AUREOMYCIN TREATMENT OF INFANTILE
DIARRHOEA AND VOMITING

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In a number of epidemics of infantile diarrhoea and vomiting that have been recorded great importance was attached to the bacteriological and virological investigations. During recent years particular interest has been aroused by a *Bacterium coli* strain, *Bact. coli* neapolitanum (B.C.N.).* Its presence was demonstrated by Bray (1945), Bray and Beavan (1948), Giles and Sangster (1948), Giles, Sangster, and Smith (1949), and by Taylor, Powell, and Wright (1949) in a number of such epidemics. Its aetiological significance has not yet been elucidated. Streptomycin treatment was given in such cases by Holzel, Martyn, and Apfer (1949), but they considered that it did not exert any specific therapeutic effect. Chloramphenicol treatment was tried out by Rogers, Koegler, and Gerrard (1949) in a small number of cases, and they found the results to be encouraging. The present preliminary report covers two epidemics in which the presence of B.C.N. could be demonstrated. Eight of the patients in the second epidemic were treated with aureomycin.

Present Series

The series consists of infants treated in the Sachs Hospital for Children between July and November, 1949. On two occasions an epidemic of dyspepsia broke out among them. The first was during July–September. Altogether 20 infants were examined with respect to the presence of B.C.N. in the stools and the respiratory tract. The second epidemic started at the end of September and continued during October and November. Fourteen infants were affected. On both occasions the control material consisted of children in hospital during the same time but with no dyspeptic symptoms.

The presence of B.C.N. was demonstrated in 19 cases in the first epidemic and in all in the second. In the control series, consisting of altogether 40 children, B.C.N. bacteria were found in the stools of one child only. In the first epidemic all the children became affected during their stay in hospital, and in the second epidemic 10 became affected during that time. Of the three infants admitted to hospital for diarrhoea, one had been treated at another children's hospital two weeks earlier and two had been at a home for post-natal care.

It is of considerable interest that in our series the strain was also found in the respiratory tract (see Table I). Special note should be made of the fact that it was relatively often found in the nose. This is in view of the recent investigations of so-called dangerous carriers, in which it could be shown by Laurell (1950) that those with coliform bacteria in the nose most easily spread the infection to their surroundings.

TABLE I

	Coliform Bacteria in Throat Only	B.C.N. in Throat Only	Coliform Bacteria in Throat and Nose	B.C.N. in Throat and Nose
Infants with dyspepsia:				
Epidemic I	7	3	7	5
Epidemic II	3	—	7	7
Infants without dyspepsia:				
Epidemic I	3	—	2	—
Epidemic II	11	—	2	—

The incubation time could be determined approximately in the case of 17 infants. In no case did it exceed 17 days, nor was it less than 4 days. In the majority of instances it varied between 8 and 12 days.

The clinical picture was the same in both epidemics, the main symptom being more or less severe gastro-enteritis usually accompanied by vomiting. In the first epidemic, with 5 deaths, 12 cases were regarded as severe or moderately severe and 8 as mild. In the second epidemic, in which no deaths occurred, 11 infants were seriously ill and only 2 had mild symptoms. All the infants were less than 1 year of age and 22 less than 1 month. It is of interest to note that 12 of the children affected (5 in the second epidemic) were admitted to hospital for prematurity. In conformity with the findings of Taylor, Roberts, and others, the youngest infants were commonly those most severely affected. In order to illustrate the clinical picture in more detail, accounts of two typical cases are given.

Typical Cases

Case A.—A newborn girl was admitted on the grounds of prematurity; weight at birth, 1,550 g. Nothing of note occurred during the first week in hospital. On the 11th day after admission there was slight diarrhoea, with a failure to gain in weight. Penicillin and "elkosin" therapy was started and aminosol glucose and Darrow's solution given subcutaneously. During the subsequent days there was a temporary improvement with a gain in weight. On the 23rd day there was a sudden exacerbation with increasing diarrhoea. Streptomycin therapy was started and fluids given intravenously. The condition nevertheless continued to deteriorate, the diarrhoea became watery and extremely severe, and death ensued on the 40th day. Pure cultures of B.C.N. were found in the stools seven days before death. Necropsy revealed no pathological condition in the intestines, but there was bilateral bronchopneumonia as well as bilateral purulent mastoiditis; clinically, the infant died from an acute intestinal infection.

