PARASITIC ZOONOSES

Clinical and Experimental Studies

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Edited by

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ACADEMIC PRESS, INC.

New York San Francisco London 1974
A Subsidiary of Harcourt Brace Jovanovich, Publishers

ACADEMIC PRESS, INC.
111 Fifth Avenue, New York, New York 10003

United Kingdom Edition published by
ACADEMIC PRESS, INC. (LONDON) LTD.
24/28 Oval Road, London NW1

LIBRARY OF CONGRESS CATALOG CARD NUMBER: 74-16429

PRINTED IN THE UNITED STATES OF AMERICA

Preface

The zoonoses, those diseases and infections naturally transmitted between animals and man, assume increasing importance in the modern world. In part, this is due to economic development. The increased contact of man with rural or sylvatic environments by tourism and increased leisure time and the increase in domestic pets in urban and suburban areas are a measure of this. In part, it is due to the increasing urbanization, and the need for companion animals, and in part, it is due to factors inimical to economic development, such as the migration of rural populations or refugees to cities, political unrest and natural disasters. Finally, in part, it is due to modifications of the environment wrought by man.

The parasitic zoonoses are represented in the spectrum of the epidemiological situations above and involve considerations related to all aspects of biomedical investigation.

Such considerations, in the past, have provided focal points for conferences of the World Association for the Advancement of Parasitology. This was the situation with the 6th International Conference of the W.A.A.V.P. which provided a forum for discussion on recent research and development in the field of Parasitic Zoonoses.

The core of the conference, and of this volume, are the invited papers by distinguished experts, who have reviewed the present knowledge in their fields of interest. Supporting these are contributions, selected from numerous short communications which are representative of the work in progress on parasitic zoonoses in various countries of the world.

As with the other International Conferences of the W.A.A.V.P., the local flavor of the venue and the hospitality of our hosts provided an added dimension to the meeting. Indeed, the "Parasitic Zoonoses" conference will be remembered by many as the Vienna Conference since the organization and hospitality provided by Professor Supperer and his staff are not likely to be forgotten.

I wish to thank the contributors to the volume for their cooperation in providing manuscripts, the majority of which were received on time To the staff of Academic Press, Inc., I extend my special thanks for their patience during the preparation of the camera-ready copy. The production of such a volume requires diligence, industry and dedication on the part of secretarial and office staff. Mrs. Margo Bradford, Mrs. Karen Bell and Miss Cleola Taylor have performed outstandingly in producing this volume, and I extend to them my deepest thanks for their assistance.

Finally, to my wife, Annette, I thank her for her patience, forbearance and support during the task of editing and indexing.

E. J. L. Soulsby

Introduction
to the

Sixth International Conference of the
World Association for the Advancement of Veterinary Parasitology

on

Parasitic Zoonoses
Clinical and Experimental Studies

Dr. Georg Lämmler, President
Institute of Parasitology and Parasitic Diseases of Animals
Justus Liebig University, Giessen
Federal Republic of Germany

Magnifizenz, Distinguished guests, Ladies and Gentlemen:

It is my special duty and high honor to call this session to order, and thus open the Sixth International Conference of the World Association for the Advancement of Veterinary Parasitology.

The subject of this conference in Vienna, "Parasitic Zoonoses," was selected in Mexico City, two years ago, with the aim of bringing this important group of diseases to the forefront of scientific interest, public discussion and public awareness.

Zoonotic diseases are problems of considerable magnitude in every country, particularly where domestic animals are the principal reservoirs of infection

since man comes into closest contact with such animals. Though once considered to be diseases of rural and sylvatic environments, the zoonoses now occur in the dense urban areas of large cities, often being associated with pet or companion animals such as the dog and cat and also with more exotic pets such as monkeys, reptiles and other animals.

Research in the field of zoonoses in the last few years (e.g., in toxoplasmosis, sarcocystosis and larva migrans) has been extremely dynamic and this conference provides an opportunity to present, discuss and analyse the recent advances in the field. Since the zoonoses represent a field of research involving both human and veterinary medicine, this conference is of interest and significance not only to comparative medicine, but also it emphasizes the need for the concept of "One Medicine" especially "One Experimental Medicine" in biomedical research on disease by veterinary, medical and natural science disciplines.

