amine and ergometrine on the veins suggests that a fall in the compliance of the systemic venous reservoir may be an important component of the circulatory changes that follow the administration of clinical doses of these alkaloids. This action may also be an important factor in the production of certain of the harmful side-effects that are occasionally observed. The aggravation of angina pectoris that sometimes follows the administration of ergotamine has been assumed to result from coronary arterial spasm, but there is no evidence to confirm this view. The constrictor action on the veins could provide an alternative explanation: the rise in central venous pressure that results will tend to increase the size of the heart and so augment the metabolic needs of the left ventricle, and this change would be expected to facilitate the development of angina pectoris in response to exercise or other stress. It is interesting to note that the circulatory actions of ergotamine are almost exactly the reverse of those of the organic nitrates which probably relieve angina partly as a result of the venodilatation that they produce.

The occasional occurrence of pulmonary oedema in women with mitral stenosis who have been given ergometrine immediately after delivery is usually attributed to a sudden transfusion of blood resulting from the powerful uterine contraction. Brown *et al.* (1947), however, who suggested this mechanism, also put forward the idea that a decreased capacity of the vascular reservoir might play a part. The finding that ergometrine induces a rapid constriction of the forearm veins

provides strong support for this view, and the resulting rise in central venous pressure may well be an important factor in the precipitation of pulmonary oedema in patients with impaired cardiac function.

The potent effect of ergotamine and ergometrine on the veins should be considered whenever these drugs are used clinically. The venoconstriction that they produce is haemodynamically equivalent to the administration of a rapid blood transfusion, and this should be borne in mind before either alkaloid is given to a patient who has a cardiac disorder.

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Coccidian-like Nature of *Toxoplasma gondii*

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Summary: Specific pathogen-free domestic cats were fed with tissue cysts containing *Toxoplasma gondii*. In two infected cats large numbers of oocysts were produced in the faeces; no oocysts were observed in the faeces of the uninfected control cat. Five days after the feeding of the toxoplasms profuse schizogonic and gametogonic stages were observed in the epithelial cells of the small intestine of one infected cat. A single schizont was observed in an intestinal epithelial cell of a second cat six days after being fed the tissue cysts. There was no evidence of schizogony or gametogony in the uninfected control cat. The stages observed in the intestinal epithelium are identical with those of the well-known endogenous cycles of coccidian parasites. The appearance of these stages, together with the nature of the oocyst, indicates that *T. gondii* is a coccidian parasite closely related to the genus *Isospora*.

Introduction

Toxoplasma gondii is probably the last protozoan parasite of medical importance whose life cycle has yet to be elucidated. Much information has been compiled on its epidemiology,

pathology, immunology, serology, and other aspects of its effect on the life of man and other animals, but it is only relatively recently that a clearer understanding of its life history and transmission has emerged. It was thought that the elucidation of its natural transmission mechanism would provide a clue to the life cycle. This has indeed been proved to be the case.

Research on transmission of toxoplasmosis employing cats was initiated by Hutchison (1965). He showed that a resistant form of *Toxoplasma* could be transmitted in the faeces of cats which had been fed with chronically infected toxoplasmic carcasses. Hutchison (1967) put forward the hypothesis that this resistant form of *Toxoplasma* was transmitted within nematode ova, but subsequent work by ourselves and others has cast doubts on the validity of this hypothesis (Jacobs, 1967; Dubey, 1968; Hutchison *et al.*, 1968; Frenkel *et al.*, 1969; Hutchison and Work, 1969a; Sheffield and Melton, 1969; Work and Hutchison, 1969a).

It was next shown by Work and Hutchison (1969a, 1970b) that the infective unit passed in cat faeces was a cyst. Moreover, they pointed out that this cyst showed remarkable similarities to the coccidian oocyst of *Isospora* (Hutchison and Work, 1969b; Work and Hutchison, 1969b). In the absence of evidence of schizogony and gametogony, however, they tentatively called their cyst "the new cyst" rather than an oocyst. Siim *et al.* (1969), using coccidian terminology, showed that within the oocyst there were two sporocysts each containing four sporozoites, thus strengthening the hypothesis that *T. gondii* is related to the genus *Isospora*. The purpose of

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the present paper is to present conclusive evidence that *T. gondii* is in fact a coccidian undergoing typical schizogonic cycles and gametogony in the intestinal epithelial cells of the cat.

