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Opportunistic Infections Caused by Protozoan Parasites

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Parasitic protozoa have played a major role in the discovery of the HIV epidemic. It was the occurrence of clustered cases of *Pneumocystis* pneumonia which caught the attention of the epidemiologists indicating that something unusual was going on. Very recently remarkable progress was made in understanding the epidemiology. Knowledge is evolving that *Pneumocystis* is host-specific to an extent which seems to justify species rank for the cause of death in AIDS patients for many years.

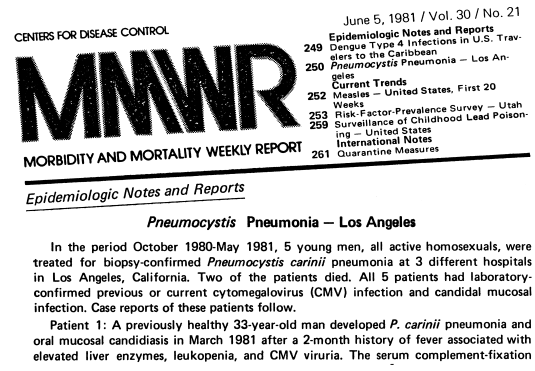
***Toxoplasma gondii* infections were also recognized very early in AIDS patients. Cerebral toxoplasmosis has now replaced *Pneumocystis* pneumonia as a fatal infection in many cases. AIDS patients with CD4 cells below 200/µl have a high risk to develop this complication.**

***Cryptosporidium parvum* was recognized as the cause of diarrhea in AIDS patients and also in immunocompetent humans where it only leads to a diarrheal episode lasting a few days. In AIDS patients the persisting diarrhea leading to loss of fluid and electrolytes can be life-threatening.**

Another group of parasites previously unknown to infect humans are the microsporidia, which are wide-spread parasites in nature. Increasing numbers of such infections are observed but many questions regarding pathogenesis and epidemiology are still unclear.

Keywords : Opportunistic protozoa, *Toxoplasma gondii*, *Pneumocystis carinii*, microsporidia, *Cryptosporidium parvum*

The concept of opportunistic infections is a rather recent concept. It evolved in close relation with the gradual progress of our knowledge about the human immunodeficiency virus (HIV) and the pandemic which sweeps over the world since nearly 15 years and which has changed the world in so many aspects, affecting the Third World in particular. The famous African writer Meja MWANGI describes the African experience in a remarkable book with the title THE LAST PLAGUE. Going through the literature I was not able to find out who coined the expression "opportunistic infection". It seems to appear all of a sudden in the literature and is used extensively. Equally difficult it is to find a satisfying clear definition of "opportunistic infection". Usually the term is explained by saying it is an infection with a facultative pathogenic organism. Certainly, this is not wrong but it does not take sufficiently into account the condition of the host, of his immune system in particular. If one tries to be more precise, one could say that opportunistic infections are caused by parasites, bacteria, fungi or viruses, which can use man as an host but only for a limited multiplication and which are not able to cause any serious pathological changes as long as the human immune system is func-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Epidemiologic Notes and Reports

***Pneumocystis* Pneumonia — Los Angeles**

In the period October 1980-May 1981, 5 young men, all active homosexuals, were treated for biopsy-confirmed *Pneumocystis carinii* pneumonia at 3 different hospitals in Los Angeles, California. Two of the patients died. All 5 patients had laboratory-confirmed previous or current cytomegalovirus (CMV) infection and candidal mucosal infection. Case reports of these patients follow.

Patient 1: A previously healthy 33-year-old man developed *P. carinii* pneumonia and oral mucosal candidiasis in March 1981 after a 2-month history of fever associated with elevated liver enzymes, leukopenia, and CMV viruria. The serum complement-fixation

Fig. 1 Morbidity and Mortality Weekly Report, June 5, 1981 reporting the unusual increase in *Pneumocystis* infections in Los Angeles.

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tioning normally. In contrast under conditions of primary or secondary immunodeficiency these agents can proliferate extensively and cause serious, life-threatening diseases. Even this definition will not cover all aspects of the disturbed relation between host and parasites as I will show later.