More than 150 zoonoses are now recognized in the world. On a world wide basis, therefore, zoonoses are the most frequent disease risks to which mankind is exposed. This is particularly true in the tropics and subtropics where arthropod vectors play an important role in the transmission of these communicable diseases. Of these zoonoses, about 100 are of major public health importance, and a considerable number of them are caused directly by parasites or are transmitted by arthropods.

The Joint FAO/WHO-Expert Committees in 1959 and 1967 defined zoonoses as *"those diseases and infection, which are naturally transmitted between vertebrate animals and man."* It has been argued that this definition is too wide and includes not only infections that man acquires from animal, but also diseases produced by non-infective agents, such as toxins and poisons, as well as infections that animals acquire from man, even if they are purely incidental infections and of no public health importance.

Despite these criticisms, the definition has been widely accepted, and is at present recommended by the World Health Organization. On the basis of this definition therefore *"Parasitic Zoonoses are parasitic diseases and infections which are naturally transmitted between vertebrate animals and man."*

Parasitic zoonoses consist predominantly of protozoal and helminthic infections. Opinions differ whether infestations with ectoparasites should be considered as zoonoses. The Expert Committee on Zoonoses of the World Health Organization concluded that if ectoparasites burrow into, or otherwise penetrate the body of the host, they should be considered as zoonoses. However, since there are no specific ectoparasites of man, except the human louse, and arthropods such as insects, ticks and mites which attack man are primarily parasites of animals, it could be debated that these are also zoonotic parasites. Regardless of this, ectoparasites are important vectors of disease, zoonotic or otherwise, and their intimate association with this is sufficient justification for their inclusion in this conference.

Parasitic zoonoses include *obligate zoonoses* which are transmitted from

vertebrates only to man and *facultative zoonoses* which will generally be transmitted from man to man or animal to animal respectively, but may infect human beings occasionally.

Zoonoses may also be classified in terms of their reservoir hosts, whether these are man or lower vertebrate animals. The term *anthropozoonoses* has been applied to infections transmitted from man to lower vertebrates and the term *zooanthroponoses* to infections transmitted from lower vertebrate animals to man. Both terms have been used interchangeably for all diseases found in both animals and man, and these terms have served to confuse, rather than clarify. The term "zoonoses" is to be preferred.

The hazards of zoonotic diseases are faced by persons in most walks of life. Traditionally, they are especially serious in agriculturists, animal handlers, meat processors and laboratory workers. Nevertheless, the city dweller may be equally exposed to entities such as toxoplasmosis and visceral larva migrans, either through direct contact with companion animals or through contamination of public places such as parks and playgrounds by domestic pets. Further, the advent of modern advances in medicine such as the immunosuppressive therapy and drugs for transplantation, cancer and allergic disorders has identified the importance of subclinical infections of entities such as toxoplasmosis, babesiosis and malaria to the well being of the immunosuppressed patient.

Therefore, there is much to discuss in this conference. The stage will be set by eight "Invited Papers" by distinguished international experts who will discuss the major parasitic zoonoses. Within this framework, the "Short Communications" will contribute a variety of research findings and epidemiological investigations.

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SOME ASPECTS OF TOXOPLASMOSIS, A WORLD WIDE ZOONOSIS

J. K. A. Beverley

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The protozoan parasite *Toxoplasma gondii* was discovered in 1908 by Nicolle and Manceaux in generalised fatal infections of captive North African rodents called gondis. At about the same time Splendore (1909) found it in a rabbit. In the ensuing years it was shown to occur in many other animal species but it was not until 1939 that it was first recognised in man by Wolf *et al.* A parasitic cyst was seen in sections of an eye of a blind infant by Janku in 1923. This is now regarded as a toxoplasma cyst. The human infection described by Castellani in 1913 is unlikely to have been toxoplasmosis. Probably the first human infection to be described even though it was not recognised as toxoplasmosis but considered to be atypical sarcosporidiosis, was one reported by Darling (1909, 1910).

