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SPECIAL TYPES OF ESCHERICHIA COLI IN INFANT DIARRHEA

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Approximately eight years have passed since the work of John Bray[1,2] in England drew the attention of English and Scotch workers to the possible role of a certain *Escherichia coli* type in infant diarrhea. Abroad a voluminous literature has been published on this subject, most of it favorable to the idea that one, and perhaps two, serologic types of *E. coli* are among the causative agents of infant diarrhea.

With what sort of a reception has this work been received abroad and in this country?

One is inclined to believe, because of the number of publications that have come from England and Scotland, that in those countries, at least, acceptance of certain coliform bacteria as etiologic agents in diarrhea of infants has been widespread. Apparently, though, nothing is further from the truth. To use a newspaper cliché, a "reliable source" has informed me that pediatricians, pathologists, and bacteriologists over there are still divided into two camps over the issue of whether or not *Escherichia coli* has anything to do with gastroenteritis of babies. Also, according to the "reliable source" feeling runs rather high among the partisans. Nevertheless, an annotation in the editorial section of the Lancet of August 16, 1952, states unequivocally that one serologic type of *E. coli* may cause infantile gastroenteritis both as a sporadic and epidemic disease.

Probably the situation in Sweden, Denmark, Germany and other continental countries is much the same as in England. However, the medical literature in those countries appears to be favorable, perhaps because the opposition has not been active in publication.

In this country, if one were to judge by publications and editorials in medical journals, there is complete indifference to the subject. So far as I am aware, not a single article has appeared in any of our pediatric or other strictly clinical journals on special serotypes of *Escherichia coli* in infant diarrhea. Publications to date have come from bacteriologists, some of whom are men with a medical degree. I know of one and perhaps two papers on coli diarrhea of infants which is under preparation by a well-known pediatrician. These will be the first clinical papers of the kind to be published in the U. S. A. It seems likely that there will be others when the right combination of medical and laboratory skills is available.

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It is a heartening sign that investigators and reviewers are coming to recognize that diarrhea of the newborn may be caused by a variety of agents, both bacterial and viral. There was a time shortly after the publications of Buddingh and Dodd[3], and of Light and Hodes[4], when reviewers were prone to discuss infant diarrhea solely in terms of a virus etiology.

One of the open minded—Clifford[5] of the Harvard Medical School—feels that the syndrome described as epidemic diarrhea of the newborn is not a pathologic entity but a miscellaneous group of cases of various etiologies, known and unknown, bound together by a common symptom—diarrhea.

Kirby, Hall and Coackley[6] of England share this view and feel that on the basis of the literature the syndrome of infant diarrhea may be broken down into six categories, according to clinical symptoms and etiologic agents.

Apparently, though, it has taken this concept some time to take root in the minds of medical investigators. Even today there is an inclination on the part of some to regard infant diarrhea as an entity with a virus as the sole causative agent.

John Bray, in England, back in 1943, evidently had an open mind about the etiology of infant gastroenteritis. His unorthodox approach to the problem is a tribute both to himself and his colleague Beavan. It was Beavan, a clinician, who suggested to him that he determine the cause of the unusual seminal odor which had been noted in the stools of diarrheal babies in outbreaks of the disease. His investigation of this lead resulted in the discovery of a single serologic type of *E. coli* organism which produced a seminal odor on artificial media and, moreover, which was present in the stools of a large percentage of diarrheal babies. The organism was found in only a small number of well babies housed in the diarrheal wards in which he conducted his studies. The name Bray gave his coliform organism was *Bact. coli* var. neapolitanum—a name now of historical interest only, since it has been supplanted by a variety of designations.

At about the time Bray concluded his work, Giles, Sangster and Smith[7], working in Aberdeen, Scotland, began studies on infant diarrhea, keeping in mind the possibilities of a bacterial or viral agent. Their search for a virus was soon dismissed as useless; likewise their search for Group D streptococci was discontinued as futile. In their search for special types of *E. coli*, however, they hit "pay dirt."

During 1947, Giles, Sangster and Smith[7] investigated 207 cases of infective gastroenteritis, chiefly in infants who were bottle-fed and under 7 months of age. Of these, 105 or 50.6 percent died. From the stools of 95 percent of the infants a special coliform organism was isolated which they named *Bact. coli* alpha. It was later discovered that *Bact. coli* alpha was identical with the coli organism of Bray.

At post-mortem 55 of the fatal cases in the Aberdeen study showed an indefinite pathology, apparently a common finding in infant diarrhea. The changes that occurred in the intestines were termed minimal, but the liver was affected in some instances, showing slight to extensive fatty degeneration.