Materials and Methods

The Beverley strain of *Toxoplasma* which was used in these experiments was maintained in Strain A albino mice. In the brains of mice which had been infected two to four months previously numerous toxoplasmic cysts developed. Only the brains of these mice containing the cystic form of *Toxoplasma* were fed to the cats; the mouse carcasses were discarded.

The cats used in these experiments had been born and raised under specific pathogen-free (S.P.F.) conditions. They were thus free of all protozoan pathogens before being infected with *T. gondii*. Consequently there was no possibility of natural coccidian infection—for example, *Isospora felis*—being harboured by them. Nevertheless, the faeces of all the cats were examined initially and found to be negative for coccidia. Before beginning the experiments, sera from all the cats were also examined by the Sabin–Feldman dye test and found to be negative for *Toxoplasma*.

The cats were designated S.P.F. 1-5. Evidence presented below was obtained from cats S.P.F. 2 and 3; cat S.P.F. 5 was not subjected to experimental treatment and was examined as a negative control. S.P.F. 2 was fed with brains from the mice chronically infected with *Toxoplasma*; this cat was killed after five days. The small intestine was removed and divided into eight equal portions. In the description which follows these portions are numbered from 1 (immediately following the stomach) to 8. The anterior centimetre was removed from each portion and fixed in Carnoy's fluid for six hours. It was embedded in ester wax and sectioned at 8 μ . The sections were stained with Alcian blue for mucus and Heidenhain's iron haematoxylin.

S.P.F. 3 was similarly infected and was killed after six days. S.P.F. 5, which was the uninfected control, was killed after seven days. The small intestines of both S.P.F. 3 and S.P.F. 5 were removed and processed in an identical manner to S.P.F. 2.

Results

Microscopical examination of the control cat S.P.F. 5 revealed no infections in the intestinal epithelium. Sections of S.P.F. 3 were next examined. This cat was killed six days after feeding with infected brains, and by this time large numbers of unsporulated oocysts were being shed in the faeces. In a section of the third portion of the intestine a small intracellular vacuole measuring 6 by 7 μ was observed in the outer margin of an epithelial cell. Closer examination showed there were six crescentic organisms at different focal planes within the vacuole. It is possible that there may have been more present which were outside the plane of the section examined. No distinct cyst wall, such as appears in the tissue cyst of *Toxoplasma*, was apparent. This structure (Fig. 1) was identical with a coccidian parasite which had undergone schizogony to form merozoites. Despite a careful search, no similar stages have yet been seen in sections from the same portion. The sections from the other portions of the small intestine of S.P.F. 3 appear to be negative.

The intestinal portions from cat S.P.F. 2, killed on the fifth day after feeding with infected brains, were next examined. Oocysts had been shed in the faeces of this animal. No infections could be detected in sections from portions 1-4 and 8. In sections from portions 5, 6, and 7—that is, the lower part of the small intestine—however, large numbers of the intestinal epithelial cells were infected with late schizonts of *Toxoplasma* similar to the single specimen obtained in cat S.P.F. 3. In addition, immature schizonts and the various stages of

gametogony were observed. The longitudinal axis of most macrogametocytes lay parallel with that of the host cells. Some—for example, Fig. 2—were unusual in that their longi-

FIG. 1.—Mature schizont of *T. gondii* in intestinal epithelial cell of cat (S.P.F. 3).

tudinal axis was at right angles to that of their host cells. Many free oocysts were seen in the intestinal lumen in section and their measurements corresponded with those shed in the faeces.

A fully illustrated account of these forms of *T. gondii* will be published later.

