Tissue Injury Induced By Candida Albicans

Mental and Neurologic Manifestations

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Introduction

Medical research of the past several decades has greatly expanded our knowledge of the deranged chemistry and physiology that characterize many individual disease states. Yet most diseases have stubbornly resisted the massive effort to unlock the secret of their etiologies. We learn more and more about the abnormalities of function that result in clinical symptoms and signs, but continue to be frustrated in our effort to discover the identity of the factor initiating the departure from normal function. It is unfortunate that the list of such diseases is headed by those that are the most frequent cause of disability and death. Among them would be atherosclerosis, most often clinically expressed as hypertension, heart attacks, and strokes; malignancies, "auto-immune" diseases, arthritis, muscle-wasting diseases, mental and neurologic disorders, and many others.

Frequently the evidence suggests that immunologic mechanisms of tissue injury are involved. The deposition of antigen-antibody complexes or the presence of "auto-antibodies" to one's own tissues are but two examples.

The same "dead end" is reached, however, when the search for a virus or other antigenic agent is unfruitful. The evidence indicates that an immunologic response is taking place and is in some way involved in the disease process, but the antigenic agent continues to elude discovery.

Or we may postulate that the immunologic process occurs secondary to toxic damage to a tissue, leading to autoantibodies and perhaps to antigen-antibody complex deposition. But again, such a toxin escapes detection, if it exists.

In presenting selected, cases treated during the past 16 years, I hope to call attention to Candida Albicans as a possible candidate for the role of etiologic agent in diseases that seem to have an immunologic or toxic basis, but for which no such factor has been discovered. This yeast probably exists in all humans as well as in many animal species. Anti-Candida antibodies are present in 100 percent of humans, as will be discussed later. If studied serially, a high percentage also will yield a positive culture of mucous membrane surfaces, as well as a positive delayed skin test to Candida.

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The very fact of its universal presence probably accounts in large part for the neglect in attempting to relate this yeast to serious disease. Instead, it is today relegated to the role of an aggravating nuisance when it infects mucous membranes, skin, and nails; the one exception is the rare septicemic dissemination to internal organs in the chronically ill, often immuno-compromised host. Since culture, skin test, and serology fail to distinguish between a well person and one in whom Candida is causing illness, there has been no reason to suspect that it may, by an entirely different mechanism, play a far more important role as an agent of tissue injury. By treating yeast infection and yeast allergy intensively where found, it has been possible to demonstrate the relationship between mucous membrane infection and abnormal function in organs distant to the yeast infection and not actually themselves infected. The cases selected for presentation also demonstrate the variety of tissues that may be injured by this mechanism, as judged by the diversity of symptoms and signs that ceased when the mucous membrane infection cleared.

Case Presentations

An incident that occurred in 1961 was the first indication that this organism perhaps is capable of causing disorders much more severe than conventionally attributed to it. A 40-year-old woman whom I was treating for allergic rhinitis and migraine headaches walked into the office with one of her severe headaches. It was readily apparent that she was also quite depressed, which was characteristic of the severe premenstrual symptoms that she experienced for one week each month. Candida Albicans was one of her allergens, and chronic yeast vaginitis worse premenstrually was a prominent complaint. A small dose of Candida extract relieved the headache, but the most startling result of the injection was the rapid and complete disappearance of the depression. Her initial unsmiling, agitated manner was suddenly replaced by a relaxed, smiling countenance. In subsequent months it was possible to duplicate this experience, both in her and in other similar cases of severe premenstrual depression and tension.

My interest then evolved to depression and anxiety not limited to the premenstrual period, and to their relationship to the chronic allergic state and to Candida in particular. I noted that in certain women the premenstrual depression would become so intense that in appearance and response they brought to mind patients with catatonic schizophrenia. I remember remarking at the time that I would like to treat the yeast infection in a schizophrenic patient to see whether there would be any improvement in the mental status if the yeast problem could be brought under control. Four years after the initial incident this opportunity was afforded me, and this patient is presented as Case No. 1.

Case #1

In 1965 a 36-year-old woman with allergic sinus headaches was brought to see me. However, her case was distinctive in that for six years she had been treated for schizophrenia. After many courses of drug and electroshock therapy, her condition had deteriorated to the point that permanent commitment to the state mental hospital had been recommended by her psychiatrist. On checking with him regarding any objection he might have to my treating her headache problem, I was told to go right ahead—that nothing could aggravate her already grave mental condition.

The patient was withdrawn, managing a yes or no answer to questions only after much effort and hesitation, so that the history was obtained from her neighbor and long-time friend. Two weeks after the first injection of extract of Candida Albicans, she was more alert and better able to answer questions. The second injection resulted in marked improvement, such that four weeks after beginning treatment she was doing her own housework, was cheerful, and "even able to get mad again." At seven weeks she stated "I'm myself again"—an appraisal to which her husband acquiesced. Chronic yeast vaginitis and menstrual spotting had stopped with the first injection, a normal

menstrual period occurring on the 26th day of treatment. Stelazine and Elavil had been discontinued at five weeks, the only remaining medication being one Librium capsule in the morning, "but not every day." She had returned to her church activities, and stated that "I'm looking for a job." She was totally asymptomatic except for mild, mid-morning "nervousness" for which she used the Librium capsule when needed. Normal menstrual cycles continued. At 12 weeks she was "taking in ironing" to supplement the family income, in addition to her housework and church activities. Her husband stated "she's sassy now."

A careful history led to the choice of treatment that resulted in this rapid recovery after six years of progressing, chronic mental illness.

Her health had been remarkably good until age 25 years. At that time her second pregnancy was complicated by hypertension and urinary frequency and burning. Following delivery, she developed vaginal discharge and a fungus infection between the fingers of both hands, both conditions recurring repeatedly thereafter.

Between ages 25 and 30 years she remained active and well, and "very energetic." During this interval she continued to have the vaginal discharge and itching and the fungus infection between the fingers. She also began to note repeated sore throat and postnasal drainage. Developing hormone problems were signaled by the onset of excessive menstruation and cramps, loss of libido, and seven to 10 days of premenstrual anxiety and depression. These symptoms would typically abate once her period started and gradually increase as she moved farther into the next cycle.

At age 30 years pain and tenderness in one breast were associated with increasing nervousness. By age 31 years she was under the regular care of a psychiatrist. On tablets prescribed by him she remained active, but with occasional "quiet spells." The premenstrual tension progressed both in severity and duration. By age 33 years the depression was severe. She stopped church activities. Headaches and back pain began.

Even as her overall condition became worse, she would still improve for seven to 10 days once her period started. Her friend stated "her face clears," "she's more active," "doesn't sit and hold her hands—not as clumsy; before her period she drops almost everything she picks up." "After her period starts it is easier to rouse her." "When I fuss at her, I think she hears me."

Physical symptoms by this time included pain in the left shoulder and back, episodes of marked abdominal distention, sore throat and headaches, fungus infection between the fingers, chronic nausea and puffiness of the eyelids, and the chronic yeast vaginitis.

The next two years saw progression of these mental and physical symptoms. Shock treatment would seem to help for three to four weeks only. One month before her first visit to me eight shock treatments helped "for a few hours—then right back down." At this point they were discontinued. Premarin, because of three months of menstrual spotting, Stelazine, Elavil, and Librium were the prescribed medications at the time her allergy treatment was begun.

This woman was treated for one year with nothing other than the Candida Albicans extract. Follow up 10 years later found her well. Three years after her Candida treatment was discontinued, she had a transient episode of mild depression which cleared quickly when her psychiatrist gave her three shock treatments as an outpatient. She had remained well for the next seven years.

This case will be discussed further later. It is of note that vaginitis and fungus infections of the fingers, both following her second pregnancy, were the earliest indicators of a change from her previously normal physiologic state, and heralded 10 years of steady deterioration in hormone function and mental status.

