collected in that area in much greater numbers than in the duodenal wall elsewhere. The muscular thickening and the concentration of ganglion cells must indicate increased muscular action where the common bile duct penetrates the circular coat of the bowel from without. No sign of any intrinsic circular muscle ring round an ampulla has been discernible. It is hoped that in the future further comparative histological investigation

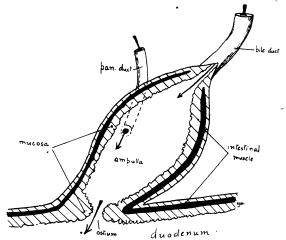


FIG. 3.—Civet (Viverra civetta): R.C.S. Museum (store specimen). Wall of ampulla formed by muscle of duodenum, which ceases abruptly at apex of ampulla. No muscle in walls of pancreatic and biliary ducts. (I.e., ampulla = intestinal pouch, not a mere dilatation of lower end of ducts.) (Cross-hatching indicates cut surfaces) indicates cut surfaces)

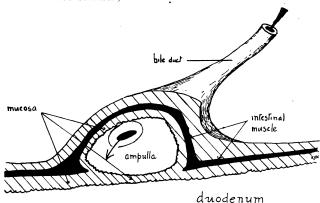


FIG. 4.—Seal (Phoca vitulina): R.C.S. Museum (store specimen). Ampulla wall formed of intestinal muscle, which is confined to the pouch and does not extend into the bile duct. (Cross-hatching indicates cut surfaces.)

may be carried out. But there is also macroscopic evidence of such a muscular relationship: thus in certain of the Carnivora—e.g., Viverra civetta—and in some Pinnipedia—e.g., Phoca vitulina—it is abundantly clear even to the naked eye that the muscular coat of the ampullated duct takes origin from the intestinal muscle tunics (Figs. 3 and 4).

#### Summary

This paper comprises two sections of a recent Hunterian

It emphasizes the low grade of malignancy of many tumours of the lower end of the common bile duct and adjacent head of the pancreas, and appeals for more radical measures in this type of case. Several personal cases of resection are quoted, and reference is made to those of other surgeons.

The diverse methods of scientific investigation lend support to the view that a special intrinsic sphincter exists at the terminal portion of the common bile duct or the conjoined bilio-pancreatic duct.

The muscle sheath of the duct is derived from the circular muscle tunic of the duodenum.

Although circular muscle derived from the bowel tunics is to be found round the basal portion of the intramural duct, only longitudinal and oblique fibres are present in the distal portion of the papilla.

Some of these fibres are prolonged as a core into the villous processes with which the wall of the terminal segment of the duct abounds.

The direction and arrangement of these fibres shows that their action is partly to retract the papilla and partly to erect or to aggregate the villous processes centripetally, thereby preventing reflux from the duodenum and controlling the exit of bile.

There is no circular arrangement of fibres close to the ostium -a reputed disposition credited with mythical properties.

There are few muscular fibres in any of the extrahepatic biliary ducts, and certainly no circular disposition of muscle fibres forming a sphincter in the hepatic duct.

The kindly co-operation of Prof. John Kirk and of Prof. A. J. E. The kindly co-operation of Prof. John Kirk and of Prof. A. J. E. Cave has been invaluable in the preparation of this lecture; my warmest thanks are due to both these friends for all their help so spontaneously and enthusiastically given. Mr. S. R. Scarfe of the Anatomical Department, Middlesex Hospital, has prepared the innumerable histological sections which have formed the basis of part of this inquiry, and to him I am indeed most grateful. My friend Col. A. E. Hamerton has generously afforded me material from the Gardens of the Zoological Society. Surgeon Commander W. A. Hopkins, R.N., and members of the staff of the pathological department of a naval hospital have readily and eagerly granted me facilities for work in their laboratory. Surgeon Vice-Admiral Sir Sheldon Dudley has always a stimulating effect on any worker, and at all times encouraged me, so that the occasional minutes and hours of surgical inactivity inevitable in war have not been idly spent, and of surgical inactivity inevitable in war have not been idly spent, and an endeavour has been made to carry on, though feebly, the spirit and tradition of the Founder of our Museum, who seized the fleeting hour for Science, even amidst the distractions and disorders of war.

