STUDIES IN INFANTILE GASTRO-ENTERITIS.

GENERAL INDEX.

INTRODUCTION.

Diarrhoea in infancy may occur as a result of a number of distinct disease processes, such as coeliac disease, the more typical forms of dysentery, ulcerative colitis, or as a terminal feature of other diseases. A large group of cases exists, however, in which the aetiology is uncertain. The cases in this group comprise a medley of clinical types which, although arising from diverse initial causes, are not readily distinguishable one from the other; for the diarrhoea and accompanying vomiting and fluid imblance may so dominate the clinical picture that the initiating causes are obscured.

For practical purposes, this syndrome is usually regarded as a disease entity, and, in the following paper, will be referred to as "infantile gastroenteritis".

Other names which have been used to describe the condition include "flux of the bowel", "cholera infantum", "diarrhoea aestiva", "Alimentary toxicosis", "summer diarrhoea", "epidemic gastroenteritis", "non-specific enteritis", or simply "D. and V. of infants". Frequently the name used has indicated the author's conception of the aetiology of the condition or described the epidemiology of his cases. All refer to the same clinical syndrome and can be regarded as synonymous.

Infantile gastroenteritis has long been recognised as an important cause of child mortality and morbidity. In the present century, despite advances in treatment, death-rates among affected infants are alarmingly high; and although the condition has been studied extensively, aetiology and pathology are obscure. The present paper attempts to add to the existing information on this puzzling disease.

The paper falls into three main parts:-

Part 1 reviews the history and literature of the disease, and describes past and present conceptions of aetiology and treatment.

Part 2 describes original investigations into some clinical aspects of the disease.

Part 3 reviews bacteriological findings, and reports an investigation into the role of Bact. coli neopolitanum in the causation of the disease.

H I S T O R Y

PART 1.

EARLY DESCRIPTIONS.

The history of infantile gastroenteritis stretches back
to earliest times. Hippocrates, as early as 450 B.C., described
the occurrence of infantile diarrhoea, and from then until the
present time, medical writings in many languages have contained
accounts of the malady. The Arabians in the 7th century and
Rhazes (900 A.D.) mention "looseness and flux of the bowels in
infants". In the 16th century, a french writer, Simon de
Vallembert, defined the syndrome thus; "Flux of the bowel in
infants may be of several varieties. We do not describe here
that in which the food is passed very much as it is eaten which
the Greeks call "lientery", nor of that with skinning of the
bowel which the Greeks call "dysentery", but only of that which
is neither of these but which the Greeks and Hippocrates call
"diarrhoea" but which we call "emotion du ventre" with which
infants are most often afflicted." This interesting definition
of the disease is almost applicable to modern usage. Later,
in England, Permmell (1653) and Harris (1647-1732) provided
additional accounts of the disease, but it was not until the
18th century that the first comprehensive description emerged.

This classic account was given by Rush (1745-1813), who investigated in Philadelphia, U.S.A., a diarrhoeal disease of infants which he named "cholera infantum".   He published a detailed description of incidence, symptomatology and aetiology in a paper entitled "An Enquiry into the Causes and Cure of Cholera Infantum".   Some excerpts from his paper, quoted here because of the excellence and accuracy of the descriptions, are as follows:-

"The disease affects children of ages between 1 and 2 weeks after birth and two years.   In the early stages, the children appear to suffer much pain..... the eyes are languid and they lie with them half-closed..... fever when present is of the remitting kind.   An intense thirst attends every stage of the disease.....   When the disease has been of long continuance, the approach of death is gradual and is attended by an emaciation of the body to such a degree that the bones come through the skin, by livid spots, convulsion and a strongly marked Hippocratic countenance".

Later clinical accounts of the condition have scarcely improved on Rush's carefully reported findings.

The literature of the late 19th and 20th centuries is abundant in all European languages, and will now be considered along with the earlier literature under the headings of "Aetiology" and "Treatment".

AETIOLOGY.

Early conceptions:-

Rhazes (900 A.D.) believed that "Flux of the bowel arises from teething, catching cold, or spoiling of the milk by choler or phlegm". Vallembert (1565) included these causes and listed an additional one of "gourmandising the child and overburdening the stomach and liver". Pemmell (1653) stressed the nutritional factor in the aetiology. He wrote .... "the cause of looseness or flux of the belly is bad concoction or corruption of the milk". Rush (1753-1813) disagreed with previous writers who had favoured ripe summer fruit as a cuase, and suggested that "the moderate use of ripe summer fruit tends to prevent rather than to cause the disease".

Dentition:-

It was believed by most of the early writers that dentition was a cause of diarrhoea. Rush (18th Century) thought that dentition, though not a main cause, acted by aggravating the diarrhoea. Towards the end of the 19th Century, this theory began to be discarded. Kassowitz (1892) pointed out that statistics showing the age and seasonal incidence of diarrhoea occurrence failed to show any correlation with dentition. Nothnagel (1904) agreed with Kassowitz in denying positively any aetiological influence to dentition, and in modern textbooks the association of dentition with the disease is not even mentioned.

Diarrhoea Biliosa:-

Authors of the 19th century applied the name "Diarrhoea Biliosa" to the condition, because they thought that summer diarrhoea was due to some perversion of liver function. This hypothesis appears to have been purely theoretical speculation and unconnected with scientific observation. It is of interest to note, that in recent years, liver damage has been found at necropsy by several investigators. However, Alexander and Eiser (1943) and others believe that the liver degeneration and necrosis are the result rather than the cause of the disease.

Environment:-

Season The terminology of the disease, "Diarrhoea aestiva" and "summer diarrhoea", indicate its seasonal frequency. Walter Harris (1641-1732) was one of the first to draw attention to this characteristic feature. He wrote "From the middle of July to about the middle of September the Epidemic Gripes of Children are so rife every year, that more of them usually die in a Month than in three or four at any other time." His explanation was that "The Heat of the Season commonly weakens them at least if it does not entirely exhaust their strength".

The summer frequency has been typical of the disease from early times until the first quarter of the present century. In the epidemic year of 1921, 64% of the cases occurred between July and September, (Findlay 1932), and Nabarro (1923) reported similar findings in his series of cases. In America, Marriott (1933) and others found that non-dysenteric diarrhoea of

children was most frequent in the autumn months.

More recent reports have indicated a change in the seasonal prevalence. Graham (1936) thought that the infant mortality from diarrhoea was now tending to show a winter instead of a summer peak, and associated this with the occurrence of respiratory infections.   Support to this view was given by Stirk Adams (1937) who found that the incidence of otitis among children in Birmingham showed a September trough and a winter crest.   Other authorities, while agreeing that the season prevalence is not so well-defined as in former years, do not support the view that infantile gastroenteritis is now more common in winter.   Cooper (1937), in a series of cases seen in Glasgow between 1931 and 1934, found that almost half occurred between August and October, and 68.8% from June to October; and Bloch (1941) in Glasgow, analysed the decennial period 1928-37 and found that the peak incidence for enteritis in infants under one year fell in the third quarter of the year with some tendency to increase in the winter quarter.

Campbell and Cunningham (1941) found that over half the cases occurred between the months of June and October. Smellie (1939) also found an increase in incidence for July to October, but he regarded this increase as insignificant and considered that the summer diarrhoea of text-books had been replaced by a disease of mixed aetiology which is present throughout the year.

Climate:-

The association of summer diarrhoeal incidence with
fluctuations in four-foot soil temperature was demonstrated
by Ballard in 1889, and Garret (1899) subsequently showed that
incidence of diarrhoea varied directly with air temperature
and inversely with the amount of rainfall.

In later years, it was generally assumed that seasonal
and climatic conditions were related to the disease's incidence
through facilitating growth and spread of the causal organisms.

Living Conditions:-

Statistics compiled by Public Health Authorities between
1900 and 1910 demonstrated the influence of home environment.
Peak points in diarrhoeal incidence were shown to occur in
urban areas.   The incidence was highest "where dwelling-places
were damp, overcrowded and ill-ventilated, where sanitation
and drainage was defective, drinking water was contaminated,
and swarming flies throve among the adjacent heaps of decaying
animal and vegetable refuse". (Local Government Board 1910).

During the past forty years, housing improvements and
reduction in horse traffic with consequent diminution of flies,
have probably helped in the decline of the disease, reflected
in the diminishing total death-rates (Table 1.)   Nevertheless,
recent reports have shown that adverse environment still plays
an important role in the predisposing aetiology.   Cooper (1937)
found a great increase in incidence in families of five and more,

TABLE   1.

Average Annual Death Rate from Diarrhoeal Disease in Infants
under One Year of Age per 1,000 Live Births. (England & Wales).

Years	Average Annual Death-rate.
1896 - 1900	31
1901 - 1905	23
1906 - 1910	18
1911 - 1915	19
1916 - 1920	9
1921 - 1925	8
1926 - 1930	6
1931 - 1935	5
1936	5
1937	5

(from Topley and Wilson 1946: Vol2. p.1581)

The declining annual death-rates from infantile diarrhoeal
disease is shown in the above table.   This is due mostly to a
decline in the total incidence of the disease which, in turn,
is largely the result of improved environmental hygiene (p.8).

and stressed the influence of overcrowding, while an analysis
by Bloch (1941) of the deaths due to enteritis in infants under
one year in the period between 1927 and 1937, revealed that 90%
of the infants came from homes that were small, and 80% from
overcrowded houses.

Infection.

In the closing years of the 19th century, the rapid
succession of discoveries in bacteriology focussed attention
on the microbic origin of the disease.   Many of the older
conceptions of aetiology were discarded when it was realised
that the epidemic nature of the malady, the spread of the
disease from sick to healthy infants, the association with
season, climate, adverse environment and artificial feeding,
were findings typically characteristic of an infectious disease
caused by specific micro-organisms.   Booker (1896) at John
Hopkins Hospital, began the search for the causal organism:
he investigated the faecal flora of a series of infants suffering
from summer diarrhoea, but was unable to reach any definite
conclusions.   Other bacteriologists followed in attempting
to find an organismal cause of the disease, among the earlier
ones being Escherich in Germany, Flexner in America, Morgan
in Britain, and Metchnikoff in France.   Research has continued
in many countries up to and including the present time, and a
detailed account of the bacteriological findings will be given
in Part 3 (P.).   Here, it will suffice to state that although
many have been incriminated in the aetiology, no one organism has

yet been established as the prime cause, and the bacterial

origin of the disease remains a matter of conjecture.

Parenteral Infection

On the other hand, the association of parenteral infection

with the diarrhoeal syndrome has long been recognized.   Many

clinicians have recorded how diarrhoea and vomiting of infants

have appeared coincident with the onset of a parenteral

infection, and have subsided in a striking manner when the

primary infection has been effectively treated, either by

medical or surgical means.   Reports of the total incidence

of primary parenteral infections occurring in any one series

of cases of infantile gastro-enteritis, have shown wide

variations (see Table 2.).   These are possibly due to

individual differences in interpretation of what constitutes

parenteral infection.   Authorities are agreed that, while all

types of parenteral infection may be implicated in the aetiology,

infections of the respiratory tract, including the middle ear

and mastoid, are in the overwhelming majority (Ellis, 1943 a).

Campbell and Cunningham (1941) found that these infections

comprised $\frac{4}{5}$ of all the parenteral infections which were found

early in the disease.

MIDDLE EAR AND MASTOID INFECTIONS.

As early as 1867, Professor Troltz of Wurzburg reported

that purulent otitis media frequently occurred in infants, and

Wredan (1868) described the finding of pus in the middle ear

TABLE.   2.

Incidence of Parenteral Infections in
Infantile Gastro-enteritis.

Author.	Incidence of Parenteral Infection per 100 cases.
Cooper (1937)	40.6
Smellie (1939)	46.2
Campbell and Cunningham (1941)	30.5
Alexander and Eiser (1944)	88.6 (including rhinitis and Pharyngitis)
Cohen (1944)	46.0.

The above table from recent literature, indicates

the variations in reports of total incidences of parenteral

infections found in different series of cases of infantile

gastro-enteritis (see text, p.11)

and mastoid of children at necropsy.   Ten years later, in

Paris, Parrot suggested that there was an association between

"arthrepsia" and otitis media, but it was Hartman (1894) who

first clearly demonstrated the link between otitis and

nutritional upset.   As a result of his investigations,

myringotomy was commonly used in Germany about 1900, as a

means of treating D. and V. in infants.   The procedure appears

to have been abused by indiscriminate application without

regard to changes in the drumhead, and it later fell into

disfavour.   Interest was renewed when Renaud (1921) reported

the finding of extensive suppuration in the middle ear and

labyrinth in post mortem examinations in a series of cases

suffering from infantile gastro-enteritis.   Blacklock, Guthrie

and McPherson (1937) found purulent material in the middle ear

in 92% of cases who came to necropsy and Ebbs (1937) found

otitis in 52% of his cases.

Whether otitis is secondary to the alimentary disorder or

vice versa, is still a matter of dispute.   Many observers

believe that otitis is frequently the primary cause.   Marriott

(1925) and Floyd (1925) suggest that streptococcal toxin

emanating from the infected middle-ear cleft, exerts a toxic

action on the capillaries of the body in general and of the

alimentary tract in particular, causing the characteristic

derangement in alimentary peristalsis.

On the other hand, Wishart (1930), from a 5 years' study

of the condition, concludes that mastoid infection is the

result rather than the cause of the syndrome.   He found that

many infants had no sign of ear infection throughout the course

of their illness, and that bilateral mastoid operations failed

to cure the condition.   Patterson and Smith (1944), comparing

post-mortem findings in 60 infants who had died of enteritis

with those of a similar number of infants who had died of other

diseases, found that there was little difference in the incidence

of ear and mastoid infections in the "enteritis group" and in

the group who had died of respiratory infections (broncho-pneumonia,

bronchiectasis, atelectasis).   Again, Smellie (1931) and

Campbell and Cunningham (1941) have drawn attention to the

frequency with which infants suffering from enteritis develop

parenteral infections (including ear infections) during their

stay in hospital.   Such observations lessen the force of the

evidence - much of it derived from post-mortem studies - that

otitis is the primary cause of infantile gastro-enteritis.

The position has been summarised by Cohen (1944) as follows:-

1.   Middle-ear infections occur in varying frequency in the

   alimentary disorders of infancy, the variant probably

   being seasonal and geographical.

2.   In some cases, it may be the primary cause, but in the

   majority of cases, middle-ear disease cannot be inculpated

   in the aetiology.

3.   Where middle ear infection is present, whether as primary

   cause or complication, the prognosis is aggravated

   considerably; and skilled treatment of the ear condition

should therefore be instituted as a means of assisting

the patient's recovery.

Other Causes.

Other causes have been postulated by various observers,
none of them supported by very strong practical evidence.
Boyd (1923) isolated a histamine-like substance from the portal
blood stream and suggested that this was implicated in the
aetiology.   The presence of certain fatty acids in the small
intestine (Catel 1937) and of products of protein decomposition,
such as choline (Paffrath, 1920) have also been blamed.
Bessau (1935) thinks that the picture of alimentary toxicosis,
with its heavy and continued loss of water and mineral salts,
is explicable on the basis of abnormal interchange of colloids
and salts through the cellular membranes with entry into the
cell-substance of Na, and Cl. ions and escape into the blood
stream of K,P, and Mg. ions.

Allergy.

In some patients, there appears to be an allergic factor
responsible for the onset of the diarrhoea and vomiting (e.g.
egg introduced into the nursing mother's or infant's diet).
(Ellis, 1943b; Lyon, 1939).

TREATMENT

External Remedies

In early times, external remedies were applied to the affected infant in the hope of alleviating the disease.   The Arabians (7th Century) advised bathing the patient in lukewarm rosewater and then applying fomentations of this water to the tibiae and feet.   Rush (1756) recommended the application to the abdomen of "plasters of Venice treacle or flannels dipped in aromatic herbs".   Today, such external applications have been completely discarded.   Emphasis is now placed on disturbing the patient as little as possible and providing warmth to minimise the shock and collapse which so frequently accompany the condition.

Diet.