Review of Conventional Role

Candida Albicans enters and colonizes newborn infants during or soon after birth. This event may be evidenced clinically as oral thrush, but in the vast majority of cases it escapes clinical detection. Nevertheless, that it occurs is apparent from the fact that by age six months, 90 percent of babies have developed a positive delayed skin test.

This, together with the simultaneous development of humoral antibodies, indicates that T- as well as B-lymphocytes have participated in the immunologic response to this yeast.

Thus soon after birth the stage is set for a lifelong battle between this yeast and the human body. That this continues throughout life is confirmed by the presence at any age of the same high incidence of immunologic response, as well as by the frequency of recurring clinical yeast infections. If we consider the fluctuating levels of humoral antibody together with the alternating pattern of positive and negative cultures of the mucosal surfaces in a given individual, the ebb and flow of the host-parasite struggle is evident. Many factors favor the yeast in its attempt to extend its total area of mucosal involvement. We may have had its growth under reasonably good immunologic control, only to have such a factor (e.g., antibiotic therapy) lead to a breakdown in this control. This may be mild or severe and may be easy or difficult to reverse. Few if any individuals over a lifetime escape repeated encounters of this type. From what is known about the genetic control of the immune response, we might predict wide variation among individuals in their ability to keep yeast growth under control; and indeed, this prediction is borne out by clinical experience.

The next point for consideration is the effect that such yeast growth has on the host. Turning to the most recent edition of the standard textbooks of medicine, we find Candida Albicans described as a fungus of widespread occurrence, usually of no importance other than for the discomfort it causes on mucosal surfaces (and occasionally the skin and nails), chief of which are soreness of the mouth, diarrhea or rectal itching, and vaginal discharge or itching. The one exception to this assigned role as a relatively minor nuisance is Candida septicemia, whereby the yeast may be disseminated throughout the body, leading to serious or fatal consequences. This occurrence is usually ascribed to a concomitant severe illness, often one associated with general immunosuppression, e.g., leukemia.

Hypothesis

The response to an anti-Candida therapeutic program, as illustrated by the cases selected for presentation, suggests the existence of an additional mechanism by which Candida may lead to symptoms. These may range from mild to severe and may represent disturbed function in a variety of tissues. In terms of human disability, both mental and physical, symptoms induced by this mechanism far outweigh the minor nuisance of mucous membrane colonization by yeast.

The distinguishing feature of this type symptom is its origin in a tissue remote from actual yeast colonization. Abnormal function in a tissue results rather from the release of yeast products into the bloodstream of the host. That at least some of these factors are antigenic is evidenced by the response of both T- and B-lymphocytes; however, there is no reason to assume that all are antigenic, or that the resulting abnormal function is necessarily mediated by immune mechanisms. The important distinction is that chronic colonization of mucous membranes may lead to serious illness apart from the purely local symptoms of soreness, itching, discharge, or diarrhea.

Possible ways in which yeast products may lead to such a result will be considered following the case presentations. Conceding for the moment the existence of such a mechanism, it becomes apparent that the proper approach to terminating such a situation is to drive the yeast out of the tissues wherever it has been able to establish itself. Although anti-yeast drug therapy and possibly diet help accomplish this, ultimate success must depend on immunological techniques designed to reestablish a competent defense against this infectious agent. The antigenic nature of Candida Albicans and the immunologic response of the human to it will be discussed in detail later. At this time, since it is an integral part of the postulated mechanism, a brief description will be given of the phenomenon of immunologic tolerance, or unresponsiveness, as it may apply in this instance.

It is possible to render an animal

unresponsive to an antigen by exposing it more or less continually to this antigen. This may be carried out with very high doses of antigen—called "high-zone tolerance"—or with very low doses, "low-zone tolerance." High-zone tolerance tends to render unresponsive both T- and B-cells, whereas low-zone tolerance weakens or blocks the T-cell response only. Thus the cellular immune response (T-cell) is more easily blocked, and such blockage is easier to sustain than is the humoral (B-cell) response. Furthermore, unresponsiveness (or "tolerance") is easier to induce with soluble than with aggregated antigens.

Thus immunologic tolerance is most readily achieved by more or less continual exposure to a soluble antigen, with T-cell paralysis being much easier to achieve and sustain.

When mucous membranes are chronically infected by yeast, cells of the immune system are exposed continually to Candida antigens, thus satisfying the conditions for tolerance induction. This weakened immunologic response allows the yeast to thrive in the tissues, and a vicious cycle is established. An analagous situation has been reported in lepromatous leprosy. In this, the widely disseminated form of leprosy, impairment of the immune response has been demonstrated in vivo by reversion to negative of the lepromin skin test, and in vitro both by impairment of the lymphocyte transformation test on exposure to the leprosy bacillus or phytohemagglu-tinin, and release of the migration inhibitory factor on exposure to the bacillus. In the tuberculoid form of leprosy, however, this does not occur. This is the localized form of the disease, which carries a good prognosis. Thus widespread involvement is associated with impairment of the immune response.

With Candida infection, as with leprosy, there may be for each individual a critical point beyond which the total area of involvement is such that the antigenic stimulus paralyzes rather than stimulates the immune system, particularly the T-cell com-partment. Until this state of immunologic unresponsiveness is broken, drug therapy of the yeast infection will be less than fully effective. This chronic state of depressed immunity allows the infectious agent to thrive and to continue to release its own products, antigenic or otherwise, into the bloodstream. If indeed such yeast products have the capacity to injure tissues in the various organs of the body, the requisites for chronic disease are present. The continued elaboration of the injurious agent is assured by an impairment of the immune response, which in turn is perpetuated by the organism elaborating the injurious factor. The clinical manifestations of chronic illness will reflect the abnormal function in the particular tissues involved. Genetic factors may be of primary importance in determining which tissues will react in a given individual.

The cases selected for presentation demonstrate the wide range of tissues and organs that may be involved, either in a given patient or among a group of patients.

This hypothesis allows the seemingly unrelated conditions represented by these cases to be tied together by a common mechanism. We have only to keep in mind that perhaps no tissue or organ is safe from such injury in order to understand how symptoms related to such diverse areas of the body as brain, skin, muscles and joints, and internal organs can respond to the same form of treatment.

Case#1

The case presented at the beginning of this paper illustrated the severity that symptoms may reach in this syndrome. It will be discussed in more detail later, but first I would like to present a less complicated case that demonstrates the principles outlined in the previously presented hypothesis.

Case #2

This young white woman was relatively free of health problems until 24 years of age. The one exception was hay fever present since childhood, nonseasonal, and aggravated by windy or damp weather and damp, musty places.

She and two other healthy young women working in the same office became ill with vomiting and diarrhea. Her two fellow-

workers recovered in the usual two to three days, but when I first saw her three years later, the patient had never returned to her former state of good health. Unlike her two friends, she had consulted her physician, who had prescribed tetracycline for the intestinal flu symptoms. She promptly developed yeast vaginitis which recurred intermittently during the next three years. Within six months she developed severe constipation. X-rays showed "megacolon." She began to have episodes of marked abdominal distention, associated with anxiety and depression. She also had noted the onset of premenstrual tension of three days' duration; this had never been a problem for her prior to the present illness. This is an important point which will be considered later. Proctoscopic examination and colon x-ray were unremarkable at the time of her initial work-up with the exception of internal and external hemorrhoids.

In order to test the idea that her three-year illness was due to Candida Albicans, and because with injection therapy there is always the possibility of nonspecific stimulation of the immune system, I chose to treat this patient only with nystatin. The sole effect of this drug is to suppress yeast growth; it is the most widely used drug for this purpose. It is used in tablet form for intestinal, suppository for vaginal, and suspension for oral yeast infections; in addition, it may be used topically for skin and nail involvement. It is absorbed from the intestine in such small amount that it is of no value for treating Candida infections of the internal organs. In fact, if it were absorbed in the small intestine, it would not reach the large intestine and would therefore be ineffective in treating yeast growth in the bowel.

Since pharmacologically this drug has no effect other than to suppress yeast growth on mucosal and skin surfaces, any symptoms that are cleared by its administration may be presumed to have been caused by yeast. This would apply not only to symptoms and signs related to the skin and mucous membrane colonization, but more importantly to those arising in an organ itself not infected by this fungus.