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# ENTERITIS IN A NURSERY HOME ASSO-CIATED WITH GIARDIA LAMBLIA\*

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The following account of a prolonged outbreak of enteritis associated with Giardia lamblia (G. intestinalis), affecting both children and adults in a nursery home for evacuees, is reported partly because little attention seems to have been paid in Great Britain during recent years to infections with this protozoon and partly because there is reason to suspect that the condition is commoner than is generally supposed.

## History

The outbreak occurred in a spacious country-house, referred to as the Grange, used both as a family residence and as a wartime nursery. The domestic arrangements of the two communities were separate, but there was naturally a good deal of communication between the two sides of the house. Consequently, the entire population, numbering 51 in Jan., 1941,

<sup>\*</sup> A Report to the Medical Research Council from the Emergency Public Health Laboratory, School of Pathology, Oxford.

was exposed to the infection, and 86% showed signs or symptoms as a result.

The infants, 31 in all, of both sexes, and aged at the time of admission from 4 to 16 months, came from poor workingclass homes in or about London. They were cared for by eight nurses under the supervision of a matron with special paediatric training. The nursery accommodation was ample and reasonably well adapted to its purpose, and the management of the children very satisfactory, so that a detailed description of the hygienic arrangements may be omitted. The first batch of infants arrived at the home on July 18, 1940, in good health. Included were twin sisters aged 16 months and a boy of 13 months, all of whom had loose stools on July 29; these were the first to be recorded. Within another week 3 more, and within six weeks all the infants, had loose stools. Further infants joined the nursery in Aug., Sept., and Nov., 1940, and in Jan., 1941, and all but 3 became similarly affected within a month-2 within as short a period as seven days and 2 within nine days.

Some of the adults soon began to have diarrhoea as well. Two nurses were attacked early in August, and other nurses, and the family in residence and most of their servants, in the months that followed. Symptoms in the nurses appeared within 10 days to 8 weeks of their arrival. Several months elapsed before some of the house servants had diarrhoea, but this can probably be explained by the fact that they had less contact with the children than the nurses and the private residents.

Between July, 1940, and Jan., 1941, 28 out of 31 infants were affected and 16 out of 20 adults. The more intensive phase of the outbreak extended from Aug. to Dec., 1940, during which time additional children arrived at the nursery in small groups. From Jan., 1941, the acute episodes were less in evidence, but the trouble continued to smoulder until May, when treatment put an end to it.

#### **Symptoms**

Infants.—In nearly all cases the earliest sign of infection was looseness of the stools. This did not at first arouse anxiety. The infants were given grey powders and were not confined to bed. A few of them rapidly got worse. stools became fluid, pea-soup or dark green in appearance, and increased in number up to ten a day. No blood was There was repeated vomiting, dehydration, loss of appetite and weight, and sometimes a rise of temperature to 100° F. In one case at least there was severe abdominal pain and tenderness. Recovery from this acute phase took place in a few days, but was sometimes delayed for two or three weeks. These urgent symptoms appeared quite soon in some of the infants, but in others they were preceded by a mild form of diarrhoea for several weeks. In all, 9 infants were severely ill; 2 of them had to be removed to hospital, where they died. In the remaining 19 infants the initial symptoms were less striking. Once started, the enteritis continued for a few days to a month or more. The stools were generally loose, though persistently fluid in a few cases, brown or green, often with a noticeable excess of mucus, but without blood, and numbering two to four in the 24 hours. Some of the infants vomited on several consecutive days or intermittently. Systemic effects were mild, and the infants were not confined to bed. A chronic stage followed the initial acute or subacute attack, except in the 2 fatal cases and in 2 that cleared up completely. In 7 cases diarrhoea was persistent till therapy was instituted. Soft green or brown stools were passed every day. One of the patients had loose green stools for seven months, and 3 whose stools were always fluid suffered impairment of appetite and growth. In the remaining cases the diarrhoea was intermittent, taking the form of subacute attacks lasting for two to four days or longer, every few weeks. Again the stools were loose, green or brown, or else fluid. As the attacks subsided in some of the infants the stools became large, soft, and white before they were normal.

