

population of the Midlands, having no obvious disease or chance infection. This being so, our results show that the average blood levels of the total carotenoids and vitamin A are lower in this part of England than those found in other countries.

In the Medical Research Council's Special Report on Vitamin A Requirements of Human Adults are assembled all the available data on the normal value for the carotenoid and vitamin A content of human blood plasma in 195 subjects, and Moore and Leitner, who carried out the investigation, point out that some American authors, in calculating the values for vitamin A, do not appear to have made any correction for the blue colour contributed by carotenoids to the antimony trichloride reaction. They also state that some of the earlier workers in America used the U.S.P. unit, which is now held by Hume (1943) to have only 87% of the value of the international unit, and that it is not always possible in retrospect to be certain which unit was really meant.

These facts may account for the apparent discrepancies between American and English results, as well as the fact that the people of Britain do not have access to unlimited fat, and have not acquired the taste for large quantities of green vegetables and salads. In our series 85% of cases have total carotenoid plasma levels lying between 40 and 120 $\mu\text{g./100 ml.}$, and vitamin A plasma levels between 80 and 130 i.u./100 ml., and these are suggested as being reasonable limits for normality under conditions prevailing in the Midland area of England during 1947.

The results of our investigation indicate slightly lower levels for vitamin A, and considerably lower levels in total carotenoids, compared with those found by other English workers (Yudkin, 1941; M.R.C., 1949).

Summary

The levels of total carotenoids and vitamin A in the plasma of 133 normal adults were estimated. The investigation took place throughout the year 1947. The normal range was found to be:

Total carotenoids ($\mu\text{g./100 ml.}$)	..	20-199	Mean	80
Vitamin A (i.u./100 ml.)	..	69-158	108

but since 85% of our cases gave values of

Total carotenoids ($\mu\text{g./100 ml.}$)	40-120
Vitamin A (i.u./100 ml.)	80-130

these are suggested as limits of normality under conditions prevailing in the Midland area of England in the year 1947.

Vitamin A levels showed a slight fluctuation during the year, while the level of the total carotenoids rose steadily from March to December.

Those subjects performing hard manual labour showed lower levels of total carotenoids and vitamin A than subjects engaged in light or sedentary occupations.

Thymol turbidity tests were performed on a series of 110 normal adults, and it was found that when allowance is made for a "blank" test the normal range is 0 to 1.5 ml. of barium sulphate suspension, with a mean value of 0.59 ml.

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CHLORAMPHENICOL IN TREATMENT OF INFANTILE GASTRO-ENTERITIS

A PRELIMINARY REPORT

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Bray (1945), Giles and Sangster (1948), and Taylor *et al.* (1949) independently noted a close correlation between the same serologically specific type of *Bact. coli* and epidemic infantile gastro-enteritis. This *Bact. coli* is referred to in this communication as *Bact. coli* B.G.T. (Bray-Giles-Taylor).

During the last ten months one of us (K. B. R.) has studied the appearance of this organism in 86 infants under the age of 1 year admitted to the Birmingham Children's Hospital. Routine rectal swabs were taken on admission and in many cases five days later, and again if a case of gastro-enteritis appeared in the ward. The first isolation of the *Bact. coli* B.G.T. from the stool was noted and the subsequent progress of the infant observed.

Epidemiology

In 17 cases it was possible to calculate the interval between the time of the first isolation of this organism from the faeces and the development of a gastro-intestinal disturbance. In all cases except one this period was less than 22 days; the exception was a case which developed diarrhoea at home 24 days after the first positive rectal swab. The shortest interval was four days, in two cases; the average interval was 11 days. It must be emphasized that in 25 of the 86 cases observed the appearance of the *Bact. coli* B.G.T. in the faeces was followed by no untoward symptoms; these cases were followed for a period of at least one month.