In 1981 an unexplained increase of *Pneumocystis carinii* infections in cities like Los Angeles, San Francisco and New York was observed. The reports which were received by the U.S. CDC indicated that something unusual was happening (Fig. 1). The enigmatic *P. carinii* was known for 70 years and suddenly this parasite made the scientific and medical world aware that a new pattern of disease was emerging (Fig. 2 - Fig. 4). Intensive epidemiological, microbiological, parasitological and virological research began, and a highly competitive field of research developed rapidly. Probably never before was so much money spent in such a short time for research into one subject.

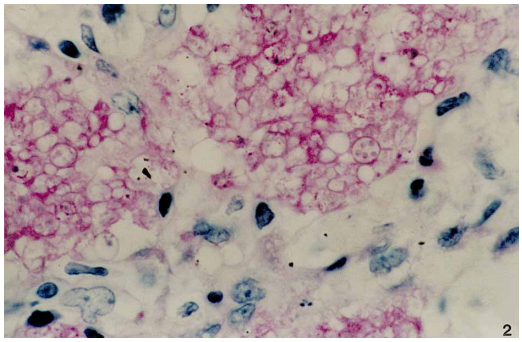

Fig. 2 Lung of an AIDS patient with *Pneumocystis* occupying the alveolar spaces as a foamy PAS-positive material. A few cysts with intracystic bodies are clearly visible.

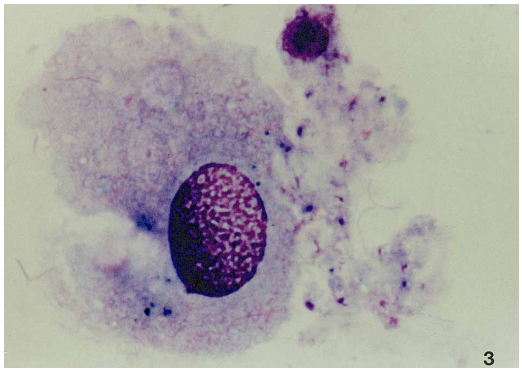

Fig. 3 Sediment from a bronchoalveolar lavage (Giemsa). Close to an alveolar cell there are a number of "trophozoites" of *Pneumocystis*.

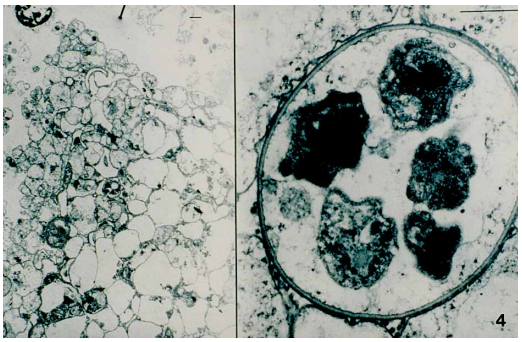

Fig. 4 Sediment of a bronchoalveolar lavage, electron micrograph, bar: 1 μm (kindly supplied by Dr. Sahm). Left: low magnification showing empty vesicles of various sizes, cysts and empty cyst walls. Right: higher magnification of a quite intact cyst with 5 intracystic bodies visible.

Let me deal briefly with *P. carinii*. In recent years modern analytical methods mainly DNA and RNA analysis showed that *P. carinii* is not a typical protozoan parasite but may be an untypical fungus. So apparently the pure bred parasitologist has to say sayonara to *P. carinii*. Before doing so, we have to state that nearly all of our knowledge regarding *P. carinii* originated from the work of classical parasitologists, and I do not hesitate to mention here Professor Yoshida and his coworkers who made extremely valuable and important contributions in *Pneumocystis* research (Fig. 5) [20]. Since modern microbiologists tell us now that *Pneumocystis* does not belong any more to our field, I will restrict myself to a few remarks on the recent developments which indicate that we might enter a new phase of *Pneumocystis* research. Already 1976 Frenkel claimed on the basis of staining properties that the rat *Pneumocystis* is different from the human *Pneumocystis*. He proposed the name *P. jiroveci* for the human parasite in contrast to the rat parasite, *P. carinii* [13]. Frenkel's proposal was not accepted generally, and the name *P. carinii* was used for all forms regardless if they came from man, rats, mice, rabbits, horses or other hosts. Today different groups have shown that *Pneumocystis* has a very high host specificity. It seems that, for example, rabbit *Pneumo-*