Adults.—Of the adults affected 6 were nurses, 4 were members of the resident family, and 6 were servants in their employment. Only 3 nurses and 1 servant appear to have been free from symptoms. In general, members of the nursing staff were the first to be affected, and the domestics the last. The onset was somewhat different from that in the children. There

was no prodromal period of mild diarrhoea, but a sudden acute and usually violent attack of diarrhoea accompanied by more or less severe abdominal pain. The stools were dark, very loose or fluid, and numbered 10 to 20 or more in the 24 hours. Blood was never noticed. The pain was of a griping nature, usually in the lower abdomen, but in some patients located in the epigastrium or the right hypochondrium. Vomiting was frequent. Additional symptoms in order of frequency were giddiness, loss of energy, weakness or faintness, anorexia, headache, nausea, flatulence, backache, and fever. When the attack was over there was usually a rapid convalescence. About onethird of the 16 adults affected had one attack, a like proportion had two, and the remainder three attacks before treatment. The interval between the attacks varied from four to eight weeks. One nurse had prolonged attacks at short intervals over a period of three months. She kept at her work, but suffered from lack of energy and "pain in the stomach and back, especially when carrying anything or making the cots." Two other nurses stated that after their last attack they had never been really free from diarrhoea, and often felt weak and faint. These nurses had apparently entered a chronic symptomatic stage of the infection like the children. The other adults felt perfectly well between attacks, and many of them remained free of symptoms for some months. No physical examination of the adults was made either before or after treatment, as all were engaged in their affairs and none was acutely ill when seen.

#### **Bacteriological Investigations**

At the request of Dr. Cowan, medical officer of health, Gloucestershire County Council, the Oxford laboratory was asked to investigate this outbreak. The Home was first visited on Jan. 29, 1941. Bacteriological examination of the stools at a neighbouring laboratory had shown organisms of the paracolon group in several specimens, and it had been suggested that these were probably water-borne. There were two water supplies available for the nursery, and both had apparently been condemned by local analysts. Our investigation of the two water supplies showed that they were collected from a hillside under almost perfect conditions, and both bacteriological and chemical examination confirmed their freedom from excretal pollution.

There were two milk supplies—one to the nursery and the other to the private residents. A sample from the nursery supply proved to be of relatively poor bacterial quality. Since, however, all milk and water for the children was boiled, it was difficult to believe that they could be responsible for the outbreak.

Specimens of faeces from 25 children and adults were examined for organisms of the dysentery and Salmonella groups, with completely negative results. Blood serum from 4 of the adults was tested for agglutinins against organisms of the Salmonella, dysentery, Brucella, Proteus X, and Leptospira groups—again with negative results. Further faecal specimens were obtained in February from 8 children with recent or current diarrhoea, special arrangements being made for their receipt at the laboratory within a few hours of collection. These were examined for protozoa. Five of them contained Giardia lamblia in either the free or the cystic form, three in very large numbers. Since, according to Dobell (1921), the infection rate in this country is between 4% and 9% for adults. and 14% and 40% for children, it seemed desirable to obtain further information on the frequency of this parasite in the Grange. Accordingly on March 3, 1941, specimens of faeces were examined from 29 children and 22 adults.

The method we used consisted in rubbing up a small portion of the faeces on a slide in a 1% solution of eosin with a wooden toothpick or platinum spatula, so as to make a moderately opaque suspension. A cover-slip was applied, and the preparation was examined at once under a 1/6-inch objective. This method has the advantage of providing a pink background, against which the unstained protozoa can be distinguished readily by contrast. Giardia appears as a pear-shaped body about 10 to 20  $\mu$  long by 6 to 10  $\mu$  wide in the free form, and 10 to 13  $\mu$  by 8 to 9  $\mu$  in the cystic form, having a faint bluish tinge. Little structure is visible, but if a second preparation is made in a drop of Lugol's iodine, the nuclei, the axostyles,

and other details can often be seen. The results of our examination are recorded in Table I.

TABLE I.—Frequency of Giardia lamblia in Faeces

		No. Examined	No. Positive	% Positive	
Children Adults	::	29 22	13 6	45 27	
Total	••	51	19	37	

The proportion of children carrying Giardia was higher than that of adults. Taking both together, no less than 37% of the 51 persons examined proved to be infected. An analysis of these figures was made in relation to (1) the presence of loose stools at the time of examination, and (2) a history of continual or intermittent loose stools for some months previously (Table II).

