The Role of Candida Albicans in Human Illness

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Manifestations of oral and vaginal thrush were described by Hippocrates over 2000 years ago. With the advent of the germ theory many centuries later, the yeast "Candida albicans" was identified as the cause of these symptoms, as well as of many intestinal and skin problems.

Normally it is confined to skin and mucous membranes, but on rare occasion may invade the blood stream and infect any organ. This often fatal eventuality is confined almost entirely to patients with a severe disease, such as leukemia, that is associated with a weakened immune system, a weakness often accentuated by drugs used in its treatment. Also it may occasionally cause such conventional allergies as hives and asthma, but for the most part, this fungus has been considered more nuisance than threat to health as from time to time it causes such skin and mucous membrane infections as vaginitis, oral thrush, diaper rash, esophagitis, and colitis.

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The frequency and severity of these infections have been aggravated greatly by a number of drugs and procedures used in current medical practice. Foremost in importance are antibiotics, birth-control pills, and drugs that weaken the immune system known as "immunosuppressants" (chief among which are the cortisone-type steroids, drugs used in chemotherapy of malignancies, and some that are used in the treatment of such inflammatory conditions as rheumatoid arthritis), and even a prolonged high carbohydrate intake. Together with repeated pregnancies, these factors have had an enormous impact on the incidence, severity, and chronicity of yeast growth in the population.

Observations made while working with this yeast as a cause of migraine headache first suggested that it might be a much more significant factor in human illness than then suspected. In 1961 an injected Candida extract relieved a headache, but surprisingly, simultaneously relieved intense pre-menstrual depression. This led to a continuing interest in and observation of literally all complaints in patients treated for chronic infection and allergy related to Candida albicans.

Complaints of depression and anxiety and impairment of memory and concentration were so prominent that initial interest focused primarily on disturbance of brain function, at times so severe as to suggest catatonic schizophrenia. But equally impressive was the response of a variety of complaints referable to other organs. Most often these were problems for which as an internist I had been able to do little, many being of the type usually considered "psychosomatic" for little reason except the absence of abnormalities on x-ray and laboratory investigation. After sixteen years these experiences were published; six cases were selected around which was built the concept that Candida albicans may cause severe chronic illness, including the type usually referred to as "mental," causing symptoms commonly considered psychological in origin, but which in reality are reflections of disturbed chemical and physiological processes in what is just another physical organ—the brain. The diagnosis in two of these patients was "schizophrenia" and in a third "multiple sclerosis." It was pointed out that, even if the diagnostic names given these diseases were incorrect, all three without question were victims of severe abnormalities in brain function, with differing clinical pictures that cleared completely with anti-yeast therapy.

Virtually any organ can function improperly in this condition, which we call chronic candidiasis. Thus a great variety of complaints may occur, their onset often coinciding with that of vaginal or intestinal yeast infection, itself often directly traceable to the influence of antibiotics or other of the factors, singly or in combination, that so adversely affect the body's control of this fungus.

Yet despite their great variety, certain manifestations occurred with such frequency as to suggest the diagnosis of yeast induced illness-mental depression, anxiety, hyperactivity, and hyperirritability; recurrent urinary tract symptoms usually diagnosed and treated as "cystitis", increased susceptibility to reactions to inhaled or ingested chemicals (including drugs and food), and many indications of interference with hormone function (acne, rough dry skin, almost any type of disturbance of the menstrual cycle, decreased or absent libido, decreased breast size, and progressively more severe pre-menstrual tension. Miscarriages and endometriosis were common.) In students, impairment of memory and concentration often resulted in deterioration of school work; coupled with the depression and anxiety, this often led to rebelliousness and association with other students similarly affected, and frequently to school drop-outs, drugs, and an end result so familiar in the past two decades. Recall that these symptoms were almost always superimposed upon the many physical manifestations originating at the sites of yeast growth or related to allergic responses.

In this connection I would like to mention a thought that recurs each time I see this condition in adolescent and young adult patients. The first broad-spectrum antibiotic, aureomycin, became available in 1947. The next 13 years saw a proliferation of articles in medical journals detailing the rapid increase of intestinal and vaginal yeast infections as these drugs attained wide useage. The first children born after the advent of the mycin drugs would have reached puberty about 1960, also the approximate time of beginning of the drug problem in adolescents in this country. I would like to read a short note that arrived in the mail from a 26-year-old woman whom I had been treating for five months; she had obtained great relief with treatment of her yeast problem, but with the intermittent relapses customary early in treatment. At the time of her initial visit I had mentioned to her this thought about yeast-induced depression and the drug problem.