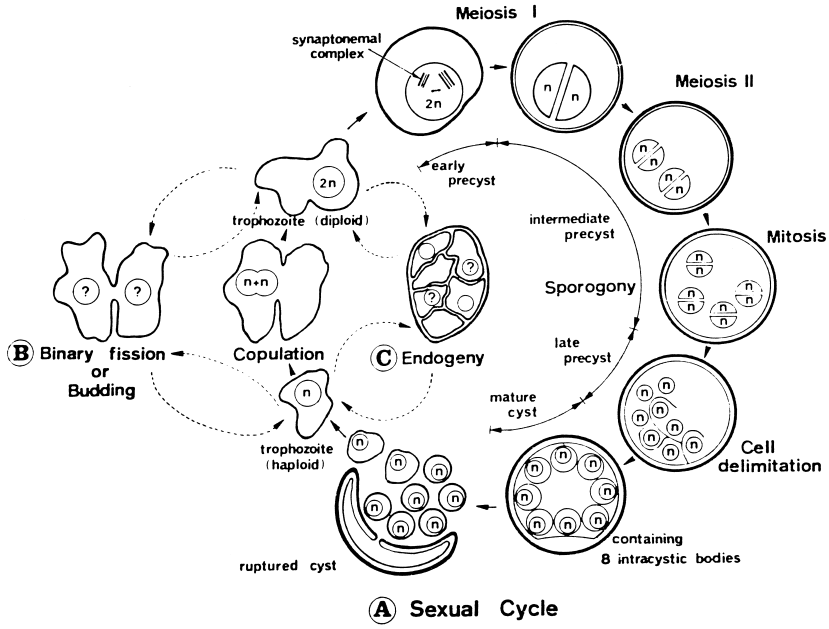

Fig. 5 Life cycle of *Pneumocystis* as proposed by Matsumoto and Yoshida.

cystis cannot be transferred to immunosuppressed rats, human *Pneumocystis* cannot infect rodents. The discussion is still going on, but there is now a clear tendency to define several separate *Pneumocystis* species.

The possibility to differentiate *Pneumocystis* strains led to another interesting finding. Very often the relapses of *Pneumocystis*-infections in AIDS patients are not caused by the same parasite, but each relaps may have its own special strain. That means it is not a relaps in the strict sense but more likely a new infection. This observation questiones the previous concept to which, I have to confess, I also adhered meaning that *Pneumocystis* is a parasite which is present in the lungs of most of us. It is suppressed by an efficient immune system and comes up only when the immune defense vanishes. This may be wrong. Still there is a possibility that normally several strains live in the lung and that they appear just one after the other. There is still a lot of research to do on *Pneumocystis*. One major break-through desperately needed is finding a method for continuous long-term cultures of *Pneumocystis* [17, 21, 27].

With rapidly accumulating experience regarding the clinical manifestations of AIDS it became clear very soon that a second protozoan parasite, *Toxoplasma gondii* (Fig. 6

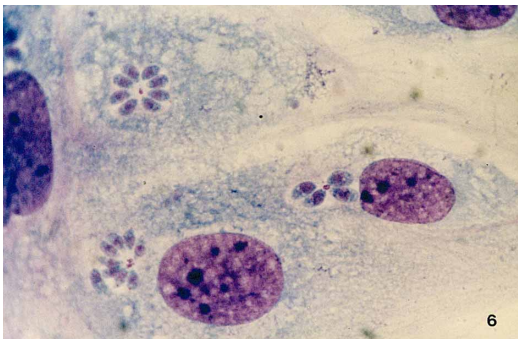

Fig. 6 *Toxoplasma gondii* trophozoites in cell culture. Giemsa stain. The parasites are enclosed in parasitophorous vacuoles. If the parasites can multiply undisturbed they tend to form rosettes in the vacuoles.