In this young woman I hoped to determine whether clearing the mucous membrane involvement in the colon and vagina would be possible with nystatin alone, and if it were, whether the central nervous system symptoms of anxiety and depression would clear. She responded quickly to this therapy; in 10 days she was totally free of all symptoms and having normal bowel movements. I discontinued treatment and within two days all symptoms returned, only to cease quickly on resumption of treatment. After three weeks without symptoms, I halved the dose from 16 to eight tablets per day. She again relapsed and again quickly cleared on return to the original dose. After another six weeks of symptom-free therapy with four tablets four times a day and one vaginal suppository twice daily, she remained well when treatment was stopped. At the time of my last contact with her one year later, she was well. Her follow-up letter to me at that time concluded with the following statement, "I personally feel that I have had a complete recovery since I no longer have any problem with waste elimination and my nerves and hay fever have caused me no trouble since I finished taking the pill which you prescribed."

Discussion of Case #2

Because of her remarkable freedom from illness of any kind until age 24 years, except for her mild hay fever, we may assume a well-functioning immunologic system, and a genetically determined ability to contain yeast in an effective way. The stimulation by tetracycline enabled the yeast to initiate the colonization of her mucous membranes and thus begin releasing its products into her bloodstream. That she soon became unable to mount an effective immunologic response to the yeast is indicated by increasing colonization in the colon and vagina. Whether or not skin and in vitro tests are adequate to document it, we must assume that her immune response to yeast had been impaired to a degree sufficient to prevent her from regaining her previous control of this infectious agent.

Also illustrated in this case are the two mechanisms of symptom induction. She suffered from conventional local symptoms

due to mucous membrane infection (constipation, abdominal distention, vaginal discharge, and itching) as well as central nervous system symptoms of depression and anxiety. Indeed, she could tolerate the symptoms of local infection much better than the anxiety and depression, of which she complained bitterly.

The recurrence of symptoms when the nystatin was discontinued prematurely and again when the dose was halved indicate that relief of both local and remote symptoms depends upon an adequate dose administered for a sufficient length of time.

This woman remained well as of the last follow up one year after treatment was discontinued. It is unusual to achieve this result with nystatin alone. Usually immunotherapy with Candida vaccine is required. But this case does illustrate in an uncomplicated way the manner in which a healthy person may become chronically ill when some factor leads to a breakdown in yeast control; how the involvement may be local or at sites distant to the yeast growth; and how the patient's immune control of the infection may be re-established, if given the opportunity, by adequate suppression of the yeast for a sufficient length of time.

Case #3

The next case is chosen to illustrate an inflammatory response in tissue distant to the site of yeast colonization. This 66-year-old man had been in excellent health until seven years before his first visit. At that time a skin lesion developed on the inner aspect of the left forearm just below the elbow. It was purple, about two inches long, one inch wide, raised one-half inch above the skin surface, and very firm. During these seven years it had not varied, and had been biopsied three times. The first was read as "lupus erythematosus"; the second as "an intense lymphocytic infiltrate"; the third "about like the first." I was able to secure the pathology report only of the second biopsy. It described "perivascular lymphocytosis, marked—suggest absolute lymphocyte count of blood and lymph node to rule out leukemia. The perivascular collections are quite prominent."

Five years earlier, which was two years after the appearance of the skin lesion, he developed exertional dyspnea with wheezing. He had never smoked. Examination and x-rays revealed no cause. His exercise tolerance had previously been exceptionally good.

Finally, three years earlier and now four years after the skin lesion had appeared, he developed what was diagnosed as "mucous colitis." A gluten-free diet helped only slightly. No cause could be found.

Thus over a seven-year period he had the sequential appearance of a skin lesion undiagnosable by three different pathologists on biopsy; dyspnea and wheezing; and the alternating diarrhea and constipation of mucous colitis.

Nystatin was started in a dose of four tablets four times daily. He reported that within 24 hours there was dramatic relief of the intestinal symptoms and within three to four days "25 percent improvement in the shortness of breath." The skin lesion became much less intense in color and less elevated. Two weeks later it was smaller, the stools were normal, and the dyspnea much better. After 10 weeks of nystatin therapy, still on a dose of four tablets four times a day, the skin lesion had disappeared and the bowel movements remained normal. The wheezing had ceased, and the exertional dyspnea was "75 percent gone."

After 12 weeks of therapy with nystatin, weekly infections of Candida extract were added because of the residual dyspnea. Six weeks later he stated that the respiratory difficulty had ceased. Treatment was continued for one year with no further recurrence of any symptom.

There was no precipitating incident to account for the onset of the present illness. The only antibiotic therapy he could recall had been three years before the appearance of the tumor. There was no history of allergy except for a penicillin reaction 20 years earlier.

Although this patient had no symptoms to implicate the central nervous system, he did have involvement of two areas distant to the yeast infection. The immediate response to nystatin indicates that the "mucous colitis"

was probably chronic yeast growth in the colon. Participation of the skin and the respiratory system in the response to the yeast infection illustrates tissue changes resulting not from yeast colonization, but from a different mechanism. This conclusion seems inescapable since the nystatin, due to its negligible absorption from the intestinal tract, would not be available in the skin and lungs. Resolution of the inflammation in these tissues, therefore, must have been secondary to the clearing of the infection in the intestine.

Case #4

The next is a case in which the central nervous system was involved. It illustrates the severity of symptoms that may result when it is the tissue of the brain that is reacting, since this young woman shot herself three times in the chest. She survived after weeks in intensive care following surgery to remove a bullet that had lodged in her heart.

I first heard of this 36-year-old registered nurse from her sister, a physician's wife who was already under my care, who told me over a period of months of the family's increasing concern for her sister's steadily progressing mental depression. She was seeing a psychiatrist regularly. At the request of the family, and after securing her psychiatrist's permission, I agreed to see her with the stipulation that she miss none of her appointments with her psychiatrist.

The initial history revealed four months of rapidly progressing depression. Preceding by several weeks the onset of the depression was gross urinary bleeding with clots. Over the next few weeks she passed several kidney stones and exhibited gross or microscopic hematuria almost continually. Wide fluctuations of weight—as much as 20 pounds—would occur over a several-day period. She had first passed kidney stones at age 25 years when six weeks pregnant. She passed several more stones in the ensuing six years.

Past history revealed grossly abnormal menstrual cycles from age 14 years, with irregularity, clots, cramps, and premenstrual tension. An 11-month period of amenorrhea preceded her only pregnancy, which was marked by pre-eclampsia at three months with hypertension, albuminuria, and gain in weight from 140 pounds to 193 pounds. One year after delivery her weight was down to 125 pounds and she felt fairly well. These evidences of severe hormone dysfunction are significant and will be considered in detail later.

Past allergies were limited to mild allergic rhinitis in the fall and winter and multiple drug allergies.

Detailed questioning concerning problems with yeast revealed the following: At nine years of age she had oral thrush requiring treatment, during which two permanent teeth "just came out." At this same age she began to have three to four bowel movements almost daily. A history of "colitis" as an infant may be significant. Within the year after her pregnancy she developed yeast vaginitis from antibiotics.

Her own description of herself at the time of her first visit was as follows: "My memory has become very poor in the past four months; it used to be excellent." "I despise my husband and child when I'm like this; as soon as they come in the door I scream at them over just anything; I don't appreciate anything."

Her initial skin tests were just slightly positive to molds, dust, and grass. Treatment was started immediately with Candida Albicans extract. Her second visit was two weeks later. She and her husband reported "great improvement" in mood; also of great interest was the fact that the kidney symptoms ceased and the urinalysis became clear of blood for 11 days after beginning the injections. Four weeks after treatment was begun, she reported "10 perfect days; then slight wheezing the past three to four days."

