TOXOPLASMOSIS IN THE ADULT*

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SAMUEL T. DARLING, a pathologist and parasitologist in Panama, to whom is credited the discovery in 1906 of histoplasmosis in man, described the case of a 20-year-old male with an acute illness characterized by fever, headache, and stiffness of muscles and joints.[1] Microscopic examination of muscle tissue, obtained at biopsy for suspected trichinosis, revealed the presence of encysted organisms which Darling interpreted, with some reservation, as sarcosporidia. Chaves-Carballo[2] suggests that Darling, whose data were collected and published in 1908 (the same year that Nicolle and Manceaux discovered animal toxoplasmosis in *Stenodactylus gundi*), should receive credit for what may be the first description of toxoplasmosis in the human adult. Kean and Grocott in 1945 initially raised the question as to the correct classification of the parasites observed by Darling, believing them to be *Toxoplasma*.[3]

A great deal has been learned about the organisms since our publication on this subject 13 years ago,[4] but there have been relatively few advances or changes in our knowledge of clinical toxoplasmosis as it occurs in adults.

Although the vast majority of cases of toxoplasmosis in adults are attributable to infection acquired after birth, as is evidenced by the increasing prevalence of antibodies with increasing age, it should be recognized that manifestations of infection acquired *in utero* may not become apparent until adult life, e.g., retinochoroiditis. In studies of toxoplasmosis in the immunologically deficient host, we often cannot ascertain whether the infection was acquired recently or whether the

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clinical syndrome and histologic findings were due to reactivation of infection acquired earlier in life—in some cases perhaps even congenitally. It is in the immunologically compromised patient that toxoplasmosis is emerging as a new and serious problem.

Despite a plethora of articles and chapters in the literature in the United States describing the clinical manifestations of toxoplasmosis, physicians rarely consider the disease in their differential diagnosis when adults with these manifestations appear in their office or hospital. Failure of appreciation of toxoplasmosis by physicians in the United States as other than "a disease of the tropics" has resulted and is resulting in erroneous diagnoses, unnecessary procedures, and potentially preventable deaths in patients subjected to immunosuppression. In addition, regrettable misinformation, in the form of advice given by physicians, has resulted in unnecessary anxiety in numerous pregnant and nonpregnant women who have *Toxoplasma* antibody titers.

The clinical manifestations of acquired toxoplasmosis in the adult are not unique to infection with this organism; the signs of the infection often mimic those of commoner diseases. Although the manifestations in adults are protean and include symptomatic and asymptomatic lymphadenopathy, myocarditis,[5] pericarditis,[5, 6] hepatitis,[7] encephalitis,[8] pneumonitis,[8, 9] myalgia and arthralgia, and maculopapular rash, which frequently lead to consideration of other etiologies, the major factor contributing to the failure to diagnose toxoplasmosis correctly in patients in the United States is the fact that physicians lack knowledge of toxoplasmosis in the adult. Most physicians state that they have "never seen a case" when, in fact, they fail even to consider the diagnosis. In some ways, the recent articles on this subject which have appeared in the lay press (some of which are sensational and misleading to a degree that approaches irresponsibility), have served to educate the physician about toxoplasmosis—not because physicians have read these articles, but because their patients, appropriately concerned, have read them and requested that the diagnosis be considered in their situation. In my own geographic area, it appears that demand from patients has impelled hundreds of physicians to educate themselves about the disease and I suspect that this may be equally true in other areas of this country. Like other contributors to this symposium, I receive numerous calls from physicians and patients who desire factual information about toxoplasmosis, especially as it pertains to pregnancy. Each year

many women are told that they should not become pregnant, because they have previously given birth to an infected child or because they had a positive serologic titer for toxoplasmosis some years previously. This is tragic. It testifies not only to a lack of knowledge on the part of the doctor, but to the fact that the literature is replete with misinformation, half-truths, and untruths. Often this is due to distortion of data because of lack of proper controls, or misinterpretation by the author of his own data or, as so often is the case, to lack of discernment by reviewers and editors. Practitioners must be more aware of the importance of considering the diagnosis in their daily practice. I intend to confine my comments to two forms of toxoplasmosis of which more physicians must be made aware: 1) the lymphadenopathic form and 2) the disseminated form in compromised hosts. The specific problem of toxoplasmosis in pregnancy will not be discussed here since it has recently been reviewed elsewhere.[10]