"Thank you so much for helping me and my sister. Thanks especially for your special attention during these 'emergencies.' P.S. When you told me your theory about drugs and the 60's I thought you were on a limb. But during the past week of 'relapse' I have definitely experienced the kind of depression that first began my drug addiction. So I see now you may have a very valid and important thought. Love and appreciation..."

This note was written by a hardened and cynical young woman who from age 14 had

experienced virtually every fashionable drug, up to and including heroin. That this illness contributed to the deterioration of this young girl's life soon after puberty is purely speculative. Yet it should not be difficult to envision for anyone who has seen a woman with severe premenstrual anxiety and depression reach for the alcohol and Valium.

One year ago a girl, also 14 years old, was brought in because of mental confusion and sudden inability to learn, associated with severe depression and frequently voiced thoughts of suicide. This condition had begun abruptly five weeks earlier, on the identical day that for the first time in her life she broke out with severe hives and developed severe asthma. The hives were severe every day and in the two weeks prior to her visit asthma had required hospital emergency room treatment three times. She had experienced menstrual periods only ten days apart after two years of normal 28-day cycles.

Five days before the abrupt onset of this illness she had begun tetracycline therapy for mild acne. Six and one-half months earlier, during an initial two-month course of tetracycline for acne, she had developed headache, vaginitis, and constipation—none having been present at any previous time in her life. During the four and a half months before the reinstitution of tetracycline therapy she was well.

Based on this history, I instituted treatment with the anti-yeast drug "nystatin" and low-carbohydrate diet; fortunately the tetracycline had been discontinued two weeks earlier. From the first dose of nystatin she never wheezed again. The hives stopped completely except for a slight recurrence six weeks later when her mother reduced the nystatin dose for two days. Her mental picture began to improve immediately, although complete return of her normal happy personality was delayed until her next menstrual period began, nine weeks after beginning the anti-yeast program.

This case illustrates almost every aspect of the candidiasis concept. A happy young girl, an A student, suddenly could not think clearly or learn, and was transformed into a suicidally depressed child. Yeast infection produced symptoms at its sites of growth in the vagina and bowel. The hives and asthma represented allergic responses to yeast products entering the blood stream in the vagina and intestine. Interference with hormone function led to two menstrual periods within two weeks after regular 28-day cycles from age 12 to 14, and it was nine weeks before her periods resumed, even though strong suppression of the yeast was indicated by cessation of the asthma and hives during this interval.

Her natural immune containment of this yeast for 13 and a half years was disrupted by the initial two-month course of tetracycline for mild acne. The initial impact of this antibiotic was expressed as yeast vaginitis, constipation and headache. Apparently during this initial course she became sensitized to yeast products released into her blood stream, so that on the fifth day after re-stimulation of the yeast by this antibiotic, the severe brain, skin, and bronchial manifestations erupted simultaneously.

The dramatic response of these severe symptoms to nystatin therapy leaves little doubt that this interpretation of these events is correct. She was referred to me quite by chance by her teacher who was also a patient. Already her pediatrician had made an appointment for her with a psychiatrist. It is not pleasant to contemplate the ensuing years if it had been concluded that these classical "mental" symptoms were the initiating factors of the illness, a conclusion that, in view of a traumatic divorce of her parents three years earlier, would have been altogether probable despite her having been happy and an excellent student between the time of the divorce and the onset of the acute illness. Hives, asthma, constipation, and menstrual problems would almost certainly have been treated in part, at least, with psychotherapy and psychiatrically-oriented drugs with their many undesirable side effects. Inevitably infections of the allergic respiratory membranes would have necessitated increasing antibiotic use, each time aggravating the underlying cause of the allergic membrane and hence of the infection. This vicious cycle might well have been further enhanced by the gynecologist's use

of birth-control pills in an effort to reestablish a normal menstrual pattern, and it is a virtual certainty that cortisone-type drugs would have been used heavily for both the asthma and the hives.

She could not possibly have done well in school, despite increasing parental pressure predicated on the belief that the problem was psychological. In fact, being physical in origin, the depression and inability to function intellectually were no more amenable to control by will than would have been a high fever originating in the heat-control center of the brain.