Now we come to an incredible occurrence. It is difficult to see how such a thing could happen, but for two months she did not return. Since she was feeling so well when last seen, and lived 220 miles away, I assumed from week to week that she was just postponing her next visit. The unbelievable fact was that no one in her family realized that she was no longer coming.

One day my phone rang. It was the

patient's sister, informing me of the near-fatal suicide attempt. After heroic surgical measures had saved her life, I was asked to resume her treatment. Again I left it up to her psychiatrist, and again he approved.

She lost 13 pounds with the first injection of Candida Albicans extract, and her depression cleared. During the next six weeks she felt extremely well, complaining only of "hot flashes" (remember the lifelong hormone problems). The extent of her improvement was indicated when her psychiatrist told her "you don't need me anymore," and to my amazement, dismissed her. Some four months after the suicide attempt, she was working regularly and soon became administrator of a 300-bed nursing home. It is now 11 years later. She has been treated without interruption, receiving Candida injections weekly. After nine years on Candida vaccine alone, I added dust, pollen, and airborne mold extracts because of some trouble with hay fever, which was in itself mild, but caused her to have hot flashes that were more troublesome than the hay fever. During these 11 years we really have had no significant problems. She has worked throughout, never feeling any indication of the old symptoms returning.

Before considering this case further, I would like at this point to discuss briefly one of the mechanisms that seems to be involved in the production of these symptoms of brain dysfunction. This consists of interference with sex hormone function, particularly in women. In the cases presented thus far, I have stressed premenstrual tension and abnormalities of hormone function as manifested by disturbances in the menstrual cycle. In almost every case I have treated, symptoms referrable to poor hormone function are among the most prominent and most intolerable to the female patient.

There is no interference with hormone production by the ovaries. The serum level and 24-hour urinary output of estrogen are normal, but there is much evidence that the tissues are not responding to this estrogen in the usual way. Skin becomes rough, dry, scaly, and prone to acne. Decreased fullness of the breasts frequently is noted, with loss of sensitivity of the nipples. Improper stimulation of the endometrium is manifested by menorrhagia, metrorrhagia, clots, and dysmenorrhea. Periods may be too close together, or too far apart. The vaginal smear often reveals poor cor-nification, and vaginal candidiasis is present on a chronic recurring basis in most patients. But by far the most devastating to the unfortunate woman with this problem are the irritability, emotional lability, mental depression, and general inability to function. Total loss of libido is particularly prominent, often adding strained marital relations to the rest of her problems. The typical woman who has reached this point has been referred to a psychiatrist with the belief that the mental problem is primary. In reality, the mental symptoms are merely the manifestation of aberrant function within the central nervous system, just as the bleeding disorders are indicators of abnormal uterine function. This interference with hormone function in the chronically allergic patient will be discussed in detail later. It is presented briefly at this point so that it may be pointed out as these cases are discussed.

Returning now to the last case presented, we recall the history of colitis as an infant and oral thrush at age nine years with the onset of several bowel movements per day. It is probable, therefore, that chronic yeast infection preceded the onset of her hormone cycle at age 14 years. Her cycles were never normal, and finally a hysterectomy was performed at age 32 years. Her only pregnancy occurred following 11 months without a period. Severe pre-eclampsia complicated her pregnancy from the third month. Hot flashes have occurred from time to time when she was troubled with hay fever.

It is not possible to say what precipitated the final plunge into severe depression. I have been unable to ascertain whether antibiotics were given when the stones and hematuria were such problems about the time the depression began to progress. It is of interest that the kidney symptoms and hematuria ceased when Candida therapy was initiated, and that this same phenomenon occurred later in her father (Case #5).

This patient's psychiatrist had diagnosed

"manic depression and schizophrenia." The case presented at the beginning of the paper had been diagnosed "schizophrenia." Other psychiatrists might have given different names to the illnesses that nearly wrecked the lives of these two women. It doesn't seem too important what name we give to these groupings of symptoms that indicate advanced deterioration in brain physiology. What is important is that such symptoms cleared completely when Candida immunotherapy was instituted, and in one of the two recurred to the point of a nearly fatal suicide attempt when treatment was interrupted, again to clear quickly and completely when therapy was reinstituted.

Case #5

This 60-year-old man developed severe chronic inflammation of the eye that resisted all forms of treatment. This had its onset following Declomycin therapy and had been present for three months when oral nystatin therapy was begun. Within three days there was marked diminution of the inflammation; it had cleared completely after eight weeks of therapy.

Severe constipation and lethargy that had been present at the time nystatin was begun were relieved almost immediately. He has continued two to four nystatin tablets daily for 12 years and remained well. Efforts to discontinue therapy invariably resulted in return of the lethargy and constipation, although not the conjunctivitis.

History in this man revealed 20 years of intermittent antibiotic therapy for chronic urinary tract infection in association with multiple kidney stones. Stones had been removed from each kidney, and many stones had been passed. The urine was reported as "4+ for pus cells" during the three years preceding the administration of nystatin, often with concomitant gross or microscopic hematuria.

Three months after beginning anti-yeast therapy, the urinalysis was normal. There has been no recurrence of kidney infection or stones during these 12 years on nystatin. There is no clue as to why this longstanding renal problem cleared so abruptly. Speculation that this unexpected development was indeed related to bringing the

chronic yeast infection under control is strengthened by an almost identical result in his daughter. This was Case #4, the 36-year-old depressed woman who shot herself in the chest. She had passed kidney stones intermittently starting at 26 years of age. Gross urinary bleeding of several weeks' duration, with the passage of several stones, preceded the onset of mental depression. As the depression deepened, her urinary problem continued unabated, and this was the situation when treatment with Candida extract was begun. The urinary symptoms and signs ceased within the first month of treatment and have not recurred during the ensuing 11 years of excellent health.

The abrupt, sustained cessation of the formation and passage of renal stones with the associated infection and hematuria, in this father-daughter pair, is intriguing. The probability of this occurring coincidentalfy rather than as a result of anti-Candida therapy seems remote. More likely is that the condition in each one was in some way related to their long-standing battle with Candida, and that genetic factors were decisive in determining that this particular organ-system would be involved.

Discussion of Case #5

In this case we again see demonstrated the clearing of a chronic inflammatory response by oral nystatin therapy. The conjunctivitis had proved intractable to antibiotic and steroid therapy. Since the involved tissue was the eye, we had another opportunity to actually see a tissue that by some mechanism was responding to Candida products as had been true of the lymphoid tumor of the arm in Case #3. In both instances resolution of the inflammation began almost at once following suppression of intestinal yeast by oral nystatin. Once again a return to normal colon function coincided with clearing an inflammatory response in a tissue inaccessible to nystatin in the form given.

This man did not demonstrate symptoms to indicate a reaction in brain tissue. His case was included because of the location of the inflamed tissue on the surface of the body. The conjunctivitis in this man and the lymphoid tumor in Case#3 were visible

examples of the inflammatory response of tissues remote from the site of yeast colonization. Because of their surface location, we could actually watch the resolution of the inflammation resulting from oral nystatin therapy. Similar processes in the internal organs, including the brain, may be part of the explanation of symptom-production in these sites.

Case #6

This 30-year-old woman developed a visual field defect in one eye on November 13, 1972, 12 months before the onset of numbness and tingling of both lower extremities from the feet to the pelvic area. The legs felt "slick" when rubbed together during this time. Symptoms gradually subsided after 10 days, to recur in the feet within three to four weeks. Numbness and tingling now also involved the hands, beginning simultaneously in the fingers of each hand and extending up the arms and into the chest area. Gradual improvement resulted in residual symptoms confined to the hands and feet, with "spot numbness" on the chest.