This organism was isolated from the stools of 86 babies under the age of 1 year, 82 of whom acquired the organism after admission to hospital; 25 patients, 10 of whom were less than 4 months old, had no intestinal symptoms, while the remaining 61 developed gastro-intestinal disturbances which varied from a severe gastro-enteritis to a mild diarrhoea with or without vomiting; of these 61 patients 13 died. All of the deaths occurred in infants under the age of 4 months, except in two who were aged 10 months. One of the two, a mongoloid idiot, collapsed and died directly after discharge from hospital, but to what extent the *Bact. coli* was responsible is not known. The other, a case of pink disease, died primarily of respiratory failure associated with an extensive polyneuritis and diaphragmatic palsy, but she also had a severe terminal enteritis. The finding that *Bact. coli* B.G.T. is more commonly associated with severe gastro-enteritis in the younger babies is in agreement with the observations of Taylor *et al.* (1949). That the appearance of *Bact. coli* B.G.T. in the stools is sometimes associated with a fulminating gastro-enteritis is suggested by such typical case histories as the following.

Case 1.—A girl aged 3 months was admitted with pseudo-paralysis due to congenital syphilis, for which she received penicillin. A month after admission *Bact. coli* B.G.T. was isolated from the faeces; 15 days later, after her transfer to another hospital for further antisyphilitic treatment, she developed diarrhoea. Four days after the onset she collapsed and died.

Case 2.—A girl aged 2 months was admitted with cystic fibrosis of the pancreas. Her progress was satisfactory at first, but five days after *Bact. coli* B.G.T. was isolated from the stools she developed a watery diarrhoea and 10 days later she died. Necropsy revealed fibrocystic dystrophy of the pancreas complicated by enterocolitis, bronchopneumonia, adhesive pleurisy, and right otitis media; clinically the severe gastro-enteritis was the cause of her sudden death.

Case 3.—A girl aged 1 month was admitted because she had vomited with increasing severity since birth and had become jaundiced. Diarrhoea was present on admission and the stools contained *Bact. coli* B.G.T. In spite of intravenous alimentation the gastro-enteritis persisted and she died 13 days later.

Case 4.—A girl aged 1 month was admitted with generalized convulsions precipitated by an otitis media. From this she made an uneventful recovery. Four days after admission *Bact. coli* B.G.T. was isolated from the stools; 10 days later gastro-enteritis developed and after nine days she died. Necropsy revealed a haemorrhagic enterocolitis with intestinal pneumatosis and an early peritonitis.

Treatment with Penicillin and Sulphonamides

All cases of severe gastro-enteritis were treated as a routine with intravenous alimentation until the diarrhoea and dehydration were controlled, followed by graded oral feeding. Initially, penicillin and sulphonamides were also administered. These agents helped to control parenteral infections, such as otitis media, but they seemed to have little or no direct effect on the gastro-enteritis. In fact, *Bact. coli* B.G.T. appeared in the stools and gastro-enteritis developed in some cases while the infant was actually receiving both penicillin and sulphonamides. Case 5 is an example.

Case 5.—A girl aged 6 months was admitted with scalded buttocks, and developed gastro-enteritis associated with the isolation of *Bact. coli* B.G.T. while on penicillin, sulphonamides, and streptomycin.

In no case did either penicillin or sulphonamides remove *Bact. coli* B.G.T. from the stools once this organism had made its appearance.

Treatment with Streptomycin

Streptomycin proved to be equally disappointing in its failure to cure gastro-enteritis. Although only 12 cases were treated with this drug, four orally and the remainder by intramuscular injection, the results did not appear to justify further investigation. Our small experience supports that of Holzel *et al.* (1949) and not that of James *et al.* (1948). In Holzel's series 50 of the 79 cases were associated with *Bact. coli* B.G.T., but this organism was not mentioned by James *et al.*, whose cases might therefore have had a different aetiological agent.

