AETIOLOGY OF JUVENILE DIARRHOEA

LABORATORY INVESTIGATION OF SPECIMENS REFERRED FROM GENERAL PRACTICES IN NORTH-EAST LONDON

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Much evidence has been published showing that certain serological types of *Escherichia coli* are the cause of infantile gastro-enteritis. The association has been found among babies in nurseries (Taylor and Charter, 1952), in hospital (Rogers and Koegler, 1951), and among hospital admissions (Ian Taylor, 1954). Such evidence refers almost exclusively to infants under 2 years old. The subject was reviewed in an editorial in the *Lancet* (1955).

Scope and Nature of Investigation

The present survey, made during the three years 1952–4, was undertaken primarily to observe the frequency with which such serotypes of *E. coli* strains occur in index cases of enteritis arising among children up to 4 years of age living in their own homes, and to compare the incidence of other infections and of the condition which has been termed "epidemic steatorrhoea" (Thomas, 1952). Within five days of the onset of a diarrhoeal illness 1,135 specimens of faeces were examined at the Edmonton Laboratory. Cases which had already had treatment were excluded. Faeces were collected in screw-capped bottles without preservative. Rectal swabs were not accepted; for it has been explained (Thomas, 1954b) that these specimens do not permit a full examination.

Technique

Specimens were studied macroscopically and microscopically, and a record was made of cells, parasites, incompletely digested foodstuffs, and other abnormalities. Cultures were made on MacConkey and deoxycholate citrate plates, and also into tetrathionate and selenite F enrichment broths, which, after overnight incubation, were subcultured on to deoxycholate citrate and Wilson and Blair plates. In 1953 the MacConkey medium was enriched by the addition of 1% of "lemco." This was found to reduce the frequency with which *E. coli* cultures showed non-specific agglutinability.

Biochemical and serological tests were used to identify shigellae, salmonellae, and other non-lactose-fermenting entero-bacteriaceae. In Edmonton six serotypes of *E. coli* were sought on the MacConkey agar by direct slide agglutination. A representative sweep of confluent growth and six isolated colonies were tested with pooled sera. Plates were forwarded to Colindale and further examined by one of us (R. E. C.). Here additional sera were used for slide testing, and suspected colonies of *E. coli* were submitted to detailed biochemical and serological tests. Slide tests were confirmed by the tube agglutination techniques described by Taylor and Charter (1952), who used heated and unheated suspensions. In general, O agglutinations only were used for routine identification of all serotypes, but complete serological analysis, including the identification of H antigen, was undertaken for O groups 111, 55, and 26.

For the first nine months of 1952 (191 cases) only six specific O sera were used—O 26, O 55, O 86, O 111, O 125, and O 126—but 18 were employed after October, 1952. Strains of *E. coli* agglutinating specifically with 16 of these 18 were isolated.

Table IV shows the serotypes isolated from 103 cases; it will be seen that 12 of these patients were first examined after having been ill for a period longer than five days or having had treatment. These cases are included with the 91 early acute index cases shown in Table I.

Results of Investigation

The findings are considered in relation to age (Table I), sex (Table II), and seasonal incidence (Table III), since differences were found in all these respects. Epidemic "summer diarrhoea" was not encountered, and more cases of enteritis were referred to the laboratory in the winter than in the summer months. There was an excess of males as compared with females in the total number of cases of diarrhoea; this excess was in the ratio 1.3 to 1, and this was true for each year of age. Table I summarizes the relation of pathological findings to the age of the patient.

Serotypes of E. coli.—Specific serotypes of *E. coli* were isolated from 13% of cases of diarrhoea occurring in babies under 12 months old and in 10.2% of cases in those aged 12–23 months. Older children showed a sharp drop in incidence of these serotypes of *E. coli* to 3.7% at the age of 2 years, and 1.6% at 3 years (Table I). Although Table II shows more cases of diarrhoea in males, sero-specific types

TABLE I.—*Analysis of Findings in Faeces Specimens from* 1,135 *Index Cases of Acute Diarrhoea in Young Children*