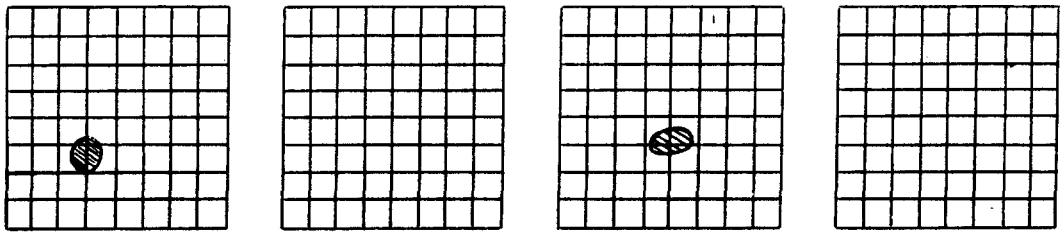
Neurological examination was unremarkable except for "some diminution in the abdominal reflexes and some unsteadiness on standing on either foot." Laboratory, x-ray, and spinal fluid studies were normal except for slight elevation of spinal fluid protein. The diagnosis of multiple sclerosis was made and discussed with the patient by her neurologist; vitamins were the only prescription.

Her opthalmologist reported the following findings: "The patient was seen originally on November 13, 1972, with a minimal visual field defect to an Amsler grid. The peripheral visual field was normal. At that time she had a vitreous detachment in the left eye with a slight wrinkling of the internal limiting membrane close to the macula corresponding to the Amsler distortion. The vision in the right eye was 20/20 and in the left eye was 20/25 with correction. She was seen again in May of 1975 with 20/20 central vision and no defect on the Amsler grid. In February of 1976, she had 20/20 vision and a slight inferior defect on the Amsler grid. In March of 1977, her vision was 20/20 and there was no Amsler defect."

The patient immediately came to me for evaluation of long-standing manifestations of allergy, with the hope that perhaps her neurologic abnormalities were related.

When the history was taken from an allergist's viewpoint, with emphasis on symptoms that might suggest a problem in coping with yeast, a different picture emerged. Perennial allergic rhinitis "all my life" led to numerous respiratory infections, at times accompanied by wheezing. Her hormone cycle had always been abnormal, including marked premenstrual tension and "paranoia." Patient states, "I was completely flat-chested and had hair growth on the lip and chin." The first four months of her only pregnancy, two years before onset of the neurological disorder, "I felt like I was losing my mind; I did not want to be around anyone." Severe constipation accompanied the entire pregnancy. Postpartum depression was severe.

One year before the onset of numbness and tingling in the extremities she developed a "blind spot" in the left eye; this had persisted for several weeks. Extreme fatigue began at the same time. Both symptoms began during a severe lung infection that lasted for four months and for which much antibiotic was given. The bowel movements had become looser, and diarrhea occurred at the time of onset of the



numbness and tingling. There was a history of blood in the stools intermittently as a teen-ager. Colon x-ray at age 21 years was normal. A vaginal yeast infection occurred 10 months before onset of the paresthesias (two months after the initial visual field defect). She also could recall episodes of vaginal discharge in childhood.

Again the total picture is one of lifelong allergy, chronic intestinal and vaginal symptoms, and poor hormone function. Many courses of antibiotic were administered from childhood on. The initial neurological symptom occurred during massive antibiotic therapy over a four-month period for the severe lung infection.

Therapy with oral and vaginal nystatin was begun three months after onset of the paresthesias, which was 15 months after the visual field defect. Improvement in energy was apparent early in treatment. It was 10 weeks before the bowel movements became normal. During the next two years of almost continuous nystatin therapy improvement was steady. The visual field defect cleared completely on examination, but recurred later.

After two years of nystatin therapy neurological examination was "entirely normal." The nystatin was discontinued. Within three to four months the menstrual periods, which had become normal at 29-32 day intervals, again increased to as much as 50-day intervals. The next two cycles were associated with paresthesias for about four days premenstrually. Also two days of vaginal bleeding and itching occurred around ovulation time in each of the last two cycles. There have been no acute attacks as severe as before nystatin treatment was begun. Mild exacerbations were noted when symptoms of vaginal or colon candidiasis increased.

Next she noted intermittent loose bowel movements; a definite decrease in energy was noted; and most important, numbness and tingling of all extremities and in the eyeball reappeared. This time she also noted soreness of the gums and small white spots on the gums. Nystatin therapy was started with tablets, vaginal suppositories, and oral suspension (to be used as a mouthwash). Improvement both in energy and local membrane symptoms again occurred quickly. Paresthesias had begun to decrease at the time of this writing, which was eight weeks after reinstitution of nystatin therapy.

Discussion of Host-Parasite Relationships

Except for occasional intra-uterine infection, colonization of the human body by Candida Albicans begins during passage through the vagina and increases very rapidly during the ensuing four weeks. In a study of 140 full-term normal babies, Russell and Lay (1973) found positive oral cultures in 5.7 percent of babies on the day of birth; by four weeks this had increased to 82 percent and by one year had decreased to 50 percent. These figures are probably low, since it is known that repeated cultures in the same individual may be alternately positive and negative.

By six months of age the immunologic response to first contact with this yeast has resulted in the development of a positive delayed skin test in 90 percent of infants. Many studies indicate that this test of cellular immunity remains positive throughout life in approximately this same percent of individuals.

Antibody formation has begun by three months of age in 9 percent of normal infants. This rises to 80 percent by the school years (Winner and Hurley, 1964). These studies were done before the much more sensitive immunologic techniques available today. Thus Axelsen (1976), using quantitative immunoelectrophoresis to Candida antigen 78, found antibody in 163 of 169 "normal controls" in unconcentrated sera. Chew and Theus (1967) had found precipitins to the mannan cell-wall antigen of Candida in 48 percent of unconcentrated sera from healthy adults. When the immunoglobulins were concentrated 15 times, precipitins were found in 100 percent of sera from these adults. Axelsen suggests that these findings indicate that differences in antibody response of candidiasis patients and controls may be quantitative rather than qualitative, and support the common belief that all, or practically all, humans have

responded to antigens of Candida Albicans by virtue of contact with this microorganism.

Candida vaginitis was shown by Stanley and Hurley (Budtz-Jorgensen, 1973) to stimulate the production of Candida precipitins. Waldman (Bach, 1971) showed that intravaginal application of Candida vaccine resulted in a rise in serum precipitin levels and in IgA precipitins in vaginal secretions.

Thus, whether we look at antibody levels, cutlures of mucosal surfaces, or the cellular immune response as represented by the delayed skin test, a picture begins to emerge of early and lifelong contact with this yeast. As the total exposure to yeast varies from time to time, so too will these parameters of the body's immunologic response. Modifying factors that enhance yeast growth in the body result in an increased antigenic load reaching the cells of the immune system. In response to this stimulus, cells in both compartments of the immune system proliferate, and each is capable of modifying the response of the other. Depending on whether suppressor or helper effects predominate, the T-cells may inhibit or stimulate antibody formation. In turn, by such phenomena as immunologic enhancement, antibodies may influence the cellular immune response.

Cultures will become negative or remain positive, depending upon whether the net effect of the responses has resulted in immunity or tolerance. Undoubtedly important in determining which outcome prevails are the immunologic status of the host, the nature of the antigens, and the manner in which they are presented to the immune system.

Immunology of Candida Albicans Candida Antigens

This subject has been recently reviewed by Axelsen (1976). Seventy-nine distinct, immunologically definable antigenic determinants have been demonstrated for Candida; this is the largest number yet found in any organism. The cell wall contains one principal antigen, mannan, which is a polymer of the sugar, mannose; water-soluble extracts of the yeast phase yield the *77* cytoplasmic antigens. In addition, the mycelial phase contains at least one antigen not demonstrated in the yeast form. Fourteen of these antigens have been found to have enzymatic activity, while nothing is known of the function of the remainder. Only mannan and a few of the cytoplasmic antigens have been purified. Most studies have used water extracts of the disrupted yeast phase, containing in some instances approximately 30 of the known Candida antigens.

Immunologic Response to Candida Antigens

With an organism of such antigenic complexity, it is not surprising that the precipitin response is equally complex. The pattern of response will vary among individuals, both in the rabbit and in the human. Antibodies of IgG, IgA, and IgE classes have been demonstrated. The pattern of antibody response will vary as the antigen load changes qualitatively and quantitatively. The role of antibody in defense against Candida invasion is uncertain.