TABLE II.—Frequency of Giardia lamblia in Relation to Diarrhoea

		No. of Positive		Observed % Difference between the Two	Standard Error of this Difference	Observed % Difference divided by its Standard	
			No.	%	Groups		Error
A. B.	Loose stools at time of examination No loose stools at time of examination	- 7 44	5	71 32	39	18-5	2·1
C.	History of intermittent or continual loose stools for some months . No history of intermittent or continual loose stools for some months	11	9	82	57	13·5	4-2

From Table II it is seen that the proportion of persons harbouring Giardia was more than twice as great in those with loose stools at the time of examination as in those without. The numbers, however, are small and the odds against getting such a distribution by chance alone are not more than 27 to 1. The proportion of persons harbouring Giardia was more than three times as great in those with a history of intermittent or continual loose stools for some months as in those without, and the odds against such a distribution are over 37,000 to 1. There appeared, therefore, to be little doubt that the association of Giardia with chronic enteritis was more than coincidental. When it is remembered that Groups B and D were not strictly control groups, practically all the patients in these groups having suffered at one time or another from diarrhoea, the association becomes even more significant. It is hardly necessary, however, to point out that such an association does not prove the causal relationship of Giardia to the enteritis, but it does add weight to other evidence that may be brought in favour of this assumption.

### **Treatment**

Since Brumpt (1937) recorded his finding that mice infected with Giardia muris could be rapidly freed from infection by the oral administration of quinacrine, several workers have successfully applied this treatment to human beings. Galli-Valerio (1937), Love and Tayloe (1940), Voltrina (1941), Nutter, Rodaniche, and Palmer (1941), and Hartman and Kyser (1941) used atebrin; but de Muro (1939) and Grott (1939) obtained better results with acranil, a hydrochlorate of a new acridinic compound prepared by Bayer. Atebrin and quinacrine, it may be noted, are different names for the same substance. Chemically this substance is an acridine compound related to the antimalarial plasmoquine, but differing from it in the substitution of the acridine for the quinoline nucleus; it has therefore no direct relationship to quinine. Since acranil was unobtainable we decided to try quinacrine.

Six children who were heavily infected with Giardia were transferred to a cottage some distance from the Grange and put in charge of two nurses. One of these was heavily

infected; the other, who had joined the staff only three weeks previously, had not suffered from enteritis and had no Giardia in her stools. All food was prepared in the cottage, and no communication, except by the matron, was permitted between the inhabitants of the cottage and those of the Grange. Before treatment began, and again after the conclusion of the first course of treatment, the cottage was thoroughly cleaned and disinfected.

Tablets containing 0.1 g. of quinacrine were obtained from Messrs. May and Baker. The children, all of whom were under 2 years of age, were given one-sixth of a tablet, and the infected nurse one tablet, three times a day for five days. As the drug is very bitter the tablets were not pulverized, but were mixed with the food at the end of a meal. A drink of milk was given immediately afterwards. The nurses were instructed to keep the children's bowels well open and to watch for toxic These comprise persistent headaches, severe symptoms. abdominal pain, cerebral excitement, and acute restlessness, and are best treated by the administration of purgatives, large doses of alkali, and plenty of sugar. The first course of treatment lasted from May 12 to May 17, 1941. Examination of the stools on May 19 showed that they were all free from Giardia. As none of the patients had suffered from toxaemia, and as the probable duration of the apparent cure was in doubt, it seemed wise to repeat the treatment. This was carried out between May 21 and May 26. Samples of faeces collected on the last day again proved negative.

The success of this treatment, as indicated by the disappearance of Giardia from the stools, seemed to warrant its application to the remainder of the children at the Grange. Accordingly 25 children, of whom 13 were known to be infected, and 13 adults, of whom 5 were known to be infected, received a first course of treatment between June 5 and June 10, and a second course between June 15 and June 20. Stools taken on June 11 after the first course and on June 24 after the second course all proved negative. Before and after the first course the nursery portion of the Grange was disinfected so far as possible in order to reduce the opportunity for reinfection. Apart from insomnia in some of the adults, and occasional slight yellow coloration of the skin and urine, no untoward effects were caused by the drug.