It takes little imagination to envision a child, so overwhelmed by medical and parental forces, reaching out to others similarly alienated from those who should be a source of support rather than blame, or to understand how the next step to any drug that might afford even momentary relief would be so easy.

This story, with minor variations, is typical of many. I have devoted to it much of my allotted time because it is so vital that these cases be recognized and properly treated.

It brings me to my second speculation. The suicide rate in adolescents has risen steadily during the same recent decades that witnessed eruption of the drug and yeast problems. If cases like that just described are occurring with increasing frequency, it would be logical for this to be reflected in the suicide rate.

Statistical associations such as these, of course, in no way prove a relationship between conditions that may only be increasing in frequency coincidentally for entirely different reasons. But they are useful in giving direction to avenues of future exploration.

This point is illustrated again by the story of a 15-year-old girl with anorexia nervosa. In nine months she had gone from 120 to 59 pounds, had not eaten for weeks, and was barely alive in intensive care as a result of tube feeding. She was noted on a Monday morning to have oral thrush, and a very small amount of liquid nystatin was administered—not with any thought that this was other than the usual colonization by this normally present yeast of the oral cavity in a patient very debilitated and close to death. The next day she ate, and three days later ate a full-course Thanksgiving dinner. Three weeks later she had gained to 72 pounds, and subsequently made an uneventful recovery. One such case, despite the dramatic response, proves nothing, but coupled with reports of a 100-fold increase in the incidence of anorexia nervosa in recent decades, again suggests further studies to determine whether there might be meaning in the simultaneous increase in incidence of two presumably unrelated conditions.

If, as I believe, chronic infection with Candida albicans can be responsible for such a variety of symptoms, the legitimate question arises as to why this has remained unrecognized by the internist, allowing the tragic misdirection to futile psychiatric therapy of patients with a medical illness. It seems to me that two factors contribute to this situation. First, the evidence is strong that this yeast lives in virtually every human being. Most individuals can be shown to have a positive skin test if vaccines of assured potency are used; it can be cultured from the mouth, stool, or vagina in most people, especially following antibiotic therapy, and it has been demonstrated that probably everyone has antibodies in the blood stream to this fungus. Now these are the three types of tests—skin tests, cultures, and antibody levels—upon which the diagnostician relies in detecting infections (and an infection with this yeast is what we are talking about.) But a moment's thought reveals that the value of each of these tests rests on its ability to demonstrate evidence of the presence of a particular germ where it should not be, e.g. a skin test for tuberculosis or leprosy; a throat culture for a pathogenic streptococcus, a positive urine culture; antibodies to the syphilis germ, or the typhoid organism, etc. Thus the value of these tests rests in their providing evidence of the past or present existence of an organism in the body, or alternatively at a particular site within the body, where it is not normally found, and this is taken as presumptive evidence of its relevance to the illness in question. Yet to demonstrate that Candida is present

accomplishes nothing, since, as we have already seen, it is universally present. Because he knows this, the diagnostician will usually, (and quite properly) ignore, for example, a positive culture, and give it no weight in arriving at his diagnosis. In such an instance it is usually termed an "opportunistic organism," which means that it has grown at the site from which it is cultured because the patient's resistance has been lowered by his primary illness.

The second factor leading, in my opinion, to the mistaken psychosomatic label is the overall clinical picture. It could hardly be a more ideal example of psychosomatic theory. Depression and agitation are almost always among the more prominent complaints. Their frequent association with complaints of loss of memory and concentrating ability sets the tone even as the internist begins the exhausting job of listening to symptoms referable to almost any system of the body, including prominently the gastrointestinal and urinary tracts, skin, menstrual cycle, a seemingly endless list of complaints such as weakness, dizziness, insomnia, fluid retention, and loss of libido, chemical intolerances, and various disturbances of smell, taste, vision, or hearing. Physical examination and laboratory and x-ray studies selected to investigate each of these complaints yield little. Consultations with subspecialists appropriate to the various complaints are equally unrewarding. Armed with all of this evidence that "there is nothing wrong physically," with anxiety and depression so evident, and secure in the knowledge that there is no conceivable medical problem that can lead to complaints in so many organs, the diagnosis of psychosomatic illness is almost irresistible. Thereafter so-called "emotional problems" are considered the original initiating factors in the illness and the cause of abnormal function in various organs that are organically sound.