Since the description of the lymphadenopathic form of toxoplasmosis in the early 1950s by Siim[11] and by Gard and Magnusson[12] this form of the infection has become recognized as the most common clinical manifestation of toxoplasmosis in man. The entity is well recognized in eastern and western Europe and in Scandinavia; a large number of publications describing it have emanated from countries in these areas. Although the disease is less well recognized in the United States, ample evidence of its presence has come from areas of this country,[13-17] especially from Kean and his colleagues at Cornell.[18-20] At the meeting of the expert committee on toxoplasmosis in Geneva in 1968, it was estimated that approximately 15% of cases of "otherwise unexplained lymphadenopathy" is due to toxoplasmosis.[21] Some patients with this form of toxoplasmosis present with adenopathy involving multiple sites and symptoms and signs which closely mimic the clinical picture of infectious mononucleosis.[13-15] The adenopathy may not be solely superficial and may involve mesenteric retroperitoneal and mediastinal nodes. Information on enlargement of the spleen and liver are meager, but Jones et al. note splenomegaly and hepatomegaly in approximately one third of their cases.[18] The hematologic picture may mimic exactly that seen in infectious mononucleosis, with lymphocytosis and atypical lymphocytes; eosinophilia has been observed in approximately 10 to 20% of cases.[18]

When an adult with either localized or generalized adenopathy

TABLE I. LYMPHADENOPATHY IN COLLEGE STUDENTS

Leukemia	Tuberculosis
Hodgkin's disease	Cat scratch disease
Mononucleosis	Metastatic disease
Toxoplasmosis	SLE*
Sarcoidosis	Rheumatoid arthritis

*Systemic lupus erythematosis.

TABLE II. ATYPICAL LYMPHOCYTES AND LYMPHOCYTOSIS

Infectious hepatitis	Viral pneumonia
Mononucleosis	Toxoplasmosis
Mumps	Exanthems of childhood
Varicella	

presents himself to the physician, among the conditions to be considered in the differential diagnosis are those shown in Table I. Although toxoplasmosis is among the diagnoses, it is rarely considered. Similarly, in patients with atypical lymphocytes, the diagnoses in Table II are among those to be considered. Here again, although toxoplasmosis may cause atypical lymphocytosis, it is rarely considered in patients who exhibit this abnormality. In the absence of demonstrable heterophile antibodies, toxoplasmosis should be considered in such patients, and appropriate serologic tests should be ordered.

Not uncommonly, adults with toxoplasmosis who present with adenopathy are entirely without symptoms. The lymphadenopathy may be localized (usually cervical and in our experience and that of Jones et al.[18] most often posterior cervical) or may involve multiple sites. In such cases, lymphoma is frequently considered and frequently leads to biopsy of lymph nodes. In such cases early serologic testing may remove the need for biopsy—but only if a rising serologic titer can be demonstrated or if the initial titer is high (e.g., greater than 1,000 in the dye test or fluorescent antibody test) in the presence of IgM-fluorescent antibodies.[22] The high prevalence of antibodies in the normal population and the fact that in some normal individuals titers of 1,000 or greater may be found[22, 23] usually precludes reliance on a single

high titer in the dye test or conventional fluorescent-antibody test as being diagnostic of toxoplasmosis.* Erroneous interpretation of serologic data in such patients may result in unnecessary hesitation to perform biopsy when it is indicated.

