regarded as an additional factor in favour of a non-bacterial causation of infantile diarrhoea.

I am indebted to Professor Stanley Graham, in whose wards these cases were treated, for generous criticism and advice in the preparation of this paper. I am grateful to Dr. A. M. MacDonald and his staff for bacteriological reports and necropsies. To Sister Sutherland and the nursing staff my thanks are due for a consistently high standard of nursing.

REFERENCES

- Campbell, R. M., and Cunningham, A. A. (1941). *Arch. Dis. Childh.*, **16**, 211.
 Cerruti, C. F., and Scarzella, M. (1950). *Minerva pediat.*, *Torino*, **2**, 220.
 Henderson, J. L. (1943). *British Medical Journal*, **1**, 410.
 Hinden, E. (1948). *Arch. Dis. Childh.*, **23**, 27.
 James, U., Kramer, I. R. H., and Armitage, P. (1948). *Lancet*, **2**, 555.
 Long, P. H., Bliss, E. A., Schoenbach, E. B., Chandler, C. A., and Bryer, M. S. (1950). *Ibid.*, **1**, 1139.
 Magnusson, J. H., Laurell, G., Frisell, E., and Werner, B. (1950). *British Medical Journal*, **1**, 1398.
 Sabin, A. B. (1951). In *Modern Trends in Paediatrics*, p. 272. Edited by L. Parsons. Butterworth, London.
 Smellie, J. M. (1950). *Proc. roy. Soc. Med.*, **43**, 766.

PHAECHROMOCYTOMA PRESENTING AS AN ABDOMINAL EMERGENCY

BY

I. C. GILLILAND, M.D., M.R.C.P.

Medical Tutor and Senior Medical Registrar, Postgraduate Medical School of London

AND

O. DANIEL, M.B., F.R.C.S.

Senior Surgical Registrar, Postgraduate Medical School of London

Phaeochromocytoma is now being recognized more frequently, not only in patients whose clinical features suggest paroxysmal hypertension (Walton, 1950) but also in those whose presenting disability is sustained hypertension (Green, 1946) or diabetes mellitus (Duncan *et al.*, 1944; Goldner, 1947). This clinical diagnosis is usually suggested by the association of two features—a liability to attacks, with palpitations, headaches, and sweating, and evidence of hypertension either persistent or observed during these attacks. In the present case, which was under observation for 18 hours, the clinical picture was dominated for that time by a state of shock with periodic exacerbations associated with severe abdominal pains. The blood pressure was either normal or subnormal, and the E.C.G. and x-ray film showed no evidence of previous hypertension. This case is reported because of its unusual presentation, which served to emphasize that the condition of shock, familiar as a post-operative or post-manipulative complication in these patients, may be the presenting clinical problem, thus masking any evidence of previous hypertension.

Case Report

A carpenter aged 29 was admitted to hospital as an emergency case of pneumonia. He had been ill for 24 hours and had become distressed and prostrate, unable even to sit up, coughing up large amounts of blood-stained sputum.

He gave a history of being suddenly struck down the day before with aches and pains all over, and complained particularly of headaches and pains in the abdomen, back, and chest. He said that for the past four months he had had an unproductive cough, which he thought brought on vomiting once or twice a day. With the vomiting he had headache, palpitation, and profuse sweating. On this account he had attended another hospital, where he had had a barium meal and was assured that he was suffering from "nerves." He had lost no weight and had been able to carry on with his work. Further details were not then available, but it was subsequently discovered that he had previously complained of attacks of vomiting, unrelated to meals, occurring almost every night. Headaches, palpitations, and profuse sweating accompanied the vomiting. On the two occasions it was tested his blood pressure was found to be normal. After treatment with phenobarbitone he seemed a little improved and had ceased attending.

On admission he was found to be a robustly built young man, limp, and ashen grey in colour; he was coughing up copious blood-stained sputum, and vomited and sweated profusely. His temperature was 96° F. (35.6° C.), pulse 100, and respiratory rate 30. His blood pressure at this time was 160/80. There were many fine crepitations, especially in the apical regions. There was tenderness in the epigastrium, especially on the left, and in the left renal angle. The urine