Findings	Age Group in Months				Total	
	0–	12–	24–	36–48	No.	%
No abnormality	119 (38·9%)	158 (42 6%)	130 (48·1%)	83 (44·1%)	490	43·2
Cells only	13	15	16	15	59	5·2
G. lamblia	1	11	8	9	29	2·6
Other parasites (*E. coli*, *I. butschlii*)	2	1	1	0	4	0·4
Excess fat globules only	46 (15%)	58 (15 6%)	31 (11·5%)	14 (7·4%)	149	13·1
Sh. sonnei	19 (6·2%)	28 (7·5%)	39 (14·4%)	40 (21·2%)	126	11·1
S. typhi-murium	9	8	10	5	32	2·8
Other salmonellae	1 (3·3%)	2 (2 7%)	Nil (3·7%)	2 (3·7%)	5	0·4
Primary culture of *Proteus* species	42 (13·7%)	35 (9·4%)	5 (1·9%)	7 (3 7%)	89	7·8
Providence	Nil	4	7	2	13	1·1
Other N.L.F.s	11	13	11	8	43	3·8
Klebsiella	3	Nil	2	Nil	5	0·4
Serological type of *E. coli*	40 (13·1%)	38 (10·2%)	10 (3·7%)	3 (1·6%)	91	8·0
Totals	306	371	270	188	1,135	

TABLE II.—*Sex Distribution of Findings in Faeces from* 1,135 *Index Cases of Diarrhoea in Children Under* 4 *Years of Age (Male Predominance)*

Findings	Male	Female
No abnormality	297	193
Cells only	35	24
Protozoa	20	13
Excess fat globules only	81	68
Sh. sonnei	71	55
Salmonellae	20	17
Proteus	46	43
All other N.L.F.s	31	25
Klebsiella species	4	1
Serological type of *E. coli*	45	46
Totals	650	485

TABLE III.—*Seasonal Distribution of Findings in* 677 *Cases in Children Under* 2 *Years (Winter Predominance)*

Findings	Summer (April–September)	Winter (January–March and October–December)
No abnormality	122	155
Cells only	14	14
Protozoa	5	10
Excess fat globules only	33	71
Sh. sonnei	21	26
Salmonellae	14	6
Proteus	38	39
All other N.L.F.s	14	14
Klebsiella species	3	—
Serological type of *E. coli*	42	36
Totals	306	371

TABLE IV.—*Serological Types of E. Coli Isolated from Children Under 4 Years, and Their Seasonal Distribution (91 Cases, Together with 12 Cases of Either More than 5 Days' Duration or Having Had Treatment)*

Serological Types of *E. coli*	Summer (April–September)	Winter (October–March)
O 26	25 (1)	10
O 111	9 (2)	9 (1)
O 55	4	6 (3)
O 86	1	2
O 125	2 (1)	2
O 126	1	4
O 119	0	1
O 128	5 (1)	0
O 127	1	1
O 114	2	1
Others of unclassified O group	7 (1)	10
Totals ..	57 (6)	46 (4)

Figures in parentheses denote number of cases with institutional history included in totals given.

of *E. coli* did not account for this predominance, as these organisms were found in 46 out of 485 females and in 45 out of 650 males. Identified *E. coli* infections showed no seasonal trend, except for type O 26, which, like the salmonellae, was commoner in summer than in winter. From Table IV it is apparent that the commonest *E. coli* serotypes to be encountered during the period under review were O 26, O 111, and O 55, which together accounted for nearly two-thirds of the *E. coli* infections recognized. The failure to demonstrate any constancy in the H antigens within the O groups 26, 55, and 111 suggested that many infections were not related. The serotypes of *E. coli* which most commonly cause outbreaks of gastro-enteritis—that is, types O 111, O 55, O 128, and O 119—were found to account for about one-third of all these sporadic coli infections, whereas the remaining two-thirds were infected with other specific types, especially O 26. In only a few of these infections was there evidence of a second aetiological agent also present—fat in three, *Sh. sonnei* in three, *Giardia* in three, and *Salmonella* in one. These second agents are omitted from Table I.

Shigellae.—Sh. sonnei was the only member of the *Shigella* group encountered. While this organism infected many children in nurseries, it was less common among young children at home. It was found in less than 7% of all cases under 24 months, but more frequently in the older age group.

Salmonellae.—These were found in 3.2% of the series. More cases occurred in summer than in winter, but there was little variation with age or sex. Of the 37 infections 32 were due to *Salm. typhi-murium.*

Proteus and Other Non-lactose-Fermenting Organisms.—The non-lactose-fermenting flora was recorded only when the growth on primary culture was profuse. Like the *E. coli* serotypes, *Proteus* strains were found more often in children under 24 months than in older children—an incidence of about 12% as compared with about 3% respectively. Most strains were *Proteus mirabilis.*

From a few children, organisms of the Providence group were isolated; in some instances they were present together with blood and pus. These organisms did not always grow reliably on deoxycholate citrate agar, but were easily isolated on MacConkey agar (Ridge and Thomas, 1955).

Fatty Diarrhoea or Epidemic Steatorrhoea

The stools from characteristic cases were very pale or putty-coloured and soft or fluid. Occasionally an aluminium sheen was evident.