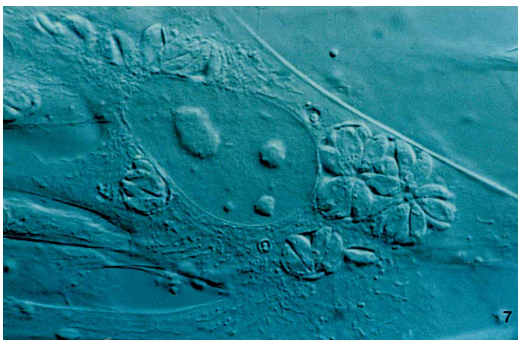

Fig. 7 *Toxoplasma gondii* in a living cell culture. Interference contrast microscopy.

- 7) was involved. Being widely distributed this parasite has apparently shared the path of evolution with many mammals including man. Under normal circumstances *T. gondii* is of very low pathogenicity for most of them. The prevalence of the infection in humans differs from country to country. It is closely related to the eating habits and to age and may reach 90% in the older age groups. In Germany, for example, the seropositivity for anti-*Toxoplasma* antibodies indicates that in the age-group of 20-30 years about one fourth of the population is infected, but clinical symptoms are very rare and transient. The infected person reaches very soon a state of immunity, the infection becomes latent. The parasites do not destroy cells any more but are confined to cysts where they do no harm. Only under severe immunodepression if, for example, in a HIV-infected person the T helper cells fall below 50/ μ l, dormant *Toxoplasma* parasites can revert to the rapidly multiplying tachyzoite phase again and destroy the cerebral tissue for which *T. gondii* has a preference - a toxoplasmic encephalitis results. The frequency of this condition varies for unknown reasons from country to country. In few AIDS-cases even a generalized toxoplasmosis develops. Protozoa are found in nearly every tissue of the body as liver, lung, bone-marrow, skin, intestine, just to name a few. Clinical overt toxoplasmosis in AIDS patients is always a life-threatening condition whether it is cerebral toxoplasmosis (Fig. 8 - 12) or generalized toxoplasmosis. Usually it responds well to treatment at least for the first time. Relapses are more difficult to treat.

Persistant diarrhoea, resistant against all trials of chemotherapy is one of the prominent symptoms associated with AIDS. Because of the high loss in electrolytes and

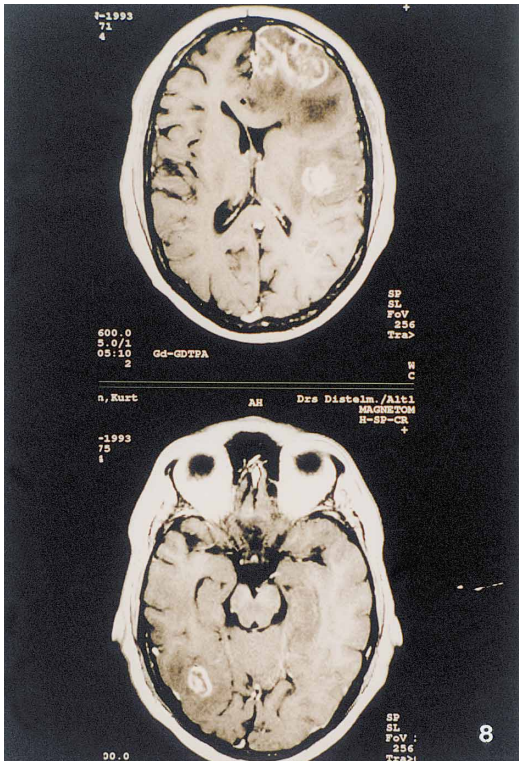

Fig. 8 Cerebral toxoplasmosis in an AIDS patient. Multiple lesions are seen in the brain. In some patients more than 10 lesions can be found.

