side-effects was not vitamin B₁₂ but an impurity present in A, absent in B, and present in traces in C. This substance was therefore probably a carry-over impurity from the streptomycetes fermentation liquor (Tables I and III). (2) People who had previously received penicillin or other antibiotics were more than twice as likely to be skin-sensitive and to develop side-effects to the "mould impurities" as those who had not been so treated (Tables II and IV).

Discussion

There is increasing evidence that unusual responses to antibiotic therapy are nearly always the result of acquired sensitivity (*Lancet*, 1951), and that non-specific hypersensitivity to fungi or mould-products may be responsible for a significant proportion of these unusual responses. The conclusions above imply an antigenic relationship between antibiotics and carry-over impurities in certain vitamin-B₁₂ preparations derived from streptomycetes: it is a reasonable corollary that the converse relationship is valid.

In themselves, the side-effects and skin reactions described above, being trivial, would be scarcely worthy of mention were it not that they indicate yet another way in which idiosyncrasy to antibiotics may be acquired. Deaths directly due to this cause are very rare, but it may prove a serious handicap in the management of infections, since people who are idiosyncratic to one antibiotic may be sensitive to all the others (Bedford, 1951b) and reactions may be so severe that antibiotic therapy becomes impossible.

This investigation does not exclude the possibility that preparations of vitamin B₁₂ derived from liver may also contain impurities capable of producing sensitivity phenomena (nor, indeed, that the pure vitamin itself may be capable of doing so); but there is no evidence that sensitivity to liver derivatives implies idiosyncrasy to antibiotics.

Cogent reasons for preferring any preparation of vitamin B₁₂ to liver extracts were low price, greater purity, relative freedom from side-effects, and the trivial nature of these when they did occur. As, however, there are now available highly purified vitamin-B₁₂ preparations from both liver and streptomycetes, against which no evidence of liability to promote idiosyncrasy to antibiotics has been adduced, the use of the cruder mould-derivatives is unjustified.

Summary

Of 100 people 14 were skin-test-positive to a vitamin-B₁₂ concentrate derived from *Streptomyces griseus*, and six suffered side-effects after intramuscular injection.

Two were skin-test-positive to a purer preparation of vitamin B₁₂ derived by crystallization from streptomycetes cultures, and none developed side-reactions to intramuscular injection.

None reacted adversely to a preparation of vitamin B₁₂ derived from liver.

Impurities carried over from the mould fermentation liquor are regarded as responsible for the sensitivity phenomena.

Both cutaneous reactions and side-effects were more than twice as common in people who had previously been treated with antibiotics.

The possibility of inducing idiosyncrasy to antibiotics is advanced against the use of impure preparations of vitamin B₁₂ derived from mould cultures.

It is with great pleasure that I express my gratitude to Mr. J. T. Marsh and Dr. H. M. Walker, of the Medical Department of Glaxo Laboratories Ltd., for supplies of vitamin-B₁₂ preparations and for information concerning them; and to the patients and staff of the Cowley Road Hospital for their co-operation in this investigation.

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"EPIDEMIC" ABDOMINAL COLIC ASSOCIATED WITH STEATORRHOEA

BY

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Many specimens of faeces from cases of gastro-enteritis and diarrhoea suspected of being infective in origin are sent to the laboratory for examination. Often a known bacterial or protozoal pathogen is found, or food-poisoning organisms are incriminated; but a number of sporadic cases and a few epidemics remain for which no satisfactory explanation is found. We have observed the occurrence of pale stools and steatorrhea among some of these unexplained cases, and an outbreak of gastro-enteritis of this kind is described here because it suggests the occurrence of a syndrome of infective intestinal disorder which is not generally recognized.

The Outbreak

In December, 1950, a number of cases of diarrhoea occurred in a day nursery accommodating 50 children under the age of 5. The course of events is summarized in the Table. After the tenth day no further cases of

Day of Outbreak	Case No.	Sex	Onset of Symptoms
1	1	M	Diarrhoea during night
	2	F	" and vomiting in morning
2	3	M	" " " " " "
	4	F	" " at midday " " "
	5	M	Severe stomach-ache in afternoon
3	6 to 16		Diarrhoea beginning at various times during the day. Case 13 had also severe vomiting
4	17	F	Diarrhoea
	18	M	Diarrhoea
5	19 to 22		Four of the staff complained of abdominal pain and flatulence with a sensation of "churning up" in the intestines.
6	23	F	Diarrhoea
	24	M	Diarrhoea
	25 to 26		Two more of the staff felt ill
7	27	M	Diarrhoea and vomiting
	28	F	" " " "
	29	M	Diarrhoea " " "
8	30	M	" " " "
9	31	M	Vomiting
			Case 6 suffered from vomiting. She had been well for the three previous days
			Case 8 had diarrhoea again. He had been well for the five previous days
10			Case 3, who had been ill for four days and better for four days, developed a second bout of diarrhoea

diarrhoea or vomiting occurred. It will be seen that fresh cases developed over a period of nine days. In all, 25 children aged from 1 to 4 years and six staff were affected—just under half the number of persons at risk. In addition four household contacts of three children (Cases 2, 3, and 6) were affected. These secondary cases developed from two to four days after the onset in the child concerned.

Clinical Picture.—The clinical picture was characteristic. The affected children showed a striking pallor with the onset of symptoms, and pain in the abdomen or vomiting (five cases) was the first complaint. The urgency of the call to stool and the apparent straining were severe, out of proportion to the degree of the diarrhoea; and a few children who cried for their pots failed to pass any faeces. The adults who were affected suffered from abdominal pain, flatulence, and nausea, and felt ill; but no adult had frank diarrhoea.