Recognition of human infections was an impetus to the development of serological tests. Of the many types of test which were evolved that which has proved to be of greatest use is the "dye test", described by Sabin and Feldman in 1948. Many surveys, both serological and parasitological were then done. These indicated that *T. gondii* had little host specificity, that any warm blooded animal including birds could be infected and that toxoplasmosis was a world wide zoonosis. While infection has been shown to be very common, only relatively rarely is it known to cause ill health.

During this period, therapeutic agents were sought. Sabin and Warren (1942) showed that sulphonamides were of use and Summers (1949) that sulphones were effective. Eyles and

Coleman (1953) discovered the synergy between sulphonamides and pyrimethamine. Garin and Eyles (1958) found spiramycin to be of value while the latest useful agent in experimental infections is clindamycin (McMaster *et al*, 1973).

No historical account, however short, should fail to mention the recent discovery of the role of the cat in transmission of infection, but more of this later.

THE PARASITE

Trophozoites

Toxoplasma trophozoites were the first forms of the parasite to be recognised. When mature these are elongated lemon shaped, are often flattened on one side and one end is more pointed than the other. They measure approximately 5.0μ x 1.5-2.0μ. The nucleus is situated nearer the rounded end. Electron microscopy shows that there are numerous sub-cellular organelles and a micropyle.

Multiplication

Multiplication occurs only in the cytoplasm of a nucleated host cell, usually close to the nucleus. Any cell will serve for this, most commonly it is a reticulo-endothelial cell, but it may even be an avian erythrocyte. A trophozoite actively penetrates the host cell wall using its more pointed end and becomes surrounded by a vacuole like structure (parasitophorous vacuole), inside which endodyogeny occurs. This is a form of internal budding in which the organelles of the parent become dismantled and then reconstructed as two smaller parasites still within the body of the parent. Eventually the original cell membrane of the parent splits open allowing the progeny to move to other parts of the vacuole, there to grow and each to have its twins.

Pseudocyst

By repetitions of this process the host cell cytoplasm becomes distended with parasites and is then known as a terminal colony or pseudocyst. This finally ruptures, liberating 16 or more parasites which tend to be more crescent or bow shaped than the mature forms. They swell in the extracellular fluids and each is then capable of invading another host cell. Spread may be local, across serous cavities, by the blood stream, or along lymphatics. In the first two of these instances the parasites are extracellular while in the last two they are more likely to be inside reticulo-endothelial cells.

Sequence of Events

Multiplication and spread continue until either the host dies or, much more usually, immunity is established. Extracellular parasites are then killed and intra-cellular multiplication is slowed. Concurrently with the development of immunity, but not necessarily because of it, tissue cysts develop. These probably arise as a result of the expulsion of a parasitophorous vacuole and its contained toxoplasma from the host cell. Such vacuoles have an elastic membrane which is made up of components from both host and parasite. Cysts enlarge slowly, taking about three weeks to double their volume and, presumbaly, to double the number of contained parasites. These are similar to, but smaller than, trophozoites and are known as zoites. A small cyst may contain only a few zoites but a large one many thousands. Intact cysts do not provoke an inflammatory reaction but should one rupture a local delayed hypersensitivity type reaction may develop. Cysts are found most frequently in the brain, less often in skeletal muscle and the heart and, more rarely, in the lung. They persist for many months or years, possibly even for the lifetime of the host.

Strain differences

Strains of toxoplasma vary in their virulence. Some kill small laboratory animals such as mice, hamsters or rabbits in 7-10 days. Others do not, but cause a life-long infection even though the animal remains apparently healthy. Infection with a strain of low virulence causes immunity to a subsequent challenge with a high virulence strain. The immunity, however, is only partial for, while the animal survives the challenge, superinfection takes place.

CLINICAL MANIFESTATIONS IN MAN

These may be the result of congenital or post-natally acquired infections.

Congenital infection

Congenital infection occurs only when a woman has a primary infection during pregnancy. While this rarely causes the mother any harm she does have a temporary parasitaemia which may lead to placental infection. When this happens minute focal lesions develop and on rupture toxoplasms are discharged into the foetal circulation. Foetal infection is at first generalised and it may cause exudates (which may be blood-stained) in the body cavities, oedema of connective tissues, lymphadenopathy, hepato-splenomegaly with or without

jaundice, and bone marrow dysfunction. If, as it often does, the foetus survives this stage the infection is cleared from the viscera and resolution of the pathological changes takes place. Even so, the infection then becomes localised in the central nervous system.