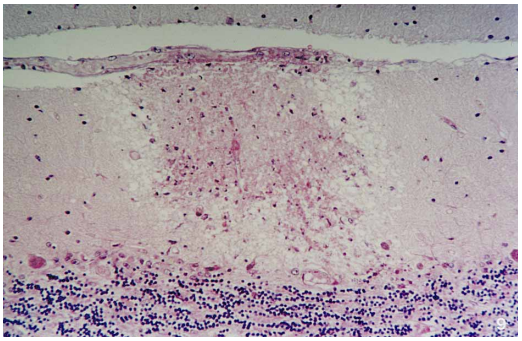

Fig. 9 Cerebellum of an AIDS patient with cerebral toxoplasmosis (HE stain). Around a small blood vessel in the cortex of the cerebellum an inflammatory focus has developed with destruction of the tissue.

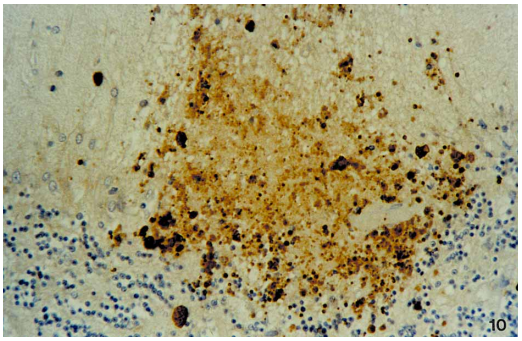

Fig. 10 Same material as Fig. 9. A neighbouring section is stained with the immunoperoxidase method using specific polyclonal antibodies against *Toxoplasma gondii*. Numerous parasites are now visible in the area of destruction.

water these diarrhoeas can be life-threatening. Quite soon it became clear that a large proportion of these diarrhoeas was caused by *Cryptosporidium parvum*, an intestinal protozoon well-known since long in veterinary parasitology for causing devastating epidemics in newborn calves. It turned out that human parasitology had to learn a lesson. After *Cryptosporidium* was recognized as a cause of intestinal disease in AIDS patients (Fig. 13), and after appropriate diagnostic methods were established in many laboratories, it became clear that already in the past *Cryptosporidia* have caused episodes of diarrhoea even in apparently immunocompetent people. I myself was able to identify *Cryptosporidia* in faecal smears made 30 years ago from patients with transient diarrhoea where we were not able to establish a satisfying diagnosis at that time. Today it is clear that *Cryptosporidia* can take hold in the human intestine for a short time, can even cause a short spell of diarrhoea but are eliminated soon. Only in severely immunodeficient individuals the infection persists as described. In severe cases the parasites spread beyond their normal habitat, which is the small intestine, into the gall-bladder (Fig.

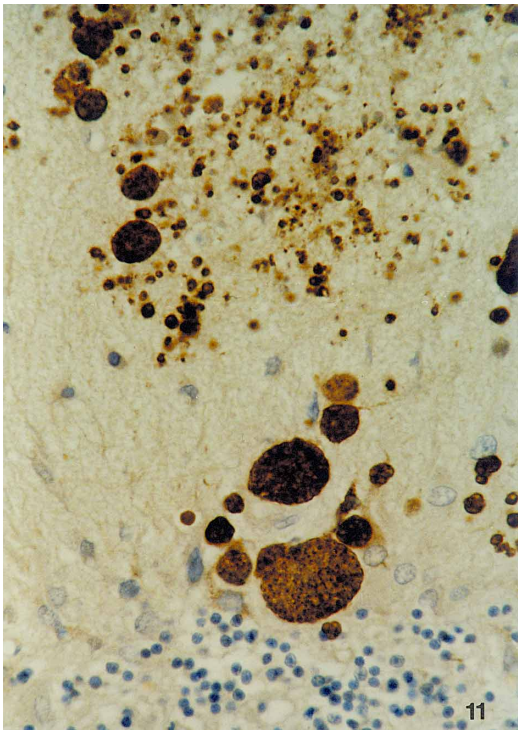

Fig. 11 Cerebral toxoplasmosis in an AIDS patient. Immunoperoxidase staining for *Toxoplasma gondii*. Trophozoites and cysts can co-exist in the same active lesions.

