Preliminary Communications

Adenovirus and Intussusception

The aetiology of intussusception in children has remained obscure, although the development of this abnormality in adult cases has often been attributed to the presence of a tumour or some similar focus. The commonest location of the lesion in intussusception is the small intestine, in the region of the ileocaecal valve, where the heaviest concentration of lymphoid tissue is to be found.

In children, intussusception has been attributed to imbalance of intestinal muscular contraction, to the presence of lymphoid tissue about the ileum, and to varying directions of peristaltic waves in this region (Anderson, 1957).

It has been known for some time that adenoviruses may be excreted in large quantities in the stool (Kjellén *et al.*, 1957; Gardner *et al.*, 1960; Duncan and Hutchinson, 1961) and for long periods of time (Gardner *et al.*, 1961). With current methods of isolation it would appear unlikely that adenovirus could be isolated so easily from the stool over long periods of time if the presence of virus was solely the result of passive swallowing from the upper respiratory tract. If this view is accepted it would appear that adenoviruses must multiply somewhere in the intestinal tract. With these observations in mind, it was decided to examine the stools of all confirmed cases of intussusception in children seen during a period of about a year. Over the same period the first specimen of faeces of all admissions was examined for viruses, and children in the equivalent age-groups whose clinical condition was unlikely to be of a viral nature were selected to act as controls. The results of the investigation, presented below, substantiate the simultaneous observations of Graham Ross and Potter (1961).

MATERIALS AND METHODS

Faeces from 10 cases of intussusception, taken as soon as possible after operation, were examined on HeLa cells, and 13 ward controls between the ages of 3 months and 1 year were similarly examined. The ward patients were those who had been admitted on account of trauma or for the treatment of a congenital hernia. Cases which might have a possible virus aetiology were excluded. Ten per cent. faeces suspension in 0.2-ml. and 0.1-ml. quantities were inoculated into HeLa cell tubes and maintained for a minimum of 28 days. It was necessary occasionally to passage agents during the 28 days for non-specific changes. Likely degenerating agents were passaged and if still present were subjected to a complement-fixation test using a standard adenovirus serum. If the result of this test was positive a neutralization test was performed, using the appropriate antisera. The methods employed were similar to those described by Munro-Ashman *et al.* (1958).

If an agent did not give a positive complement-fixation test with adenovirus antisera, neutralization with a rabbit herpes simplex antiserum was attempted, followed by inoculation on to the chorio-allantoic membrane of 10-12-day-old fertile hens' eggs.

Monkey-kidney tubes were inoculated when available, and 7 out of the 10 cases of intussusception and 5 out of the 13 controls were thus examined.

RESULTS

Of the 10 cases of intussusception examined (seven males and three females), all were under 1 year except one girl aged 2½ years. The results are shown in the Table.

Analysis of Cases of Intussusception

Case No.	Sex	Age	Adenovirus	Other Viruses
1	F	2½ years	—	—
2	M	8 months	—	—
3	M	10 "	—	—
4	M	5 "	—	Herpes simplex
5	M	5 "	+	—
6	M	5 "	+	—
7	F	9 "	+	—
8	M	6 "	+	—
9	F	6 "	+	—
10	M	4 "	+	—

In three cases no viruses were isolated in HeLa cells. From the remaining seven, six stools yielded adenovirus, while the seventh yielded herpes simplex. Four of the adenoviruses were type 5, one was type 4, and one was type 7. None of the 13 control infants had any viruses in their stools as detected by HeLa cells. In none of the faeces examined in this investigation were any enteroviruses detected either on HeLa cells or monkey-kidney cells when used. In two cases adenoviruses were isolated on both monkey-kidney and HeLa cells.

As this was by way of an exploratory investigation no blood specimens were taken from this young age-group, nor were follow-up faeces, except in one case (No. 10) in which the same adenovirus type 5 was being excreted two months later.

DISCUSSION

Though the figures were small the results indicate that virus was being excreted in large quantity in the faeces of 70% of cases of intussusception, 60% being adenovirus. Three of the cases gave a history of upper respiratory infection, which may have been the source of their infection. However, the experience gained in the study of adenovirus excretion in a closed community (Gardner *et al.*, 1961) showed that adenovirus, particularly type 5, could be excreted for a long time without apparent ill-health. This may be of interest, as four of the six adenoviruses isolated were types associated with long-term faecal excretion. The possibility exists that the adenoviruses multiply in the lymphoid tissue of the bowel, perhaps in the Peyer patches and the terminal ileum, and result in the enlargement of this tissue. This factor, either alone or in association with physiological upset due to a change to mixed feeding or some dietary indiscretion, may lead to the start of an intussusception. Abdominal symptoms are certainly not uncommon in adenovirus infections (Gardner *et al.*, 1960), and they have been found in the mesenteric glands (Kjellén *et al.*, 1957).

It must be emphasized that this is a preliminary report and adequate confirmation of these results is necessary. One could speculate that intussusception was just one of the rarer manifestations of adenovirus infections of the bowel in the young, while many more children of this age-group may present with diarrhoea and perhaps in the older child as mesenteric adenitis. Suitable cases at operation should be examined and compared with normal children and children with diarrhoea, mesenteric adenitis, and perhaps acute appendicitis, before a clearer picture emerges of the part played by adenoviruses in the aetiology of intussusception and other bowel diseases.

SUMMARY

Ten cases of intussusception are reported. An adenovirus was isolated from the faeces of six of these patients and herpes simplex from the faeces of one. Thirteen subjects of a similar age examined as controls were negative. The possible role of adenovirus in the aetiology of intussusception is discussed.