Many types of evidence indicate that the cellular immune response is the more important in resistance to Candida. In syndromes characterized by deficiency of the thymus, yeast infection is prevalent. In conditions characterized by inability to form antibodies, yeast is not a problem (e.g., agammaglobulinemia). If a previously healthy individual develops a disease that compromises the cellular immune response, there is a strong likelihood of a yeast infection which is usually resistant to anti-fungal therapy. In the limited number of cases in which it has been possible to repair the defect in cellular immunity with transplants of thymus or bone marrow, or administration of transfer factor, the yeast infection has cleared.

Budtz-Jorgensen (1973) studied the serum agglutinins in 180 subjects, as well as the cellular immune response as measured in vitro by the production of the migration inhibitors factory (MIF). In addition to normal controls, 55 patients had Candida-induced denture stomatitis while others had traumatic (non-Candida) stomatitis. Others had Candida vaginitis, dermatitis, Candida

leukoplakia, and chronic mucocutaneous candidiasis. Candida-induced denture stomatitis exists in two forms, termed simple and granular. The simple is characterized by a general erythema and inflammatory response. The granular type is more extensive and shows less inflammation. The percentage of patients in each group exhibiting a positive cellular immune response as measured by the MIF test was as follows: normal controls, 50 percent; traumatic (non-Candidal) stomatitis, 94 percent; Candida vaginitis, 80 percent; Candida dermatitis, 67 percent; simple Candida stomatitis, 76 percent; granular Candida stomatitis, 28 percent; leukoplakia and chronic mucocutaneous candidiasis, 0 percent.

Antibody response increased as the level of cellular response decreased in the various groups. In other words, in the syndromes characterized by impairment of cellular immunity, antibody titers are much higher, so that in patients with chronic mucocutaneous candidiasis, levels are as high as those reached in rabbits during the production of Candida antisera.

In 12 patients the palatal candidiasis was treated topically for one week with am-photeracin B. In all 12 cases, marked inhibition of leucocyte migration was found after treatment, indicating that suppression of yeast growth resulted in restoration of the cellular immune response. Showing the greatest increase were those in whom the cellular immunity was most depressed prior to treatment.

Several important aspects of the immune response to Candida are illustrated in this study. It appears that up to a point the T-cells respond to Candida; as the antigenic load increases (or perhaps changes-qualitatively) there is a progressive impairment of cellular immunity, associated with an increase in antibody response. This reaches its peak in chronic mucocutaneous candidiasis, as evidenced by high antibody levels together with total absence of in vitro MIF production.

Following suppression of yeast by topical therapy for denture stomatitis, and by systemic as well as topical treatment in chronic mucocutaneous candidiasis, the MIF response returned to normal. As the yeast growth gradually returned in the cases of chronic mucocutaneous candidiasis, once therapy was stopped, the cellular immune response again ceased as measured by the MIF test.

In an effort to clarify the sequence and relationship of the humoral and cellular response to Candida, Budtz-Jorgensen (1973) induced candidiasis of the palate in monkeys both with and without prior treatment with azathioprine, an inhibitor of the T-cell response.

In the untreated monkeys, migration inhibition was significant in one week and lasted five months, indicating an early and persistent response within the T-cell compartment. In two weeks the Candidal lesions had healed. Antibody could not be detected until four weeks, after which the antibody level continued to rise for eight months (at which time the experiment was terminated). As the antibody level rose, the MJF response decreased. At the end of eight months the MIF response was back to the pre-infection level, but the antibody titer was at its peak.

Palatal smears during the two-week infection showed acute inflammation and a moderate number of hyphae of Candida. By culture as well as biopsy, the lesions were healed in two weeks, which was a full two weeks before the antibody response was first detectable.

When a similar group of monkeys was pretreated with azathioprine, a different response ensued. It should be noted that azathioprine acts selectively on T-lymphocytes while having no effect on antibody formation. This effect is transient, the immunosuppression decreasing by 75 percent within 12 hours after administration (Bach, 1971; Bach and Dardenne, 1971; Bach etal., 1972).

In this group of monkeys the antibody response was earlier and strong, beginning at two weeks (while the animals were still receiving azathioprine), reaching a maximum titer in three to four weeks, and declining thereafter. (This titer had been reached only after eight months in the normal monkeys.) The onset of MIF production was delayed three to six weeks; in each case

it did not occur until one week after cessation of immunosuppressive therapy. Thus the reciprocal response of T-and B-cells is again demonstrated; when the T-cell response is suppressed, the B-cell response occurs in two rather than four weeks. The B-cell response declines rapidly as the T-cell response begins (three to six weeks). In contrast, in the normal monkeys the T-cell response occurred early and the B-cell response began only as the T-cell response started to subside.

The findings on histologic examination of biopsy specimens of the Candidal lesions are equally significant. In the monkeys not given azathioprine, a strong inflammatory response occurred with an atrophic appearance of the palatal mucosa and absence of hyphae (in contrast to those seen on the palatal smear). There was complete healing in two weeks' time. This may be considered the "normal" response.

In the monkeys receiving azathioprine, thrush-like lesions were produced. These were different on microscopic examination in that little inflammatory response was present and invasion by hyphae was pronounced. Healing of the palatal yeast infection did not occur until after the azathioprine had been discontinued and MIF production had begun.

These studies indicate that thrush-like lesions do not ensue when the immunologic response is primarily cellular rather than humoral. Hyphae, indicative of the invasive or mycelial form of Candida, are seen on smears, but not on biopsy. Healing is rapid and complete well before the antibody response is detectable. This is the pattern that might be considered the normal response in a healthy individual.

When, however, the initial response is one of rapid and strong antibody formation without a detectable response of the cellular immune system, thrush-like infection occurs, characterized histologically by marked depression of the normal influx of inflammatory cells. The finding of hyphae indicates a transition from the yeast to the mycelial phase, typically seen with invasive candidiasis. The infection is able to persist and spread despite high antibody levels.

Only when the suppressive influence of azathioprine is removed is the cellular immune system able to mount an effective response. As this becomes progressively stronger, the palatal lesions begin to heal concomitantly with a falling antibody titer.

These findings in general support the findings in humans with candidiasis in various sites of the body. In the syndromes with the most extensive yeast colonization (chronic mucocutaneous candidiasis) we find the association of high antibody levels with poor cellular immune response, as measured in vitro by the MIF and lymphocyte transformation tests, and in vivo by the delayed skin test. (The MIF test is the most consistently abnormal. In certain instances a positive transformation test or delayed skin test may be found despite the absence of MIF production.)

In clinical conditions that are characterized by intermittency, e.g., vaginitis, lower humoral and higher cellular immunity is found. As long as this immunologic pattern persists, the host seems to be able to eradicate the infection. When one of the factors favoring yeast growth again exerts its influence, the cycle repeats itself.

At such point that the colonization of the tissues becomes sufficiently extensive to produce a state of tolerance in the T-cell response, the situation becomes analagous to that in the azathioprine-treated monkeys. The yeast transforms to the mycelial phase, and the lesions become thrush-like. As the area of colonization increases, so will the antigenic load. In addition, antigens characteristic of the mycelial phase increasingly exert their influence on the immune response. Assuming that as the condition progresses, cells still in the yeast phase begin to rupture, then the large number of soluble cytoplasmic antigens heretofore shielded within the yeast membrane enter the blood stream to further stimulate or compromise the immune response of the host.

Thus is the immune system presented with an antigenic load of great complexity that is subject to wide fluctuation, both quantitatively and qualitatively. Among the better known factors that favor yeast growth

in the body and therefore alter the pattern of Candida antigens presented to the immune system of the host are antibiotics, birth control pills, pregnancy, and steroids. Further, any congenital or acquired condition that results in general impairment of the T-cell response of the host favors the yeast in the continuing host-parasite encounter. Well-known examples of such conditions are Hodgkin's disease, Boeck's sarcoid, lymphoma, and Di George syndrome. Immunosuppressive therapy, for whatever reason administered, leads to a similar result.