The stools of many of the patients were re-examined at intervals up to Feb., 1942. During this time only two of the previously positive children relapsed or became reinfected—it was impossible to say which. One showed a few Giardia in the stools in Aug., 1941, and the other a very scanty infection in Feb., 1942. Two fresh cases, however, were detected in children and one in a nurse whose stools had been repeatedly negative. These occurred in July and Aug., 1941, and in Feb., 1942. All five cases cleared up at once after a single course of quinacrine treatment. So far as the elimination of Giardia infection was concerned the treatment was undoubtedly successful. The failure to achieve complete sterilization may perhaps have been due to the presence of infection in two or three of the adults who were unwilling either to provide stools for examination or to undergo treatment.

#### Clinical Results of Treatment

Before treatment started, and again 8 to 9 months later, the children were physically examined, and blood counts were made on a number of those who were most heavily infected. At the first examination, 5 to 9 months after their admission, most of the 31 infants were fairly well nourished, but 26% had skin infections of one type or another, including eczema, and in 40% muscle tonus was poor. Many of them had diarrhoea or loose stools at the time, or gave a history of enteritis in the recent past. At the second examination their nutritional state and general well-being had improved; only 4% now had skin infections, and muscle tonus was good in all but 16%. Diarrhoea had ceased for several months and loose stools were unusual. We had hoped to find out whether the beneficial effect of treatment was reflected in the rate of growth, but we were unable to make use of the figures available because the weight and height of the infants were taken at irregular intervals, and the numbers falling into appropriate age periods were too small for comparison with normal standards. In the adults diarrhoea had likewise ceased, and those who had previously suffered

from abdominal discomfort, weakness, giddiness, and anorexia now appeared to be quite well again.

Before treatment the average number of red blood cells in 7 of the infected infants studied in April, 1941, was 4,700,000 per c.mm., and of white blood cells 8,100 per c.mm. After treatment the corresponding figures obtained in Feb., 1942, on the same infants were 4,800,000 per c.mm. and 11,000 per c.mm. respectively. These differences are of little importance. The haemoglobin content of the blood, on the other hand, showed a considerable rise. Before treatment the figures varied from 60 to  $88\,\%$  , with an average of  $74\,\%$  , and after treatment from 80 to 94%, with an average of 85%, thus showing an average increase of 11%. Before treatment some degree of hypochromasia, polychromasia, and basophilic stippling was common, whereas after treatment the red cells were normal except in one child in which they showed slight anisocytosis. A remarkable feature of the differential white cell counts in Feb., 1942, was the finding of a mild degree of eosinophilia, varying from 4 to 14%. Observations on two occasions for *Enterobius* made by the cellophane swab technique were negative, so that a helminthic infection seems improbable. What the explanation is must remain undecided, but it is thought worth while reporting this finding in case others meet with a similar degree of eosinophilia in Giardia infection treated with quinacrine.

#### Discussion

It is not our purpose here to discuss in detail the vidence for and against the pathogenicity for man of Giardia lamblia. Those wishing for fuller references should consult papers by Lyon and Swalm (1925), Véghelyi (1938), Manson-Bahr (1940), and McGrath, O'Farrell, and Boland (1940). Opinion is divided between those who regard this organism as a harmless parasite and those who believe that it may give rise to symptoms of disease.

So far as children are concerned one of the most careful of recent studies is that of Véghelyi (1938, 1940), who made observations on 92 infected and 92 control children aged 2 to 17 years at the children's clinic, Budapest. He found that in the infected subjects the occurrence of anorexia, headache, dizziness, abdominal pain, irregular bowel movement, and anaemia was much more frequent than in the controls. Of the infected children 86% were below average weight and 75% showed signs of disease. Studies in the laboratory revealed that fat absorption was defective, and that excretion of biliary pigment in the urine was much below normal. Véghelvi attributes this to the mechanical effect of the parasites in covering to a greater or less extent the wall of the intestine and rendering it impermeable. The resulting interference with absorption he regards as being sufficient to account for the anaemia and retardation of development. Great clinical improvement followed eradication of the organism by

Hartman and Kyser (1941), who described 100 cases of Giardia infection at the Mayo Clinic, all but 5 of the patients being over 14 years of age, found that 89% had symptoms of illness. The commonest complaints were diarrhoea and abdominal pain. In a small number of cases which were treated with atebrin and followed up, clinical cure resulted. Nutter, Rodaniche, and Palmer (1941), in a study of 14 infected adults, noted the following symptoms in order of frequency: diarrhoea, fatigue and weakness, abdominal pain and flatulence, blood in the stools, insomnia, dizziness, nervousness, and loss of weight. The symptoms disappeared after treatment with atebrin.