In three of our cases which received streptomycin *Bact. coli* B.G.T. was actually isolated from the faeces for the first time while streptomycin was being given for other conditions (miliary tuberculosis, a large infected naevus, and infected scalds of buttocks). Two of these cases developed a severe gastro-enteritis necessitating intravenous alimentation; the third had no more than a mild diarrhoea preceded by a loss of weight. Of the remaining nine patients one died, a second deteriorated whilst on streptomycin, and seven recovered, but only one made a quick recovery. *Bact. coli* B.G.T. disappeared from the stools of only one child while it was receiving streptomycin.

Chloramphenicol

When it was decided to investigate the efficacy of one of the newer antibiotics, chloramphenicol ("chloromycetin") was chosen because all strains tested were sensitive to this drug; they were also sensitive to "aureomycin," but chloramphenicol was used because of its relative stability. Chloramphenicol was first described by Ehrlich *et al.* (1947), who mentioned that *Bact. coli* was sensitive to it. It is felt that the results with this

Table Showing Cases Treated with Chloramphenicol

Case	Sex	Age in Months	Reason for Admission	Days After Admission Before Onset of G.E.	Severity	Duration of Treatment with Chloramphenicol in Days	Complications	I.V. Alimentation	Days Taken to Clear <i>Bact. coli</i> B.G.T.	Result	Comments
S.B.	F	6	Scalds of buttocks	13	Severe	13	Infected scalds and G.E.	Yes	5	Died	Died 9 days after disappearance of <i>Bact. coli</i> B.G.T. from stools but after diarrhoea had ceased
M.C.	M	2	Otitis media	18	Severe	15	None	Yes	3	Survived	Readmitted with G.E. 10 days after discharge from original admission for nutritional disorder and pink disease
G.H.	M	8	Pink disease	On readmission	Moderate	10	Sore buttocks	No	3	"	
N.H.	M	3	Otitis media	11	Severe	10	Mastoiditis	No	2	"	Bacteriological relapse 7 days after cessation of chloramphenicol. Had been clear 15 days
J.M.	F	1	Marasmus	12	Severe	11	Sore buttocks	Yes	3	"	
R.M.	M	1	Pyloric stenosis	17	Moderate	9	None	No	?	"	Bacteriological relapse 1 day after cessation of chloramphenicol; had been clear for 5 days
L.P.	F	5	G.E.	On admission	Severe	7	Staphylococcal septicaemia and osteomyelitis	Yes	3	"	
W.R.	F	4½	Thrush and parotitis	11	Severe	13	Sore buttocks	Yes	5	"	Readmitted with G.E. 4 days after discharge from original admission for otitis media and asthma
D.S.	M	5	G.E.	On readmission	Severe	14	None	Yes	7	"	
R.S.	M	8	Pink disease	15	Moderate	12	"	No	8	"	Discharged from another hospital 8 days before admission
S.S.	F	5	G.E.	On admission	Moderate	13	"	No	3	"	
D.T.	M	1½	Meningitis	40	Severe	14	Sore buttocks	Yes	4	"	(Twin died of G.E. associated with <i>Bact. coli</i> B.G.T. and received no chloramphenicol.) Readmitted with G.E. 13 days after discharge from original admission for otitis media
J.C.	F	3	Prematurity	On readmission	Severe	13	Otitis media	Yes	5	"	
J.N.	M	2½	G.E.	On admission	Mild	6	None	No	3	"	Attending a day nursery
J.P.	F	2	Marasmus	27	Mild	9	"	No	Never	"	

J.C., J.N., and J.P. were carriers who had recovered from their initial G.E., but who still excreted *Bact. coli* B.G.T.

G.E. = Gastro-enteritis.

antibiotic are hopeful enough to warrant a preliminary communication, although it is realized that the number treated is small. The age groups in the different series are not strictly comparable; moreover, individual cases vary so much in severity that, with small numbers, comparisons are invidious. These results can best be illustrated by the following case histories. (For further details of cases see table.)