To me it has always seemed that the psychosomatic concept has allowed us internists to pretty much eliminate the category of "I don't know" in cases with any component of anxiety or depression. Psychosomatic theory gets much emphasis in medical schools, so that in making a diagnosis of psychosomatic illness, not only do we escape the erosion of ego associated with having to say "I don't know," but we do so with a diagnosis that makes us feel very educated and medically sophisticated. Yet the vast imperfections in our knowledge of physiologic disturbances, especially of the brain, together with the relative crudeness of our laboratory and x-ray diagnostic methods (modern and scientific though they appear) seem to me to make totally indefensible the conclusion that, by exclusion, the illness must be psychological in nature.

On the other hand, from the viewpoint of the allergist, the brain is just one of many organs participating in the allergic response. Depression, anxiety, and memory and concentration problems are seen as the outward expression of interference with the chemical and physiologic reactions responsible for intellectual functions and for the expression of emotion. With clearing of such conditions as asthma, or hives, or hay fever, comes simultaneous disappearance of these so-called "emotional" symptoms, which are thereby revealed to have always been secondary to allergy and never psychiatric in nature and hence not the cause but a result of the illness.

In summary, then, it is my belief that Candida albicans has not been related to many problems it causes for these two reasons— the ready availability of the alternate psychosomatic explanation, and the lack of a definitive test to tell not that this yeast is in the body (which we already know) but when by allergic and possibly toxic mechanisms, it has begun to cause disturbances of function in the various organs of the body.

I would like now to review briefly a phenomenon known as immunologic tolerance, sometimes called immunologic paralysis or unresponsiveness. Stated simply, this refers to the inability of one's immune system to respond to substances that are capable of stimulating an immune response under other circumstances. In general terms, an immune response tends to occur when something foreign to our own body is recognized by certain of our white blood cells. This triggers a complicated sequence of

events, involving among other things, other white blood cells—some producing antibodies, some killing on contact living foreign cells, others becoming activated and therefore capable of helping or suppressing the antibody-producing cells and probably the killer cells as well. In other words, some cells produce antibodies and some kill foreign cells by direct contact, both immunologic functions being more or less "turned on" by helper cells, and "turned off" by suppressor cells when continuation of the immune response might be injurious to the body.

These responses may occur spontaneously as when we contact various infectious agents, or by design in response to vaccines given to stimulate protective immunity. It is this same immune response that leads to rejection of a transplanted organ because, unless donated by an identical twin, the immune system recognized its "foreignness" and immediately sets about to destroy it. And when a cell suddenly undergoes malignant change, it is thought that it is treated by the immune system much as if a surgeon had transplanted it into the body; its "foreignness" to any of the body's normal cells is quickly recognized and the killing response "rejects" it, i.e. destroys it much as in the example of the transplanted organ.

It should be readily apparent that to a great extent the integrity of this immune process determines the state of one's health. Immunologic paralysis (or unresponsiveness) refers to the loss of this response, usually to a single foreign invader (although at times it may be a general loss of response). Studies in patients with such slowly progressing infections as leprosy have revealed in the early stages a strong immunologic response which is subsequently lost. As the number of foreign bacteria in the tissues becomes progressively greater, increasing quantities of its metabolic products circulate in the blood stream. The term "antigen" refers to a substance capable of stimulating an immune response, in this illustration the metabolic products of the leprosy bacteria. As the disease progresses, a critical point is reached beyond which the total "antigenic load" more or less overwhelms the cells of the immune system and immunity drops, often to an undetectable level. Thus "paralysis" or "unresponsiveness" has replaced the strong immune response present when the "antigenic load" was small. The immune system has lost its ability to fight back and is now "tolerating" the leprosy germs in the tissues—hence the term "immunologic tolerance." Similarly, an impairment of the immune response may allow a malignant cell to escape destruction, enabling it to divide repeatedly and become what we know as a "cancer."'

As an explanation of the chronic illnesses represented in the six published cases, it was postulated that this phenomenon of immunologic tolerance occurs when Candida albicans slowly increases its total area of tissue invasion after years of repeated stimulation by antibiotics, birth-control pills, immunosuppressant drugs, pregnancies, and diets high in carbohydrates and in foods with a high mold or yeast content.