Among the dietary treatments recommended by early clinicians were "concoctions of barley water with juice of isinglass and egg albumin" (Arabians 7th Century);   "bread boiled in water with rosewater and sugar" (Pemmell, 1654);   and "demulcent and diluted drinks and clysters of flax-seed tea" (Rush, 1756). Pemmell (1653) was one of the first to recognize that milk was badly tolerated by patients during the acute phase of the disease.   He warned that milk should not be given at the onset of the illness "lest it curdle in the stomach".

At the present time, paediatricians are agreed that patients should not receive milk during the acute stages. Most modern authorities advise an initial starvation period

of 12 to 48 hours during which time the infant receives small
frequent feeds of saline (normal or half-normal) or 5% glucose
in N/2 saline or half-strength Hartman's solution, the fluid
intake being supplemented, if necessary, by parenteral routes.
Subsequently, diluted milk is given, the dilution being
progressively lessened until normal amounts are taken.
Carbohydrates and solids are added to the diet only when the
stools are normal.   During the initial stages, Lelong (1938)
and other French writers have reported favourably on the use
of vegetable soups and cereal concoctions; but this treatment
has been little used in this country.   In the transition period
when acute symptoms have subsided, some authors advise continuation
of the milk-free diet.   Thus, Czerny and Keller (1928) recommend
the use of whey with later the addition of a 10% rice gruel.
Other authorities use "protein-milk", or unsweetened skim milk
or half-cream milk during the transition period, proceeding on
the principle that infants with gastro-enteritis have impaired
digestion for fats and carbohydrates.   Others, again, advise
citrated or lactic acid milk.   Buttermilk has also been used
in various countries for several centuries, and in Germany,
good results have been reported following the use of commercial
preparations, by Engel (1930), Studer (1935), and others.

   The apple diet was first introduced by Moro (1929) but
subsequently, various authors have reported such widely
divergent results that this form of treatment has been relegated
to the background, only to be revived by enthusiasts from time

to time. Campbell and Cunningham (1941) using diets of finely
divided apple and ☞ a commercial apple preparation, reported
no benefit in young infants, although in infants with sub-
acute illness and over eight months of age, the apple dietary
seemed to be helpful.   The elements reputed to be of specific
value in the apple diets are pectin and cellulose, and Winters
(1939) and Howard and Thomson (1940) have reported excellent
results using a standard pectin-agar milk mixture.

From the multiplicity of dietary remedies in current use,
it can be deduced that no one remedy is completely satisfactory.
In this disease which is of unknown aetiology, dietary remedies
have, of necessity, remained empirical or symptomatic.   Never-
theless, the provision of a suitable dietary according to the
patient's digestive capacities and nutritional needs is of
utmost importance as a means of assisting recovery.

Vitamins.

Vitamin supplements are recommended by modern authorities.
Alexander and Eiser (1944) add vitamins A.B.C. & D. to the feeds
from the first day and continue administration throughout stay
in hospital.   This is also advised by Lyon (1939), and Casparis
(1939) suggests that infants with diarrhoea should receive larger
doses of vitamins than are recommended for normal infants.   In
the present series of infantile gastro-enteritis, it was found
that in the acute phases, many infants were unable to take the
fat-soluble vitamins orally, and in these, Vitamins A & D were
successfully administered by a daily inunction of 1 to 2 drams
of 20% Adexolin ointment.

Parenteral fluid administration.

The introduction of parenteral fluid therapy marks a mile-
stone in progress in the treatment of infantile gastro-enteritis.
The knowledge of the importance of biochemical changes resulting
from dehydration, and the discovery of effective means of
carrying out the necessary technical procedures has resulted in
the widespread adoption of parenteral means of fluid administration.
The pendulum of medical opinion has thus completely swung round
from the viewpoint previously held that venesection should be
performed on the seriously ill patients. (Rush 18th Century).
Fluid can be introduced by subcutaneous, intraperitoneal, intra-
venous and intramedullary routs, but the administration of fluid
through the anterior fontanelle has now been abandoned by most
authorities.   The fluids used include saline (normal or half
normal), 5 to 10 per cent glucose in saline, Hartmann's solution,
Ringer's solution, blood serum and plasma, synthetic plasma
substitutes such as "periston", whole blood, protein hydrolysates
such as "Casydrol", and various combinations of these solutions.

Saline, Hartmann's solution, glucose saline, and plasma may
be given by subcutaneous injection.   Where dehydration is
severe and speedy therapy is required, administration is best
performed by intravenous or intraperitoneal routes.   Govan and
Darrow (1946) recommend that potassium chloride be added to the
parenteral fluid mixture, and also to the oral feeds which are
given subsequently.   They claim that this restores the normal
electrolyte balance in the intracellular fluids, the balance

having been previously upset by severe loss of potassium during the acute phase of the disease; (however, this claim awaits confirmation).   Blood transfusion is recommended only for older infants (over 9 to 12 months), after the acute phase has subsided and for **chronic** cases of the disease (Campbell and Cunningham, 1941).

The use of "intra-gastric drip" to treat dehydration is described in detail in Part 2, page 67.

Amount.

Care must be taken not to administer excessive amounts of fluid, otherwise oedema and overloading of the circulation are liable to occur.   The required daily fluid volume is generally reckoned as $2\frac{1}{2}$ ounces per pound body weight plus an allowance of 3 per cent to 6 per cent body weight for dehydration in the first 24 to 48 hours. (Alexander and Eiser, 1944)

Drugs.

Formerly a wide variety of drugs was employed in treatment, the choice of drug being based on the character of the stool and the stage of illness.   Today, apart from the use of sulphonamides and penicillin in certain cases, drugs play an unimportant part in the treatment of the disease, and modern authorities make use of them sparingly.   Even the initial purge that used to be given to all patients has now been discarded as a routine and is now used only occasionally for the older children.   However, although drugs have a small role in the therapeutic regime, some are still employed in treatment, and

if used judiciously they have undoubted value in affording
symptomatic relief.

Some drugs still used in present-day practice and their
indications, are as follows:-   Bismuth mixtures, aromatic powder
of chalk, grey powder or kaolin are sometimes useful in
checking diarrhoea.   To allay restlessness, choral hydrate,
chlorodine or nepenthe may be used in appropriate doses; and
Gunn (1945), recommends the use of small doses of phenobarbitine.
(In the author's opinion, the giving of phenobarbitone during
the acute stage is not altogether free from risk in view of the
probable presence of liver and renal damage).   Brandy, given
well diluted in repeated doses has been recommended by several
authors as a stomach sedative and general stimulant to combat
shock; but others such as Keller (1932) believe that alchohol
is completely contra-indicated.

Coramine and adrenaline have their place in the treatment
of the collapse as also has oxygen administration by nasal
catheter.   (In one case in the author's experience, the prompt
giving of intravenous coramine into the anterior fontanelle
proved a lifesaving measure in a child who had collapsed
suddenly and in whom pulse and respiration had ceased.)

"Eumydrin" (Atropine sulphate solution $\frac{1}{1000}$) though not
generally mentioned in the literature, has been used and found
of value in the present series.   Given orally or by subcutaneous
injection 15 minutes before feeds, in doses of $\frac{1}{2}$ to 2 c.c., this
drug was efficacious in alleviating vomiting, especially during

the sub-acute stages of illness.

Sulphonamides.

The reports from Britain and America on the use of sulphonamides in infantile diarrhoea are conflicting.   American observers are almost unanimous in claiming favourable results from sulphonamide therapy, whereas, in Britain, the results have been variable and, in the main, disappointing.   However, the cases of the disease which occur in the two countries are not strictly comparable;   in America, 40 - 60% of the cases are due to dysentery infections, and the mortality-rates are low (1.5 - 10%); whereas in Britain, a very small proportion of cases are due to dysentery infections and the mortality-rates are higher (20 - 40%).   It may be best, therefore, to discuss the findings for the two countries under separate headings.

American Reports.

Halpern (1942) from observations on 63 infants, reports that sulphathiazole and sulphadiazine are equally effective in checking diarrhoea and in promoting recovery.   (The dosage employed was 1.5 grains per pound body-weight per day).

Menchaca (1944) employed sulphadiazine in infantile diarrhoea in daily dosage of 0.1 to 0.15 G per kilo body-weight. From observations on 20 infants, he concluded that this drug was an efficacious aid in the treatment of infantile diarrhoea.

Tudor (1942), from observations on 31 cases, reports that sulphathiazole and sulphaguanadine are equally effective in

both dysentery and parenteral diarrhoea.   (Sulphathiazole

dosage was 1 G. initially and 0.25 G. four-hourly, and Sulpha-

Guanidine dosage was 2 G. initially and 0.5 G. four-hourly).

Altenfelder and Correa (1945) treated 236 cases with

thiazamide (0.1 G. per kilo body-weight daily in divided doses

given 6 hourly), and in most cases, the diarrhoea ceased after

2 - 3 days' treatment.

It can be concluded that in America, the sulphonamide drugs

are a valuable means of treatment of infantile diarrhoea, and

the different varieties of sulphonamide - sulphathiazole,

sulphaguanidine, sulphadiazine, thiazamide - are equally

efficacious in treatment.

British Reports.

The following reports illustrate the diverse findings

obtained by British observers :-

McSweeny (1943) states that he observed no benefit from the

use of sulphaguanidine treatment in infantile Diarrhoea.

Gunn (1945) agrees that sulphaguanidine and sulphasuccidine

have little value as "intestinal disinfectants" but believes

that sulphadiazine may be of value in cases with parenteral

infection.

On the other hand, Gairdner (1945) reports that sulpha-

succidine (1.5 - 3 G. daily) benefited 16 patients who exhibited

no signs of parenteral infection, whereas, in 56 patients with

demonstrable signs of parenteral infection or unexplained

pyrexia, sulphapyridine or sulphadiazine therapy had no effect in

reducing the mortality-rate (which, in these cases, was as
high as 50%).

These diverse findings are to be attributed to the diverse
nature of the disease which is labelled "infantile diarrhoea"
or "infantile gastro-enteritis".   Under the latter designations
are included a medley of conditions ill-definable from one
another clinically, but of widely differing aetiology and
prognosis.   Members of different groups differ in their response
to sulphonamide therapy, and in considering the efficiency of
sulphonamide therapy each case must be considered on its own
merits.   In the meantime it can be said that sulphanamide
therapy is probably of value in most patients with parenteral
infection, and may be of some value in some cases where the
diarrhoea is of mild character.   Sulphaguanidine therapy is
probably worth while employing in neonatal diarrhoea, for
Henderson (1943) and Twyman and Horton (1943) have reported encouraging
results from its use.

Penicillin.

Penicillin therapy is of undoubted value in cases showing
signs of parenteral infection.   It has particular application
in patients who have not responded to sulphonamides or who cannot
tolerate drug administration by mouth.

Burns and Gunn (1944) recommend its use in the treatment of
mastoiditis, and also in the post-operative period where
operation has been performed: The dosage recommended is 40,000

units daily.   Buchanan (1946) advises that in infancy, penicillin should be given in dosage of 4,000 units per pound of expected weight per day; and shows that in infants under 6 months, owing to the low stomach hydrochloric acid concentration, satisfactory results can be obtained by oral administration.

PREVENTION.

All authorities stress the importance of breast-feeding. Still (1933) recorded that 96% of his fatal cases of infantile diarrhoea had occurred in artificially-fed children.   Graham (1936) laid emphasis on breast-feeding, hygiene, and the maintenance of weight;   he ascribed to children in Glasgow under 70% of their normal weight, a diarrhoea mortality of more than twice as high as among children of normal weight.   Cruikshank (1937) specified raised external or internal temperature as important adverse factors.

The condition and management of the home also undoubtedly play a part in the aetiology of the disease.   Diarrhoea is much less liable to occur in a clean well-ventilated nursery, where the infant is fed regularly and allowed to lie quietly after its feeds, than in a dirty overcrowded home, where such discipline is neglected.

Ward management of hospitalised infants is described by Campbell and Cunningham (1941), and the value of task-nursing and its method are dealt with in M.R.C. War Memorandum No. 11 September, 1944.

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Part 2.

INVESTIGATIONS INTO CERTAIN CLINICAL ASPECTS.

(a)   OCCURRENCE OF OEDEMA.

(b)   EVACUATION TIME.

(c)   INTRA-GASTRIC DRIP FEEDING.

C L I N I C A L   S T U D I E S.

THE OCCURRENCE OF OEDEMA.

The occurrende of Oedema during infantile gastro-enteritis has been recorded in the past by various writers, but few have provided detailed descriptions of the conditions.   Arabian writers (7th Century A.D.) record that "in the course of the disease, the child may become bloated throughout the body or in part";   and Rush, in the 18th Centruy in America, observed that "during summer diarrhoea a swelling frequently occurs in the abdomen and limbs".   Hume (1911) appears to be the only writer who has described symptomatology and discussed aetiology in some detail.   In a paper entitled "General Oedema following Gastro-enteritis in Children", he described 13 instances of the complications in children of ages ranging from 1 - 4 years, who developed oedema of the hands and feet, three to four weeks after the onset of an attack of diarrhoea and vomiting.   Hume's other findings are discussed elsewhere in this paper.

More recent references provide little additional infirmation. Morris & Graham (1933), Kutumbia (1941) and Dieckhoff & Kunstler (1944) make only brief comment on the occurrence of the phenomenon, as do Thomson and Findlay in their textbook on Children's Diseases.   In other modern paediatric textbooks, however, although descriptions are given of "overhydration oedema" following excessive parenteral fluid administration, and

of "nutritional oedema" in marasmus and the wasting diseases,

the oedema of gastro-enteritis per se is not even mentioned.

Present Investigation

In view of the paucity of information on the subject,
further study seemed desirable.   This was begun in the
infantile gastro-enteritis wards at Belvidere Hospital, Glasgow
in the summer of 1945.

The following plan of investigation was adopted:-

(1) All routine admissions to the wards were observed closely
for the occurrence of oedema.   The nursing staff,
especially the morning staff who bathed the babies, were advised
to be on the alert for its presence.

(2) When it was noted, the patient was weighed immediately
and thereafter, daily records were charted.

(3) Careful notes were taken of the course of the oedema and
of the concomitant clinical features.

(4) Casydrol feeds were given to alternate patients (a) on
admission and (b) at the onset of oedema.   The purpose
of this feeding experiment was to discover whether protein
feeding was of value as a means of prevention or of
treatment of the condition, and thus test the validity of
the hypothesis that the oedema was due to hypoprotinaenemia
of nutritional origin.

GENERAL DESCRIPTION OF CASES.

A total of 176 patients was observed in the infantile
gastro-enteritis wards between 11th June 1945 and 1st January 1946.

They presented the usual age-incidence found in the disease,
87% being within the 0-18 months age-group.   Sex-incidence was
the normal 3:2 male preponderance.

Clinical features accorded with those customarily found in
gastro-enteritis, inasmuch as vomiting, frequent stools and
dehydration of varying degree were present.   Parenteral
infections, mainly respiratory, were noted in 46% of cases.
Although the severity and stage of illness varied from case to
case, all exhibited evidence of toxaemia or dehydration or both,
sufficiently grave as to warrant hospitalisation.

Treatment followed the usual lines, the main points being
as follows:-

After an initial starvation period, when only saline or
5% Glucose in $\frac{N}{2}$ saline feeds were administered, every alternate
patient was given "Casydrol" feeds (a protein hydrolysate). Milk
feeds, diluted as required in half-normal saline, was the
alternative diet, and this was given also to those infants who
could not tolerate "Casydrol".   The feeds were then built up
gradually until a full dietary, suitable for the patient's age
could be administered.   All patients received Vitamin B complex
tablets and Vitamin C (mg.50) tablets, t.i.d., and daily
inunction of adexoline ointment (20%).   Sulphadiazine and
sulphaguanidine, and in a few cases penicillin, were administered
where indicated.   Gastric lavage and replacement of fluid by
"intragastric" drip or by parenteral routes were administered
when necessary.

DESCRIPTION OF OEDEMA CASES.

Clinical Features.

