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ing host resistance to the parasite and for the potential design of cytokine-based immunotherapies for *Toxoplasma* in AIDS patients.

It is now clear that the outcome of infection with *T. gondii* is dependent on the genetics of both the host and parasite. While the clear-cut MHC restriction of host resistance has provided us with important clues as to how the immune system recognizes *T. gondii*, the recent classification of the species by Sibley and Boothroyd into virulent and avirulent genetic groups has important new implications for both pathogenesis and the induction of natural immunity against parasite populations.

As described in the lead article of this Forum, the Pasteur Institute and its scientists have played a key role in both the discovery of *T. gondii* and the development of research on toxoplasmosis. We hope

that the present issue will provide a modern testimonial to this long-standing scientific association and we thank the participants for contributing their work, ideas and discussion to what we hope is a unique overview of a vital and rapidly expanding field.

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Historical introduction: the Institut Pasteur's contribution

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In 1964, Colin Beattie delivered the Lister lecture on toxoplasmosis at the Royal College of Edinburgh (Beattie, 1964). *Toxoplasma* was characterized as a very unusual parasite: "it pays scant respect to boundaries of zoology or geography, it is widespread among mammals and birds of many, probably all species and remains in them for long periods, in some at least for the duration of their natural lives." Beattie concluded by saying that it is an "exceptionally good parasite, very rarely doing any harm to its host" (Beattie, 1964).

These lines defined the common sense on toxoplasmosis in the sixties: a rather uninteresting, or a remarkably well-behaved parasite, as one might put it. Only under two special circumstances did this mild pathogen become harmful: during pregnancy, and in case of chorioretinitis (Frenkel, 1954). Again, in terms of contemporary wisdom at the time, both cases shared the common feature of causing relative impairment of the immune system, due either to a temporary downregulation of immune reactions or to estrangement from the centres where this response

was elaborated (physiological "sequestration" of the eye antigens from a normal environment). In 1964, both situations were referred to as natural tolerance. Embryo tolerance accounted for the first successful cultures of the parasite on chick embryo (Brumpt, 1949).

The contrast between the rarity of the disease and the high frequency of infection provided guidelines for the future immunobiology of the parasite. Why the parasite has been able to successfully invade nearly all nucleated cells, including red blood cells of birds, and to survive unnoticed in large cysts in brain and muscle in so many species still remain to be explained. In the last decade, this intriguing model of parasitic life has been recognized as a core immunological enigma, as its ubiquitous presence was felt to be a potential epidemic threat for humans.

The benign account of Prof. Beattie's Lister lecture of 1964 may obscure the fact that the early period of toxoplasma studies was marked by a passionate interest in epidemiology and pathogenicity of

the new parasite when it emerged in 1908, in the context of research on cutaneous and visceral leishmaniasis.

Ironically, *Toxoplasma*, discovered by the French Pastorian Charles Nicolle, was to provide a striking illustration for his concept of inapparent diseases, an idea which he elaborated at the same time (Nicolle et Lebailly, 1919) in the case of experimental typhus and further offered as a general explanatory model for the emergence of new epidemics (Nicolle, 1925). Charles Nicolle had come to the direction of the Pasteur Institute of Tunis, ten years after its founding, in 1903. In the intervals of the epidemics of plague and typhus recurring in the Regency period, he explored infantile splenomegaly already described in India as kala-azar, and the Oriental sore locally known as Gafsa pimple. Nicolle succeeded in culturing the parasite from the leg ulcer of a camel driver of Tozeur on the NN medium which he improved (Nicolle, 1908). Having established leishmania cultures, he embarked on an experimental and epidemiological study of the disease.

Nicolle suspected that rodents played the same role in the oriental sore as dogs did in kala-azar. In order to capture rodents in the Djerid desert, Nicolle recruited a military doctor, Louis Manceaux. The gondi, a North African rodent (*Ctenodactylus gondi*, Pallas, 1778), covered roughly the same geographical areas as the "clou de Gafsa". Nicolle had been familiar with the gondi since his trip to Djerba island, where he investigated an ancient leprosy focus and considered it as a possible "clue to the oriental sore" (Nicolle, 1908).