Case 5 (already referred to).—In spite of treatment with sulphonamides, penicillin, and streptomycin her gastro-enteritis continued, but within five days of starting chloramphenicol *Bact. coli* B.G.T. disappeared from the stools and the diarrhoea ceased. Unfortunately she died from complications due to burns nine days after the disappearance of *Bact. coli* B.G.T. from the faeces. A post-mortem examination was not made.

Case 6.—A boy aged 5 weeks was admitted with meningococcal meningitis. Nineteen days after the first appearance of *Bact. coli* B.G.T. in the stools, and while receiving both sulphonamides and penicillin, he developed a severe gastro-enteritis. No improvement followed the administration of streptomycin, but within three days of starting chloramphenicol therapy the diarrhoea ceased; a day later *Bact. coli* B.G.T. disappeared from the stools. Further recovery was uneventful.

Case 7.—A boy aged 8 months was admitted with pink disease. Fifteen days after admission he developed gastro-enteritis associated with the isolation of *Bact. coli* B.G.T. from the faeces. With penicillin and sulphonamide therapy there was little improvement, but on chloramphenicol the organism disappeared within eight days, the diarrhoea ceased, and he started to gain weight satisfactorily.

Case 8.—A girl aged 4½ months was admitted with thrush and a left parotitis. The infection subsided with the application of gentian violet locally and penicillin systemically, but 10 days after the isolation of *Bact. coli* B.G.T. from the stools she developed diarrhoea and lost 12 oz. (340 g.) in weight in three days. The enteritis did not respond to symptomatic treatment, but when chloramphenicol was given the diarrhoea ceased; *Bact. coli* B.G.T. disappeared from the stools in five days.

In eight additional cases the administration of chloramphenicol, in conjunction with intravenous alimentation where necessary, and graded feedings, was followed by rapid amelioration of the diarrhoea, and *Bact. coli* B.G.T. could no longer be recovered from the faeces. In three cases there was a bacteriological relapse, although no case had a recurrence of the diarrhoea.

Carriers.—Three children who had had diarrhoea associated with the presence of *Bact. coli* B.G.T. but had recovered from their diarrhoea still excreted this organism in the faeces. They were given chloramphenicol. In one case *Bact. coli* B.G.T. was not recovered from the faeces after the third day of treatment. In a second the organism was not recovered from the fifth day of treatment until four days after the cessation of treatment, when a bacteriological relapse occurred. In the third case this organism was still present in the faeces after nine days' treatment.

Clearance of the Organism.—The average time for chloramphenicol to effect a clearance of *Bact. coli* B.G.T., except in the carriers already mentioned, was four days, within the limits of two and eight days. In two cases the organism reappeared in the faeces one and seven days after cessation of treatment which had lasted seven to eleven days respectively, but the organisms were still sensitive to chloramphenicol. These cases may have been either true relapses or reinfections, as neither had been discharged from the infected ward.

Parenteral Infection.—Six cases were admitted with otitis media. No *Bact. coli* B.G.T. were isolated from their faeces, but before these infants were fit for discharge they had not only acquired the organism but had also developed gastro-enteritis. It is understandable that, in the absence of recognition of any organism as a potential pathogen

in the stools, the diarrhoea might be ascribed to the inflammation in the ears. In point of fact, the sequence of events would seem to have been an initial infection necessitating admission to hospital, followed by a subsequently acquired intestinal infection. An otitis media was present at the onset of the gastro-enteritis in two cases; in three additional cases an otitis media developed from five to ten days after the onset of the gastro-intestinal infection. In no case was *Bact. coli* B.G.T. isolated from the middle ear.

Other Cases

Case 9 is worthy of special mention as it was the only one in which a primary urinary infection with *Bact. coli* B.G.T. was encountered.