Although it has been suggested that the localized form of adenopathy is more common in adults,[24] classifications which suggest a significant difference in presentation of the lymphadenopathic form in children as opposed to adults are most probably artificial and are due largely to the clinical exposure of those who perform the studies.[25] There are no clear-cut data which reveal a definite difference between the lymphadenopathic form in children and that observed in adults. In the series of cases of acquired toxoplasmosis in children reported by Lelong et al.,[24] 11% had localized adenopathy and 51% showed involvement of multiple sites. These figures do not differ significantly from those obtained in a series of adult cases reported by Piguet et al.[26]

In Europe the diagnosis of toxoplasmic lymphadenopathy has been made for years by pathologists who accept the almost characteristic criteria originally described by Piringer-Kuchinka[27] and confirmed by others.[28] In the United States these characteristic histologic changes are often reported as "reticulum-cell hyperplasia, etiology unknown." Until recent years, this was true also at Stanford Medical Center. In 1968 Dr. Ronald Dorfman, a recognized authority on the pathology of lymph nodes, came to Stanford to head the Division of Surgical Pathology. At Stanford we have a large and active radiotherapy and chemotherapy program for patients with Hodgkin's disease and non-Hodgkin lymphoma. Consequently many patients are referred for biopsy of lymph nodes. Soon after his arrival, Dr. Dorfman told me that he was looking at a node taken from a case of suspected Hodgkin's disease and that he considered the probable diagnosis to be toxoplasmic lymphadenopathy. Serologic testing in that patient revealed a dye-test titer of 1:64,000 and an IgM-IFA test titer of >1:640. Dr. Dorfman and I embarked on a prospective, blind study to determine how frequently his histologic diagnosis would correlate with serologic test titers compatible with a diagnosis of acute toxoplasmosis in patients who came to Stanford for biopsy of lymph nodes. Since we began our study, and without any prior knowledge of serologic results or history, Dr. Dorfman has suggested the

*A diagnosis made from a single high titer is sometimes justifiable in patients who have adenopathy and extraordinarily high titers (e.g., 32,000 or greater).

TABLE III. PREVALENCE OF DYE TEST ANTIBODIES AMONG UNITED STATES MILITARY RECRUITS IN 1962*

Geographic area	*No. tested*	*% positive*†
Northeast	109	20
North Mid-Atlantic	193	16
South Atlantic	469	18
East North Central	549	18
East South Central	256	19
West North Central	315	12
West South Central	201	13
Mountain	182	3
Pacific	406	8

*Adapted from Feldman, H. A.: A nationwide serum survey of United States military recruits, 1962. VI. Toxoplasma antibodies. *Amer. J. Epidem. 81*:385-91, 1965.

†Dye-test titer positive at 1:16 or greater.

Aproximately two thirds of the recruits were 17 to 20 years of age and fewer than 5% were more than 23 years of age.

diagnosis in more than 40 cases. The serologic results were compatible with the diagnosis in every case; all the patients in the series had dye-test titers of 1,000 or greater; 81% had titers of 4,000 or greater; all but one were positive in the IgM-IFA test.[29] Thus, there is no doubt that the diagnosis can be made by histologic means and in many instances by histologic diagnosis alone. His results support the contention of Tenhunen,[30] who states that at least 90% of cases of the lymphadenopathic form of toxoplasmosis can be diagnosed solely by histologic criteria.