Among these 176 cases, no less than 35 exhibited oedema
in one or more situations during their stay in hospital.   The
first indication of the oedema was usually on the dorsal
surfaces of the feet and hands.   The swelling was of rapid
onset and development.   It did not readily pit on pressure,
but rather imparted a feeling of resilience to the examining
fingers.   This oedema of the feet and hands was a feature of
all the cases, although not infrequently, the loose tissues
round the eyes were involved, and, more rarely, oedema was
noted in the sacral region.   In several patients the abdomen
seemed distended, and some free fluid may have been present.
The urine of all oedematous patients was clear; and in no
case was abnormality found in the cardiovascular system.
Indeed, apart from the weight changes (which are described
below) no other outstanding clinical abnormalities could be
detected in the oedematous patients.   Most of these infants,
however, showed some degree of microcytic hypochromic anaemia
(Hb ranging from 40 - 70%: R.B.C. from 3 - 3.5 millions/cu.mm:
W.B.C. from 6000 - 13000 cells/cu.mm. and films showing normal
cells or ring-staining microcytes).   Although parenteral
administration of fluid was pursued in all acutely dehydrated
patients, this form of treatment was required soon after admission,
and, in no case, did oedema develop during the administration or
within the 72-hour period following.   Thus the oedema which was

being observed was not the well-recognised type of "overhydration

oedema" which is due to administration of excess parenteral fluid.

Three cases had received intra-gastric drip therapy (see P.67)

prior to the onset of the oedema.   The fluid administered was 5%

glucose in $\frac{N}{2}$ saline, and daily volumes of 30 cc/kilo body-weight

had been introduced.

The general treatment of the oedematous patients differed

in no way from that of the non-oedematous, but approximately

half of the oedematous patients were fed on Casydrol, the

remainder continuing to receive their previous diet, which in

most cases was diluted milk feeds.

COURSE OF OEDEMA.

The course of the oedema was unexpected.   Except for four

infants who died while oedema was still present, spontaneous

subsidence of the oedema occurred in all cases.   This occurred

even in patients whose dietary and therapeutic regime had not

been altered.   The duration of visible oedema in most cases was

found to range from 2 - 8 days (Table 3).   Recurrence of oedema

was noted in only one case.   Here the initial oedema had lasted

for two days;   seven days later, it recurred on hands and feet,

and again subsided after four days.   This child, subsequently,

was discharged well.

PROGNOSIS.

Of 35 oedematous patients, 11 died (31.4%) whereas of the

141 non-oedematous patients, 25 died (17.7%).   Although a χ^2
test showed that there was no significant difference between these
death-rates, the clinical impression was that oedematous patients
had a poorer prognosis than the non-oedematous.

In four fatal cases, oedema was still present when death
occurred.   The remaining seven fatal cases were oedema-free at
the time of death;   the time interval in these cases, between
the subsidence of oedema and the onset of death being from 7 -
14 days.

POST-MORTEM EXAMINATIONS.

Two of the fatal cases were examined post-mortem.   In one
child, no obvious lesions were found: in the other, who died
while oedema was still present, histological examination of
liver by Dr. Reynolds (Pathologist to Glasgow Corporation Public
Health Department) revealed extensive fatty degeneration.

Post-mortem examinations in 10 of the non-oedematous cases
gave results as follows:-

    Four cases .... No abnormality detected.

    Three cases .... Broncho-pneumonia.

    Two cases   .... Mastoiditis and Broncho-pneumonia.

    One case   .... R.mastoiditis and Brain Abscess.

WEIGHT CHANGES.

Weight changes were a striking feature, found in almost all
the cases, and they provided objective confirmation of the

presence and course of the visible oedema.   A high increase in
weight appeared with the onset of the oedema.   The maximum
increase occurred within 24 hours of onset;   subsequently, the
weight-chart showed a downward trend corresponding with the
diminution of the visible oedema.

The weight increases accompanying the oedema varied from 4 to
58 ounces, the average being 22.1 ounces with a S.D. of ± 11.9

The initial losses in weight which occurred simultaneously with
the subsidence of the visible oedema were rapid and were
accompanied by diuresis.   The figures varied from 7 to 30 ounces;
the average being 16.8 ounces (S.D. of ± 7.8).   Subsequently,
during the following 7 - 14 days, most patients continued to lose
weight, although in amounts not as high as the initial weight
loss.

Note: S.D. = Standard Deviation.

Part 2

Oedema

(C)   DETAILED ANALYSIS OF OEDEMA CASES.

Table 1

Oedema-Incidence and Age of Patient.

Age in Months	Total Cases	Oedema Cases	Percentage of Oedema Cases.
0 - 3	46	8	17.4
4 - 6	33	8	24.2
7 - 9	26	9	34.6
10 - 12	16	4	25.0
13 - 15	19	5	26.3
16 - 18	13	1	7.7
19 - 21	4	0	0
22 - 24	1	0	0
25 - 27	8	0	0
Total	176	35	19.9

(The oedema-incidence in separate months is shown in Table 1a
 in the Appendix, p. 56   )

Fig.1

Percentage of Oedema Cases Classified by Age of Patient.
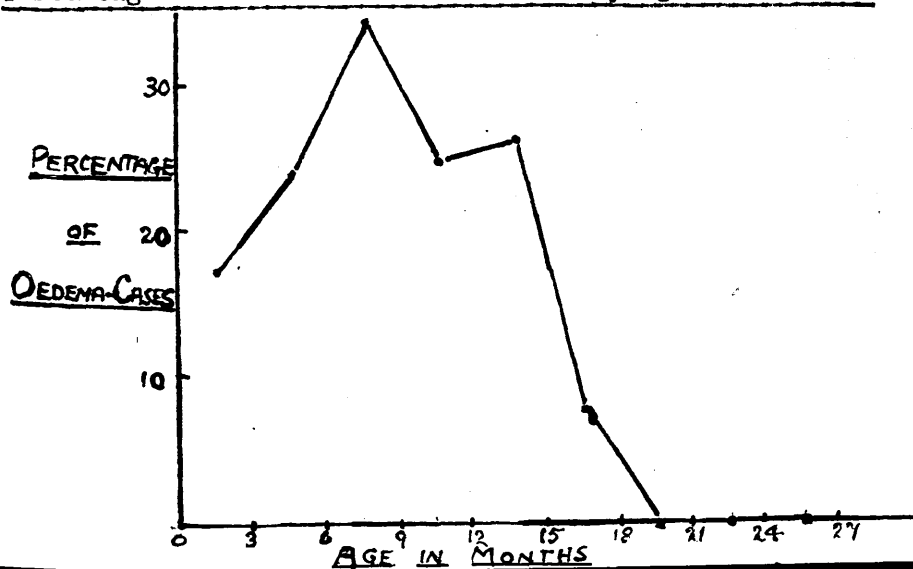
Oedema

Table 1 shows that oedema was confined to patients in the 0 - 16

months age-group, and that 83% of the oedema-cases were one year of

age and under.

Table 2

Oedema-Incidence and Duration of Illness
(from onset of illness to onset of oedema)

Duration of Illness in Days (from onset of illness to onset of oedema)	1	2	3	4	5	6	7	8	9	10	11	12
Number of Oedema Cases	0	0	0	0	1	2	3	2	6	1	4	2

| Duration of Illness in Days (from onset of illness to onset of oedema)	13	14	15-21	22-28	29 plus
Number of Oedema-Cases	2	2	5	1	4

Table 2 shows that oedema was never observed during the first four

days of illness. Thereafter, it occurred in 19 cases (55.7%) during

the 2nd.weeks of illness; in 6 cases (17.1%), during the 5th.-7th

days of illness, i.e. during the 1st week; in 5 cases (14.3%) during the

3rd.week of illness; and in 5 cases(14.3%) during and after the 4th.

week of illness.

(It should be noted that in the above table the time-intervals are of

unequal duration. For convenience of representation, cases of oedema

occurring after the 14th.day are grouped in 7 day intervals, and the

last group comprises all cases occurring after the 29th.day of

illness.)

Table 3

Duration of Oedema and Number of Cases

Duration of Oedema in Days	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Number of Cases	0	6	7	4	6	3	2	1	0	0	0	1	1	0

(Note: Four patients who died while oedema was still present are not included in above table.)

Fig. 2   Duration of Oedema and Number of Cases
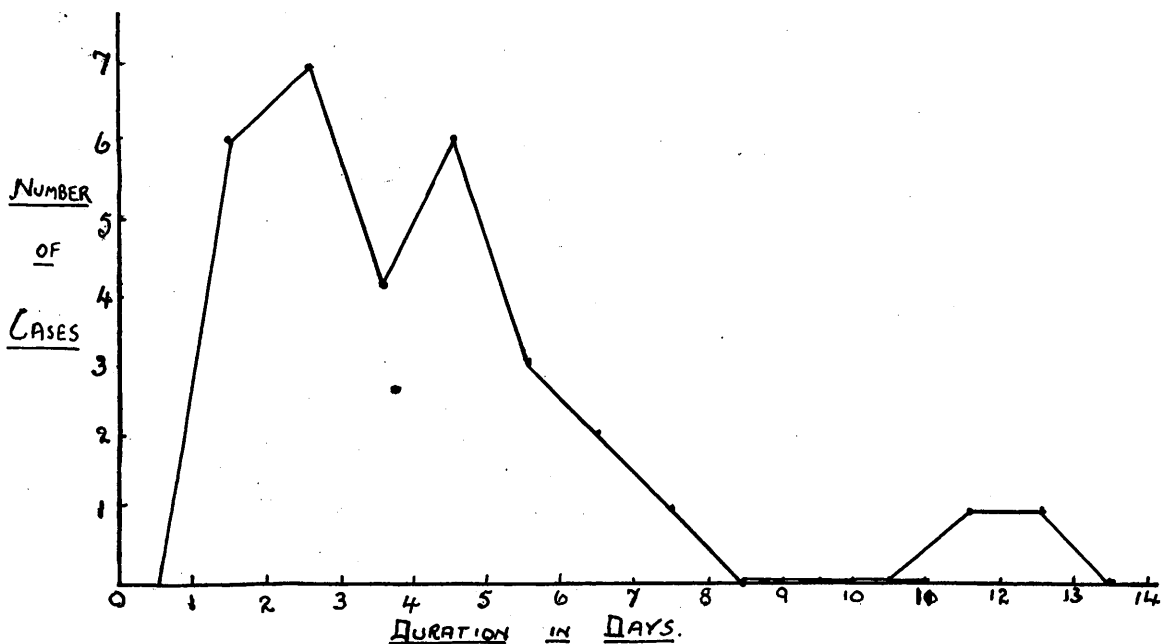
Thus, 2-8 days was the duration of the visible oedema in 93.5% of the 31 oedematous patients, and in 23 patients the duration of visible oedema was only from 2-5 days.

The Casydrol Experiments

(a) Casydrol-feeding of alternate patients on admission.

(b) "   "   "   "   "   at the onset of oedema.

(a) Casydrol and Prevention.

Many infants, on admission, could not tolerate Casydrol, and were given diluted milk feeds instead.   Thus, only 1 in 3 of the total patients observed, received protein feeds rather than 1 in 2 as had originally been intended.

Table 4 shows that, despite Casydrol feeding, 10 patients developed oedema, and that the frequency of oedema-occurrence in Casydrol-fed infants was little different from the frequency in milk-fed infants.

Table 4.

Oedema-Incidence and Type of Feed Given on Admission.

Type of Feed given on Admission.	Total No. of Cases.	Cases who developed Oedema.	
		No.	Percent.
Diluted Milk.	113	23	20.4
Casydrol.	61	10	16.3

Thus, it can be concluded that Casydrol was ineffective as a means of prevention of oedema.

(NOTE:-   Two patients who developed oedema within 48 hours after admission are not included in Table 4.).

(b) Casydrol and Treatment.

The duration of oedema was regarded as an index of efficacy of treatment.   Since the duration may have been influenced by the diet received prior to the onset of oedema, it was thought desirable to consider the combined dietary which the patients

had received.   Thus, the oedematous patients fall into the

following four groups:-

1. Patients given MILK before onset and MILK after onset of oedema.

2.   "   "   MILK   "   "   " CASYDROL "   "   "   "

3   "   " CASYDROL "   "   " CASYDROL "   "   "   "

4.   "   " CASYDROL "   "   " MILK   "   "   "   "

TABLE   5.

Duration of Oedema and Type of Diet.

	Group 1.	Group 2.	Group 3.	Group 4.
Diet before Oedema. Diet after Oedema.	Milk Milk	Milk Casydrol	Casydrol Casydrol	Casydrol Milk.
Number of cases.	18	8	6	1
Duration in Days.	2 2 2 3 3 3 4 4 4 4 5 5 5 6 6 7 13 14	2 2 2 3 5 7 8 8	3 3 3 5 6 8	4
Mean duration of Oedema in Days.	5.11	4.82	4.67	4.0.

A test of significance shows that there is no significant

difference between the mean duration of oedema in groups 1, 2

and 3.   Group 4, which contained only one patient was not

included in the significance test (shown in Appendix, p.**57**)
However, this does not materially affect the conclusion, which
is - that Casydrol feeding had no effect in shortening the
duration of the oedema.

Duration of Oedema and Sulphonamide Treatment.

    Of 31 oedematous patients, 8 patients had received no
drug treatment, 12 had received sulphaguanidine, and 11 had
received sulphadiazine.   The duration of oedema in each of the patients
in these three groups is shown in Table **6**. below:-

TABLE   6 .

Duration of Oedema and Sulphonamide Treatment.

Duration in Days.		
Group 1. No Drug.	Group 2. Sulphaguanidine.	Group 3. Sulphadiazine.
Number of Cases. 8	12	11
2 2 2 3 5 6 7 13	2 3 3 3 4 4 4 5 5 5 6 7	2 2 3 3 4 5 5 6 8 12
Mean Duration in Days. 5.0.	4.2	4.8.

    In Group 1 (no drug treatment) the mean duration of
oedema was 5.0 days;   in Group 2 (sulphaguanidine), the mean

duration was 4.8 days.   No significant difference was found

between the means of each group.   (The statistical analysis

is shown in Appendix, p. 57).

Hence, the giving of sulphonamide had no influence on the

duration of the oedema.

TABLE 7.

Death-Rates Classified by Oedema-Incidence.

	Deaths.	Total Cases.	Death-Rate per 100 Cases.
Cases which developed Oedema.	11	36	31.4
Cases which did not develop Oedema.	25	141	17.7
Total	35	176	19.9.

ASSOCIATION

A X^2 test shows that the difference between the percentage

of deaths in oedema cases, viz., 31.4%, and the percentage of

deaths in the non-oedema cases, viz., 17.7%, is not significant.

(The calculated value of X^2 was 3.23, and the value of X^2

required for significance at the 5% level is 3.8.)

However, these X^2 values are sufficiently close to one

another to indicate a tendency for mortality in oedema cases

to be higher than in cases without oedema.

D I S C U S S I O N.

At first, it was difficult to understand why this
complication of gastro-enteritis - apparently not an uncommon
one - had received so little mention in the literature.   The
explanation of this, however, may lie in its unobtrusive and
inconspicuous nature.   Characteristic features of the oedema
observed in the present study were.... Its brief duration,
its swift and spontaneous subsidence, its rare occurence during
the acute stage of the illness, and the lack of obvious changes
in the accompanying clinical picture.   Observers who were not
specially on the look-out for this complication may, therefore,
have missed instances of its occurrence, or have regarded it
as occurring much less frequently than it actually does.

Weight Changes.

These occurred rapidly and varied greatly from patient
to patient.   Although no definite correlation was possible
between the amount of weight changes and the extent of visible
oedema, it seemed that weight changes were higher in the
patients who had more widespread oedema.   Other diseases in
childhood which are complicated by oedema - such as nutritional
oedema of premature infants, serum disease and nephritis, are
also associated with spurious gain in weight.   In nephritis, the
patients may gain as much as 16 to 32 ounces (Holt, 11th edition).
and in overhydration oedema following the giving of excessive
amounts of parenteral fluid, gains of 5 - 6 kilos may occur.
(Brown, Clark, Jones, Walther & Warren, 1943).