A record of excess fat globules in Table I does not refer to the results of chemical analyses, which were often within the normal range for healthy children, but indicates that numerous globules of neutral fat (staining with Sudan III) of diameter 2 to 20 μ were visible in every microscopical field. Liquid paraffin had not been administered, and castor oil in three cases only, which were discounted. In normal stools at any age the only fats recognizable microscopically in quantity are soaps. While diets grossly over-supplied with fat may disturb the balance, no oily globules were seen in the faeces of 647 healthy control children under the age of 5 years who were taking a daily dose of cod-liver oil under supervision; 133 of these healthy children were under 1 year.

Steatorrhoea in this sense appeared as an independent abnormality, not as a complication of the symptom of diarrhoea, since it was eight times commoner in the absence of other abnormalities than in their presence. In very few cases indeed was undigested starch also seen. The incidence was highest in children under 24 months old, and it showed a winter rise in prevalence.

In our experience it was not associated with giardiasis, for it was not found either in the 29 cases included in Table I or in a further 92 contact infections under the age of 5 years.

As is shown in Table I, fat globules were the sole abnormality in 13.1% (149 cases) of the whole series. On only 14 occasions were these globules found when known potential pathogens were also present.

Visits to the homes of affected children revealed that more often than not other persons in the household had had diarrhoea or vomiting a few days before or after the onset of symptoms in the index case. The severest illnesses were among pre-school children, who might ail for a fortnight, whereas older persons were seldom upset for more than two or three days, and it was rarer for fat globules to be seen in their stools. Examination of the urine from typical cases revealed no bile or sugar, but a gross excess of urates was often found. Two cases of coeliac disease were discovered, and were excluded from the series.

Discussion

In this survey of diarrhoea in pre-school children the proportion of cases showing certain abnormalities in the faeces has varied in a definite manner with sex, age, and season. Male cases predominated. Both in the 306 infants under 1 year old and in the whole series of 1,135 children the ratio of male to female was 1.3 to 1. This figure compares closely with the findings of Ian Taylor (1954) and of Scott (1953) in the London County Council area. The exception to this rule was a very slight female excess among the *E. coli* infections. There was a clear age trend; *Sh. sonnei* and *G. lamblia* infections rarely affected children under 1 year old, but became progressively commoner thereafter, whereas serological types of *E. coli* were identified in 11.5% of all cases of diarrhoea occurring in children under 2 years old, but in only 2.8% of those aged 2 and 3.

A form of "fatty diarrhoea" was common up to 3 years and still fairly frequent in the 3-year-old group. Indeed, this "steatorrhoea" was the most frequent single finding in the whole series, being present in 13.1% of the 1,135 cases. This finding is associated with pale stools, purging, nausea, and dehydration, and has already been described (Thomas, 1952, 1954a). It was very rare to find either cells or undigested starch in such stools.

During the acute stage, when these patients eat poorly or not at all, the percentage of fat in dried stools from representative cases has ranged from 5 to 60 g.%. In spite of the microscopical recognition of numerous globules of neutral fat, biochemical examination revealed more than half of the *total* fat weight to be in the split form, and gross amounts might fall within normal ranges. Some temporary failure of fat emulsification and of bile secretion, perhaps with an associated defect in absorption, appeared characteristic of this disease in young children. There was no evidence of failure to digest starch.

The brief but variable duration of the condition makes standard fat studies difficult; but a search for sequelae might be rewarding, for Sheldon (1955) suggests the possibility that coeliac disease may follow infantile gastro-enteritis. During these studies two first attacks of fatty diarrhoea were encountered in children subsequently thought to have coeliac disease.

This fatty diarrhoea may be the juvenile form of one of the "winter vomiting" group of diseases, such as types of

virus enteritis described by Gordon (1954). Its more general recognition might protect some infants from the misapplication of antibacterial drugs, which appear to be ineffective in treatment. Our experience has been that sulphonamides often provoke vomiting, but seldom control the diarrhoea.

The summer incidence of diarrhoea, as represented by the numbers of stool specimens sent to the laboratory, was lower than that in winter. Epidemic steatorrhoea was responsible for many winter cases, and such cases were often part of a household outbreak of vomiting and diarrhoea. Only salmonellae and *E. coli* O 26 showed a summer increase in prevalence, perhaps representing food-borne infection, since these organisms and O 114 have been found in animal infections (Ørskov, 1951 ; Charter, 1956).

Bacillary dysentery accounted for only 11.1% of all cases of diarrhoea. This and the low incidence of salmonella infection corresponds with the experience of Boardman, Cassel, and Kahn (1955), who studied 200 African children, but contrasts with the view put by Felsen (1945) that most cases of diarrhoea were demonstrably due to shigellosis. During and after epidemics shigellae may predominate temporarily, but any aetiological picture must alter as circumstances change.