In persons who are immunologically normal, treatment of lymphadenopathic toxoplasmosis is rarely indicated. This form of the infection is almost always self-limited and has no untoward sequelae. In such cases, the use of pyrimethamine and sulfonamides, which are potentially toxic, is probably not justifiable except in patients who are seriously ill with this form of the infection.[31] If drugs become available which have few or no serious side effects, treatment might be considered in all such patients in the hope of reducing the number of organisms in the acute stage, thereby reducing the number of organisms which persist in the host. The value of totally preventing or of at least reducing the level of latent infestation with *Toxoplasma* will be readily apparent from the discussion of toxoplasmosis in the compromised host which is given below. It is in later life that patients who have

TABLE IV. PREVALENCE OF DYE TEST ANTIBODIES IN FIVE HUMAN POPULATIONS IN THE UNITED STATES*

Age group (years)	Per cent positive				
	Portland, Ore.	St. Louis, Mo.	Syracuse, N. Y.	New Orleans, La.	Pittsburgh, Pa.
10-19	21	20	13	27	30
20-29	25	29	35	35	24
30-39	26	33	36	42	45
40-49	15	40	36	36	68
50+	16	39	44	45	67

*Adapted from Feldman, H. A.: Toxoplasma and toxoplasmosis. *Hosp. Pract. 4:* 64-72, 1969; and Feldman, H. A. and Miller, L. T.: Serological study of toxoplasmosis prevalence. *Amer. J. Hyg. 64:*320-35, 1956.

acquired toxoplasmosis in the past may be more seriously threatened—when they are treated with cytotoxic drugs and cortiscosteroids for malignancy, to prevent rejection of organ grafts, etc.

There is an extensive literature on the serodiagnosis of acute toxoplasmosis,[22] and no attempt will be made to review this facet extensively here. It is essential to recognize that in adults the serologic diagnosis of acute acquired toxoplasmosis is complicated by the high prevalence of antibodies in the normal population. The prevalence of dye-test antibody titers in the normal adult population of the United States ranges from approximately 10 to 20% in young adults, to approximately 35 to 70% in older persons (Tables III and IV).[32, 33] Such antibody titers (IgG) usually reach levels of 1,000 to 64,000 or greater during the acute stage, may remain elevated at levels of 1,000 or greater for 10 years or more, and persist at lower titers, usually for the life of the individual.[7]

Although a number of serologic tests have been described for diagnosis of toxoplasmosis in adults, I shall mention briefly only those few which the majority of physicians in the United States should know and which are available to them. The titers in only two of the serologic tests which are now performed routinely can be interpreted with accuracy in an individual case—the Sabin-Feldman dye test and the conventional (indirect) fluorescent antibody test. The complement-fixation test is performed by only a few laboratories in the United States, and mainly for purposes of research. The agglutination test,[34, 35] precipitin

test,[36, 37] and IgM-fluorescent antibody test[38] are still being evaluated. Although the hemagglutination test is used by a number of private and public laboratories and the test is available commercially in the form of a kit, the titers vary widely among different laboratories and often are difficult to interpret. The hemagglutination-test titers usually appear somewhat later than in the dye and fluorescent antibody tests; interpretation can be facilitated if the hemagglutination test is standardized so as to reflect the magnitude of titers found in the dye and fluorescent antibody tests. The hemagglutination test is valuable in surveys but has yet to see its value established in diagnosis of the acute acquired infection in adults, except in the hands of experts in the serology of toxoplasmosis, such as Lunde.[39]

A relatively new method for diagnosis of the acute infection in adults is the IgM-fluorescent antibody method. This is now being used by some state and local laboratories and is being prepared as a kit for commercial distribution. Recent results from a number of different laboratories attest to its diagnostic value.[40-44] This test is based on the fact that in most infections of man, IgM antibodies appear very early and thereafter fall to low titers and may even disappear as IgG antibodies are still rising. In more than 100 cases of acute acquired toxoplasmosis studied in our laboratory, IgM antibodies were demonstrable if the test was performed early in the acute infection. In many instances, the titers remained elevated for several months, thereafter falling to levels of 1:20 or less. In some patients, IgM titers fall to low levels or disappear after one month. This was true in a member of our staff who recently became infected in a laboratory accident, the date of which was known. Since in some cases IgM-antibody titers persist at low levels for a year or longer and in others they disappear early only to appear again later, studies are in progress to define further the variability in the IgM-antibody response in acquired toxoplasmosis and to gain more knowledge about IgM *Toxoplasma* antibodies per se. From the data accumulated up to the present time we consider the demonstration of *Toxoplasma* antibodies (dye test or conventional fluorescent antibody test) in the absence of IgM antibodies in a normal person to reflect infection that has advanced beyond the acute stage. As absence of IgM antibodies almost always signifies that the infection is not acute, once the IgM method has been standardized it should be useful as a screening device in adults in order to determine whether the infection

is acute. An example of its use in this manner has recently been described by Desmonts.[40]