Aetiology.

The present investigation has not solved the problem of aetiology.   Such information as has accrued has been of negative character only and the true cause or causes are unknown. However, the negative findings obtained here may be of some value in enabling the exclusion of some possible causes of the condition.   It is proposed to review these now, and then proceed to consider the probably hypotheses of aetiology which remain.

Nutritional Hypoproteinaemia.

Although this hypothesis is favoured by Morris and Graham (1933), the findings in the Casydrol experiments do not support this view.   The Casydrol feeding provided an adequate protein intake, but did not prevent the occurrence of oedema (Table 4.) and was ineffective as a means of treatment, inasfar as it did not shorten the oedema's duration (Table 5).   While it might be argued that the Casydrol was not absorbed by the severely ill patients on account of rapid peristalsis or derangement in gastro-intestinal function, this argument is refuted by the experiments of Shohl (1943) on the nitrogen balance of infants suffering from acute diarrhoea.   The latter found that despite the presence of vomiting, diarrhoea and acidosis, nitrogen was absorbed and retained when given orally in the form of Casein hydrolysate.   Also, in the present series, oedema usually occurred after the acute phase had subsided, when stools were formed and vomiting had ceased;   and this suggests that normal gastro-intestinal function and normal absorption were present

prior to the onset of oedema.

On the whole, therefore, it seems unlikely that nutritional hypoproteinaemia is a major factor in the aetiology.

Vitamin B. deficiency.

Likewise, Vitamin B. deficiency does not appear to be a major aetiological factor.   Here, there is no experimental evidence available to show that the Vitamin B. preparation which was administered routinely to all patients during their stay in hospital, had been absorbed.   On the other hand, had Vitamin B. deficiency occurred to an extent sufficient to cause oedema, other signs of Vitamin B. deficiency would have been present. These (described by Fehily, 1947) were never observed in the oedematous infants.   Moreover, as stated above, in most cases the gastro-intestinal tract appeared to have resumed normal function prior to the onset of oedema.

Therefore, Vitamin B. deficiency can probably be excluded as a cause of the condition.

Possible Causes.

Albuminuria, heart disease, and macrocytic anaemia (described by Holmes, 1945) are other possible causes of oedema, but these were never found in the patients in the present series.

"Overhydration oedema" due to administration of excessive amounts of parenteral fluid has already been excluded as a cause of the condition. (p.35)

Hume (1911) suggested that the oedema was related to a

deficiency in secretion of the suprarenal glands, for he found
fibrosis in these glands in two cases at necropsy.   He also
reported that oedematous children, treated by injections of
adrenalin hydrochloride, appeared to show improvement.   However,
Hume's hypothesis is based on very slender evidence and the
finding of suprarenal fibrosis has not been confirmed by other
workers; while, in the view of the characteristic tendency of
the oedema to spontaneous cure - as observed in the present
series - the therapeutic efficacy ascribed to adrenalin
injections is open to doubt.

The Remaining Possibilities.

        When the above have been excluded from the list of
possible causes, the range of hypotheses is narrowed and attention
can be focussed more closely on the possibilities which remain.
The potential causes of the oedema which now emerge for
consideration are (a) Impairment in function of capillary
                                        endothelium,

                    (b) Impairment in liver function,

                    (c) Impairment in renal function.

These will now be discussed in turn.

(a) Impairment in Function of Capillary Endothelium.

        Damage to the capillary endothelium is well-recognised
as a cause of oedema.   Diekhoff and Kunstler (1943) favour
this hypothesis to account for the oedema of gastro-enteritis,
and Sheldon (1943) states that "oedema which occurs in marasmic

and severely-wasted infants is attributable to changes in permeability of the capillary walls resulting from their poor nutrition." The oedema of acute nephritis appears also to be due to this cause, since the oedema-exudate has a high protein content (usually over 1%) and changes in the peripheral vessels can often be found (Cumulative Supplement, 1947).

Unfortunately, there is no scientific evidence to confirm that capillary damage is a cause of oedema in infantile gastro-enteritis. Also some features of the condition are not readily explained by the hypothesis. Thus, if the oedema were due only to the effects of toxaemia on the capillaries, it should surely have become manifest at the early stage of the illness when toxaemic effects were maximum, rather than during the 2nd and 3rd weeks, when the oedema usually occurred. Also, if the spontaneous subsidence of the oedema is to be accounted for by rapid recovery of capillary function, the reason for this rapid recovery is not quite clear.

It must be concluded that although impairment of capillary function is a possible cause of oedema, it does not alone account satisfactorily for all the observed features of the condition.

(b) Impairment in Liver Function.

Thomson (1936) reported the occurrence of oedema in patients in whom the underlying cause appeared to be a deficiency in the physiological mechanism for manufacturing

serum proteins. He suggested that this deficiency arose from

the presence of zonal atrophy of liver lobules, which occurred

in marked degree in patients who were examined post-mortem.

Lawrence (1946) has recently confirmed that faulty liver

functioning may impair the formation of serum proteins and

cause hypoproteinaemia and oedema.

Now, in infantile gastro-enteritis, liver damage is a

common - in fact the only common - pathological finding. It

is possible, therefore, that malfunctioning of this organ may

be the explanation of the oedema.   So, the long time-interval

between the onset of the illness and the onset of oedema could

be the time-interval required for the exhaustion of the infant's

reserve protein stores, plus that required for the occurrence

of sufficient liver damage to cause hypoproteinaemia.(Morris

and Graham(1933),who hold the oedema is due to hypoproteinaemia

of nutritional origin, suggest that this delay is due to the

presence of acidosis which masks a serum protein deficiency).

Again, since the liver is an organ which has strong powers of

regeneration, it is feasible that the spontaneous subsidence

of oedema was due to the occurrence of compensatory, regenerative

changes in the liver.

The defect in this theory, as with the one previously

discussed, lies in the fact that it possesses no sdientific

confirmation.   Fluctuations in serum protein levels coincident

with the waxing and waning of the oedema, are essential to

this hypothesis - but although serum protein levels both in

normal infants and in dehydrated infants suffering from
diarrhoeal disease have been ascertained by Teitelman (1944),
Bridge and Associates (1941) and others, there is no information
available to indicate whether variations in serum protein
levels occur in infants with gastro-enteritis who have developed
oedema.

(c) Impairment in Renal Function.

The important experiments by McCance and Young (1943)
on the kidney function of infants have demonstrated clearly
the relative inefficiency of these organs during the first
year of life.   These workers showed that, at low urine flows,
the concentration of solids in the infants' urine does not
increase as it would do in adults, and that, if oliguria occurs
as a result of dehydration, some degree of salt and water
retention inevitably occurs.   Simmons (1944) has summarised
the situation in these words.. ".... the infants' urine is
always a dilute urine.   Therefore, any infant short of water
is likely to have renal failure with retention of salt and
urea, and with oedema due to salt-bound water".   It is thus
apparent that infants with gastro-enteritis who suffer from
oliguria, are liable to develop oedema due to salt retention.

Hume (1911), who has already been mentioned as one of the
first to describe the oedema of gastro-enteritis in some detail,
was ignorant of the details of kidney physiology elucidated by
the above workers, but he recognised then that salt retention
might be a cause of the oedema.   In an endeavour to test this

hypothesis, he fed large quantities of salt to the oedematous children, but found that this had little effect on the curve of salt-retention or on the body-weight, and that the oedema steadily subsided during the period when the large quantities of salt were being ingested.   Although Hume was led to conclude that salt retention was not the cause of the oedema, his observations have not been confirmed.   Also, since his experiments were performed on a small series of 13 children and all were over one year of age, his findings may not be applicable to the present series where oedema was never observed over the age of 16 months and 83% of the oedematous infants were under one year.

The theory of salt-retention as a cause of the oedema possesses several points in its favour which may be worthwhile enumerating.   These are:-

1. Oedema incidence was restricted to the young age-
    groups in whom renal function is least efficient.

2. Artifically fed infants have a greater load placed
    on their excretory apparatus than breast-fed infants,
    since cow's milk contains more protein and salt than
    breast-milk; and young infants with gastro-enteritis
    who are artificially-fed, have thus an increased
    liability to develop renal failure.

3. The spontaneous subsidence of the oedema can be
    explained by this hypothesis as the return of the
    infant to a normal state of water excretion, since
    the cessation of the diarrhoea and vomiting may have

made available a sufficiency of fluid to excrete
retained salt and allow the release of salt-bound
water.

4. The continued loss of weight after subsidence of
oedema can also be explained by continued excretion
of salt and water from tissues which, although relieved
of visible oedema, were still relatively water-logged.

Whether this theory provides a complete answer to the
problem of pathogenesis is uncertain, but it seems reasonably
certain that impairment in renal function is at least an
important factor in the aetiology of the condition.

SUMMARY   AND   CONCLUSIONS.

In a series of 176 cases of infantile gastro-enteritis, oedema occurred as a complication in 35 (19.6%)

The preponderant incidence was in the 0 - 12 months age-group, although oedema was noted in patients up to 16 months.

Spontaneous subsidence of the oedema occurred 2 - 8 days after its onset.   In this series, oedema never occurred before the 5th day of illness, but appeared thereafter in more than half of the cases during the second week of illness, and in almost a third during the third and fourth weeks of illness.

Appart from weight changes which fluctuated parallel with the waxing and waning of the oedema, and from the presence in a few cases of a microcytic hypochromic anaemia there was no other clinical abnormality detected.

The occurrence and duration did not seem to be influenced by the diet.   Thus, Casydrol feeds had no effect on frequency and duration of the oedema, and Vitamin B. deficiency did not appear to be related to the condition.

Comparison of patients treated by sulphonamides with those untreated, indicated that neither sulphaguanidine nor sulphadiazine were related to the production or duration of the oedema.

The death-rate in the oedematous patients was 31.4% (11 out of 35) and in the non-oedematous, 17.7% (25 out of 141).

Although the clinical impression was that the oedematous patients had a worse prognosis than the non-oedematous,

statistically, there is no significant difference between
these death-rates.

The aetiology is obscure, and the present investigation,
while enabling the exclusion of some of the possible causes,
has not solved this problem.   Probably several factors are
implicated;   of these, the likeliest appear to be

(a) impairment in capillary function.

(b) impairment in liver function.

(c) impairment in kidney function.
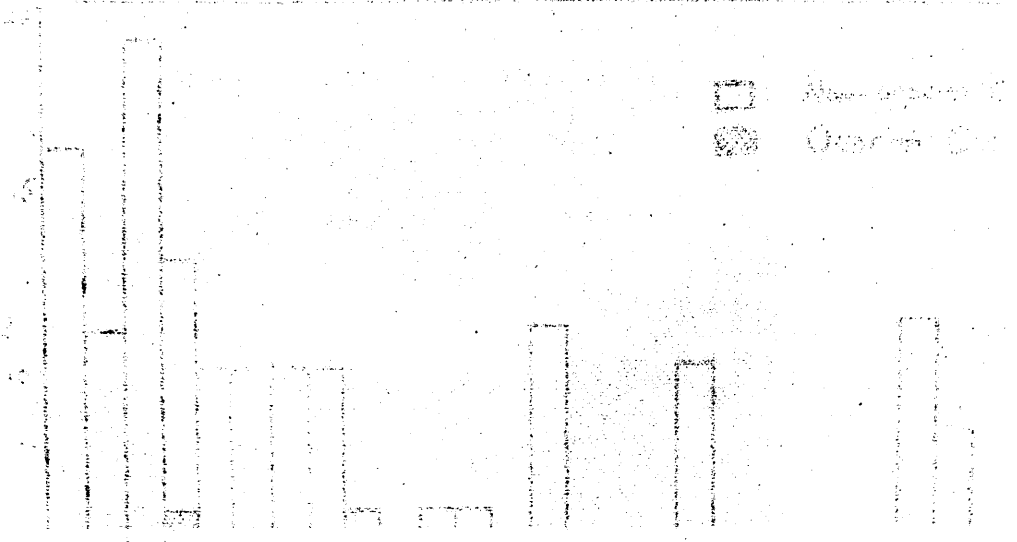
APPENDIX 1.

Table 1a.　　Number of Cases Classified by Oedema-Occurrence and Age.

Age in Months		1	2	3	4	5	6	7	8	9	10
Total Cases		16	11	19	13	10	10	10	10	3	4
Oedema Cases	Number	3	2	3	6	1	1	2	4	3	0
	Percentage	19	18	16	46	10	10	20	40	50	0

Age in Months		11	12	13	14	15	16	17	18	19	20	21	22	23	24	24 plus
Total Cases		6	6	5	10	4	3	0	10	1	1	2	0	0	11	8
Oedema Cases	Number	1	3	2	1	2	1	0	0	0	0	0	0	0	0	0
	Percentage	17	50	40	10	50	33	0	0	0	0	0	0	0	0	0

Fig. 1a.

NUMBER OF CASES CLASSIFIED BY OEDEMA-OCCURRENCE AND AGE [IN SEPARATE MONTHS].

NON-OEDEMA CASES.

OEDEMA CASES.

No. OF CASES

AGE IN MONTHS.
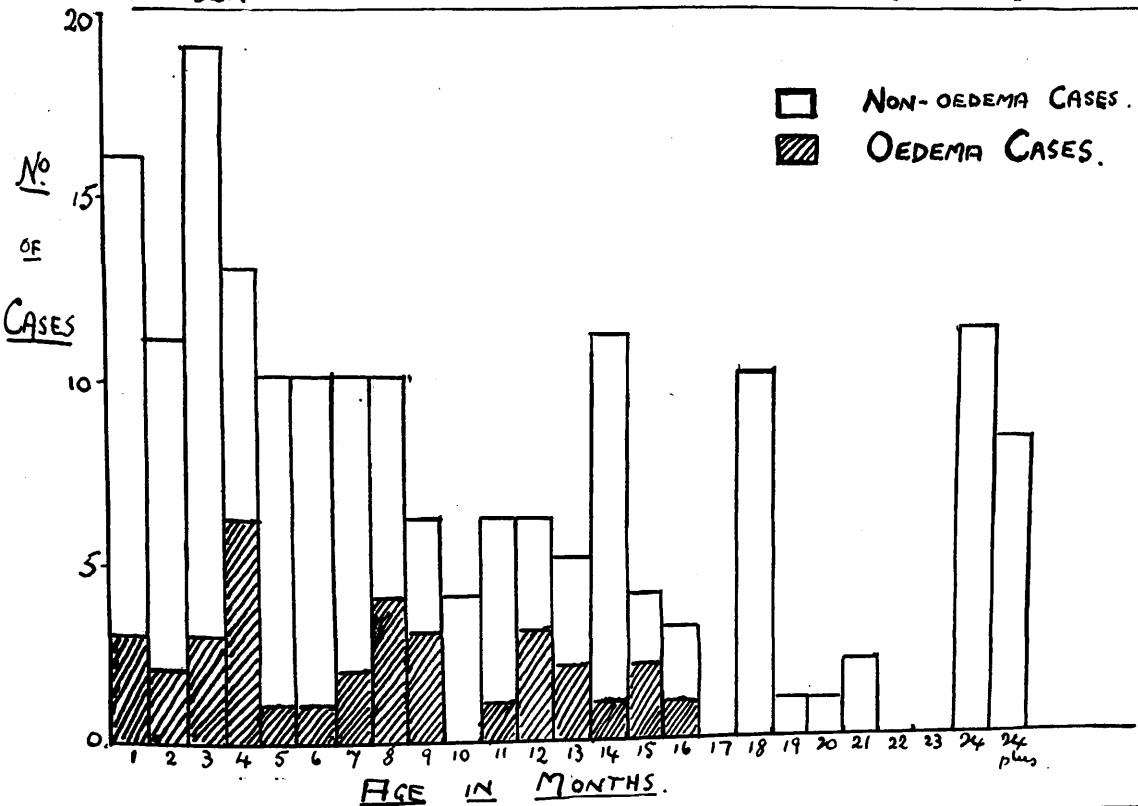
APPENDIX 2

Analysis of Variance of Table 5.