Abortion

The severity of clinical manifestations varies enormously and depends on the degree of foetal damage. This in turn depends partly on the virulence of the infecting strain and partly on the duration of gestation at the time of foetal infection. Thus, infection early in pregnancy probably leads to abortion and toxoplasma has been isolated from the products of abortion (Magnuson, 1951; Wildfuhr, 1954). This does not mean that toxoplasmosis is a common cause of abortion; Feldman and Eichenwald (1953) failed to find evidence of active toxoplasmosis in any of 95 women who had abortion and Kimball *et al* (1971) found that none of 260 abortions were due to toxoplasmosis. If infection occurs late in pregnancy the child may appear normal at birth only to develop signs of infection when 4-12 weeks of age. Between these extremes, infection leads to signs of active disease at birth, if infection has occurred earlier, to a live child with quiescent or even healed lesions, while if the infection is still earlier it may lead to intrauterine death. It is not uncommon for each of twins to be infected but only one of them to have signs; the reasons for this are unknown.

Pathological changes are found more frequently in the central nervous system than in the viscera and somatic tissues. By far the commonest site is the eye and the basic change is a focal infiltration with round cells which, in the case of a large focus, tends to undergo central necrosis. The foci vary in number as well as in size. They may be so numerous and so close together that they become confluent.

Ocular disease

Very occasionally infection spreads throughout the globe causing a panophthalmitis and leaving a useless microphthalmic eye which is generally noticed at or very soon after birth. Nearly always, however, the changes are confined to the posterior chamber and involve both the choroid and retina. One or both eyes may be affected and lesions may be multiple though commonly they are single. Areas of acute choroidoretinitis or areas of destroyed uveal tissue are readily seen with an ophthalmoscope. The former are irregular shaped yellowish raised areas with imprecise edges and are often found alongside or bridging the retinal vessels. Inflamma-

tory exudates cloud the vitreous so making the view of the fundus hazy or even obscuring it. As the acute processes subside, the vitreous clears, destroyed retina and choroid are removed leaving the underlying white sclera clearly visible. Sometimes the ciliary vessels can be seen crossing such a scar and proliferation of choroidal pigment can be seen at the edges of the lesion or even straddling it.

When very large areas are destroyed, a white reflection instead of a red one may be noticed on shining a light into the eye and be seen by an observant mother or midwife. A smaller lesion involving the macula will cause a squint, often first noticed at about the time the child should be developing binocular vision. If both macular areas are affected, a searching nystagmus occurs instead of a squint. The squint may be convergent, divergent or vertical. Lesions near but not involving the macula may not be found until early school age when defective vision is first suspected. Others in more peripheral areas may not cause signs and symptoms until early adulthood when a reactivation may occur and cause exudates in the vitreous and cloudiness of vision. Such reactivations are commoner in women especially in relation to pregnancy and lactation. Other lesions may not be found until still later when a complication such as detachment of the retina develops or when the presbyopic age is reached and an ophthmoscopic examination is made for the first time.

Intracerebral calcification

Changes may also occur in the brain. While some of them are uncommon they are more dramatic. The lesion is basically the same round cell infiltration. Meningeal signs may develop but these are rarely a predominant feature. Much more often the principal change is in the brain. Here the infiltrations are focal, are accompanied by oedema and glial proliferation and tend to undergo necrosis. Healing is often accompanied by calcification which may be sufficiently dense to be visible on x-rays. A common site for these calcified lesions is the sub-ependymal tissues of the walls of the ventricles. Here calcium is deposited in thin sheets which in "end-on" views appear as curvilineal streaks in line with the ventricular walls. Elsewhere, calcified areas are of irregular shape. In x-rays of some patients, both types can be seen.

Hydrocephalus

Should flakes of necrotic tissue in the walls of the lateral ventricles be shed, reach the aqueduct of Sylvius and