In two gondis which died and displayed splenomegaly upon post-mortem examination, Nicolle and Manceaux observed parasites both free and within mononucleated cells, and both isolated and in clumps (Nicolle et Manceaux, 1908) which were very similar to leishmania. One end was more tapered than the other. Nicolle initially called it *Leishmania gondii*. But the parasite could not be cultivated. Later, the plates which his Academy correspondent Laveran had omitted (Nicolle, 1908) appeared in print, showing small asymmetrical crescents grouped by pairs indicating their binary mode of division. Nicolle suggested the name *Toxoplasma* (from the Greek toxon, or arc) for a new genus, distinct from *Leishmania* in the absence of a centrosome, and from *Piroplasma* in its location in the white cells (Nicolle, 1909; Nicolle et Manceaux, 1909). *Toxoplasma gondii* was born.

Since this was not a leishmania, the new disease merited further investigation. The original context of leishmaniasis research nevertheless strongly influenced Nicolle's initial views of the new parasite. He inquired about an insect vector (flea or tick) which would explain the peak of the disease during the cold

season (Nicolle, 1916) and assigned the new parasite to the general chapter of Mediterranean splenomegalies. Toxoplasmosis, both natural and experimental (Nicolle et Conor, 1913) was viewed as a disseminated infection with involvement of the spleen, liver, lymph nodes, lungs and kidneys. The parasite was sometimes found in the blood and bone-marrow, and more often in mononucleated cells than in polynucleated, another similarity with *Leishmania*.

Following the pastorian protocol, Nicolle passaged the new virus on gondis by intraperitoneal inoculation and reproduced the disease. Although the guinea pig finally revealed itself to be sensitive to the disease, the animal of choice was found to be the mouse (Nicolle, 1914) whose voluminous ascites contained great amounts of parasites, thus enabling researchers to cope with failure to culture the parasite. The pigeon reacted with torpor, and for the first time, involvement of the central nervous system was suggested (Nicolle et Conor, 1913).

Alfonso Splendore worked in a very similar context, far from his native Italy, in Sao Paulo, where the Oriental sore was identified following completion of construction, by a French company, of a railway through the Matto Grosso. Two days after Nicolle's findings were read, he presented his work on a new rabbit disease before a scientific society in Sao Paulo, emphasizing the similarity with kala-azar (Splendore, 1908). Although both papers converged in a kidney-shaped, asymmetric morphology, they differed on two points. Splendore identified schizogony or "multiple endogenous division" (Nicolle later mockingly coined the term "schizontiens" for partisans of schizogony, before being convinced by his assistant Georges Blanc) (Nicolle, 1916). He considered that the parasite formed true cysts, while Nicolle denied any formation of a real membrane wall and mentioned only "gangues", simple artifacts resulting from the destruction of the host cell. These points deserve being addressed, since we now admit both endodyogeny and schizogony, the latter typical of coccidia in *Toxoplasma*. We also view the wall of the mature cyst as a combination of host and parasitic components, a membranous network involving redistribution of the major outer membrane proteins of the *Toxoplasma* cell (Sibley and Krahenbuhl, 1988) and contributing to intracellular survival. Splendore called his parasite *Toxoplasma cuniculi* (Splendore, 1909).

As early as 1900, the French parasitologist Laveran had described a similar parasite in *Padda oryzivora*, an Asian sparrow (Laveran, 1900), but following Nicolle's description, the diagnosis of toxoplasma spread epidemically in the circle of Pastorian correspondents during the years of intense activity in tropical medicine preceding World War I (Senaud, 1967). The parasite was identified in numerous species: insectivorous and carnivorous, primates and

birds. Half the papers appeared in the *Bulletin de la Société de Pathologie exotique*, a journal of the society of which Nicolle was a prominent member. On the German side, Prowazek also described a case in a mole from Japan (von Prowazek, 1910). In humans, Castellani in Ceylon attributed a feverish splenomegaly to a protozoon which he named *Toxoplasma pyrogenes* (Castellani, 1914). Fedorovich did the same with blood collected during an anti-malaria campaign on the Black Sea (Fedorovitch, 1916).