(1) Sum of Squares between Groups $= \dfrac{(92)^2}{18} + \dfrac{(37)^2}{8} + \dfrac{(28)^2}{6} - \dfrac{(157)^2}{32}$

$$= 1.73$$

(2) Total Sum of Squares $= 2^2 + 2^2 + 2^2 + 3^2 + \ldots \text{to 32 terms} - \dfrac{(157)^2}{32}$

$$= 268.72$$

Variation due to	Degrees of Freedom	Sum of Squares.	Variance	Ratio of Variances
Groups	2	1.73	0.87	0.09
Residual	29	266.99	9.21	
Total	31	268.72		

Hence, the difference between the means is not significant.

Analysis of Variance of Table 6.

(1) Sum of Squares between Groups $= \dfrac{(40)^2}{8} + \dfrac{(51)^2}{12} + \dfrac{(53)^2}{11} - \dfrac{(144)^2}{31}$

$$= 3.21$$

(2) Total Sum of Squares $= 2^2 + 2^2 + 2^2 + \ldots \text{to 31 terms} - \dfrac{(144)^2}{31}$

$$= 215.10$$

Variation due to	Degrees of Freedom	Sum of Squares	Variance	Ratio of Variances
Groups	2	3.21	1.605	0.212
Residual	28	211.89	7.568	
Total	30	215.10		

Hence, difference between mean durations is not significant.

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(b)   <u>EVACUATION   TIMES.</u>

EVACUATION TIMES.

The purpose of this investigation was to measure the
time of passage of food material through the alimentary tract
in the acute phase of gastro-enteritis.   Although the time
is undoubtedly diminished, the exact extent of diminution
does not yet appear to have been measured.   It therefore
seemed worthwhile to undertake the following experiments to
provide an index of this time - referred to hereafter as
"evacuation time".

Two groups of infants were studied: Group A.
consisted of 20 infants with normal stools, and Group B. of
20 infants suffering from acute gastro-enteritis.   In both
Groups, ages ranged from 1 - 18 months.

Method:

Each infant was given $\frac{1}{2}$ to 2 teaspoons of charcoal mixed
in a little water before the first morning feed (6 a.m.).
The time when charcoal first appeared in the stool was care-
fully noted, and the difference between the two times was the
"evacuation time".   It was found that the charcoal produced
an obvious darkening of the stool easily detectable by the
nurse.   In some gastro-enteritis patients, vomiting was a
difficulty, but this could usually be overcome by administering
the charcoal more slowly and on a subsequent occasion.   In a
few patients, however, persistent vomiting prevented the
experiment from being performed.

RESULTS

The results of the investigation are shown in the table below.

Table 8

	Number Examined	Age-Group in months	Evacuation Time		
			Average (hours)	Range of 2/3 of Cases (hours)	Extremes (hours)
Group A Normal Stools	20	1 - 18	19.6	16 to 23	12 and 37
Group B Loose Stools (Acute Gastro-Enteritis)	20	1 - 18	10.8	7 to 14	2 and 21

Fig. 2

Frequency Distribution of Evacuation-Times in Normal Infants and in

Infants suffering from Acute Gastroenteritis.
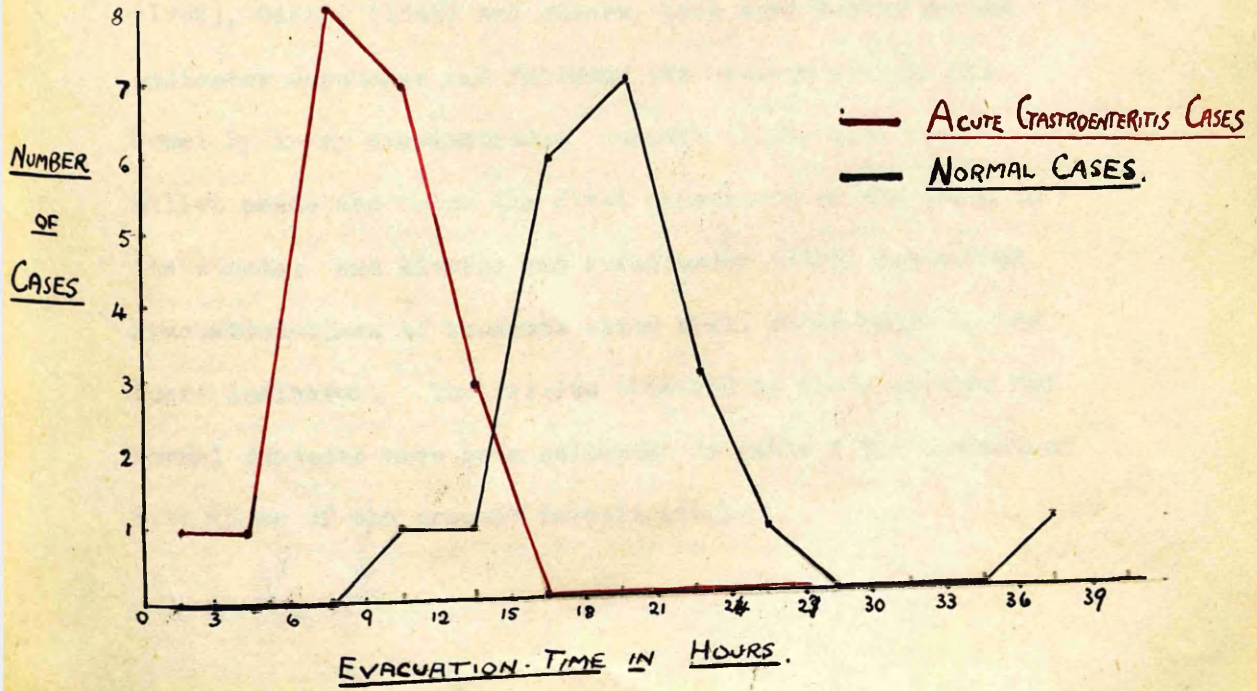
RESULTS (Cont.)

There was wide variation in the evacuation-times found in infants in both groups.   A few normal infants had rapid evacuation-times, which were even less than times found in some patients with gastro-enteritis, but on the whole, the times in the gastro-enteritis series were less than the normal ones - on the average about half as long.

The charcoal was not evacuated completely in the first stool, but traces of charcoal appeared in the stools of infants in both groups for as long as 36 - 96 hours after the first administration.

D I S C U S S I O N.

Other substances besides charcoal have been used by investigators to determine the evacuation-times of normal subjects.   Radiologists, such as Kantor (1927), Barclay (1936), Caffey (1945) and others, have used barium as the indicator substance and followed its passage through the bowel by X-ray examinations: Burnett (1923) used French millet seeds and noted the first appearance of the seeds in the stools; and Alvarez and Friedlander (1924) determined evacuation-times of students using small glass beads as the inert indicator.   The results obtained by above methods for normal subjects have been collected in Table 9 for comparison with those of the present investigation.

TABLE 9.

Comparison of Present Findings with others reported in the
literature.

Author	Subject of Investigation.	Method Employed. (Indicator substances).	Average Evacuation-time (hours)
Present Series.	Normal infants.	Charcoal.	19.3 (range of 2/3 of cases was 16 - 23 hours)
Caffey (1946)	Normal infants.	Barium and X-ray exam.	about 24.
Alvarez and Friedlander (1924)	Normal adolescents.	Glass beads.	about 24.
Kantor (1927)	Normal adults.	Barium and X-ray exam.	about 24.
Barclay (1936)	Normal adults.	Barium and X-ray exam.	about 24.

All observers have reported wide variations in the
evacuation-times of different subjects, and the results obtained
in the present series of normal infants can be regarded as
corresponding in the main with those of other observers who used
different methods of estimation.   It is interesting to note
that Barclay (1936) who compared evacuation-times of charcoal
biscuits and barium in 11 healthy adults, found that "Charcoal
appeared in the stools in approximately the same time as the
barium had taken in each case".   It can therefore be concluded
that the charcoal method described here provides a fairly
reliable index of the evacuation-time.

The occurrence of residues in the stools for periods 2 - 4
days after ingestion, have also been reported by the authors

mentioned above.

The diminished times found in the gastro-enteritis group were only to be expected.   Noteworthy was the child who had an evacuation-time of only 2 hours.   This child, aged 5 months, had a watery diarrhoea of 6 - 8 stools in the day, and died 3 days after admission.

SUMMARY   AND   CONCLUSIONS.

The evacuation-time in two groups of infants was estimated by feeding charcoal and noting its first appearance in the stools.   Wide variations in times were found in infants in both groups.

In the normal group, the avarage evacuation-time was 19.6 hours, the range of 2/3 of cases varied from 16 - 23 hours, and extremes were 12 and 37 hours.

In the acute gastro-enteritis group, the average was 10.8 hours, the range of 2/3 of cases varied from 7 - 14 hours, and extremes were 2 and 21 hours.

Charcoal residues occurred in the stools of infants of both groups for 36 - 96 hours after ingestion.

The findings for normal infants corresponded with those of other investigators who used other methods of estimation, and it is concluded that the charcoal-method employed here is a reasonably accurate and convenient means of determining evacuation-time.

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(c)   <u>INTRA-GASTRIC   DRIP   FEEDING.</u>

INTRA GASTRIC DRIP FEEDING.

A number of important biochemical and metabolic changes occur in greater or less degree during the course of infantile gastro-enteritis.   Fig. 4. shows how these changes reinforce eachother to produce a state of acidosis which, if unresolved, will lead to metabolic failure and death.

Fig. 4.

Biochemical Changes in Infantile Gastro-enteritis.
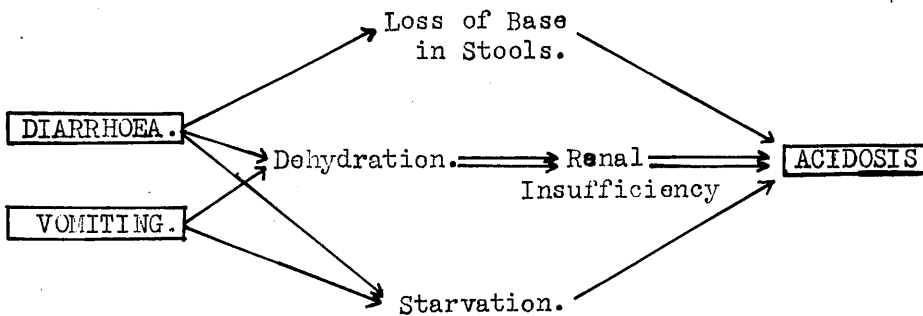
Fluid and readily assimilable carbohydrates are urgently needed to restore renal function and correct acidosis. Where vomiting or weakness of the child preclude adequate oral administration, both fluid and carbohydrate may be given parenterally.   However, the usual methods of parenteral therapy have certain disadvantages.   Some discomfort is inevitable and is poorly tolerated by the toxic collapsed patient.   In addition, the risk of sepsis complicates intraperitoneal, subcutaneous and intramedullary methods of administration: excess fluid is liable to be given by intravenous and intra-medullary routes, and insufficient by intraperitoneal and subcutaneous routes;

the risk of shock occurs with intraperitoneal injection:
technical difficulties may prevent intravenous therapy, and
constant supervision is required for all methods, except the
intraperitoneal.

In view of the drawbacks associated with parenteral
therapy, it seemed desirable to find a method which would over-
come the usual difficulties of oral feeding.   Paediatric
textbooks state that feeds of small volume, frequently repeated,
may be retained by an infant, even though normal-sized feeds
are being vomited.   It was reasoned that if this principle
were extended to the feeding of drops of fluid at time-intervals
of a few seconds between each drop, a large cumulative volume
might be administered during the day and that the fluid might
be retained by the infant.   The procedure, which was named
"the intra-gastric drip" was tried first in June 1945, on a
moribund infant, and the results of the trial were satisfactory.
Subsequently, it was used on many infants with similar success.
The technique which was finally evolved is described below.

METHOD.

A linen draw-sheet is used to immobilise the child's arms
and body in order to prevent struggling and movement which
interfere with the subsequent procedures.   The child is placed
on the draw-sheet, which is then firmly swathed round the body
and pinned in place, so that the arms are pinioned to the sides
and only the face is exposed.   A fine rubber catheter (No.5)
lubricated with liquid paraffin is passed into the stomach

through the nose, and fixed to the forehead with adhesive tape.
To facilitate the passage of the tube, the infant is given
small sips of water to drink as recommended by Hamilton Bailey
(1938).   Gastric lavage is now performed with 1% warm sod.
bicarb. solution. (This removes mucus and indigested milk curds
which are present in a high proportion of the patients).   In
the meantime, a drip apparatus has been prepared at the bed-
side.   This consists of a graduated flask containing the warm
fluid to be administered, a drip chamber, long rubber tube and
clip.   The Murphy drip apparatus was found quite satisfactory.
When the stomach washings are being returned clear, the funnel
and tube of the gastric lavage apparatus are disconnected,
and the stomach catheter is connected to the tube of the drip
apparatus.   Fluid is then allowed to flow into the stomach
and the rate is regulated to 20 drops per minute.   Faster
rates than this were found liable to cause vomiting.   As this
stage, the child is usually given a sedative dose of chloral
hydrate, which is either administered by spoon or is instilled
into the stomach tube and flushed into the stomach with the
drip fluid.   Hot water bottles are placed alongside the rubber
tubing to maintain the warmth of the fluid.   The fluids commonly
used were $\frac{N}{2}$ saline (N= Physiological), $\frac{N}{2}$ saline with 5% glucose,
$2\frac{1}{2}$% Casydrol with 5% glucose.   Hartmann's solution and other
types of fluid could also be used if desired, and the composition
of the fluid altered as necessary.

The daily fluid needs of the infant have been assessed as

Fig. 5.

Intra-Gastric Drip Feed in Progress.

$2\frac{1}{2}$ oz. per pound body-weight and an additional allowance of
3 - 6% if dehydration is present.   It was found that with
the use of the intra-gastric feed, the necessary daily amount
could easily be introduced.   In fact, care had to be taken not
to induce overhydration.   The intra-gastric drip was used in
most cases for periods between 12 and 48 hours, after which
normal oral feeds could usually be successfully started.
When the stomach tube had been in situ for a 24-hour period,
it was the practice to remove and re-sterilise it along with
the whole apparatus.   If further treatment were necessary,
the catheter was replaced and fluid administration recommenced.

Subsequent supervision is simple and is undertaken by the
nursing staff.   The main points requiring attention are:-

1. Maintenance of an even rate of administration of 20 drops
            per minute.

2. Replacement of the flask when it is empty with a full
            container.
    (to avoid the possibility of overhydration, instructions
    are left with the nurse of the total daily fluid volume
    which is required).

3. Maintenance of the temperature of the fluid by changing
            the hot water bottles as they become cold.

4. Stoppage of fluid administration on the occurrence of
            vomiting.   A doctor is then summoned.

5. Replacement of the stomach tube should it become
            displaced.

DISCUSSION.

Theoretically possible objections to the method are
vomiting, broncho-pneumonia arising from aspiration of
regurgitated material, ulceration of laryngo-pharynx and
oesophagus, and the effects of prolonged immobilisation.
In practice, none of these gave rise to difficulty.   Of the
36 patients who received intra-gastric drip therapy, vomiting
occurred in only one, who soon responded to repetition of
gastric lavage and a slower rate of administration of drip-
fluid.   Broncho-pneumonia was never observed clinically as
a result of the procedure;   post-mortem examination of one
infant who died on the third day after administration, when
intra-gastric drip therapy had been given for the previous
48 hours, revealed no evidence of damage to pharynx or
oesophagus, or of broncho-pneumonia.   No obvious ill-effects
from prolonged immobilisation of the infants' arms and shoulders
were found.   Most of the patients, being collapsed and
disinclined for movement, became rapidly accustomed to the procedure.
Ransome, Gupta and Paterson (1944) who used continuous drip
therapy in 355 adult cases in tropical practice, reported a
similar absence of ill-effects.   In 19 cases who came to
necropsy, none showed evidence of broncho-pneumonia or
ulceration of the laryngo-pharynx.