Unfortunately, the major deterrent to rapid acceptance and distribution of this method is the lack of monospecific fluorescein-tagged antisera to IgM. Over a period of several years, we and others have tested the specificity of a number of such antisera, sold by a variety of companies in the United States and Europe. Some of them were, as stated on the label, specific only for IgM. But many had appreciable titers (several greater than 1:1,000) of antibody to IgG, and still others were so dilute as to compromise the sensitivity of the serologic test, thus making them worthless.

Many laboratory directors are unaware that such antisera must be tested for specificity before being applied to clinical specimens. Further, many routine diagnostic laboratories do not have personnel sufficiently trained to evaluate the specificity and sensitivity of the antisera. Even if the laboratory personnel are aware of the requirements for testing, the task is often time-consuming and requires special reagents, such as purified antibody of various immunoglobulin classes. Because the problem is not widely understood, laboratory personnel are apt to accept on faith the assurance of the supplier that the antisera are suitable for diagnostic use. The risk of obtaining false-negative or false-positive results is great.

Any diagnostic method, the results of which are important in the care of patients, must have proper quality control before it is applied clinically. In most routine diagnostic laboratories it is not always feasible to conduct the tests that assure the monospecificity of fluorescein-tagged antisera. This leaves the patient, the physician, and the laboratory at the mercy of the standards of the supplier. This places such reagents in much the same classification as drugs and biological products; they should be under scrutiny and testing by a central authority such as the Division of Biological Standards of the National Institutes of Health. Certification that the antisera meet the most rigid standards of control for specificity and sensitivity must be required of all sera available commercially, and suppliers should be required to conform.[45]

In general, the definitive diagnosis of acute toxoplasmosis can be made readily if the proliferative form of the parasite can be demonstrated histologically in tissues.[22] Such demonstration has been invaluable[39, 46] in biopsies of the brain. A promising method for the demon-

stration of *Toxoplasma* antigen and organisms in tissues obtained by biopsy, such as lymph node, liver, and lung, and tested by the fluorescent antibody method, has been described by a number of laboratories.[25, 47]

Isolation of the parasite from tissue or from blood samples does not necessarily signify that the infection is acute.[22, 48] Cysts persist in human tissue: e.g., muscle, heart, and brain[49, 50] for years and isolation may merely reflect past infection. An exception, still controversial, is the idea that cysts may not persist for years in lymph nodes. When isolation from enlarged nodes is successful, this may reflect acute infection. The criteria for establishing a diagnosis of acute acquired toxoplasmosis have already been published.[22]

Toxoplasmosis is a major problem in the compromised host.[51] *Toxoplasma*—along with *Pneumocystis carinii*, certain fungi, gram negative bacteria, and DNA viruses—has emerged as an important opportunistic pathogen in patients whose resistance to infection is compromised by underlying diseases, such as Hodgkin's disease, non-Hodgkin lymphoma, hematologic malignancy, and systemic lupus erythematosus, or by the drugs employed to treat these diseases: e.g., corticosteroids and cytotoxic agents, or to prevent rejection of organ grafts.[52] Such patients appear to be strongly predisposed not only to initial infection with *Toxoplasma* but to reactivation of the latent infection.