In Tunisia, the war delayed the epidemiological work Edouard Chatton resumed in 1916. The "zoologist fond of toxoplasmas" as Nicolle called him (Nicolle, 1916) worked in Gabes, south of Tunisia. Blanc joined him, back from the Serbian front. In their monograph (Chatton et Blanc, 1917), published in 1917, Chatton and Blanc raised the question of captivity as triggering the pathogenicity of a natural parasite: at the Pasteur Institute, the gondi was deprived of its natural milieu and lazy life on sunny pebbles, even deprived of its natural ectoparasites, and was exposed to overcrowding. Frenkel also suggests that cats were permitted to roam animal quarters (Frenkel, 1970). Kept for beyond a month in a case, nearly half of the animals perished of toxoplasmosis. *Toxoplasma* was a "latent parasite", active only in the "physiologically depressed host", a perfect intellectual challenge for the "Pastorians gathering around their elder, during the warm evenings of Africa" (Chatton et Blanc, 1919). Nicolle conceived "the probable existence of a *latent form*" and incriminated cold for the acute illness, later reintroduced as a component of "stress".

Chatton and Blanc suggested the unity of the different animal strains, supported by Laveran (Laveran et Marullaz, 1913a,b). In contrast with most parasites, *Toxoplasma* seemed to lack host or tissue specificity and was ubiquitous. The list still goes on today, with parasites being described in Atlantic cetaceans (Inskip, 1990b) and arboreal South American marsupials (Hartley, 1990a) and antibodies identified in Canadian mouse (Siepierski *et al.*, 1990) as well as Australian dingos (Johnson *et al.*, 1990) and macropods (Johnson *et al.*, 1988). How then to understand infection and "resistance"? Chatton and Blanc (1917) concluded that the chapter on immunity in toxoplasmosis "has to be constructed from A to Z".

In 1920, at the Pasteur Institute of Bruxelles, while writing his synthesis on immunity (Bordet, 1920), Jules Bordet remarked that his knowledge came mainly from microbiology, but admitted that the mechanisms of defence against protozoa were roughly the same as against bacteria: phagocytes dispose of parasites with the help of opsonizing antibodies. But he also mentioned the power that most parasites possess to become "seroresistant" (Bordet, 1920), in a manner comparable to that of chemother-

apy resistance (as found in *Trypanosoma*) and illustrated by present description of mutants (Pfefferkorn, 1988). "Immunization of protozoa against the organism's weapons accounts for the chronicity of symptoms or the simple persistence of germs in subjects who appear to be cured" (Bordet, 1920). Relying on the example of malaria and piroplasmiasis, Bordet noted that "so-called immunity", rather, expresses a state of equilibrium between the organism and its pathogen, which can be overturned in case of intercurrent infection.

The following studies at the Pasteur Institute of Paris focused on immunopathology in the spirit of the Metchnikovian experimental tradition. Constantin Levaditi, investigating encephalopathies (Levaditi *et al.*, 1923), intracerebrally inoculated rabbits with rabbit and monkey nervous substance. The rabbits developed meningoencephalopathy, and Levaditi had the surprise of identifying inflammatory nodules with *Toxoplasma* bodies in enlarged monocytes (Levaditi *et al.*, 1927). However, the hypothesis of autoimmunity linked to infection, although traditional in the Pastorian school since the 1900s, was not explicitly reactivated.