Sera of 21 out of 41 infants who excreted the alpha organism were found to have an antibody titer varying from 1 in 40 to 1 in 640, while no significant agglutinins for *B. coli* alpha were detected in the sera of 53 normal infants. A study of fecal material from normal children and normal adults revealed that *Bact. coli* alpha was present in a very small percentage of cases.

During the latter part of 1948, the Aberdeen group found that the alpha organism occurred infrequently in diarrheal infants in that area. Instead a new type of coliform bacterium, called *Bact. coli* beta, appeared with increasing frequency. During 1949-50[8] the beta type occurred in infant diarrhea nearly to the exclusion of the alpha type. At the same time a considerable lowering of the mortality rate took place. It seems possible that better care, together with the use of chloromycetin, influenced the death rate, perhaps as much as a change in the type of organism.

The next work of significance was reported in 1949 by the English workers Taylor, Powell and Wright[9] who investigated outbreaks of diarrhea and vomiting among infants in several nurseries located in the London area. They found no recognized pathogenic bacteria but demonstrated a single serologic type of *Escherichia coli* organism in a high percentage (100 and 91) of infants in 2 nurseries; a moderate percentage (43) in a third nursery; one fifth of the cases in a fourth nursery; and none in a residential nursery with endemic diarrhea and vomiting. Their coliform organism they called *Bact. coli* D_{433}, but it was identical serologically and biochemically with the organism of Bray, and with *Bact. coli* alpha.

Bact. coli D_{433} was not isolated from 208 normal babies, nor was it found 3 to 6 months later in 82 infants occupying nurseries and wards where it had been found earlier. The organism was found, however, in 4 of 84 adult contacts and from 9 of 34 baby contacts.

Attempts to demonstrate a virus in post-mortem material from 4 babies who had excreted *Bact. coli* D_{433} were unsuccessful. A variety of animals was used and various routes of inoculation were attempted. This work, carried out by F. O. MacCallum[9], is the only significant attempt to date to demonstrate a virus in either post-mortem or fecal material from infants infected by one of the special coliform organisms.

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The work just reviewed should justly be considered the pioneer work which other investigators have expanded or have challenged. It is not possible at present, nor would your patience tolerate, a detailed review of all the publications which have been made on this subject. Instead, I wish to sum up for you the evidence for and against regarding these bacteria as causative agents of diarrhea in infants.

First, though, in the interests of sanity, it is necessary to clear up the matter of nomenclature of the special *E. coli* organisms. The British Medical Journal urges that the designations of Kauffmann, the Danish bacteriologist, be accepted internationally. For that reason I shall use the Kauffmann formula 111, B_4 for

the organism first described by Bray, and formula 55, B_5 for the *B. coli* beta of Giles, Sangster and Smith.

The following points are presented on the "pro" side of the argument in regard to etiology:

Point 1. From the standpoint of geographic distribution it is clear that *E. coli* 111, B_4 is not a purely local type, but has been found associated with infant diarrhea in England[1,9], Scotland[7,8], Sweden[10], Germany[11], Denmark[12], France[13], the U. S. A.[14,15], The Netherlands[16], Israel[17], Mexico[18], and Japan[19]. This type is either more virulent than *E. coli* 55, B_5 or else more widely distributed; or perhaps its virulence accounts for its more frequent discovery and therefore its apparent wider distribution. The 55, B_5 type has been found in Scotland, in England, in Michigan, and within the last year in Montreal, Canada[20].

Point 2. It is noteworthy that in infant diarrhea the special coliform organisms, when present, are found in nearly pure culture in the feces during the diarrheal stage. In convalescent infants who have received no treatment, both the 111, B_4 or 55, B_5 organisms tend to disappear and are replaced by other flora.

Point 3. Of particular interest is the fact that *E. coli* 111, B_4 has been found frequently in the nasopharynx of diarrheal infants excreting the same organism in the feces. Neter, Webb et al.[21] have pointed to the analogy to Salmonella infection in infants in which the same observation has been made.

Point 4. Chloromycetin, aureomycin, terramycin, and lately, neomycin have been found effective in the treatment of diarrheal infants infected with the 111, B_4 organism. It has been noted by some investigators that as clinical improvement occurs after therapy, the special coliform organism disappears from the nasopharynx and stools.

Point 5. It is controversial in England, at least, as to whether or not infected infants develop an agglutinin titer for 111, B_4 organisms. The evidence of Giles, Sangster and Smith[7] has been quoted. We have found in Michigan titers of 1:256 in convalescent infants. Dutch investigators[16] also report the development of agglutinins in infants who have had diarrhea in which this bacterium was present.