Case 9.—A boy aged 7 weeks was admitted with anaemia, mild jaundice which developed during the week before admission, severe urinary-tract infection, and bilateral otitis media. The urine contained many pus cells, casts, and a few red cells, and gave a heavy pure growth of *Bact. coli* B.G.T. There was no evidence of any abnormality in the blood apart from anaemia. Gastro-enteritis developed three days after admission, but *Bact. coli* B.G.T. were not isolated from the faeces. The urinary infection was not influenced by penicillin, given on account of the otitis media, or by sulphonamides, but responded dramatically, as did the enteritis, to chloramphenicol.

Bact. coli B.G.T. may be associated with diarrhoea in older children; the oldest child known to be affected in this hospital was a girl 4 years old, and although, because of her age, she is not included in this series, her case history is of considerable interest. Soon after she had successfully negotiated a Blalock-Taussig operation she developed severe enteritis in which the only potential pathogenic organism that could be isolated was *Bact. coli* B.G.T. After three days' treatment with chloramphenicol, given for seven days, the diarrhoea ceased and *Bact. coli* B.G.T. was no longer isolated from the stools. Before this case occurred no gastro-intestinal disturbance associated with the presence of *Bact. coli* B.G.T. had been discovered in the general wards of this hospital. The enteritis in this 4-year-old girl began 15 days after a baby who was excreting the organism had been transferred to her ward.

Administration of Chloramphenicol

Chloramphenicol is marketed in 250-mg. enteric-coated capsules, but as infants cannot swallow these the drug has been given as a suspension with tragacanth flavoured with syrup of raspberry and chloroform water. The babies have needed little encouragement to take it in spite of its bitter taste. The dosage given has been 75 mg. per lb. (165 mg. per kg.) body weight per day in six or eight divided doses; the initial dose was twice the maintenance dose.

Complications of Chloramphenicol Therapy

The administration of chloramphenicol has occasionally coloured the stools bright green. Four of the cases developed sore buttocks followed by a spreading generalized dermatitis which cleared only after two weeks, but it is not established that chloramphenicol was responsible. Apart from this possible toxic reaction, no untoward effects have been noted; routine blood counts and urine examinations on all cases have shown no abnormalities.

Further Investigation

A trial with chloramphenicol is now being undertaken on all severe cases of infantile gastro-enteritis, irrespective of the presence of the known specific strains of *Bact. coli*. Although *Bact. coli* B.G.T. is often associated with gastro-enteritis there is no proof of its actual pathogenicity, and, moreover, a number of babies who excrete this specific strain of *Bact. coli* never develop symptoms: there may

have been a previous undetected infection with *Bact. coli* B.G.T. in these cases. On the other hand, an appreciable number of children are admitted with primary gastro-enteritis without any identifiable specific strain of *Bact. coli* in their faeces.

Bacteriology

Routine Examination.—Faeces from cases of gastro-enteritis were examined to exclude the presence of protozoa and cultured on Leifson's desoxycholate citrate medium as well as in selenite enrichment medium to exclude the presence of salmonellae and shigellae. A MacConkey plate was also inoculated and at least four representative colonies were tested by slide agglutination, using Bray and Beavan's (1948) technique, which gave very clear-cut and reliable results. All positive colonies were inoculated into sugars, and a culture was sent to Dr. Joan Taylor, who very kindly confirmed their identity.

Sensitivity of the Organism to Chloramphenicol.—*Bact. coli* B.G.T. was inhibited in concentrations of chloramphenicol varying between 2 to 4 $\mu\text{g./ml.}$ Tests were made using representative colonies from each specimen from which *Bact. coli* B.G.T. was isolated whilst the child was on chloramphenicol treatment or if the organism reappeared after treatment had been stopped. No change in sensitivity of the organism was shown in these experiments. This is in agreement with the work of Smadel *et al.* (1949) and Alexander *et al.* (1949). This result is very different from those obtained with streptomycin, when insensitive variants began to appear in nearly all cases within 24 hours of the initiation of treatment. In most of the antibiotic-treated cases specimens of faeces were obtained once or twice daily during treatment and daily for two weeks after its cessation or until the patient was discharged.