Genetic Factors

Thus Candida Albicans is demonstrably an infectious agent of great antigenic complexity. The extent and form of its colonization of human tissue are influenced greatly by extrinsic factors (antibiotics, steroids, pregnancy, contraceptive hormones, etc.). Antigens of the yeast cell wall, of the mycelial phase, and of the yeast cytoplasm are presented to the immune system in a constantly changing spectrum, its pattern at any given moment determined largely by the extent of mucous membrane involvement, the relative amounts of yeast and mycelial phase in the tissues, and the rate of rupture of yeast cells with release of cytoplasmic antigens into the host.

The state of the immune defenses of the host at the time this array of antigens is presented to it will be critical in determining the outcome of the encounter. While the overall condition of the immune system is influential, of greater concern is the degree to which the host is capable of mounting an effective response specifically to Candidal antigens. The single most important factor in determining this capability is the genetic make-up of the individual. Axelsen (1976) has pointed out the variability in the extent to which given individual members of the species (human or rabbit) respond to the different antigens of Candida. This observation in rabbits, noted during the raising of an-tisera for investigational use, is of special significance since stimulation was with Candida extracts in the absence of actual yeast infection, and it was possible to control other variables (e.g., nutrition) that might in humans account for the variation of antibody response.

Immune-response (IR) genes, found in association with the major histocom-patability locus, determine the extent to which a given individual is able to respond to an antigen. When this capability is absent genetically, nothing can cause that individual to respond (except, theoretically, a gene transplant). On the other hand, the genetically determined ability to respond may be greatly influenced by other factors. Adjuvants may cause a greater than natural response. A response less than the genetic capability may result for many reasons (states of immune tolerance, immunosuppressive agents, and diseases characterized by immunosuppression).

Familial susceptibility to yeast is frequently seen. Mother-daughter combinations are common wherein the daughter may suffer from oral and/or vaginal yeast infection from early childhood. (An example in this paper is the father with the chronically inflamed eye, one daughter who attempted suicide, and another daughter with severe chronic yeast vaginitis.)

It seems probable that an individual endowed genetically with a limited ability to respond to Candida antigens will be more susceptible to the yeast-stimulating influence of such extrinsic factors as antibiotics, steroids, and hormones. A sudden increase in antigenic load can more easily upset the state of limited control of yeast growth that has previously prevailed, and allow progressive tissue penetration by Candida and a chronic state of paralysis of the immune response. The continuation of the yeast presence in the tissues allows the release into the host of products, antigenic or otherwise, on a chronic basis that may last for years. Accepting for the moment the capacity of such products to produce tissue injury in the host at sites distant to the actual infection, we have the ingredients of chronic illness. By such a mechanism we can explain the variety of otherwise unrelated symptoms represented in these case reports.

Discussion

As we attempt to interpret the meaning of these cases, two facts stand out. All responded to treatment of Candida Albicans with clearing of their symptoms and signs, and symptoms and signs reflected involvement of a variety of tissues in the body. Follow up of at least three years in each instance has indicated that the benefits have persisted. What diseases, then, have been controlled or "cured" by this approach?

Most diseases were first described many years ago. When a new condition was first described, rarely was there any indication of the cause of the disease. As a result, the name given to the condition was of necessity descriptive of the symptoms (e.g., schizophrenia, manic depressive), of the signs (e.g., rheumatoid arthritis, lupus erythematosus), or of the name of the person credited with its recognition (e.g. Hodgkin's disease, Reiter's syndrome, Bechef s disease). Therefore the name of the disease usually reflected the tissue or tissues involved rather than its etiology. Usually no one patient would have all of the reported symptoms or signs, indicating that the same combination of tissue involvement was not found in every case. Thus a "new disease" might be nothing more than a different combination of involved tissues. When a common etiologic basis has later emerged, a new designation denoting this common factor has replaced the original individual names. For example, once the basic cause linking them was discovered, "atherosclerosis" replaced the various names for "stroke" and "heart attack." Or, "myxedema" is now "hypothyroidism," "Graves' disease" is "hyperthyroidism," etc.

The importance of this discussion becomes apparent if we look at the "diseases" represented in these cases. Taken together, involvement is seen of the tissues of the eye, skin, sinuses, vagina, uterus, colon, bronchial tubes, kidney, and central nervous system. Case #1 was the woman diagnosed by several psychiatrists as "schizophrenia." Her gynecologist was treating "metrorrhagia," and her allergist would have been dealing with "allergic sinusitis." The common response to Candida extract of all three conditions surely
suggests a common etiology. Different tissues were reacting in the same individual; yet it was one rather than three "diseases." Recalling Case #3, the tumor on the arm had been suggestive of lupus erythematosus to two different pathologists by biopsy, and of "leukemia" to yet another pathologist. Two years after the appearance of the tumor, he developed "bronchial asthma" and again two years later "mucous colitis." Since nystatin by mouth cleared all three conditions, Candida Albicans was apparently causing tissue abnormalities in the skin, bronchial tubes, and colon. Thus a common etiology may cut across conventional diagnostic lines and explain the common response of such diverse "diseases" as "schizophrenia," "multiple sclerosis," "asthma," and "mucous colitis."

Great care must be exercised in attempting to define the "diseases" that responded to this anti-yeast approach. Even though diagnosed by competent specialists, were these truly cases of schizophrenia or multiple sclerosis? As stated earlier, whether they were or not doesn't alter the fact that symptoms of central nervous system involvement were profound and prolonged, indicating that brain tissue was functioning abnormally even though manifesting this dysfunction differently in each individual. These cases were chosen to illustrate how a variety of "diseases" may have a common cause.

The mechanism by which yeast produced these tissue abnormalities, and the factors that determined which tissues reacted in each instance, must remain speculative at this stage. Endotoxin activity has been attributed to Candida Albicans, and this is one possibility. Immunologic mechanisms of tissue injury, any one of which may be applicable, are being investigated in many diseases. Evidence for impairment of the immune response to Candida was presented earlier. This in itself results in an increased susceptibility to the penetration of tissues by yeast, so that tissue injury may result from the immunologic response of the host. Cellular damage initiating auto-immune responses is suggested by the frequent finding of auto-antibodies to various tissues in patients with widespread

yeast growth (as in chronic mucocutaneous candidiasis). A cross-reaction between Candida antibodies and tissue cell-surface antigens is another possibility. Candida antibodies have been found to cross-react with human blood Group A antigens. Research should be initiated to determine whether certain of the 79 Candida antigens, given the right combination of conditions in the parasite and in the host, may stimulate antibodies which will react with human tissue antigens. In view of the array of available Candida antigens as well as the genetically determined variability in cell-surface antigens in the different tissues of the host, immunologic techniques more sophisticated than presently available may be required to demonstrate such a cross-reaction if it exists. One aspect of the mechanism that does seem clear is that the yeast is able to release into the host a factor that ultimately results in tissue injury. Nystatin is able to suppress the release of this factor; and the tissues are then able to recover, both functionally and histologically. Alternately, suppression of the yeast may be achieved immunologically by injections of Candida extract. Why this is effective is again speculative. Selective suppression of the T-cell response is known as immune deviation. Breaking such a state of immune deviation or tolerance by injecting a cross-reacting antigen might be an example of how such injection therapy could lead to the suppression of yeast growth, since cellular immunity is the chief defense against fungus infections.

Thus treatment at this time consists of suppression of yeast growth either directly with antifungal drugs, or immunologically by restoring a state of competence to the immune response in the compromised host. Irrespective of the basic mechanism of tissue injury, driving the yeast out of the tissues, wherever it may have succeeded in establishing a colony, must remain the ultimate goal of treatment.

There are, however, additional measures to be taken. Whereas antifungal therapy and immunotherapy are active forms of treatment, much help in controlling this condition is available through passive treatment in the form of avoidance. To state the obvious, our goal is to weaken the parasite and strengthen the resistance of the host. To be avoided, then, are those factors that strengthen the parasite and compromise the host.