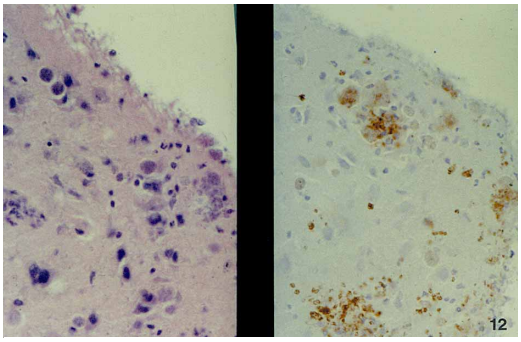

Fig. 12 Brain biopsy in a patient where a brain tumor was suspected. After brain biopsy a cerebral toxoplasmosis was diagnosed and afterwards the patient was found to be HIV positive. On the left side: the routine HE staining, on the right side: specific immunoperoxidase staining.

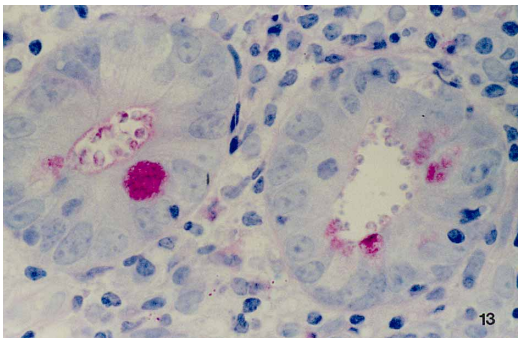

Fig. 13 *Cryptosporidium parvum* in a duodenal biopsy from an AIDS patient. PAS staining. Various stages of the *Cryptosporidia* are seen in the microvillous layer of the crypts.

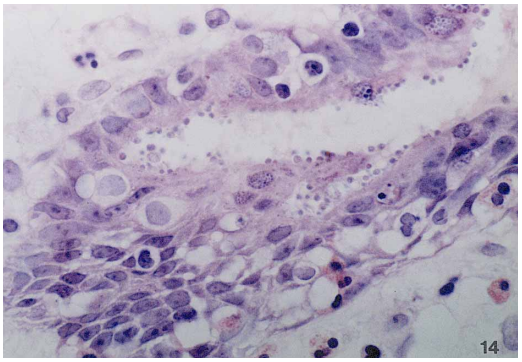

Fig. 14 *Cryptosporidia* lining the epithelium of the gall-bladder. HE staining.

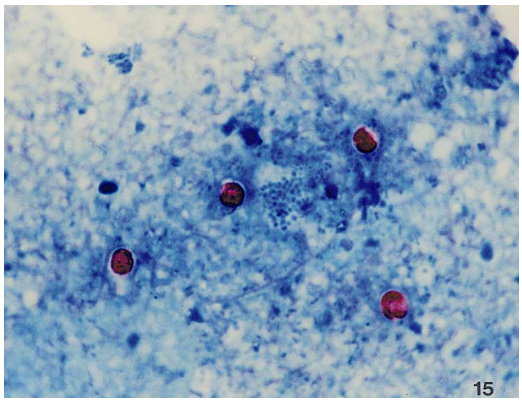

Fig. 15 *Cryptosporidium parvum* in the sputum of an AIDS patient. Kinyoun staining.

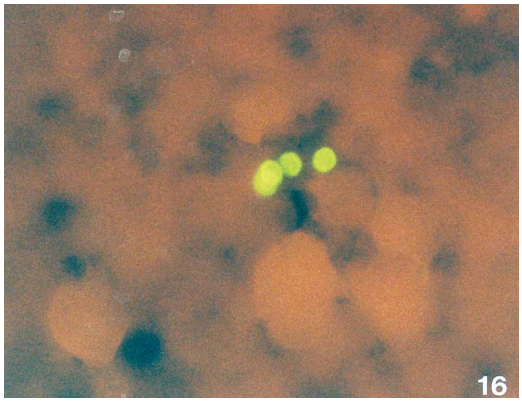

Fig. 16 Three *Cryptosporidium* cysts in a sample of drinking water. Immunofluorescence staining (Photograph kindly supplied by Dr. Karanis).

14) and even into the bronchial system (Fig. 15).