No case was ill for longer than four days, but three cases relapsed and had a second bout of diarrhoea or vomiting a week after the onset of their first attack. Six of the children had slightly raised temperatures. One child had jaundice a fortnight after his diarrhoea.

Laboratory Findings

Stool specimens from 24 of the 25 affected children were sent to the laboratory on the first or second day of illness. It was noticed at once that 17 of these were unusually pale in colour, and most were fluid. Fourteen were given careful microscopical study as well as a bacteriological examination; 10 were examined bacteriologically only. The bacteriological examination included a special search for heat-resistant strains of *Cl. welchii*, and for *Bact. coli* of the possibly pathogenic D 433 and "Aberdeen beta" types; but these organisms were not found; nor were shigellae or salmonellae. All organisms isolated were recorded; but not one organism of any kind was common to even a majority of cases. It thus appeared that no help could be obtained from the bacteriological examination; and attention was redirected to the microscopical findings. No cysts, worms, ova, or protozoa had been found, and no leucocytes or red cells; but globules of neutral fat (staining with Sudan) had been seen in 9 of the 14 cases examined microscopically. These globules were mostly from 10 to 30 μ in diameter, and were numerous in every microscopical field.

Castor oil, paraffin oil, and cod-liver oil were considered; but the first two had not been given; and faeces specimens from children from another nursery, in which a similar diet and the same amount of cod-liver oil were being given, did not show this undigested fat.

It therefore seems that steatorrhoea was an abnormality associated with the outbreak of gastro-enteritis described, and that the characteristic stool was pale or putty-coloured, fluid, and acellular, with, in most cases, much undigested fat recognizable microscopically.

Discussion

A great deal of gastro-enteritis occurs in the community, and often no attempt is made to obtain an explanation. When multiple cases occur within an institution, however, a single cause is reasonably suspected and it is usual for some investigation to be made.

In the majority of such outbreaks referred to this laboratory shigellae, salmonellae, or *Giardia* have been incriminated; but in four recent incidents of the kind, including that described above, no pathogen was isolated from the faeces and the circumstantial evidence did not suggest food-poisoning. An additional search for heat-resistant *Cl. welchii* and for *Bact. coli* of types associated with infantile enteritis was without result. It was noticed, however, that the stools of these patients were often of a pale putty colour, and that on microscopical examination leucocytes were almost always absent, however fluid the faeces, while globules of undigested fat were quite often present in specimens from children.

The occurrence of multiple cases of this condition, some of which exhibited fever over periods of four days, suggested an infective agent, but the negative results of many bacteriological examinations imply that the organism, if it exists, is not easily cultivated, and perhaps a virus aetiology should be considered.

The disorder would seem to have affected the digestion of fat in the small intestine, since it started as central abdominal colic with flatulence and was often followed by the passage of pale fatty stools. The absence of leucocytes indicated that there could not have been much inflammation of the large bowel mucosa.

In addition to the minor epidemic incidents referred to, sporadic cases of gastro-enteritis with similar features have been encountered, but in these isolated cases many explanations are possible, and such conditions as subicteric infective hepatitis, idiopathic steatorrhoea, and unsuitable diet have to be considered in diagnosis. It would be of value in such cases, and especially when they occur in outbreaks, to

have a biochemical analysis of the stools, and to examine blood and urine for bile factors. Bile has not been found so far in a few urine specimens from similar cases.

The syndrome can be recognized. Further observations are needed to determine whether it is rare or common, and to throw light on its cause or causes.

DEATH FOLLOWING A BARIUM ENEMA IN A CHILD WITH HIRSCHSPRUNG'S DISEASE

BY

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It is generally recognized that barium enemata must be given with caution in cases of megacolon, because of the danger of precipitating intestinal obstruction. The following is an account of a case in which a child suffering from megacolon died after a barium enema, but from a different cause.

Case Report

The patient, a boy aged 3 years and 10 months when he was admitted to hospital on November 28, 1949, was the third child of healthy parents. The family history revealed nothing of any significance. There was no previous history of fits in the patient or in the family. He had been constipated since birth and had regularly been given soap suppositories. With this stimulation a hard brown stool was passed every three or four days.

Examination showed that the abdomen was grossly distended and tympanitic. In contrast, his limbs were wasted. His weight was 35 lb. (15.9 kg.). No other abnormalities were discovered. Before a barium enema he was given soap enemata daily. Less than 1 pint (570 ml.) of fluid was given on each occasion without ill effect. His bowel appeared to have been satisfactorily cleared of faeces on the day of the investigation, although the abdomen was still distended.

Four pints (2.3 litres) of barium emulsion was introduced and the x-ray films showed the typical appearance of Hirschsprung's disease with a short aganglionic segment. An attempt was made to siphon back the emulsion without result, and on return to the ward it was noticed that the child's condition was unsatisfactory. He was cold, collapsed, and sweating. In an effort to retrieve the enema emulsion, a soap enema of 1½ pints (850 ml.) was introduced, but this too was retained. The sweating persisted and he began to vomit dark-coloured fluid. About seven hours later he lapsed into coma, became cyanosed, and began to have generalized convulsions. This condition persisted through the night and sedatives were given repeatedly. It was noticed that large quantities of very dilute urine (S.G. 1001) were being passed. Examination of the central nervous system at this stage showed no abnormal physical signs apart from the unconsciousness, dilated pupils which reacted sluggishly to light, and bilateral Babinski reflexes. He eventually died in a convulsion 20 hours after the enema had been given.

Permission for necropsy was not obtained, so the cause of this sudden death cannot be proved with certainty, but it seems probable that it was due to water intoxication.

Discussion

In this connexion Rowntree (1926) demonstrated certain phenomena in man and in experimental animals. If a patient with diabetes insipidus began treatment with pituitrin but did not at the same time limit his excessive water intake