Case B.—A newborn boy was also admitted on the grounds of prematurity; weight at birth 2,370 g. Initially there was nothing of note, but on the seventh day in hospital frequent defaecations and a loss in weight began. Sulphonamide was given by mouth, penicillin intravenously, plentiful fluids (Darrow's solution and aminosol glucose) subcutaneously, and breast milk, arobon, and glucose solution by mouth. There was no improvement; on the contrary a marked exacerbation occurred on the 13th day after admission, with pronounced symptoms of shock, bad colour, depression of the fontanelle, appreciable loss of weight, and 10 to 13 watery, violent, and mucous defaecations a day as well as frequent vomiting. He was put in an oxygen tent, streptomycin being administered by mouth and serum intratibially. During the following week his general condition varied, but there was no marked improvement. The administration of sulphonamide and antibiotics was therefore stopped. B.C.N. was found in the stools on the 17th day of illness and in the nose and stools on the 28th day. An intravenous cannula had been inserted earlier (on the 20th day of illness), and during the next six days he was mainly nourished in this way. There was then a rapid progress with a considerable

*The strain has also been described under the name of *Bact. coli* D 433 and B.G.T. (Bray, Giles, Taylor). Kaufmann classified the strain as O 110, B 4 in Kaufmann-Vahne's coli antigen list.

gain in weight and an improvement in the stools. The improvement continued and the patient was discharged from hospital with a weight of 2,560 g.

Treatment

During the first few days after the development of gastro-enteritis fluids were given liberally in the form of plasma, aminosol glucose, and Darrow's solution subcutaneously or intravenously and arobon and carrot soup by mouth. The basic food was breast milk.

Penicillin and sulphonamide compounds were tried in the majority of cases in both epidemics, but they had no effect on the gastro-intestinal symptoms. We noted, as did Rogers *et al.* (1949), that in several cases the gastro-enteritis had its onset in the course of penicillin and sulphonamide therapy. Streptomycin was given as well in 17 cases, but no specific therapeutic effect was seen. In this respect our results were in agreement with those reported by Holzel *et al.* (1949) and by Rogers *et al.*

"Aureomycin" Therapy

As mentioned earlier, eight patients in the second epidemic were treated with aureomycin after it had been found that the bacteria were sensitive to this antibiotic. The resistance varied inappreciably, and lay between 0.16 and

bacteria gave rise to no pathological symptoms. The clinical improvement in connexion with aureomycin therapy was striking. In order to illustrate the effect of treatment the most important clinical data are assembled in Table III and a brief account is given of the course of the illness in the patients treated.

Case 1.—The patient, a newborn infant, was admitted to hospital on the grounds of prematurity. After 17 days, in the course of penicillin treatment, he became ill with acute gastro-enteritis, manifested in vomiting and frequent watery defaecations. The constitutional disturbances became increasingly evident, the abdomen was moderately distended, and the colour ashen-grey. Streptomycin therapy was started and fluids given subcutaneously. As there was no improvement after three days and B.C.N. had been found on culture from the faeces, aureomycin treatment was begun. After 24 hours' treatment the stools were of half-solid consistency but still frequent. From the fourth day of treatment there was a good daily increase in weight and the stools were normal.

Case 2.—The patient, a newborn infant, was admitted to hospital for debility. After 12 days, in the course of penicillin therapy, gastro-enteritis developed, with frequent watery defaecations, vomiting, and loss of weight. The colour was ashen-grey and constitutional disturbances were present. Streptomycin therapy was started and fluids were given subcutaneously. B.C.N. was then found in the stools. There

TABLE II.—Presence of B.C.N.

Case No.		No. of Positive Tests Before Treatment	Day of Treatment with Aureomycin												
			1*	2	3	4	5	6	7	8	9	10	11	12	13
1	Faeces + nose	3	+	0	0	0	0	0	0	0	0	0	0	0	0
	Stools	3	+++	+	0	0	0	0	0	0	0	0	0	0	0
2	Faeces + nose	1	+++	++	++	+	++	+	+	+	0	0	0	0	0
	Stools	1	+++	+++	0	0	0	0	0	0	0	0	0	0	0
3	Faeces + nose	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Stools	2	+++	0	0	0	0	0	0	0	0	0	0	0	0
4	Faeces + nose	2	++	0	0	0	0	0	0	0	0	0	0	0	0
	Stools	2	+++	+	+	0	0	0	0	0	0	0	0	0	0
5	Faeces + nose	4	++	++	0	0	+	+	+	0	0	0	0	0	0
	Stools	6	+++	++	0	0	0	+	0	0	0	0	0	0	0
6	Faeces + nose	1	+	0	0	0	0	0	0	0	0	0	0	0	0
	Stools	1	+++	0	0	0	+	0	0	0	0	0	0	0	0
7	Faeces + nose	6	+++	0	0	0	0	0	0	0	0	0	0	0	0
	Stools	7	+++	+++	0	+	0	0	0	0	0	0	0	0	0
8	Faeces + nose	0	0	0	+	+	0	+	0	0	0	0	0	0	0
	Stools	1	+++	+	+	0	0	0	0	0	0	0	0	0	0

+++ = Plentiful. ++ = Moderate. + = Sparse (enrichment performed). 0 = B.C.N. not demonstrable (enrichment performed). * The first day of treatment denotes the day on which aureomycin therapy was started.