It was suggested that, in addition, the immune response to factors other than Candida might be altered because of alterations induced by this yeast in the balance or functional capacity of the cells of the immune system. Such an effect of yeast products released over an extended period would increase the likelihood of any of the many illnesses to which we are rendered susceptible by a poorly functioning immune system.

The discussion so far has focused on the importance of the immune system in the rejection of things we don't want in the body if we are to stay healthy-such things as viruses, bacteria, fungi, and malignant cells. In these instances, a state of immunologic tolerance is highly undesirable in that agents of disease are allowed to survive and to multiply.

On the other hand, it is equally disastrous when our immune system begins to respond to any of our own normal cells and tissues. We don't want normal cells rejected; therefore a state of immunologic tolerance to normal cells is just as vital to continued good health as it is harmful when continued good health depends on the rejection of a foreign invader, be it infectious agent or cell turned malignant. Thus a state of immunologic

tolerance to our own cells is normal; if lost, disease occurs, its exact nature depending on which tissues are attacked. As a class they are known as "auto-immune" diseases, and include such familiar conditions as rheumatoid arthritis, multiple sclerosis, systemic lupus erythematosus, myasthenia gravis, scleraderma, and probably many others.

It is now believed that the class of lymphocytes called "suppressor cells" plays a central role in preventing immunologic responses to our tissues. In other words, we are capable of mounting an immune response to our own organs but are prevented from doing so by cells that suppress such a damaging phenomenon. In autoimmune disease antibodies may appear in the blood in response to an immunologic attack; symptoms in turn reflect the inflammation and resulting abnormal function.

Evidence both clinical and laboratory is now accumulating in support of the original concept that Candida albicans, in interfering with the cells of the immune system in a way that prevents its own rejection from the tissues, also impairs this ability of the immune system to suppress immune responses to normal cells, thereby allowing autoimmune processes to occur.

The clinical evidence consists of cases that will be summarized briefly, each representative of a particular disease generally thought to be autoimmune. Considered as a group, they seem to support the further concept presented originally that one etiology (or cause) could theoretically underlie what appear to be different diseases, but which in fact may be one disease manifested in ways determined by the combination of tissues involved, each major combination long ago having received a name descriptive of its particular clinical picture.

The first case is that of a three-year-old boy who developed severe autoimmune hemolytic anemia at 11 months of age. His immune system attacked his own red blood cells, destroying them in massive amounts in crises that continued until institution of therapy with the anti-yeast drug nystatin. On one occasion heart failure had occurred when his immune system destroyed two-thirds of his red blood cells and he had so little hemoglobin to carry oxygen to his tissues that his heart could no longer function properly. Only massive therapy with predisone had kept him alive. With nystatin therapy his multiple loose bowel movements immediately dropped to normal and his extreme hyperactivity abruptly ceased; within eight weeks his red blood count was climbing toward normal. It reached adult levels in 14 weeks and he is well now two years after treatment was started, having been off nystatin for three months with as yet no recurrence.

The next is a case of myasthenia gravis in a 22 year-old woman with severe yeast vaginitis from age eight years and chronic diarrhea for many years. Myasthenia developed at age 21 and was very severe despite maximum doses of Mestenon, the drug used in its treatment. This disease is thought to be an autoimmune response represented by an abnormal antibody that forms to a normal protein located on the end of individual muscle fibers. It is the function of this protein to accept the acetyl-choline molecule that is released by the adjacent nerve fiber in the process of activating the muscle. It is thought that the antibody reacts with the protein and more or less gets in the way (at least partially) of the acetyl-choline molecule, so that muscle contraction is inhibited. After 12 weeks on nystatin a young woman who could hardly talk, and could not wrinkle her forehead, was jogging three miles, working regularly, had reduced her Mestenon from two tablets every hour to one-half tablet every three hours, and was having one or two bowel movements per day instead of five or six. Nystatin was started over two years ago. As yet she has not been able to dispense entirely with the Mestenon but neither has it been possible as yet to prevent some recurrence of yeast symptoms in both bowel and vagina. Her need for Mestenon parallels the activity of her yeast infection.

This case assumes special importance in demonstrating that an abnormal antibody to the normal acetyl-choline receptor protein can block the full expression of acetyl-choline. In this instance it was muscle function

that was impaired. But acetyl-choline blockade in the central nervous system leads to severe loss of memory and concentration and grossly alters the acetyl-choline.dopa-mine relationship.