Let me go back for a second. *Pneumocystis carinii* or better *P. jiroveci* is a typical parasite of man but it appears only when a pronounced immunodeficiency is present. The parasite takes advantage of the hosts weakness and proliferates. If a need for an anthropocentric interpretation is felt this may be called an opportunistic behaviour but only in a rather trivial sense, since under the prevailing conditions *Pneumocystis* will kill its host, a highly foolish kind of opportunism. The same is true for *T. gondii*, probably also a parasite well established in the species of man. With *Cryptosporidium* we have a different relation. Since the infection is only of short duration and is eliminated quickly the immunocompetent human being very likely is not a suitable host for *C. parvum*. This is in contrast to the immunocompromised state where a so to say new type of host offers living and proliferation space to the parasite. The enormous amounts of oocysts which are produced by *Cryptosporidium*-infected AIDS patients can be regarded as a definitive success for the parasite because they may contribute to the spread of the species.

Figure 17 shows an intestinal biopsy from a young HIV-positive drug addict who complained about diarrhoea and vague abdominal symptoms. Repeated microscopic stool examinations were negative. The pathologist saw granular material in the subepithelial layers but was not able to determine their nature. For the parasitologist it is easy. Already the routine slide shows under high magnification rounded cells, many of them with a clearly visible kinetoplast. This is a case of visceral leishmaniasis. Many cases of visceral leishmaniasis have been observed in AIDS patients in the last years. Visceral leishmaniasis is considered to be an opportunistic infection in AIDS patients. But there is convincing evidence that non AIDS-related visceral leishmaniasis, Kala Azar only develops if the *Leishmania*-infected person has a certain, although limited immune dysfunction which makes it impossible to overcome the parasite. Taken strictly all cases of overt visceral leishmaniasis are opportunistic infections since they can only develop under a state of immunodeficiency. The same is true by the way for leishmaniasis recidivans, too. So the term "opportunistic infection" broadens into the realm of normality.

One area remains to be covered where research is fast moving but where our

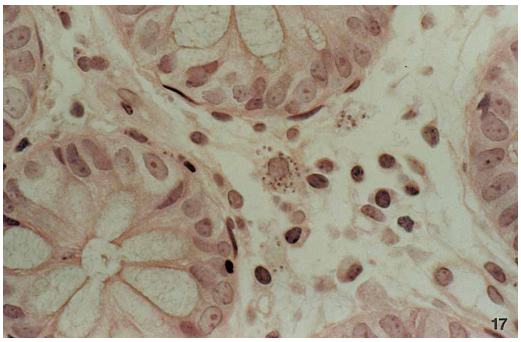

Fig. 17 *Leishmania donovani* in an intestinal biopsy from an AIDS patient (HE stain).

knowledge is extremely insufficient at the moment. I hope the presentations at this symposium will contribute to our further understanding. Several members of the phylum Microsporidia Balbiani 1882 [26] (Fig. 18 - 21) were recently detected in humans (see Table 1). Please do not expect any comments on taxonomy from my side, I think the questions are not settled yet. Apparently, there are microsporidia which are of zoonotic origin. They can infect humans only if they suffer from a severe immunodeficiency. There are other microsporidia which are considered to be true human species, at least no animal host is known at the moment. Their ways of circulation in nature is largely unknown.

I am convinced that the research regarding the complex issue of microsporidial infection which goes on in many laboratories will produce results which again will influence our understanding of the so-called opportunistic infections. If one imagines that even insect parasites under certain conditions are able to infect mammalian cells and are able to proliferate in these cells, it is

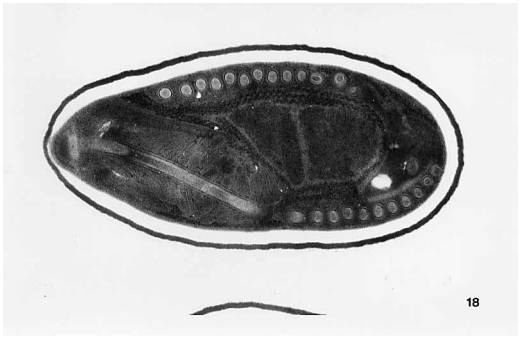

Fig. 18 *Nosema algerae* : electron micrograph of a mature spore showing the diplokaryon and the polar tube (kindly supplied by Dr. Chioralia).