0.6 µg./ml. (resistance tests made in thioglycollate broth). The aureomycin was given by mouth in doses of 25 mg. six times a day. The results of the bacteriological investigations to determine the presence of B.C.N. after the inception of aureomycin therapy are given in Table II.

During the first few days after the institution of treatment coliform bacteria were found that were not identical with B.C.N. These also disappeared later and *Monilia albicans* was then the micro-organism most often encountered both in the stools and in the respiratory tract. *Pseudomonas pyocyanea* was found in three of the infants. These

was a successive marked exacerbation, and streptomycin was therefore withdrawn on the fourth day and replaced by aureomycin. During the subsequent 24 hours the condition was unchanged, but after this time the stools became considerably firmer and less frequent and vomiting ceased entirely. From the fifth day of treatment the faeces were normal and there was a satisfactory daily gain in weight.

Case 3.—A 2-day-old girl was admitted on the grounds of prematurity. After 10 days her motions were frequent and loose. Although her general condition remained good and the gain in weight was satisfactory, penicillin and streptomycin were given as well as fluids subcutaneously. Her

TABLE III.—Clinical Data

Case No.	Sex	Age in Days	Weight	Reason for Admission	Severity	Days after Admission before Onset of Gastro-enteritis	Complications	Intravenous Alimentation	Results
1*	M	1	1,480 g.	Prematurity	Severe	17	Sore buttocks	No	Recovered
2*	F	1	2,010 g.	"	"	12	" "	"	"
3*	F	2	1,980 g.	"	"	10	" "	"	"
4*	F	2	1,990 g.	"	"	15	" "	"	"
5	F	18	2,620 g.	Gastro-enteritis	"	On admission	" "	Yes	"
6*	M	2	2,550 g.	Delayed emptying of stomach	"	14	" None	"	"
7	M	22	2,790 g.	Gastro-enteritis	"	On admission	Sore buttocks	"	"
8	M	1	1,480 g.	Prematurity	"	8	" "	No	"

* In none of these cases could B.C.N. be demonstrated before the onset of gastro-enteritis.

general condition gradually deteriorated and the stools became still looser and more frequent. As B.C.N. was found to be present in them, aureomycin was given. During the first four days there was still some loss of weight, but thereafter rapid improvement ensued with a satisfactory daily gain in weight.

Case 4.—This patient, a twin sister of Case 3, was also admitted for debility. Her development was at first normal, but after two weeks there was a sudden acute onset of gastroenteritis with frequent watery motions, vomiting, and a loss of weight. B.C.N. was isolated on culture and aureomycin therapy was started on the second day. After 24 hours the stools were of half-firm consistency and the loss of weight ceased. From the fourth day of treatment there was a satisfactory daily gain in weight and the stools were firm in consistency.

Case 5.—An 18-day-old baby girl had suffered from vomiting and frequent mucous or watery motions for a week before admission to hospital. At the onset of the illness she was in a home for post-natal care. B.C.N. was found in the faeces on the day of admission. At first streptomycin and penicillin were given as well as fluids by the intravenous route. There was an initial improvement for a few days, but thereafter a marked exacerbation with vomiting and increasingly abnormal motions. Aureomycin therapy was started, and as soon as 48 hours later the stools were half-firm and a satisfactory gain in weight was noted. Improvement continued and the faeces rapidly became normal.

Case 6.—A 2-day-old boy was admitted to hospital for dyspepsia and mucous defaecations. Examination revealed delayed emptying of the stomach, but repeated cultures failed to demonstrate the presence of B.C.N. in the faeces. Penicillin was administered as well as fluids subcutaneously. There was gradual improvement, but after 14 days an acute exacerbation occurred with vomiting and loose stools. Culture then revealed B.C.N. in the faeces, and aureomycin therapy was therefore started. The stools rapidly became normal, but frequent vomiting still occurred and the loss of weight continued. Only after persistent plentiful administration of fluids intravenously did the general condition improve and an increase in weight take place. The protracted course of the illness is presumably to be ascribed to the basic disorder.