Point 6. Our staff at Lansing has carried out fairly large-scale feeding experiments[22,23] on adult volunteers during the last two years, using 111, B_4 and 55, B_5 organisms. These tests convince us that both types of bacteria are markedly different than *E. coli* from normal individuals. A total of 114 men were used in the first experiments and 71 in the second. It was demonstrated that 111, B_4 organisms in large dosage would cause gastroenteritis similar to food-poisoning, and that individuals ingesting the test cultures developed specific agglutinins for them. The 55, B_5 type produced milder but definite symptoms of gastroenteritis. *E. coli* organisms from normal babies produced no illness even when fed in very heavy dosage. In addition, no volunteer showed an agglutinin rise from ingesting the latter type of culture.

The work of Neter and Shumway[14] may be known to many of you, but it will bear repeating. These investigators fed a 2 month-old infant with congenital defects 100 million *E. coli* 111, B_4 organisms, in formula, and produced diarrhea and weight loss within 24 hours. The organism was subsequently demonstrated both in the nose and throat and in feces. Clinical improvement followed treatment with terramycin and the organism disappeared within 48 hours after therapy was begun.

Point 7. Rogers[24], Rogers and Koegler[25] in Birmingham, England, have presented bacteriologic evidence of how epidemics of infantile gastroenteritis spread from hospital to hospital, as well as within hospital wards. They have described three such outbreaks, in 2 of which the *E. coli* 111, B_4 organism was associated with the cases of diarrhea, and another in which the 55, B_5 type was present. The epidemiological evidence is strong, according to them, that both types of *E. coli* are of etiologic significance in certain epidemics of infant diarrhea.

In presenting considerations against regarding the special *E. coli* organisms (particularly the 111, B_4 type) as among the causative agents of infant diarrhea, I admit that I am handicapped by a definite inclination toward the "pro" side of the argument. However, there is another side.

Point 1. about which there can be no disagreement, is the fact that no one, as yet, has carried out careful, large-scale attempts to demonstrate a viral agent in material from diarrheal infants excreting either *E. coli* 111, B_4 or 55, B_5. Until this is done, perhaps with humans as test animals, there will always remain a doubt. It has been pointed out by Bray[1] that the presence of *E. coli* 111, B_4 in infant diarrhea may be analogous to the situation in hog cholera, where a virus is the causative agent but *Salmonella choleraesuis* is frequently present.

Point 2. The majority of investigators have found the 111, B_4 type to occur in only a small number of the normal individuals examined. Two papers, however, have been published which cast some doubt on this point. The work of Payne and Cook[26], and of Cathie and MacFarlane[27], needs careful consideration, for they have found quite a number of strains of 111, B_4 in non-diarrheal infants. It may be that in both normal infants and adults many carriers exist, just as Salmonella carriers exist in all age groups. The authors cited, however, present their findings as reasons for not regarding the 111, B_4 organism as a pathogen.

Point 3. In some outbreaks of infant diarrhea the special coliforms have been found in only a varying percentage of diarrheal babies. Why were they not present in all infants affected?

I cannot answer this, but I will hazard a guess that part of the difficulty may be the inadequacy of selective media for demonstration of the organisms sought. During the diarrheal stage, if an infant has not received treatment with antibiotics, selective media are not important. The organisms are nearly always very abundant. However, if treatment has begun, discharge of the coliforms may be intermittent or the number may be small.

Point 4. One would think that organisms capable of causing severe diarrhea in one type of mammal would cause distinct symptoms when tested in other animals. This is apparently not the case with *E. coli* 111, B_4. Taylor[9] made repeated attempts to demonstrate some difference in pathogenicity between the 111, B_4 type and serologically unrelated coli strains isolated from healthy babies. All strains gave much the same results when given to guinea pigs, mice, rabbits or monkeys, the degree of pathogenicity being dependent upon the route of inoculation.

Point 5. It is very difficult for pediatricians or bacteriologists to accept as a pathogen a member of a bacterial group regarded as essentially commensal in the intestinal tract. This perhaps has as much to do with the controversy over the special serotypes of *E. coli* as purely scientific considerations. I make this as the final point because I can recall my own hesitancy in regarding the 111, B_4 and 55, B_5 organisms as significant.

* * * *

In Michigan for a period of nearly 7 years we have been conducting investigations on hospital nursery outbreaks of infant diarrhea. Within the last 4 years our interest has been centered on the occurrence of the special coliforms. Our experience bears out the fact that serotypes 111, B_4 and 55, B_5 are closely associated with at least one kind of infant diarrhea. The evidence to date is rather convincing that the 111, B_4 type, at least, should be considered among the causative agents of diarrhea of the newborn.