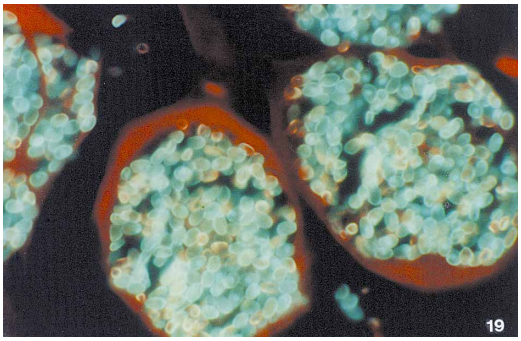

Fig. 19 *Nosema algerae* : experimental infection of a nude mouse (Fluorescence staining). The spores were injected into the tail of the mouse, they multiplied within the muscle cells and destroyed them to a large extent.

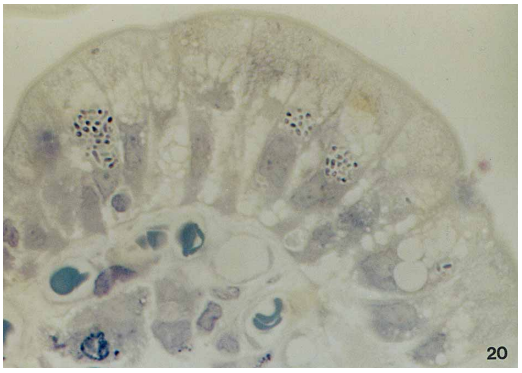

Fig. 20 *Encephalitozoon intestinalis* in a duodenal biopsy, modified Giemsa stain. Several epithelial cells harbor classes of parasites, but typical for *E. intestinalis* is that also parasites occur in the subepithelial tissue.

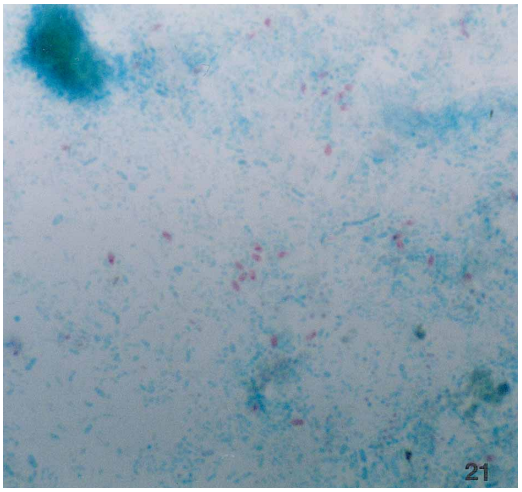

Fig. 21 *Enterocytozoon bieneusi* : faecal smear, AIDS patient. Trichrome stain. The parasites are rather small (1.5 μm) but clearly visible if properly stained. A number of them exhibits the typical dense "belt".

Table 1 Species of Microsporidia Reported to Infect Humans

Species	Sites of infection	First report(s)
Enterocytozoon bieneusi	small intestine, gallbladder, respiratory tract	[9]
Encephalitozoon intestinalis (previously *Septata intestinalis*)	disseminated, small intestine	[3, 15]
Encephalitozoon hellem	disseminated, corneal and conjunctival epithelia	[10, 14]
Encephalitozoon cuniculi	disseminated, brain	[8, 11, 28, 31]
Trachipleistophora anthropophthera	disseminated, brain	[29, 30]
Trachipleistophora hominis	skeletal muscle	[12, 16]
Pleistophora sp.	skeletal muscle	[6, 18]
Brachiola vesicularum	skeletal muscle	[4, 5]
Brachiola connori (previously *Nosema connori*)	disseminated, skeletal muscle	[5, 19, 25]
Vittaforma corneae (previously *Nosema corneum*)	corneal stroma	[7, 23, 24]
Nosema ocularum	corneal stroma	[2]
Microsporidium ceylonensis	cornea	[1]
Microsporidium africanum	cornea	[22]

clear that the severely immunodepressed host, the AIDS patient for example, is something like a challenge for the evolutionary forces which drive parasites to explore the possibility of finding new niches.

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