The principle of continuous drip alimentation through a
stomach tube left in situ is not original.   It has previously
been employed in the treatment of adult medical and surgical

conditions, such as head injuries, peptic ulceration, severe
malnutrition and dehydration due to tropical fevers.   On the
other hand, the use of the procedure in diseases of infancy
has been surprisingly neglected.   In current paediatric text-
books, and in recent reviews of the treatment of dehydration
in infancy by Simmons (1944) and Levine (1945), the procedure
is not mentioned.

When the intra-gastric drip feed was first introduced
at Belvidere Hospital, its application to paediatric practice
was thought to be original, but it was later found that Allen
and Rutherford (1945) had used a similar procedure, and Sequel
(1945) in South America had employed a nasopharyngeal catheter
for continuous drip therapy in dehydrated infants.

The procedure described here, however, contains some
contributions to the technique which have not been described
elsewhere.   These points are of importance in minimising
discomfort, and their omission has been found by experience
to result in administration difficulties and struggling and
exhaustion of the patient.   Important details are the
preliminary immobilisation as described (arm splints or
tying the hands to the sides of the cot, do not prevent
struggling and are unsatisfactory);   the use of gastric
lavage prior to the commencement of drip therapy;   and the
administration of chloral hydrate in appropriate dosage
after gastric lavage.

S U M M A R Y.

A method of continuous drip feeding through nasal catheter
is described for the treatment of infantile gastro-enteritis.
The procedure is free from the disadvantages of parenteral
therapy and was found simple, safe and effective.   Some
original points in the technique are described and recommended
for facilitating administration.

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BACTERIOLOGICAL   FINDINGS.

The rôle of Bact.coli.neapolitanum.

BACTERIOLOGICAL FINDINGS.

List of Tables (cont).

List of Figures.

BACTERIOLOGY

The bacteriological findings in infantile gastro-enteritis are extremely conflicting.

As early as 1896, Booker of John Hopkins University made an extensive bacteriological study of summer diarrhoea in infants.   He was unable to find a single organism as the specific cause of the disease, but concluded that among the incriminated bacteria, aside from the streptococcus, Proteus vulgaris ranked first.   In Paris, Metchnikoff (1914) isolated Proteus vulgaris constantly from cases of gastro-enteritis, and showed that experimental infection of mice, rats and chimpanzees with this organism produced a disease resembling "cholera infantum" in its clinical and post-mortem appearances.   His pupil, Bertrand (1914) studied 55 cases of the disease in London Hospital, and isolated Proteus in every case.   In Dublin recently, Sevitt (1945-1946) reported that in 400 cases of infantile diarrhoea, Proteus was isolated from almost 50%, as against 16% in 100 non-contact controls.   He concluded that this organism may be one of the causes of the disease, for he found that correlation existed between the isolation of Proteus and the severity and fatality of the disease, particularly in the 1 - 3 months age groups.   However, many other investigators, both in these and other countries, have been unable to confirm these findings.

In America, in 1902, Duval and Bassett (1904) concluded

that the dysentery bacillus was an important, if not the most
important, cause of summer diarrhoea.   In the following year,
an investigation at the Rockfeller Institute for Medical
Research into the occurrence of B.dysenteriae in the summer
diarrhoea of infants in the United States of America was
conducted by Duval and Shorer (1904), Wollstein and Dewey
(1904) and other workers under the direction of Flexner. The
results of the survey showed that dysentery bacilli occurred
in the stools of 69% of the patients, while in normal infants
they were uncommon.   Of the dysentery bacilli found, 90% were
of the Flexner type.   Similar results were obtained in Boston
by Tenbroeck and Norbury (1916) who found Flexner's bacillus
in 51 (68%) of 75 infants.   Again, in 1919, Davison in
Birmingham U.S.A., found 69% cases were due to dysentery bacilli,
Flexner being twice as common as Shiga infections; while in
Baltimore, 82% of the cases were due to dysentery bacilli.

Doufort (1928) also reported the occurrence of dysentery
organisms in cases in France; and Hormaeche, Suracco, Peluffo
and Aleppo (1943) in Uruguay, found a high incidence of Shigella
and Salmonella infections among infants with enteritis,
actually in 61% of 668 cases.   In Germany, the findings have
been diverse.   Gildemeister and Baerthlein (1913) examined
the faeces of 70 infants suffering from diarrhoea in the summer
of 1912.   Organisms of the Salmonella group, especially the
"Dahlem" bacillus, were found in 27 instances, and Flexner's
bacillus in 9.   The following year, Baerthlein and Huwald

(1914) found a similar distribution of Salmonella and as many
as 21 cases of Flexner dysentery in a study of 72 cases.   In
Australia, Harper (1932) stated that Tidswell found a greatly
increased incidence of non-lactose fermenting organisms in
cases of infantile diarrhoea.   Of 206 non-lactose fermenters
isolated from different patients, 69 belonged to the dysentery
group and 137 to the Salmonella - the latter organisms being
mainly Bact. paratyphosum A and B., and Bact.typhi-murium.
In Britain, Flexner dysentery organisms have been uncommon,
but B.dysenteriae Sonné has occurred in certain sporadic and
epidemic outbreaks of gastro-enteritis.

It is certainly true that the syndrome of diarrhoea,
vomiting and collapse may sometimes be caused by infection
with specific pathogens such as B.dysenteriae and members of
the Salmonella group.   In such patients, blood and mucus are
usually present in the stools and ileo-colitis is the common
pathological finding.   These cases, differing from the other
cases of infantile gastro-enteritis in symptomatology,
pathology and bacteriology, are nowadays recognised as forming
a separate group which are specific in origin.

Another group of diarrhoeal diseases has occurred during
the past ten years in epidemic form among infants in the first
month of life in both the United States of America and Great
Britain.   Observers in these countries have commented on the
restriction of these epidemics to maternity homes and
institutions, to the occurrence of most of the cases during

the first week of life, the absence of parenteral infection,

of seasonal periodicity, and of known pathogens in the stools,

and the high incidence of the disease among breast-fed infants.

On account of these outstanding differences in epidemiological

and clinical features, neonatal diarrhoea, which is also

referred to as "epidemic diarrhoea of the new born" has been

regarded by most observers of the present time as a separate

disease entity, and distinct from the non-specific diarrhoeas

of the wider range of age-group distribution.   However, this

segregation of cases of neonatal diarrhoea into a group apart

from the other infantile diarrhoeas should not be too rigidly

applied; because occasionally, sporadic cases of diarrhoea,

occurring among infants of neonatal age, do not possess the

features of the epidemic form of the disease and cannot be

clearly demarcated from cases which occur in the other age-

groups.   The result of bacteriological investigations in

epidemics of neonatal diarrhoea have been inconclusive (Frant

and Abramson, 1938; Forbes and Olsen, 1939: Crowley, Downey,

Fulton and Wilson, 1941) and there is no general agreement

as to the cause of this type of infantile diarrhoeal disease.

Some workers have commented on the occurrence of outbreaks of

neonatal diarrhoea in institutions concurrently with epidemics

of influenza among adult population (e.g. Bloch,1941).   Light

and Hodes (1943) claim to have found a filterable agent in the

stools capable of causing acute enteritis in calves.   This

work, however, awaits confirmation and in the meantime, the

cause of epidemic diarrhoea of the newborn is unknown.

The flagellate Giardia lamblia occasionally has been reported as giving rise to enteritis in infants and young children.   The symptoms are usually mild and chornic, with 3 - 4 loose, copious, foul motions in the day;   although some-times, the disease may be severe with continuous vomiting and severe diarrhoea.   In Syria, Moore and Davis (1942) have reported that 10% of all cases of infantile diarrhoea are due to Giardia infection.   In this country, Ormiston, Taylor and Wilson (1942) have described an outbreak of a chronic type of diarrhoea in a residential nursery in which a high proportion of the children aged 2 months to 2 years were affected by Giardia lamblia infection.   However, in Britain at any rate, protozoal infection of this type is rare and accounts only for a negligible proportion of the cases of infantile diarrhoea.

It has also been suggested by Lyon (1940) and others, that enteritis in infants may be due to the ingestion of food-stuffs which contain toxins of bacterial origin.   Topley and Wilson (1946) indicate that some toxin-producing strains of staphylococci are known to give rise, under favourable conditions, to acute gastro-enteritis, and that the toxin has been found in milk.   They suggest that infants and young children fed on raw cow's milk may occasionally be exposed to this toxin. However, the demonstration of such bacterial toxins in food-stuffs is difficult and no evidence is available to support the suggestion.   Further, it does not explain the transmission

of infection in an institution from sick to healthy infants,
the occurrence of relapse during convalescence, and the absence
of local irritative lesions which usually occur with toxins of
bacterial origin.

Other organisms such as Cl.welchii and Ps.pyocaneus
(Weidenmuller, 1942) have been also inculpated by other workers.

Many investigators have found that non-lactose fermenting
organisms are increased in summer diarrhoea in this country.
However, Lewis showed that the faeces of infants fed on cow's
milk contained more non-lactose fermenters than did the faeces
of breast-fed infants, and since the majority of infants with
diarrhoea have been artificially fed, the significance of the
occurrence of non-lactose fermenters is difficult to assess.

The majority of cases of infantile gastro-enteritis
comprise a heterogeneous group which are of non-specific or
uncertain aetiology.   Since, in Britain, Flexner's bacillus
has seldom been isolated from cases of infantile diarrhoea,
and Salmonella and other specific infections have been recorded
but rarely, this heterogeneous non-specific group comprises
the large mass of cases with which British workers have been
concerned.

Early bacteriological investigation of this non-specific
group suggested the importance of an organism known as Morgan's
No.1 bacillus (Proteus morgani).   In the summer of 1905 at the
Lister Institute, London, Morgan (1905) found his bacillus in
28 out of 58 cases;   in the faeces of 20 normal infants it was

not found once.   Morgan and Ledingham (1909) from the results

of 4 years' investigations, concluded that this bacillus was

one of the important causes of the disease.   Lewis (1911-12)

at Birmingham, likewise found a high incidence of Proteus morgani

in the stools of patients with diarrhoea.   He found Morgan's

bacillus in 101 out of 140 cases (72.1%) and in 17 out of 100

normal children under 5 years of age (17%).   Also, of 20 strains

isolated from diarrhoeal children, 14 proved fatal to rats on

feeding.   Further, he was successful in isolating the organism

from 5 out of 18 bottles of milk from homes in which there were

at the time or recently had been cases of diarrhoea.   Graham-

Smith (1911-12), examining flies collected at Cambridge and

Birmingham, found bacilli of the Morgan type in 5.3% of flies

captured in diarrhoea-infected homes and from only 0.6% of

flies captured in homes free from diarrhoea.   On the other

hand, Ross (1910-11) in Manchester and O'Brien (1910-11) in

London, found this organism comparitively infrequently - 5%

and 14% respectively;   and Orr (1910-11) at Shrewsbury, did

not find it once in examination of 19 cases.   Alexander (1911-

1912) at Liverpool, encountered Morgan's No. 1 Bacillus in only

23 out of 174 cases (13.2%) and he found it in 5 out of 75

normal children (6.7%).   Of recent years, Morgan's bacillus

has not been found so frequently in this country.   Nabarro

(1923) examining 68 cases of summer diarrhoea during the

epidemic of 1921 did not encounter it once.   On the other

hand, he isolated from 21 of his cases an organism which in

the light of subsequent work, was probably Sonné's bacillus.
(Nabarro, 1927).

When the bacteriological findings in infantile gastro-
enteritis are surveyed as a whole, it is apparent that a
multiplicity of organisms have been incriminated in the
aetiology.   Workers in different countries have found such
different organisms as members of the dysentery group,
Salmonella, Proteus morgani, Proteus vulgaris, Ps.pyocaneus,
Cl,welchii, protozoa such as Giardia lamblia, and viruses,
but no single organism has been demonstrated by everybody.
Even in the same country, widely different results have been
obtained.

How are these diverse findings compatible with a disease
process which reaches its maximum about the 32nd to the 36th
week of the year in London, Paris, Berlin, Moscow, Chicago and
New York (Topley and Wilson 1936), which causes a clinical
syndrome of diarrhoea, dehydration and collapse, and which is
specially fatal for infants under two years of age?   If some
single bacterium caused the disease among all the infants
affected, the differences in bacteriological findings would be
inexplicable.   Nowadays, however, the tendency is to believe
that infantile diarrhoea, though apparently an epidemological
and clinical entity, is not a disease entity.   Diarrhoea in
infancy is a symptom and the initiating causes may be widely
different.   Fairly well-defined groups of cases have now been
distinguished, each possessing its own aetiology.   It is

recognised that infantile diarrhoea may be due to a number of
different organisms and disease processes, just as dysentery
is due to a number of different organisms.

Nevertheless, the problem of aetiology is complex and
far from having been solved.   One of the major difficulties
in assessing the bacteriological findings is the confusion
that exists in the classification of the disease.   It must
be rememberd that in any series of cases of infantile gastro-
enteritis, a proportion is liable to be non-infective in
origin.   Such cases include those arising from dietetic causes,
allergic upsets, or secondary to general diseases.   They are
not readily distinguished from the infective cases, because in
all types of diarrhoea, the complicating features of dehydration
and biochemical change may so dominate the clinical picture
that the individual initiating cause is often obscured.
Further, there are cases of the disease distinctly associated
with parenteral infection, such as mastoiditis, and these may
or may not be suffering from coincidental infections.   With
the recognition of the many accessory factors, there is often
doubt whether the bacteriological findings of different
investigators have been obtained from comparable series of
cases and the significance of their findings is diminished
accordingly.   Nevertheless, after splitting off from the
infantile diarrhoea the infective cases due to recognised
pathogenic bacteria such as dysentery bacilli, staphylococci
and organisms of the Salmonella group, there remains an

extensive series of cases, undoubtedly infectious in type, in which no recognised pathogens can be detected.

It is possible, therefore, that in those so-called non-specific cases of infantile gastro-enteritis, the causative organism or organisms may belong to groups which are normally non-pathogenic, but which may have the power to acquire pathogenicity under certain circumstances or in certain age-groups.

Coliform Organisms.

Wright and Wright (1946) have recently suggested that Coliform organisms might thus be incriminated in the aetiology of infantile gastro-enteritis.   In a careful epidemiological survey of "diarrhoea and enteritis" deaths of children under two years of age, in an area of London during the decennium 1928-38, these observers were satisfied that most of the cases of unknown aetiology were of infectious origin since they occurred in groups which were associated in time and place. They suggested that this "clustered distribution" of cases might have resulted from the dissemination among the community of one or more strains of coliform organisms which were relatively harmless for adults and older children, but which were potentially pathogenic for infants under two years of age.

Earlier observers have also put forward hypotheses incriminating the coliform bacillus.   For example, Mayer (1919) suggested that colitis could be caused by coliform bacilli which had altered from the saphrophytic to the pathogenit state.

Kleinschmidt (1935) thought that coliform bacilli under

abnormal conditions could ascend from the lower portions of

the intestinal tract into the duodenum and upper jejunum, and

thus give rise to gastro-enteritis;   and Marriott (1931)

thought that overfeeding might favour this occurrence by

preventing emptying of the duodenum, and providing a continuous

culture tube of partly digested foodstuffs through which

coliform organisms could ascend from the lower portions of the

intestinal tract.   Arnold (1928) has brought evidence suggesting

that high summer temperature causes a decrease in the secretory

activity of the infant's stomach and interferes with the gastro-

disinfecting mechanism which is responsible for keeping the

upper part of the intestine free from bacteria.   Blacklock,

Guthrie and McPherson (1937) linked these theories into an

ingenious and attractive hypothesis to account for the

pathogenesis of the disease.   They suggested the following

sequence of events:-

1. Depression of the gastric secretion, which in any case

    is low in infants, occurs as a result of interplay of

    one or more of the following factors -

    (a) high external temperature,

    (b) pyrexia.

    (c) swallowed mucus from respiratory or naso-
        pharyngeal infection,

    (d) the ingestion of casein in cow's milk.