During this period of concentration on *E. coli* types we have carried out laboratory and some field work on 13 outbreaks of diarrhea in nurseries. Statistics are not available for all of the outbreaks, but in the two largest ones *E. coli* 111, B_4 was isolated from a large percentage of diarrheal babies. In the remaining 11 investigations, the 111, B_4 type was found associated with diarrhea in 9 nurseries while the 55, B_5 type was present in a high percentage of diarrheal infants in a 10th nursery. In the 11th outbreak no known pathogens such as Salmonellae or Shigellae were found and neither of the two types of *E. coli*. Thus, in 12 out of 13 outbreaks either the 111, B_4 or the 55, B_5 type was associated with the diarrhea.

We have isolated the 111, B_4 type from over 225 different infants and the other type from 10.

It is worthy of mention that the one outbreak, in which neither of the special coliforms was present, was different in that both adults and infants were involved. Although our specimens came only from infants and children who were hospitalized, diarrhea was present in both adults and younger individuals throughout the city in which the hospital was located. No evidence of a viral agent was secured from an examination of blood and stools from the diarrheal infants.

We have, like everyone else, been curious about the occurrence of the special coliform types in normal newborn babies. Our work to date along this line has been limited but interesting. It suggests to us that more work is justified. From one of the Lansing hospitals which has been free of nursery diarrhea for nearly 6 years, our laboratories cultured the stools of 1200 newborn babies. In addition

we examined 900 meconium specimens from some of the same infants. Isolation of *E. coli* 111, B_4 was successful from 3 of the stools. The 3 infants excreting the organism did not have diarrhea at the time specimens were taken; one developed diarrhea within 3 to 4 days, the other two remained well. We obtained no *E. coli* special types from meconium examinations.

Naturally, in all of the outbreaks investigated it has been customary to take specimens from doctors, nurses, mothers, and other persons in contact with the babies. Our results have been disappointing. We obtained the 111, B_4 type from the stools of 4 nurses who were in direct contact with diarrheal infants, and from 2 mothers who had sick babies. I know, however, of an outbreak in which 9 of the nursery personnel were found to be carrying 111, B_4 organisms. Some of these individuals had had diarrhea just preceding culture.

One of the first and largest outbreaks involving *E. coli*, which was investigated by our Department, occurred in Port Huron. Dr. Cummings, our Director, did the field work on that occasion. He noted at the time that certain clinical manifestations were somewhat different than those he had seen in previous epidemics. He has characterized the disease at Port Huron as one of exacerbations and remissions. The common clinical picture in the infants was: elevated temperature, sometimes up to 104°F; leukocytosis; foul-smelling stools; diarrhea not necessarily profound; the infants were toxic, acidotic; dehydration was pronounced; vomiting occurred with large numbers of infants. According to Dr. Cummings' experience at the time, the high temperatures, the leukocytosis, the foul-smelling stools and the considerable number of remissions were unusual.

I am not, as you can well appreciate, prepared to discuss the clinical picture of outbreaks investigated by our department, or the treatment. Certain details, however, come to the attention of a bacteriologist which may be of interest. It is noteworthy that from some of the early outbreaks we isolated streptomycin-sensitive and chloromycetin-sensitive strains of 111, B_4[15]. Treatment with chloromycetin appeared to be successful. Later the organisms isolated were streptomycin-resistant and some resistance to chloromycetin was noted. In one hospital outbreak the chloromycetin resistance of 111, B_4 strains was marked and therapy was changed to terramycin or aureomycin. This was not uniformly successful. The antibiotic spectrum indicated that neomycin might be effective. Treatment with this drug has been successful.

Dr. Warren Wheeler of Children's Hospital, Columbus, Ohio, has had experience with an outbreak of diarrhea recently in which *E. coli* 111, B_4 was isolated. He has permitted me to say that treatment with neomycin was very satisfactory. Current practice makes use of neomycin in infant diarrhea in a dosage of 50 to 100 milligrams per kilogram daily, over a period of 7 to 10 days. In the Michigan hospital mentioned a moment ago, the dosage was adjusted on a 50 milligram per kilo basis.

Because of the variety of antibiotics used today, it is only sensible to determine the drug sensitivity of a strain of 111, B_4 or 55, B_5 at the beginning and during

the course of an outbreak. We now make this service routine and it appears to be appreciated by physicians.

I have been asked repeatedly, could these special coliform organisms, like Salmonella, be of animal as well as human origin? Apparently they can. Hans Fey[28] of Zürich, Switzerland, has just announced the finding of the 111, B_4 organism on the prepuce of a bull. The 55, B_5 type has been recovered by him from bovine mastitis.

Another finding that points to the resemblance of the special coliforms to Salmonella is the fact that 111, B_4 and *Salmonella adelaide* are completely similar insofar as their 0 antigens are concerned. Since 0 antigens apparently account for virulence, you have an answer as to why this coliform is different from most members of its genus.

In conclusion, weary though you may be of hearing the formulae 111, B_4 and 55, B_5, I urge that you keep them in mind—particularly when you have cases of infant diarrhea under your care.

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