Toxoplasma encysts in many tissues and organs throughout the body. These cysts persist in a latent form in the human host for life.[49, 50] They create a hazard in the immunosuppressed host, not dissimilar to the situation with respect to the tubercle bacillus, *Coccidioides immitis*, herpes simplex, varicella zoster, and cytomegalovirus. It is not clear whether exacerbation (reactivation) is due to uncontrolled multiplication of parasites released from cysts or of organisms which persist within cells of the host in other than the encysted form. The intracellular persistence of the proliferative form of the parasite in man is probable. Evidence for this derives from experimental observations in a number of mammalian species,[53, 54] and persistent parasitemia has been demonstrated in human beings.[48] In addition, there is the constant antigenic stimulus to account for the persistence of *Toxoplasma* antibodies for years after the acute infection. Antigen-specific lymphocyte transformation has been demonstrated in persons who had acquired *Toxoplasma* infection as long as 19 years previously.[55]

Three purposes are obviously important and require the integrity

TABLE V. UNDERLYING CONDITION ASSOCIATED WITH TOXOPLASMOSIS IN 59 PATIENTS

Underlying condition	*No. of cases*
Lymphoma	
Hodgkin's disease	21
Lymphosarcoma	4
Histiocytic lymphoma	1
Lymphogranuloma*	4
Leukemia	
Acute lymphocytic leukemia	4
Chronic lymphocytic leukemia	5
Acute myelogenous leukemia	2
Chronic myelogenous leukemia	4
Myeloid metaplasia	1
Carcinoma	
Ovary	1
Bronchogenic	1
Breast	2
Neuroblastoma	1
Multiple myeloma	1
Malignant melanoma	1
Organ transplant	
Renal	4
Heart	1
Liver	1

*Diagnostic term employed in author's publication.

of both humoral and cellular mechanisms; the continued proliferation of *Toxoplasma* in initial infection must be prevented, latent infections must be debarred from reactivation, and uncontrolled dissemination must be prevented.

Defects in cellular immunity (as in Hodgkin's disease), in inflammatory response (as in acute leukemia), and in antibody formation (as in congenital hypogammaglobulinemia, multiple myeloma, and chronic lymphocytic leukemia) predispose to fatal dissemination in initial infection and in the relapse of a latent infection.This predisposition to uncontrolled dissemination is increased by the use of corticosteroids and cytotoxic drugs.[52] The untoward effect of such treatment on the immune system has been reviewed elsewhere.[56] It should not come as a

TABLE VI. THERAPY FOR UNDERLYING DISEASE IN 59 CASES OF TOXOPLASMOSIS IN COMPROMISED HOSTS

Therapy	*No. of cases*
Cytotoxic drugs	51
Steroids	48
Radiotherapy	37

TABLE VII. SITE OF INVOLVEMENT WITH *TOXOPLASMA* ORGANISMS IN 37 AUTOPSIES OF COMPROMISED HOSTS*

Site	*No. of cases*
Central nervous system	34
Heart	14
Lung	10
Liver	4
Kidney	4
Skeletal muscle	3
Lymph nodes	2
Spleen	2
Bone marrow	3
Other (pancreas, testes, stomach)	4

*In a number of cases, no mention is made as to whether tissues other than brain were examined histologically.

surprise that disseminated toxoplasmosis causes death in such patients, since this parasite is one of the most common latent infectious agents of man the world over.

Sporadic reports of life-threatening infections with *Toxoplasma* in patients with cancer have appeared for several years. The reports of Vietzke et al. from the National Institutes of Health[57] and of Carey and his colleagues from the Memorial Sloan-Kettering Cancer Center in New York[31] have served to emphasize the magnitude of the problem as it occurs in hospitals in which neoplastic disease is treated. Similar reports have begun to appear from groups which deal with transplantation.[58-60] Recently we have had occasion to review numerous published and unpublished cases of toxoplasmosis complicating malignancy and organ transplantation.[61] Although our data are still incomplete, they are presented here to give at least a partial picture of the problem. In Table