2. Impaired secretion of lipase and amylase results from

the lowered gastric secretion, and this causes

maldigestion of fats and carbohydrates.

3. Irregular and occasional reverse peristalsis accompanies

the derangement of digestive function and coliform

bacilli are projected into the upper jejunum and

duodenum.

4. In their new environment, the coliform bacilli attain

exaltation of virulence and cause gastro-enteritis.

Unfortunately, although there are many theories involving

the coliform organisms, few practical investigations on this

group have been performed.   Bacteriologists have concentrated

their attention more on the non-lactose fermenting organisms

than on the lactose-fermenting coliforms which were regarded

as saprophytes and largely neglected.   Indeed, some observers,

such as Gil (1941), believe that coliform organisms are never

pathogens bur occur only as secondary invaders or as contaminants.

The concensus of opinion, however, does not favour this extreme

view.   Nowadays, most observers agree that outside their

normal environment, the coliform organisms are undoubtedly

pathogenic to the human species.   In infants they may give

rise to a severe type of meningitis and in all age groups may

be responsible for such infections as appendicitis, peritonitis,

and pathological processes of the renal and biliary tracts,

(Topley and Wilson, 1946),   Steinberg and Eker (1925) have

described the presence of soluble toxic substances in young

broth cultures of B.coli, and Doufort (1928) found that B.coli

isolated from cases of infantile diarrhoea, were more toxic

to guinea pigs than B.coli isolated from normal infants.

In view of the suggested pathogenicity of certain strains

of B.coli and their possible rôle in the aetiology of some

cases of infantile gastro-enteritis, Bray's report on the

coliform flora in this disease was of particular interest.

Bray (1945) noted the occurrence in stools from gastro-enteritis

cases in London, of a particular strain of coliform bacillus.

This strain was identified first by its characteristic smell

but later was proved to be serologically homogeneous.   From

its cultural characters and its fermentation reactions, it was

considered to be a strain of Bact.coli neapolitanum (MacConkey,

1905); Winslow, Kliger and Rothenberg (1919).   It was

isolated in 42 out of 44 cases of summer diarrhoea in London

and only in 4 out of 100 healthy controls.   This apparently

significant association of Bact.coli neapolitanum with gastro-

enteritis suggested an investigation along the same lines in

Glasgow for the following reasons:-

1. If Bray's results were confirmed, further investigations

    could be undertaken to assess the pathogenicity of Bact.

    coli neapolitanum (hereinafter referred to by the

    abbreviation "B.c.n.")

2. Even if the B.c.n. did not act as a pathogen, the finding

    of a definite alteration in the intestinal flora during

    the disease might provide the clue from which the ultimate

    solution of the aetiology could be obtained, and

3. Such an investigation would be a useful preliminary to
a more general assessment into the role of the lactose-
fermenting organisms in infantile gastro-enteritis.

THE   PRESENT   INVESTIGATION.

THE   OCCURRENCE   OF   BACT.   COLI   NEAPOLITANUM.

A series of infants clinically classified as suffering
from gastro-enteritis, was studied along with control series
of normal infants and infants suffering from other diseases.

METHOD.

Selection of Specimens.

The method of investigation of diarrhoea and control
cases was the same.   In the diarrhoeal cases, to avoid any
possibility of hospital or institutional bacteria confusing
the picture, stool specimens were taken from the napkin the
child was wearing or from the first stool which the child
passed in hospital.

Culture and Selection of Organisms.

Organisms were isolated on MacConkey plates (it seemed
undesirable to use the desoxycholate medium which is known to
inhibit certain members of the coliform species): 2 - 3 pink
lactose-fermenting colonies were selected at random from each
case, and each of these were plated on agar.   Smooth colonies

were selected from the agar sub-cultures and maintained on

inspissated egg-media in the refrigerator.

Fermentation reactions of the isolated organisms were largely

neglected, because Bray (personal communication to Dr. R.D.

Stuart) had indicated that his later work showed lack of

correlation between this property and the serological groups

concerned.

Serological Investigations.

Kauffmann (1943) has recently described a new thermo-

labile somatic antigen - the "L" antigen - in strains of

B.coli.   Although in may respects similar to the Vi.antigen

of Bact.typhosum, it differed by losing its capacity to absorb

specific agglutinins after it had been heated at 100° C for $2\frac{1}{2}$

hours, or after it had been treated with 50% alcohol for 20

hours; whereas the Vi. antigen under these conditions retains

this capacity.   Otherwise it resembled the Vi.antigen in its

loss of agglutinability on heating to 60° C and its retention

of agglutinogenicity after treatment with alcohol.

In a further investigation of the serology of the coliform

group, Kauffmann (1944a) stressed the importance of the O and L

antigens for identifying such bacteria.   By their use, he was

able to divide coliform bacteria into a number of distinct

groups and also to show that certain types appeared to be

especially associated with acute infalmmatory disorders such

as appendicitis and peritonitis. (Kauffmann, 1944b)

The serological methods used in the present investigation followed as accurately as possible the lines laid down by Kauffmann in his reports quoted above.   "O" and "OL" antisera, the latter containing both "O" and "L" anti-bodies were used. Absorptions were not attempted.

Preparation of Antisera.

Cultures Gr.1945 and Lindsay 535, representative strains of B.c.n. obtained from Dr. Bray, were used.   The strains were serologically identical.

"O" Antiserum .   20 hours broth cultures, steamed for $2\frac{1}{2}$ hours were innoculated into rabbits intravenously at 5-day intervals, the initial dose being about 250 million organisms, increasing to a final dose of about 2,000 million organisms.

"OL" Antiserum.   20 hour living agar cultures suspended in saline were used, the dosage being similar to that employed in the "O" antigen preparation.   Satisfactory titres of between 1/1250 to 1/2500 were obtained in all animals.

Agglutination Tests.

"O" Agglutination: "O" antigens were 20 hour broth cultures steamed for 1 hour and treated with 0.5% formalin.   These were prepared from all investigated strains.   They were tested against appropriate dilutions of "O" antisera and the tests were read after 20 hours in a water bath at 50° C.

"OL" Agglutination: "OL" antigens were 20 hour living agar cultures suspended in saline.   These were tested against "OL"

antisera and the results read after 2 hours at 37° C. and again
after about 20 hours at room temperature.   Controls were
included in each batch of serological tests.

Interpretation of Results.

Most organisms considered similar to the specific strain
of B.c.n. agglutinaged to full titre with both "O" and "OL"
antisera.   Whenever any doubt existed, the result of the "O"
agglutination was selected as the more reliable, and in the
following account, the positive cases mean cases from whom an
organism was isolated, the "O" antigen of which was agglutinated
to titre by the specific B.c.n. antisera.

General Description of Cases and Controls.

Gastro-enteritis cases.

A total of 151 cases of infantile gastro-enteritis were
investigated between October 1945 and January 1947.   Sex-
incidence was the usual 3:2 male preponderance.   Age-incidence
is shown in Table 4;   the large majority of cases (120) being
under one year of age.

Clinically, the 151 cases were classified into "severe"
(51 cases), "moderate" (61 cases), "mild" (21 cases), and
"chronic" (18 cases) according to the classification suggested
by Cooper (1937).   In the text, two main groups of cases are
described according to the year in which the majority of the
cases in the group occurred;   they are referred to as "1945
series" and "1946 series" but these names are used as

convenient labels and not in their strict chronological sense,
for the "1945 series" includes some cases which were examined
in the early months of 1946 and the "1946 series" includes some
examined in January, 1947.   Both series contain an approximately
equal number of infants (75 and 76 respectively).   The patients
in the 1945 series all came from the same hospital;   the 1946
series comprised patients derived from three different hospitals
sited in different parts of the city.

A senior worker in the same laboratory undertook the
bacteriological investigations of 31 cases in the "1946 series"
and his results provide a useful means of checking the author's
bacteriological technique.   They are listed separately in
Tables 1 and 9, but in all other tables, in view of the concordance
between the two sets of results, they receive no special
analysis, and are grouped along with the others in the 1946
series.

Control Cases.

Of 92 control cases investigated between August 1946
and April 1947, 57 were healthy infants, 13 were infants
suffering from non-diarrhoeal disease (such as scarlet fever,
measles, whooping cough and pneumonia), and 25 were infants
suffering from dysentery.   The healthy cases were selected
at random from Day Nurseries in the Glasgow area, and others
were patients in Ruchil and Knightswood Hospitals.   All
control cases were in the age-group 0 - $2\frac{1}{2}$ years.   None were
breast-fed at the time of investigation.

R E S U L T S.

(a) Frequency of Isolation of B.c.n. in Gastro-enteritis Cases.

Table 1.

Frequency of Isolation of B.c.n. in 1945 and 1946 Series.

Series.	Total Cases Examined.	B.c.n. +ive Cases. No.	(%)
1945.	75	8	(10.6%)
1946 Author.	45	9	(20.0%)
1946 Other Worker.	31	5	(16.1%)
1946 Total.	76	14	(18.4%)
TOTAL 1945 and 1946.	151	22	(14.6%)

Table 1. shows that, out of 75 cases examined in 1945,

B.c.n. was isolated in only 8, (10.6%); and in the 1946 series,

of 76 cases, B.c.n. was isolated in 14 (18.4%).   Thus, in both

series, Bact.coli.neapolitanum was found comparatively infrequently.

Table 1. also shows the similarity in the two sets of

results obtained in 1946.

Table 2.

Frequency of Isolation of B.c.n. in Gastro-enteritis Infants
Resident in Different Hospitals.

Series	Hospital	Time of Investigation	Total Cases	B.C.n. +ive Cases No.	(%)
1945	Belvidere.	Oct.45 - Mch.46	75	8	(10.6%)
1946	Belvidere.	Sept.46 - Oct.46	33	6	(18.1%)
1946	Ruchill.	Aug.46 - Jan 47	36	6	(16.7%)
1946	Stobhill.	Aug.1.'46 - Aug.30.	7	2	(28.6%)
	TOTAL.		76	14	(18.4%)

Table 2 shows that there was little difference in B.c.n. incidence in patients examined from Belvidere and Ruchill Hospitals; and in the small number who were examined from Stobhill Hospital, B.c.n. incidence was not significantly high.

(B) Frequency of Isolation of Bact. coli neapolitanum in Control Cases.

Table 3.
CONTROL SERIES

	DATES OF EXAM.	TOTAL CASES	B.c.n. CASES
HEALTHY CONTROLS	Nov.46 – Apr.47	57	.0.
NON-DIARRHOEAL DISEASES	Nov.46 – Dec.46		
Pneumonia		2	0
Broncho-pneumonia		3	0
Whooping-cough		2	0
Whooping-cough and pneumonia		1	0
Whooping-cough and measles		1	0
Measles		1	0
Scarlet Fever		3	0
TOTAL		13	0
DYSENTERY	Aug.46 – Dec.46		
Flexner		11	2
Sonné		9	1
Clinical		5	0
TOTAL		25	3

SUMMARY OF TABLE 3. (CONTROL SERIES)

	TOTAL CASES	B.c.n. CASES
HEALTHY	57	0
NON-DIARRHOEAL DISEASES	13	0
DYSENTERY	25	3

Table 3 shows that B.c.n. was never isolated from the normal infants who were examined or from those suffering from non-diarrhoeal disease, but was found in 3 out of 25 infants who had dysentery infections.

(C)   Analysis of Gastro-enteritis Cases   -   showing B.c.n. Incidence

Classified for Age-group, Type of Illness, Duration of Illness, and

Mortality.

Table 4
Number of Cases classified by Age-Group and B.c.n. Incidence.

Table 4a   1945

Age-Gps. by Months	Total Cases	B.c.n. +tive Cases
0-	47	6
6-	11	1
12-	11	1
18+	6	0
Total	75	8

Fig. 4a   1945
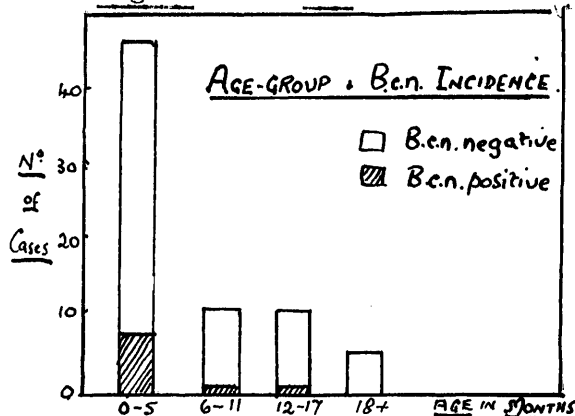
Table 4b   1946

Age-Gps. by Months	Total Cases	B.c.n. +tive Cases
0-	47	11
6-	15	3
12-	10	0
18	4	0
Total	76	14

Fig. 4b   1946
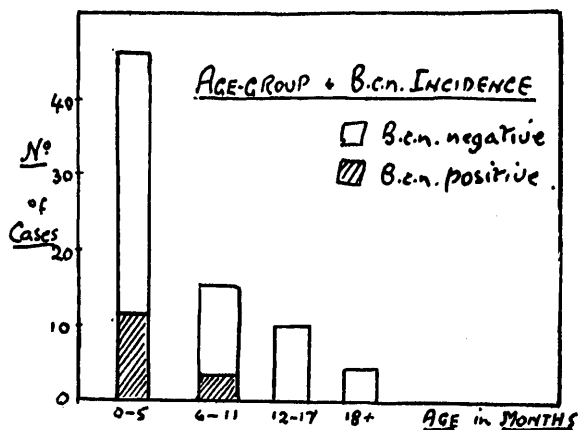
Table 4c Combined Series 1945 and 1946.

Age-Gps. by Months	Total Cases	B.c.n. +tive Cases
0-	94	17
6-	26	4
12-	21	1
18	10	0
Total	151	22

X^2 TEST (Table 4c)

Calculated Value of X^2 = 3.73

Significant Value of X^2 = 7.815 (at 5% level of significance with 3 degrees of freedom)

Hence, association is not significant.

ASSOCIATION: A X^2 test showed that age-group and B.c.n. occurrence

are not significantly related to one another.

Table 5

Number of Cases Classified by Clinical Type and B.c.n.Incidence.

Table 5a   1945

Type	Total Cases	B.c.n.+ive Cases
Severe	28	3
Moderate	30	2
Mild	8	3
Chronic	9	0
Total	75	8

Fig.5a   1945
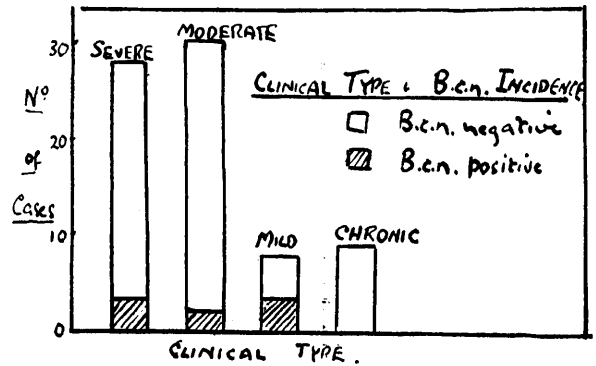
Table 5b   1946

Type	Total Cases	B.c.n.+ive Cases
Severe	23	8
Moderate	31	4
Mild	13	1
Chronic	9	1
Total	76	14

Fig.5b   1946
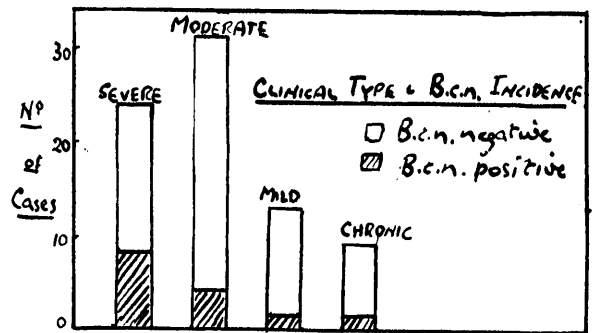
Table 5c   Combined Series 1945 and 1946

Type	Total Cases	B.c.n.+ive Cases
Severe	51	11
Moderate	61	6
Mild	21	4
Chronic	18	1
Total	151	22

X^2 TEST (Table 5c)

Calculated Value of X^2 = 3.87
Significant Value of X^2 = 7.815
(at 5% level of significance
with 3 degrees of freedom)

Hence, association is not significant.