Levaditi mentioned in retrospect that in 1923, J. Janku had described in Prague a case of hydrocephalus in a child with retina coloboma (Janku, 1923). In the outer layer of the choroid, he had described "an oval sporocyst... that contained numerous small, dark brown spots... which represented sporozoites" (Janku, 1923) but he did not examine the brain. C. Magarinos-Torres also reported a case of an encephalopathy in a newborn with cell nodes containing a parasite intermediary between the genus *Encephalitozoon* and *Toxoplasma* (Magarinos-Torres, 1927). Levaditi challenged the coincidence and suggested the responsibility for *Toxoplasma* in nervous diseases of an unknown nature (Levaditi, 1928).

Byzantine discussions on the taxonomic identity of the parasite emphasized its active role in penetrating the host cell. Biologists pleaded (Levaditi, 1929) that only a protozoon well-equipped with lytic enzymes could display locomotive features such as twirling and sliding, attributed to *Toxoplasma* since Laveran (Laveran, 1915). Modern presentation emphasizes the membrane fluidity and the role of actin and myosin for microtubule-dependent movements which are a prelude to cell invasion (Endo *et al.*, 1988).

In another series of experiments, S. Nicolau, working in his group, described the emergence of a toxoplasma encephalitis (ascertained by successful transmission to the animal) in the course of a series of rabies inoculations in rabbits (Nicolau, 1932). Again, the role of an adjuvant pathogen (here rabies virus) was put forth for the genesis of a genuine tox-

oplasmic disease, with primary involvement of the nervous system. Recently, additional proof has been brought that prior infection interferes with subsequent penetration of the cells by *Toxoplasma* (Black *et al.*, 1990).

This program was pursued from 1937 by Wolff and Paige working in New York. In their report of encephalomyelitis with an internal hydrocephalus resulting from stenosis of the aqueduct and chorioretinitis (Wolf and Cowen, 1937), they identified the parasite, both isolated and in cysts, which resembled the sporozoon seen in spontaneous encephalitis of rabbits and mice. They discussed Levaditi's hypothesis of a *Toxoplasma* but found their observation differed slightly from his description. Two years later, in *Science*, they finally established toxoplasmosis as a characteristic encephalopathy of young infants and detailed the first experimental transmission of a toxoplasma which they called *Toxoplasma hominis* to mice and rats inoculated with the spinal fluid of the infant (Wolf *et al.*, 1939, 1939). The possibility of foetal transmission through the genitals had been suggested by the Pastorian protozoologist Mesnil since 1913 (Mesnil et Sarrailhe, 1913).

Referring back to Janku's original plates, with the central mother cyst surrounded by smaller cysts scattered without inflammatory reaction in the retina, they describe rather well the central enigma of toxoplasmosis: the latency of cysts in the nervous system long after primary infection. Each brain focal lesion is the histological correlate of a single ruptured cyst from which parasites emerge and destroy surrounding cells. Nicolau considered that chronic infection resulted "from a balance between parasite activity and tissular tolerance (Nicolau, 1937; Kopciowska)". Since 1963 (Walls, 1963), these cysts have been well documented both in healthy individuals and in immunodepressed patients (Ruskin and Remington, 1976), illustrating Nicolle's concept of unapparent infection, rephrased as "a chronic asymptomatic toxoplasmosis in the individual host (Walls, 1963)". Cysts are an excellent paradigm for the study of parasite-host interaction and may be viewed as a marker of the function of immune surveillance in the era of the immune system.

Complement fixation proved itself to be of poor reliability, but demonstrated the existence of antibodies fixed on tissues (Nicolau et Ravelo, 1937). Sabin at the Rockefeller Institute developed the dye-test in 1948, which provided a tool for scientific investigation (Sabin and Feldman, 1948). In the 1960s, serology was developed as a tool appropriate for the early detection of infection and the follow-up of pregnant mothers in order to prevent mother-child transmission. Tests enabled the screening of asymptomatic acute and chronic infections and revealed the dynamics of humoral immunity. IgM and IgA arise as the first line of defence; IgG rise up secondarily and

decline slowly before becoming established at a slowly declining rate. That was common sense before the emergence of AIDS.