Discussion

The advantages of using S.P.F. cats for these experiments are numerous. The most important is that intestinal protozoan pathogens are absent, and consequently we could be certain that the infections of the intestinal epithelium which we observed were related to the *Toxoplasma* which we had administered orally. It could, of course, be argued that by feeding the toxoplasmic mouse brains to the cat we were introducing with the mouse brain some unknown coccidian stage which

FIG. 2.—Maturing macrogametocyte within a vacuole in intestinal epithelial cell of cat (S.P.F. 2).

developed in the cat gut and produced coccidian oocysts concurrently with a faecally transmitted form of *Toxoplasma*. We consider this to be unlikely and have overruled the possibility

by experiments in which the brains of *Toxoplasma* dye-test-negative mice were fed to an S.P.F. cat. No cysts appeared in the faeces (Hutchison, Dunachie, Siim, and Work, unpublished work). The coccidian nature of the life cycle of *T. gondii*, which has now been unfolded, did not come as a surprise, in view of the coccidian characteristics of the oocyst which had already been observed. In addition to its morphological and developmental similarities, this oocyst of *Toxoplasma* resembled those of the coccidia in its ability to withstand chemical action (Hutchison *et al.*, 1969).

It was disappointing to find only a single schizont in S.P.F. 3, especially since such large numbers of oocysts had been produced. It must be conceded, however, that only a relatively small region of the cat's intestine was examined. The entire intestine of this cat, however, has been fixed, and we feel that further investigations of other regions may be worth while. So far as we were concerned, the importance of this single schizont was that we were given an indication of what to search for. In addition, we were also convinced that our staining procedures were adequate.

In cat S.P.F. 2 the infections of the intestinal epithelial cells were profuse and were in the posterior region (portions 5, 6, and 7) of the small intestine. It must be pointed out that we are dealing in this instance with a single cat and that many more cats must be examined before the sites of schizogony and gametogony can be established with certainty. In this preliminary investigation we obtained the impression that most schizogonic cycles were occurring in a portion of the gut anterior to that containing the gametogonic stages.

Our findings certainly resolve some of the problems of the taxonomist with regard to the classification of *T. gondii*. This organism has been considered to be a member of the class Toxoplasmea within the Subphylum Sporozoa. Now that schizogonic and gametogonic processes identical with those of

the coccidians have been described for *Toxoplasma* there seems to be good reason to classify this organism under the order Eucoccidia, suborder Eimeriina. The possibility that the disease of toxoplasmosis might now be referred to as coccidiosis is an interesting but less important outcome of this work.

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Prevalence and Morbidity of Heart Block in Devon

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Summary: In a survey in the Exeter area 139 patients with some degrees of abnormal atrioventricular conduction were notified by 282 family doctors. Per 100,000 of the population the prevalence of second-degree and third-degree heart block was estimated to be 17.3, of complete block past or present 15.6, and of complete block at the time of survey 13.1. Heart block was commoner in men than women, the sex ratio being 1.4 to 1; its prevalence increased steeply with age, and the morbidity rate was less than that reported by others. If the morbidity figures quoted in this survey are representative of the general population, it reaffirms the policy that pacemakers should be recommended for selected patients only.

Introduction

The use of artificial cardiac pacemakers is now a practical long-term treatment for the patient with heart block, and the organization of a pacemaker service requires knowledge of the prevalence and (and incidence) of this condition. As Siddons and Sowton (1967) pointed out, however, statistics of the prevalence and incidence of heart block in the general population are very approximate, since they are based on the

number of patients attending hospital departments. The aim of this study was to carry out a more accurate survey of patients with heart block by a direct approach to the family doctor. This preliminary report describes the prevalence of the condition.

Population and Plan of Study

Letters were sent to 290 family doctors practising in the Exeter clinical area asking for details of any patients with heart block or bradycardia (pulse rates less than 56 beats per minute). If a reply to the first letter was not received, further inquiries were made, up to a total of three letters. The date of the family doctor's initial reply was taken as the date of survey of his practice and patients diagnosed subsequently were not included. All notified cases were investigated and, where available, previous hospital records and cardiograms obtained. Unless preliminary inquiry indicated that atrioventricular conduction was normal, the patients were seen by a member of the cardiac department, provided that both the family doctor and the patient agreed to the examination. In addition to cases notified by the family doctors patients were studied from two other sources: (1) those known to have heart block who were attending the outpatient department of the Royal Devon and Exeter Hospital and whose family doctors practised within the

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