ASSOCIATION:

A X^2 test showed that clinical type of illness and B.c.n. occurrence are not significantly related to one another.

Table 6

Number of Cases Classified by Duration of Illness and B.c.n. Incidence.

Table 6a   1945

Duration in Days	Total Cases	B.c.n.+ve Cases
0 - 7	51	6
8 - 14	19	2
15 +	5	0
Total	75	8

Fig. 6a. 1945
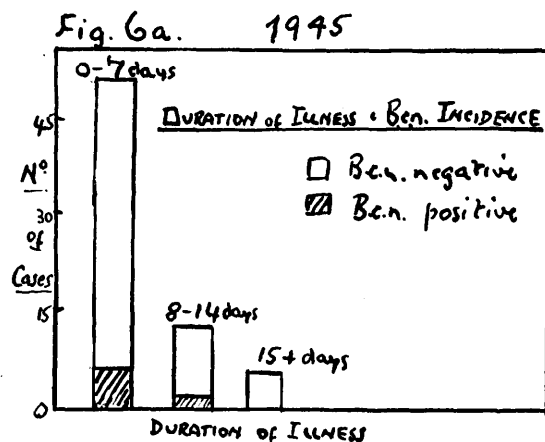
Table 6b   1946

Duration in Days	Total Cases	B.c.n.+ve Cases
0 - 7	41	5
8 - 14	20	8
15 +	15	1
Total	76	14

Fig. 6b 1946
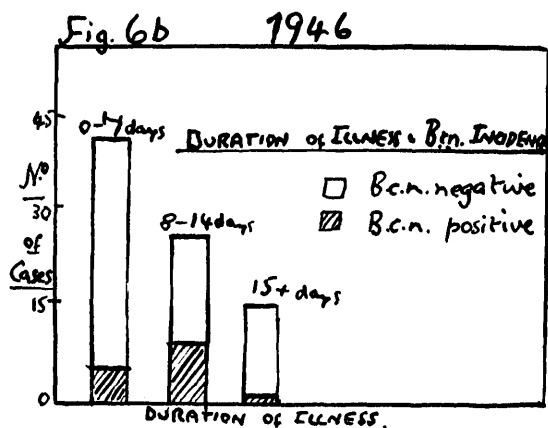
Table 6c   Combined Series 1945 and 1946

Duration in Days	Total Cases	B.c.n.+ve Cases
0 - 7	92	11
8 - 14	39	10
15 +	20	1
Total	151	22

χ^2 TEST (Table 6c)

Calculated Value of χ^2 = 5.83
Significant Value of χ^2 = 5.99
(at 5% level of significance with 2 degrees of freedom)

Hence, association is just not significant.

ASSOCIATION: Although just short of significance level there is a tendency for duration of illness to be associated with B.c.n. occurrence. It should be noted that the greatest contribution to χ^2 comes from the (8-14 days) duration group, and that this group contains the highest proportion of B.c.n. positive cases.

TABLE 7

DEATH RATES Classified by B.c.n. INCIDENCE.

Table 7a. 1945 Series.

	Deaths	Total No. of Cases.	Death Rate per 100 cases.
B.c.n.+	3	8	37.5
B.c.n.-	13	67	19.4
Total	16	75	21.3

Table 7b. 1946 Series.

	Deaths	Total No. of Cases.	Death Rate per 100 cases.
B.c.n.+	6	14	42.9
B.c.n.-	12	62	19.4
Total	18	76	23.7

Table 7c. Combined Series 1945 & 1946.

	Deaths	Total No. of Cases.	Death Rate per 100 cases.
B.c.n.+	9	22	40.9
B.c.n.-	25	129	19.4
Total	34	151	22.5

ASSOCIATION:-

A χ^2 test applied to table 7c showed that death-rate and B.c.n. occurrence are significantly related to one another.

(The calculated value of χ^2 was 3.81 and the value of χ^2 required for significance is 3.8)

TABLE 8.   (Contingency Table)

Total Cases Classified by Age Groups and Type of Disease.

Age-Group in months.	Severe	Moderate	Mild	Chronic	Total
0 - 6	40	38	11	8	97
6	9	8	3	5	25
12	4	6	6	4	20
18 +	-	6	2	1	9
TOTAL	53	58	22	18	151

ASSOCIATION:

A χ^2 test just failed to show association between age-groups and clinical type of disease.   However, these variables, if not significantly related to one another, are at least closely related, for the calculated value of χ^2 was found to be 16.04 and the value of χ^2 which determines significance is 16.92.

REPEAT SERIES.

     In order to determine whether a period of hospitalisation affected the occurrence of B.c.n. in the faeces, "repeat specimens" were examined in 39 patients in the 1946 series. The second specimen was obtained 7 - 10 days after admission. Of the 39 repeat specimens, 15 were examined by a senior worker in the same laboratory and his results are indicated separately, below.

<div align="center">

TABLE 9.

"Repeat Series" 1946.

</div>

	No. of Cases Examined.	Results of 1st Specimen Examination.		Results of 2nd Specimen Examination.	
			No. of Cases	B.c.n. +ive	B.c.n. -ive
Author	24	B.c.n. +ive	5	3	2
		B.c.n. -ive	19	6	13
Other Worker	15	B.c.n. +ive	3	2	1
		B.c.n. -ive	12	3	9
TOTAL.	39	B.c.n. +ive	8	5	3
		B.c.n. -ive	31	9	22

FIG. 9.

B.c.n. -ive Cases
(on admission).
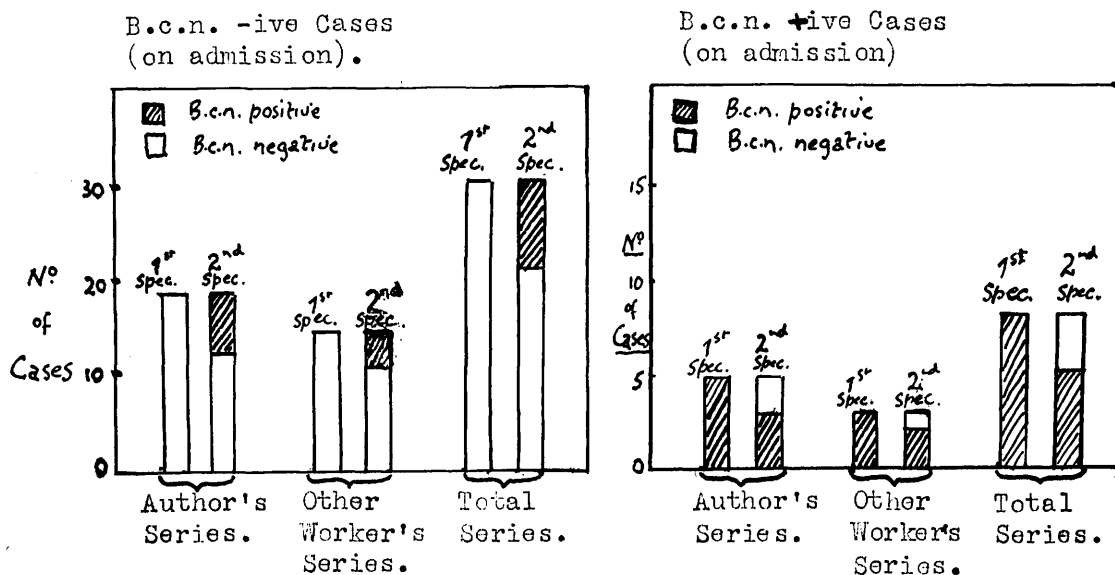
B.c.n. +ive Cases
(on admission)

Table and Figure 9. show that the other worker's findings agreed with the author's.   In both series of cases it was found that, after 7-10 days' hospitalisation, some of the cases, originally B.c.n. negative, became B.c.n. positive; and some B.c.n. positive cases became B.c.n. negative. Actual figures for the combined series are as follows:-

Of 31 B.c.n. negative cases (on admission) 9 cases (29%) became B.c.n. positive after 7 - 10 days' hospitalisation: and of 8 B.c.n. positive cases (on admission) 3 cases (37.5%) became B.c.n. negative after 7 - 10 days' hospitalisation.

D I S C U S S I O N.

The negative findings in the normal cases confirm Bray's
view that Bact.coli neapolitanum is not a common inhabitant
of the normal infant's intestinal tract; and the results in
the small series of infants studied here, who were suffering
from diseases other than gastro-enteritis, suggest that
this organism is rarely associated with diseases which are
non-diarrhoeal in nature.

In the present investigation, although the incidence of
B.c.n. in stools of infants with gastro-enteritis was
appreciably higher, both in the 1945 and 1946 series, than
its incidence in infants with normal stools, there was no
correspondence with Bray's findings of almost 100% incidence
of this strain of B.c.n. among diarrhoeal cases in London.
In the present series, B.c.n. was isolated in 1945 and 1946
in only 10.6% and 14.6% of cases respectively.

The method of sampling used here was essentially equivalent
to Bray's, but this low incidence in B.c.n. occurrence found
in the present series is in marked contrast to Bray's findings.
However, it must be pointed out that the present investigation
differed both in time and place from that carried out by Bray,
and that there was a difference in the type of cases which
were examined.   Bray's cases were studied in London in 1944
during an epidemic of the disease, whereas the present cases
were studied in 1945 and 1946 in Glasgow, where there was no

real epidemic of gastro-enteritis and the cases were of

sporadic type.   In the meantime, however, it can be said that

in whatever capacity B.c.n. was associated with infantile

diarrhoea in London in 1944 - whether as primary incitant,

concomitant, or secondary invader - its role in any of these

capacities cannot have been significant among Glasgow

infantile gastro-enteritis cases in 1945 and 1946.

It should be noted that this finding does not disprove

the hypothesis suggested by Blacklock, Guthrie and McPherson

(1937); Wright and Wright (1946) and others, that the

disease is due to coliform organisms.   The Wrights' hypothesis

was that certain coliform organisms which were circulating in

a community could, under certain conditions, become pathogenic

for infants under 2 years of age.   There are many thousands

of seriological variants of B.coli, and more than one strain

may possess this potential pathogenicity for infants.   There

is evidence from Farr (1936) that in the adult community the

predominating coliform strains are continually changing, and

Wallick and Stuart (1945) state that "in healthy adults, any

particular strain of B.coli tends to remain dominant in the

intestine for several weeks or months at a time, only to be

succeeded by another temporarily dominant resident of the

same species".   The patients in the present series also

exhibited this tendency to alteration in their intestinal

flora, for it was found here that, after 7 - 10 days in

hospital, certain infants who were previously "B.c.n.negative"

became "B.c.n. postivo" and certain "B.c.n. positive" cases

reverted to "B.c.n. negative".   (Table 9. p. 105).

Further, a difference in locale also appears to play a part

in determining differences in predominating coliform strains,

for Stuart and Van Stratum (1945) who investigated the faecal

flora of normal infants in two institutions, found that

distinctly different types of B.coli predominated in each

institution.

There are, therefore, grounds for believing that the

dominant strains of B.coli differ among different communities,

and that even in the same community, the dominant strains are

continually changing.   It follows that, should there be

several strains capable of giving rise to gastro-enteritis,

the causal strain in one group of cases is liable to be

different from that in another group, which occurs at another

time or place.   Thus, the lack of agreement between Bray's

and the present findings cannot be regarded as evidence

against the hypothesis that the disease may be caused by

coliform organisms.

SUMMARY   AND   CONCLUSIONS.

The bacteriological findings in infantile gastro-enteritis are reviewed.   Attention is specially directed to hypotheses incriminating the coliform organisms in the aetiology, and an investigation into the occurrence of one of these - Bact. coli neapolitanum - is reported.

During 1945 and 1946 in Glasgow, two distinct series of sporadically occurring infantile gastro-enteritis were studied. Bact.coli neapolitanum was found in 8 cases (10.6%) in the first series, and 14 cases (18.4%) in the second series. This organism was isolated in 3 instances from 25 patients with dysentery, but was not isolated from 57 healthy infants, or from 13 infants suffering from non-diarrhoeal disease. Examination of "repeat specimens" in 39 cases, revealed that of 31 cases which had been B.c.n. negative on admission 9 cases became B.c.n. positive after a week's hospitalisation; and out of 8 cases, B.c.n. positive on admission, 3 cases became B.c.n. negative after a week's hospitalisation.   The reason for this alteration in the infants' intestinal flora is not known.

Statistical analysis showed a significant association of Bact.coli neapolitanum with mortality and a tendency to association with duration of illness.   There was also a tendency to association between age-group and clinical type of illness.   However, this organism was found not to be

significant either in its incidence in gastro-enteritis, or in its relation to age-group or clinical type of disease.

Although Bact.coli neapolitanum does not occur in a significant proportion of all cases of infantile gastro-enteritis, the present investigation does not rule out the possibility that it may assume a significant incidence during an epidemic period, nor does it invalidate the hypothesis that several different serological variations of B.coli may be concerned in the aetiology of the disease.

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GENERAL SUMMARY OF THESIS AND FINDINGS.

The Thesis has been divided into three parts.

In Part 1. an account has been given of early historical references to gastro-enteritis in infancy. Recent work on epidemiology and treatment has been reviewed.

In Part 2. certain clinical aspects have been investigated under the following headings:-

(a) Oedema. Oedema has been found to occur in 35 cases out
of 176 cases of infantile gastro-enteritis investigated.
The oedema was confined to patients in the 0 - 16 months
age-group and was never observed before the 5th day of
illness. The oedema subsided spontaneously, in most
cases its duration being from 2 - 8 days. Weight-
changes which accompanied the oedema, were found to
fluctuate parallel with the rise and fall of the visible
oedema. Several oedematous patients were found to have
a microcytic hypochromic anaemia, but none showed signs
of albuminuria, heart disease,macrocytic anaemia, or
Vitamin B. deficiency. The oedema was not related to
the giving of excessive parenteral fluid or to sulphonamide
therapy. Experimentally, it was found that protein
feeding had no effect in reducing the incidence or
duration of the oedema. The mortality in oedematous
patients was 31.4% and in the non-oedematous, 17.7%

Hypothetical explanations for the condition have been discussed. Of these, the likeliest has been considered to be one or a combination of the following:- impairment in capillary function, impairment in liver function and impairment in renal function.

(b) <u>Evacuation Time</u>. The time taken for food to pass through the alimentary tract in patients suffering from acute gastro-enteritis, has been investigated by administering charcoal orally and noting the time when it first appeared in the stools. The findings have been compared with those in a number of similar children not suffering from gastro-enteritis. The results indicate that in gastro-enteritis, this evacuation-time is much reduced: in one patient the charcoal appeared in the stool in only two hours after its ingestion.

There was wide variation in evacuation-times in individuals in both groups, and all infants investigated showed charcoal residues in the stools for 36 - 96 hours after its first administration. The findings for normal infants have agreed with those of other investigators who used different methods of estimation and it has been concluded that the charcoal method was a reasonably accurate and convenient means of determining the evacuation-time.

(c) <u>Intra-Gastric Drip Feed.</u> A method of intra-gastric drip

feeding has been described for the treatment of
vomiting and dehydration in infantile gastro-enteritis.
The procedure is free from the disadvantages of parenteral
therapy. It has been found simple, safe and effective.
Some original points in the technique have been described
and recommended for facilitating administration.

In Part 3. the bacteriological findings in infantile gastro-
enteritis have been reviewed and discussed. The occurrence
of a certain strain of coliform bacilli, Bact.coli.neapolitanum,
recently suggested to be of aetiological importance in the
condition, has been investigated bacteriologically and sero-
logically. This organism was found not to occur in a
significant proportion of the cases investigated, although
statistical analysis revealed a significant association with
mortality and a possibly significant association with duration
of illness. This organism was found also in children suffering
from diarrhoeal diseases of known specific aetiology, but not
in healthy controls. The findings have been reviewed
statistically and the general implications discussed.

---ooOoo---