I am indebted to the Child Health Department, Newcastle upon Tyne, and the clinicians at Sheriff Hill Hospital, Gateshead, from whom specimens were obtained.

ADDENDUM.—Since this investigation was completed three further cases of intussusception have been examined; two were associated with adenovirus excretion.

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Medical Memoranda

Case of Mesenteric Reticulosarcoma Associated with Gluten-sensitive Steatorrhoea

[WITH SPECIAL PLATE]

Several authorities have recently demonstrated that the majority of cases of idiopathic steatorrhoea, or adult coeliac disease, will respond to a gluten-free diet. In fact Cooke (1958) states: "From reports in the literature and from personal experience it does seem justifiable to assume, should clinical cure result, that the patient was suffering from adult coeliac disease."

The patient concerned in this report suffered a severe degree of steatorrhoea and died of mesenteric reticulosarcoma. For 18 months there was a complete response to a gluten-free diet.

CASE HISTORY

The patient first sought advice in October, 1955, when aged 49. Previously his health had been good and he had led a normal, active life. He gave a history of loss of weight (at least 28 lb.—12.7 kg.), anorexia, fatigue, and sore tongue for the previous year. The stools had become unusually bulky and occasional nausea and vomiting occurred.

Examination revealed a tall man of normal skeletal proportions. There was evidence of recent loss of weight and pallor. The abdomen was mildly distended; there were no other abnormal physical signs.

Investigations gave the following results:—Blood count: Hb 9.8 g. per 100 ml.; packed cell volume 27%; W.B.C. 3,800 per c.mm., normal differential. Sternal marrow biopsy: megaloblastic. Barium meal: normal, rapid passage of barium into large intestine. Gastric secretion: free acid present. Oral glucose-tolerance test: very flat curve, fasting blood sugar 67 mg. per 100 ml. Stool occult blood: absent.

Since there was no response to injections of vitamin B₁₂, folic acid was given for the anaemia and full metabolic studies for calcium, phosphorus, and nitrogen were begun (see Graph). On a daily fat intake of 75 g., 20 g. per day appeared in the faeces, thus confirming the diagnosis of

steatorrhoea. Urine calcium was 150 mg. per day, but faecal calcium exceeded the intake so that a strongly negative balance resulted. A gluten-free diet was tried (Period 4). There was only a slight reduction in faecal fat and calcium—not enough to justify continuation of such a complicated regimen—and a low-fat diet was given (Period 11). Weight increased and anaemia diminished. The patient left hospital in March, 1956 (corresponding to Period 16), three months after admission, and attended as an outpatient. This improvement did not support an earlier suggestion of malignancy.

However, he failed to regain perfect health, and a gluten-free diet was reintroduced in July, 1956. In January, 1957, the haemoglobin had risen to 13.7 g. per 100 ml., normal weight had been regained, and the patient felt well. In view of the biochemical interest of the case he was admitted for further metabolic studies in February, 1957. There was considerable improvement in the balance. After only six days on a normal diet containing gluten the patient felt ill, with nausea, stomatitis, abdominal pain, and bulky, offensive stools. A return to a gluten-free diet became essential (Period 21). Stool fat rose for several periods, reaching a maximum of 27 g. per day. There was an associated rise in faecal calcium, making the balance negative again. Improvement followed resumption of the gluten-free diet (Periods 24 and 25). Streptomycin was given at this time, but its effect was equivocal.

By July, 1957, three months after returning to a gluten-free diet, normal health was regained. Later in the year the patient reported a small loss of weight and fever, and he was readmitted to hospital in January, 1958. The fever was persistent, remaining between 101° and 104° F. (38.3° and 40° C.) for four or five days at a time and then falling to 99° F. (37.2° C.) for two or three days. Three weeks later the tip of the spleen became palpable. The haemoglobin fell to 8.8 g. per 100 ml.; white cell count 4,000 per c.mm. with a normal differential. Investigations to establish a cause for the fever (stool and blood culture, serum agglutination, barium studies, intravenous pyelography, etc.) were negative. Oral glucose tolerance was normal. Plasma proteins totalled 5.5 g. per 100 ml. (albumin 2.9 g., globulin 2.6 g.). Electrophoresis showed decreased albumin with increased α -globulins. Mantoux-testing was negative at 1:100 old tuberculin and a chest radiograph was normal. At this stage the stools were normal in consistency and the fat content was only 22 g. per 100 g. dried weight. The effect of intramuscular penicillin was equivocal in that he became afebrile for a few days, but this was not sustained.

Laparotomy was performed and showed splenomegaly, small, firm peripheral mesenteric lymph nodes, and a mass of enlarged nodes at the root of the mesentery. Dr. C. F. Ross reported on the biopsy specimens as follows: "Liver: mild passive congestion only. Peripheral mesenteric node: old inflammatory change and fibrosis only. Lymph node from root of mesentery: normal structure replaced by mass of reticulum cells with much necrosis (Special Plate, Fig. 1). Reticulin impregnation shows marked network throughout the gland (Special Plate, Fig. 2). No Schiff-positive macrophages present. The appearances are those of reticulosarcoma."

Following laparotomy the patient's condition deteriorated and he died three weeks later after transfer to another hospital for radiotherapy. Unfortunately necropsy was not performed.

DISCUSSION

It is possible that this case represents a random association between idiopathic steatorrhoea and reticulosarcoma, or mesenteric reticulosarcoma complicating a case of occult idiopathic steatorrhoea and rendering it overt. However, mesenteric lymphoma, including reticulosarcoma, associated with steatorrhoea is a well-recognized entity, though gluten sensitivity has not previously been noted in such cases. The later age