TABLE VIII. NEUROLOGICAL SIGNS AND SYMPTOMS IN 37 CASES OF TOXOPLASMOSIS IN COMPROMISED HOSTS

Neurological signs	*Cases*
Confusion, lethargy, or disorientation	14
Motor impairment	12
Obtundation, coma	11
Seizures	9
Headache	5
Abnormal reflexes	6
Vomiting (projectile)	2
Sensory impairment	2

V the underlying condition in 59 such cases is shown. Of the various tumors, lymphoma and leukemia appear to predispose most strongly to the disseminated lethal form of toxoplasmosis. This is exemplified by the recent report of Carey et al.[31] As can be seen in Table VI, the majority of these patients had been treated with immunosuppressive drugs. In Table VII the organ involvement at autopsy is shown in 37 of the patients in whom sufficient data was available. The brain and heart—where acute necrotizing myocarditis is common—were the organs most often involved. Of interest is the fact that each of the six cases described from the National Cancer Institute by Vietzke and his colleagues also showed multiple foci of necrotizing pneumonitis associated with *Toxoplasma*.[57] In at least 37 of the cases there was significant involvement of the central nervous system prior to death; some of the neurologic signs and symptoms in these cases are presented in Table VIII. In some cases the signs were difficult for us to judge, since they may have been associated with either the underlying disease or with concurrent infection caused by other organisms.

As pointed out by Vietzke and his colleagues,[57] in such patients the differential diagnosis of the lesions of the central nervous system must include toxoplasmosis as well as cerebral or dural involvement by tumor, cryptococcosis, progressive multifocal leukoencephalopathy, as well as the more familiar bacterial, viral, and fungal infections, and hemorrhage. Lunde et al. have suggested a realistic approach to the serologic diagnosis of toxoplasmosis in these patients.[39] Despite the great importance of the publication of Vietzke et al., the information which it contains unfortunately has not been disseminated widely enough. The result is

that in such cases toxoplasmosis is not considered; several of the patients might have had their lives prolonged by appropriate treatment. Thus, the diagnosis of toxoplasmosis in these patients is not simply of theoretic interest. Effective drugs are available and if used early enough may prove lifesaving. In all such patients we consider treatment imperative and recommend a loading dose of 100 to 200 mgm. of pyrimethamine on the first day (given in divided doses) and 25 mgm. daily thereafter for at least one month, combined with sulfadiazine or triple sulfonamides in doses of 6 to 8 gm. a day, after a loading dose of 4 to 6 gm. Folinic acid (leucovorin) or yeast or both may be given as suggested by Frenkel[62] to protect the bone marrow. Unfortunately many of these patients are already receiving cytotoxic drugs which are toxic to the bone marrow, or they have ablated marrow awaiting return of—it is hoped—normal elements which may be affected by pyrimethamine.[63] This apparent therapeutic enigma has not been solved and awaits introduction of new and less toxic drugs effective against *Toxoplasma.*

It should be apparent from the above that toxoplasmosis must be considered in the differential diagnosis in any immunosuppressed patient who has clinical or laboratory evidence of damage to the central nervous system. As is the case with many immunosuppressed patients, infection with *Toxoplasma* is frequently associated with other opportunistic pathogens.[52] For instance, in one of our heart-transplant patients at Stanford who came to autopsy, *Toxoplasma* was found in the transplanted heart and in the brain and lung. In addition, *Aspergillus*, *Pneumocystis*, and cytomegalovirus were found at autopsy, and a bacteremia with two gram-negative organisms was present immediately before death.[60] Such cases attest to the severe compromise of resistance which results solely from the use of immunosuppressive drugs. This patient had no underlying disease which might predispose her to infection with opportunistic organisms.

It is hoped that the information presented above will serve to help physicians recognize patients in whom toxoplasmosis should be included in the differential diagnosis. When such patients are recognized, a concerted effort should be made to establish the diagnosis and provide appropriate therapy.

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