The incidence of overt yeast infection in humans increases sharply with the use of antibodies, birth control pills, cortisone-type steroid hormones, and other immunosuppressant drugs. Even in those who escape symptomatic infection there is the strong probability that the yeast is able to expand its antigenic influence in varying degree. The reported incidence of overt yeast infection for each of these four types of drugs is the same 35 percent known to be characteristic of pregnancy; this may represent that portion of the population with the greatest genetic susceptibility. It will be recalled that these forms of therapy appeared on the scene in the late 1940's with the advent of aureomycin. Cortisone, birth control pills, and additional immunosuppressants came into general use during the next 10 years. Frequently two or more would be used simultaneously, often with pregnancy an additional factor.

I have often thought of the young adult of the 1970's as belonging to "the antibiotic generation." I would like to describe a hypothetical young person 16 years of age in 1977, and show how these factors that can so profoundly alter the yeast host-parasite relationship may have come into play during his lifetime.

Typically, his mother would have used birth control pills for a year or more prior to conception. Already weakened in her response to yeast, she enters the yeast-associated condition of pregnancy. Any of the 79 yeast antigens that cross the placental barrier will result in intra-uterine exposure with its tolerance-inducing influence on the unborn child. It is almost a certainty that antibiotics would have been prescribed intermittently during these years of pregnancy and "the pill." Should she have had asthma, arthritis, or any one of a number of other conditions, cortisone or other immunosuppressant drugs might have added their influence.

Soon after birth, yeast enters the

newborn child, establishes itself permanently, and perpetuates the state of partial tolerance established in utero. If his immune response (IR) genes dictate a reasonably strong resistance, he may overcome this situation as his immune system matures. If on the other hand he has inherited genes that allow him a limited defense at best against Candida, he has little chance of overcoming the state of unresponsiveness. Antibiotics soon after birth and intermittently thereafter continue to stimulate the yeast. Allergic membranes with frequent infections are common, increasing the need for antibiotics.

Had this hypothetical young person been born 25 years earlier, his genetically determined ability to control yeast growth in his tissues would have been influenced only by the pregnant state. If, as I believe and as I think the cases presented illustrate, there are mechanisms whereby yeast may cause serious illness, it is apparent that many individuals are being done much harm by these drugs.

A particular case in point is the widespread use of tetracycline for the treatment of acne. As many as four capsules daily for many years without interruption are used. This is deeply disturbing to me, because I have seen a number of patients who were in a state of chronic illness as a result. Widespread mucous membrane involvement, lethargy, depression, and chronic aching are among the numerous complaints.

Birth control pills are almost predictably poorly tolerated by a woman with a history of a yeast problem, or inhalant mold allergy. Their use is usually associated with depression, emotional lability, yeast infections, and general lethargy.

One additional "passive" treatment that may well be beneficial is a low-carbohydrate diet. Carbohydrate is the chief nutrient of Candida; its restriction in the diet may slow down the rate of growth and division of yeast and thereby reduce the antigenic load reaching the host. The reported benefit of such carbohydrate restriction in certain schizophrenics is of interest in this connection, as is the fact that lithium in relatively low concentration halts yeast growth in vitro.

Better drugs and better extracts should increase the effectiveness of active therapy of yeast infections. Nystatin is effective and virtually free of side effects. Extracts, however, are crude and variable in antigenic content. This has been a problem in the laboratories of the most skilled investigators, and is not a reflection on commercial sources. Frequently a given batch will not produce a positive skin test in an individual who reacted positively to a previous lot. Studies are badly needed comparing the cell wall, cytoplasmic, and mycelial antigens as to their ability to induce immunity as opposed to tolerance. One might well be much more effective in stimulating the cellular immune system, while another might be tolerance-inducing.

This variability in extracts may in part account for the difficulty in arriving at one dose schedule suitable for all patients, although variation in the immune response genes is probably equally important. Candida Albicans extract may be ordered as a 10,000 protein nitrogen unit/cc concentrate. Serial 1:10 dilutions are made down to a strength of $10"^{8}$ PNU/cc. Either alum precipitated or aqueous extracts may be used.

Most patients will respond to .1 cc doses subcutaneously at intervals of three to four days or longer of the weakest strengths (10" 8, $10"^{7}$, etc.), or to doses one to two times per week of 100-500 PNU. However, it is not possible to determine in advance the strength at which the patient will first begin to show a response as indicated by the relief of symptoms. Further, as the patient begins to improve, the strength may have to be increased somewhat. Close attention to each patient is required; we are trying to activate an immune response to an organism at the same time that it is actually infecting the tissues. This is not a form of extract treatment that lends itself to a predetermined schedule of injections administered by the nurse.

It is preferable to determine the maximum benefit from antifungal therapy before adding extract treatment. If nystatin

quickly alleviates symptoms of poor colon function or of oral or vaginal yeast infection, it is better to persist with drug therapy for several weeks before adding immunotherapy.

The selection of patients who may be manifesting this type of tissue reaction to Candida Albicans rests at present entirely on clinical grounds. Neither skin tests, antibody studies, nor culture techniques distinguish these patients from normal, since such a high incidence of positive tests is found in asymptomatic individuals. If a patient is having symptoms of mucous membrane infection, nystatin therapy is justified. The aim of treatment should be the suppression of growth wherever it is accessible to nystatin. Close observation of the response of other symptoms will enable an evaluation of their possible relationship to the yeast infection.

Colon function frequently becomes normal within several days after nystatin therapy is started. Therefore diarrhea, constipation, or diagnoses such as "spastic colon" or "mucous colitis" are frequent indications of underlying yeast growth in the colon. Oral and vaginal infections are usually clearly indicated by the familiar symptoms of infection in these areas.

Thus far treatment has been limited to patients with such symptoms of mucosal involvement, but Case#3 demonstrated that the remote tissue reaction may antedate symptoms of mucosal involvement by several years. The lymphoid tumor of the arm actually preceded the "mucous colitis" by four years, during which time there would have been nothing to suggest the relationship to yeast indicated by the rapid regression of the tumor with nystatin therapy.

The purpose of this paper is not to report the treatment of a group of patients with one diagnosis, but rather to show that a variety of tissues may show this response. Controlled studies of patients with the same diagnosis are needed to determine the importance of Candida as an etiologic agent in a given disease. If tissue injury is by an immunologic mechanism, Candida may be just one of many antigenic substances capable of initiating such a response. Yet its position is unique, both in its antigenic complexity and its opportunity to disseminate these antigens into the host on a chronic basis. Until elucidation of the process by which tissue injury occurs leads perhaps to a laboratory method of diagnosis, patient selection must remain on clinical grounds.

Summary and Conclusions

Sensitive immunologic techniques indicate that probably everyone has responded to the antigens of the yeast, Candida Albicans. Evidence from the literature indicates a lifelong host-parasite struggle in which many factors favor the parasite. The resulting fluctuations in yeast growth and phase lead to variation in the pattern of stimulation by the 79 known antigens. Under the proper conditions, perhaps dictated largely by the nature of genetically determined tissue antigens, the immunologic response of the host results in tissue injury. It is possible that no tissue is insulated from such injury, hence the great variety of symptoms and signs that may result from the same underlying mechanism.

A close look at "diseases" and "syndromes" of unknown cause is indicated, to detect a relationship to yeast growth if it exists. Conditions that seem to be on an immunologic basis deserve special attention. Candida Albicans is only one of many antigenic agents confronting the immune system. It is certainly one of the most complex, and it is probably with each of us at all times. Much work is needed to determine whether the conditions described herein, all of which responded to an anti-Candida program, are representative of many more patients with chronic disorders or merely represent isolated occurrences.

In view of the complexity and chronicity of antigenic stimulation by this fungus, it would not be surprising to find this a mechanism of tissue injury in many diseases. In fact, should it prove to be so, the surprising thing would be that for so long it should have been considered possible for the human body to tolerate such an incessant immunologic stimulus without frequent harm to the tissues.

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