Blood Levels.—Estimations of chloramphenicol blood levels were made; the technical difficulties were not fully overcome, but by the use of a modification of the technique described by Fleming and Smith (1947) levels up to 120 $\mu\text{g./ml.}$ were obtained. The test organism used was a strain of *Bact. coli* B.G.T. from Case 5. There seemed to be definite individual variations in the absorption of the drug by the patient, so a relatively high dose of chloramphenicol was employed.

Summary

In Birmingham, as in many other parts of Great Britain where it is sought, *Bact. coli* B.G.T. has been found to be intimately associated with epidemic infantile gastro-enteritis. The enteritis did not respond to the administration of sulphonamides, penicillin, or streptomycin, but the response, both clinically and bacteriologically, to chloramphenicol has been most encouraging.

We would like to express our thanks to the staff of the Children's Hospital, Birmingham, especially to Professor J. M. Smellie for his encouragement and most valuable criticism, to Sister M. Coker for her co-operation, and to Dr. Joan Taylor for much advice and help; also to Dr. C. Giles, who supplied the first antisera used in this investigation.

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PARATYPHOID B FEVER TREATED WITH CHLORAMPHENICOL

BY

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The clinical course of paratyphoid fever is subject to much variation. Compared with typhoid fever it is in general a milder disease, although attacks of paratyphoid fever occur which both in severity and in duration rank with typhoid even of the most severe form. Owing to this variation in degree of clinical illness it is difficult to assess the response to any particular form of treatment. Reports on paratyphoid B fever treated with chloramphenicol (chloromycetin) have been few. Christie (1949) has reported briefly on seven cases, and Kiledjian (1949) and Montuschi (1949) have each reported on a single case. As much investigation remains to be done before the full effect of the drug on paratyphoid fever can be finally assessed, and as it will be some time before an optimum scheme of dosage can be arrived at, the following report may be of interest.

Between June and October, 1949, six clinical cases of moderately severe paratyphoid B fever were admitted to Sheriff Hill Infectious Diseases Hospital. The diagnosis was confirmed in all cases by culture of *Salmonella paratyphi* B. All patients had been ill for some days before admission; treatment with chloramphenicol was started in three cases at the end of the first week, in two cases during the second week, and in the sixth case early in the third week of disease. The dosage and the period of administration of the drug varied, patients who were admitted later in the series receiving larger doses over a longer period. The frequency of administration remained constant, the drug being given at four-hourly intervals.

In addition to the above cases, three apparently healthy faecal carriers of *Salm. paratyphi* B were admitted and treated with chloramphenicol.

Case 1

A girl aged 11 was admitted on June 21, 1949, complaining of malaise, headache, anorexia, diarrhoea, and abdominal pain of five days' duration.

On examination she was obviously toxic, cerebation was dull, her mouth was dry, and her tongue was heavily furred. The abdomen was tumid and slightly tender. The spleen was just palpable. Her temperature was 99.4° F. (37.4° C.) and pulse 120.

Progress and Treatment.—On admission penicillin (200,000 units four-hourly) and sulphasuxidine (8 g. daily) were given and continued for five days. There was no improvement; diarrhoea, abdominal pain and tenderness, pyrexia, and drowsiness persisted. *Salm. paratyphi* B phage type 3A was cultured from faeces. On the tenth day of disease a course of chloramphenicol was

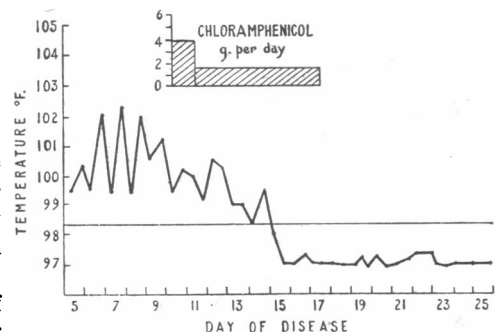


Chart 1.—Case 1.