Our own observations support the conclusions of other recent workers in indicating that Giardia infection may not be without a detrimental effect on the health of the patient. It is difficult to estimate the exact part played by this organism in causing enteritis at the Grange, since other causes cannot be excluded with certainty. During the last two or three winters a disease, which for want of a better term we refer to as "non-specific enteritis," has been common in many parts of the country, giving rise to acute transient attacks of vomiting and diarrhoea. Opportunities for a thorough examination of cases have been few, but so far we have failed to find any evidence of bacterial or protozoal infection. This disease may have been responsible for some or all of the acute cases of enteritis at the Grange,

though probably not for the chronic cases. frequency of Giardia in the patients suffering from chronic diarrhoea than in those with normal stools is very suggestive; but too much weight should not be put on this finding alone, since there is presumably a greater chance of finding cysts in the faeces when the stools are loose than when they are normal. Taken, however, in conjunction with the clinical improvement after treatment, it does suggest fairly strongly that the presence of Giardia was more than a fortuitous association.

Undoubtedly one of the factors that has most influenced recent opinion in favour of regarding Giardia as potentially pathogenic is the disappearance of symptoms, even of longstanding diarrhoea, after treatment with one of the new specific remedies. Such an observation was not possible for a worker like Boeck (1927), who, on statistical grounds alone, was unable to satisfy himself that Giardia was more than a harmless parasite.

How infection was introduced into the Grange is not known. The matron who opened the nursery, and who shortly afterwards left, was suffering from enteritis on her arrival; she may have been responsible, but this can be no more than a surmise.

#### **Summary and Conclusions**

An outbreak of enteritis, much of it of a chronic type, affecting a high proportion of both children and adults in a residential nursery for evacuees is described.

Giardia lamblia was found in 71% of children and adults having loose stools at the time of examination and in only 32% of those with normal stools.

Giardia lamblia was found in 82% of children and adults with a history of intermittent or continual loose stools for some months and in only 25% of those without such a history.

Cure of the infection was quickly and successfully accomplished by the use of quinacrine, given in two 5-day courses.

The symptoms-chronic diarrhoea and some degree of anaemia in the children, and diarrhoea with giddiness, loss of energy, anorexia, headache, and epigastric discomfort in the adults—disappeared after treatment, and the general nutrition of the children improved.

The high frequency of Giardia in the stools of the patients with long-standing diarrhoea and the favourable effect of treatment suggest that this organism may have been responsible. for the chronic enteritis observed in the nursery. Further observations, however, are necessary to establish the exact degree of pathogenicity of Giardia for man.

We should like to express our thanks to Dr. Cowan, Dr. Goodwin, Dr. Gordon, Lady Ismay, and Sister Houchin for their generous help in this investigation. We are particularly indebted to Prof. Leiper of the London School of Hygiene and Tropical Medicine not only for his frequent advice but for showing us an advance copy of the property of the Medical Preserve Council on the incidence of of the report to the Medical Research Council on the incidence of protozoa and helminths in the faeces of certain groups of the population in this country which Miss Young made while working in his department. REFERENCES

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F. Clifton and S. M. Laird (J. R.A.M.C., 1941, 77, 318) record two cases of acute meningococcal conjunctivitis in soldiers aged 21 and 23. In both a diagnosis of gonococcal conjunctivitis had been made before admission to hospital, but the absence of any evidence of infection in the genito-urinary tract suggested that the correct diagnosis was one of meningococcal conjunctivitis. One patient had received sulphapyridine before cultures were made, but in the second case the diagnosis was confirmed by bacteriological examination. Neither case showed clinical evidence of involvement of the cerebral nervous system.