A few cases of toxoplasmic encephalitis have been described in "**compromised hosts**" (cancers and transplantees) since 1976 (Ruskin and Remington, 1976), but a dramatic change occurred with the increase of encephalitis in AIDS (Luft, 1989), most of them caused by *Toxoplasma*, as proved by histologic post-mortem sections showing brain abscesses. *Toxoplasma* joined the group of **opportunistic pathogens** which, for a parasite, may sound like a teleological truism.

The failure of serology in providing a tool for the surveillance of immunodepressed patients is paradoxical in appearance only. In the past, *Toxoplasma* was shown by Remington's school to be altogether a non-specific stimulating and immunosuppressing factor (Luft, 1989). On the one hand, toxoplasma infections seem to confer upon mice a remarkable long-term non-specific resistance to a broad spectrum of infections with non-related pathogens. On the other hand, chronic toxoplasmic infection has been demonstrated to interfere with the capacity of mounting an immune response. Is the presence of antibodies at a high rate synonymous with infection or with resistance? The question had already been raised by early serology (Moulin, 1991). Attempts to differentiate between protective and non-protective antibodies have thus far been inconclusive. Another paradox is that *Toxoplasma* immunity has been linked to the persistence of life-long antigenic stimulation, in contrast to the selective viewpoint generally accepted for antibody formation.

The questions of classical immunology remain pending in toxoplasmosis. Those parasites, against which immunity is predominantly T-cell-mediated, are likely to be more severe in AIDS patients than in immunocompetent individuals. Toxoplasmic encephalitis usually occurs in patients with a low CD4 account. This was to be expected, as T helper cells may facilitate the killing of toxoplasma by macrophages and liberate lymphokines (interferon...) which enhance macrophagic toxic action. They also promote the activity of cytotoxic cells. The immune mechanism of encephalitis may be understood through reference to a mouse model (Vollmer, 1987) using an anti-CD4 monoclonal antibody in mice chronically infected by *Toxoplasma*. The depletion of T helper cells leads to the breakdown of tissue cysts and to tachyzoite proliferation.

However, the respective parts of cellular and humoral immunity in the hatching of new cysts remains unclear. There seems to be no recrudescence of cysts in muscles among AIDS patients. In a comparative spirit, it is interesting to note that HIV infection does not seem to impair immune responses to malaria at

any stage of life, including pregnancy (Fleming, 1990), while cases of severe cutaneous leishmaniasis have been reported (Fleming, 1990). In molecular terms, the question is phrased today: what enables *Toxoplasma* to adapt to different type cells and why can they invade the surrounding tissues? More precise knowledge of its flexible metabolism is urgently needed. Frenkel, who contributed so much to the understanding of the parasite cycle, made the distinction between tachyzoites and bradyzoites (Frenkel, 1974). Again in molecular terms, how can we understand the shift from activity to "latency", from rapid division (tachyzoite stage) to partly inactivated bradyzoites (which are antigenically different) and what factors permit the reversion to tachyzoites in AIDS patients? How could we establish rational serologic monitoring based on the dynamics of an immunologic marker, perhaps an antibody directed against a secreted-excreted antigen (Decoster, 1988) or a stage-specific antigen (Kasper, 1989)?

Looking back at past research may provide us with inspirational insights. Current knowledge of this unconventional coccidia widens our concepts of protozoan natural cycles and host and tissue specificity in parasitic life. The 60-year history of *Toxoplasma* from discovery to recognition of the sexual cycle presented exceptions to the rule. With the multiplication of toxoplasmosis in the compromised host, the exception is becoming the heart of the matter. With *Toxoplasma*, the enigma of latent infections, perceived very early by the first generation of parasitologists, was formulated for each period in terms of contemporary immunologic wisdom and is today brought into sharp focus. AIDS once more has not created new questions, but emphasizes that we are still unable to solve old ones. Genetic and molecular immunology are now at work on the barrier, perhaps or what might more aptly be termed the frontier, between *Toxoplasma* and its host.

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