Summary

Faeces were examined from 1,135 children aged up to 4 years within five days of the onset of a diarrhoeal illness. Excess fat globules were found in 13.1% of these cases, and the significance of the finding is discussed. *Sh. sonnei* was found in 11.1%, *Salmonella* species in 3.2%, and serological types of *E. coli* in 8%. The incidence of the latter and of *Proteus* species was very much higher in those under the age of 2 years. Diarrhoea was more common in winter than in summer months, and affected more boys than girls.

We are grateful to the several laboratories which have carried out fat analyses for us. Much of the bacteriological technical work was carried out with great care and accuracy by Mr. J. H. Cowlard and Miss M. Kinsley, to whom our thanks are due. We are grateful to Dr. Joan Taylor, Colonel H. Bensted, and Dr. G. S. Wilson for reading the manuscript and for helpful advice.

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Speaking on July 27 at Aston Hall Hospital, a mental deficiency hospital near Derby, the Minister of Health, Mr. R. H. TURTON, reviewed the problem presented by the long waiting-lists for beds in such hospitals. The position was far from satisfactory, he said. At the end of last year there were nearly 7,000 mentally deficient patients on local authorities' waiting-lists, more than half of them really urgent cases ; but in spite of wars and financial difficulties there were 51,334 patients in mental deficiency hospitals, although some of these hospitals, like Aston Hall, were very overcrowded. The Government's programmes for building "that we have at present approved or are considering," continued Mr. Turton, would provide 5,400 new beds for mental defectives. Of these beds 4,400 came into the centrally financed programme announced by his predecessor two years ago. This was building work of essential national importance. "This was recognized," said Mr. Turton, "when the Government declared that nearly alone of all building programmes, this hospital building programme should suffer neither postponement nor cut."

A FAMILY HISTORY OF UTERINE AND GASTRO-INTESTINAL CANCER

BY

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Since Paget (1857) reported uterine cancer in a mother, daughter, and granddaughter, numerous pedigree charts showing familial occurrence of uterine cancer have been published. Atthill (1868) related that a woman of 28 years, her mother, and two sisters died of uterine cancer, and Cullen (1900) reported cancer of the uterine body in three sisters. Hutchinson (1901) details a family in which the grandmother, mother, two maternal aunts, and two sisters all died from uterine cancer.

Sir Halliday Croom (1912) recorded uterine cancer in identical twins. Both began to menstruate on the same day ; both developed menorrhagia at the age of 30 years ; both reached the menopause at 50. At 53 years one sister had the uterus removed ; it contained a degenerating fibroid and a fundal carcinoma. Her sister died in the same year, and necropsy revealed a uterus with a degenerating fibroid and a carcinoma of the fundus.

More recently, Auvray (1927) reported cancer of the corpus uteri in a grandmother, mother, and daughter ; and Purdie (1944) recorded that two sisters, one a multipara of 34 and the other a nullipara of 32 years, had cancer of the corpus, their mother having died from rectal cancer.

Warthin (1913, 1925) investigated a very comprehensive pedigree of "family G." The family consisted of 146 members, of whom 28 died from cancer. In females the cancers predominantly involved the uterus and in males the gastro-intestinal tract. The uterine cancers were all adenocarcinomas. When followed up in 1936, 174 members had reached the age of 25 years. There were 43 cancers in 41 members, and with two exceptions all involved the gastro-intestinal tract or uterus. The 23 uterine cancers were endometrial in origin, and no cancers of the cervix were found.

Cholewa (1932) published two family pedigrees showing a genetically determined localization of cancer. In one of the families the mother had cancer of the uterus and the father carcinoma of the stomach. Of the eight children, one of three sons died from gastric cancer and three of five daughters died from uterine cancer. In the other family the mother developed uterine cancer at the age of 70, unilateral breast cancer at 71, and breast cancer in the other side at 72, from which she died. Two sons were cancer-free, but of 10 daughters three have died from uterine cancer, one from ovarian cancer, and one from breast cancer.

History of "Family N"

In three generations there are 19 members of this family, and nine members have had confirmed cancers (see Family Tree). One of the four male members has had cancer and died, and of the 15 female members eight have had cancer and six have died : one had carcinoma of the rectum, one had carcinoma of the stomach, and four had carcinoma of the uterus (see Table). The two surviving females had multiple primary cancers and are still alive.

Case 9.—In November, 1949, when the patient was 48, total hysterectomy and bilateral salpingo-oophorectomy were performed and a uterus containing a small intramural fibroid and a columnar-cell papillary adenocarcinoma of the body was removed. The patient kept well until January, 1956, when a mass