Case 7.—A 22-day-old boy had suffered from vomiting and mucous defaecations for one week before admission with an appreciable loss of weight from 3,430 g. to 2,790 g. During the first week of life he was at another hospital for children. On admission he was pale and dehydrated, and there was slight peripheral cyanosis. Oidium was present in the oral cavity. The abdomen was distended and blood oozed from the umbilicus. There was violent watery diarrhoea and vomiting. Fluids were administered intravenously, but he got worse and the loss of weight continued. The presence of B.C.N. was demonstrated already on the day of admission, but aureomycin was not given until the seventh day of illness. After 48 hours the stools became normal and the increase in weight satisfactory. Improvement continued.

Case 8.—A 1-day-old boy was admitted because of prematurity. Apart from the difficulty of keeping his temperature up, there was nothing of note the first week. On the eighth day he became acutely ill with vomiting and watery diarrhoea. The abdomen was distended and his colour was ashen-grey. B.C.N. was present in the stools and aureomycin therapy was started next day. After 24 hours a definite improvement could be noted, and after three days' treatment the stools were normal and the gain in weight satisfactory.

Summary

An investigation at the Sachs Hospital for Children in Stockholm revealed the presence of a special strain of *Bact. coli*—that is, *Bact. coli neapolitanum* (B.C.N.)—in the stools and at times in the respiratory tract of babies suffering from infantile diarrhoea and vomiting. This agrees with the findings of other authors. Eight of the patients were treated with aureomycin. Its effect was marked. Even after a few doses the B.C.N.

present in the stools before the inception of treatment could no longer be found. Only in a few cases did it persist somewhat longer in the respiratory tract. Parallel with this bacteriological effect there was an improvement in the clinical condition.

REFERENCES

- Bray, J. (1945). *J. Path. Bact.*, **57**, 239.
— and Beavan, T. E. D. (1948). *Ibid.*, **60**, 395.
Giles, C., and Sangster, G. (1948). *J. Hyg., Camb.*, **46**, 1.
— and Smith, J. (1949). *Arch. Dis. Childh.*, **24**, 45.
Holzel, A., Martyn, G., and Apter, L. (1949). *British Medical Journal*, **2**, 454.
Laurell, G. (1950). In press.
Rogers, K. B., Koegler, S. J., and Gerrard, J. (1949). *British Medical Journal*, **2**, 1501.
Taylor, J., Powell, B. W., and Wright, J. (1949). *Ibid.*, **2**, 117.

NITROUS OXIDE ANAESTHESIA WITHOUT HYPOXIA

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Nitrous oxide possesses many qualities which meet both the clinical and the physical demands for a safe anaesthetic. The ever-present explosion hazard with the inflammable anaesthetics has been increased by the surgical trend towards greater use of the high-frequency electro-surgical unit and has challenged the anaesthesiologist to provide general anaesthesia with non-inflammable and non-explosive agents of low toxicity.

Neff, Mayer, and Perales (1947), in a preliminary report, outlined a method of potentiating the anaesthetic action of nitrous oxide by the intravenous administration of "demerol" (pethidine hydrochloride). Thompson (1950), in an experimental and clinical investigation of two new analgesics closely related to pethidine, during nitrous oxide anaesthesia compared the effects of these drugs with morphine and pethidine. Neff and Thompson (1948) later concluded that these new analgesics were less satisfactory than pethidine for fortifying the anaesthetic action of nitrous oxide. Mushin and Rendell-Baker (1949) confirmed the efficacy of pethidine for the supplementation of nitrous oxide anaesthesia, and Brotman and Cullen (1949) emphasized its usefulness in geriatric anaesthesia.

An extensive study of the problems incident to the use of nitrous oxide and pethidine anaesthesia has been in progress for the past five years. During this period nitrous oxide anaesthesia has been employed for all kinds of intra-abdominal, intrathoracic, and other extensive operations. Experience gained through the administration of nitrous oxide on several thousand occasions since the preliminary report has provided the stimulus to attempt to review and re-evaluate the present status of this gas.

Nitrous Oxide Anaesthesia without Oxygen Restriction

Modern anaesthesia with gases or volatile liquids presupposes a combination of these agents with oxygen. One uses the terms ether anaesthesia, cyclopropane anaesthesia, and chloroform anaesthesia, but in the case of nitrous oxide the more cumbersome and very often less descriptive