Thus should a similar abnormal antibody impair the response in brain tissue to this important neurotransmitter, it would have the potential for causing severe manifestations that could vary greatly in their clinical expression, depending upon the degree of impairment in the various functions of the brain.

Time allows only the briefest description of several patients with multiple sclerosis:

Case 1: The story of this 30 year old woman was published as one of the original six cases. She is entirely well now seven years after nystatin was begun. She went through pregnancy with no trouble and delivered a normal baby.

Case 2: A 31 year-old woman developed MS three years before nystatin was started one year ago. She started improving immediately and was asymptomatic by eight months unless, as she says, she would go "on a carbohydrate binge." This would induce abdominal bloating, diarrhea, and faint suggestions of tingling in her extremities.

Case 3: A 27 year-old woman, beginning seven years ago, developed numbness of both lower extremities, both forearms and hands, and the front of her chest. The so-called "neurogenic bladder" characteristic of MS was severe. She stated that for one month, by her watch, in every instance it required 10 minutes before the bladder would begin to empty. This cleared in five days on nystatin, coinciding with clearing of constipation and a great increase in energy. After 13 weeks on nystatin both lower extremities are entirely normal, as are the upper extremities except for the slightest residual numbness of the left hand. The numbness of the front of the chest has started to decrease. She is most emphatic about the great increase in energy.

Cases 4 and 5: Two men in their mid-thirties have multiple sclerosis that started in their early twenties. In each several manifestations have improved after 12 and six weeks of treatment with nystatin.

Case 6: One case of Crohn's disease of the lower colon has cleared.

In addition I know of two additional different autoimmune diseases, systemic lupus erythematosus and thrombocytopenic purpura, that have responded, and of a published case report of sarcoidosis, (yet another autoimmune disease) that recovered completely with anti-Candida treatment.

One of the sub-groups of patients with chronic candidiasis consists of those with severe intolerance to virtually all chemicals (including foods, drugs, and inhaled chemicals). It was also in the early 1950s, the same time that Candida growth became so widespread from the mycin drugs, that Dr. Theron Randolph began reporting this condition. At one of the ecology units where these patients are studied in an effort to help them learn environmental factors to avoid, about one-third have been found to have low T cells (this is the class of white blood cells in which are found helper and suppressor cells). It is becoming increasingly apparent that these chemical sensitivities are disappearing with nystatin, and the T cells are returning to normal (in one case, as soon as one month after nystatin was prescribed), indicating that the low T-cell counts were caused by Candida albicans.

Two such chemically sensitive patients were found to have very high counts of suppressor cells and a reversal of the ratio of helper to suppressor cells. This finding emerged from a recently instituted study involving a very sophisticated analysis of the cells of the immune system at the Tumor Institute of the Medical College of Alabama, under the direction of Dr. Max Cooper. These abnormalities will be followed and correlated with clinical improvement, which in both patients has already occurred.

When these studies were done in the two men with multiple sclerosis, a striking abnormality was found in a recently discovered class of lymphocyte known as a "natural killer cell." With normal being 16 percent, one was at 0.6 percent — the other at 1.9 percent. After three weeks on nystatin, the former had increased from 0.6 to 3.5 percent. After 12 weeks on nystatin, the latter

rose from 1.9 to 10 percent.

It is far too soon to evaluate these findings, but the finding of such striking abnormalities in these and in two cases of severe Crohn's disease gives a measurable abnormality that can be followed and correlated with the clinical course. More important, it offers laboratory evidence of an imbalance in the numbers of the various subclasses of lymphocytes in patients with these autoimmune diseases as well as in the two chemically intolerant patients. The clinical response of both chemical intolerance and multiple sclerosis to anti-yeast therapy relates this fungus to these abnormalities. The effects of these distortions on the various functions of the immune system remain to be studied.

To conclude, I will summarize the categories of illness in which I feel the relationship to yeast is well-established, those in which the evidence is strongly suggestive, and those that I believe deserve careful study with respect to the possibility of such a relationship.

1. Infants and children with frequent infections and much antibiotic. Bowel disturbances, oral thrush, diaper rash, and respiratory allergy are common. Chronic irritability and hyperactivity, and even one case of stuttering, have been seen in children, many of whom carry the diagnosis of "learning disabled."

2. The manifestations of candidiasis after puberty, illustrated by the story of the 14-year-old girl: Interference with sex hormone physiology is added to the manifestations of the childhood years, often with devastating effect on mood and on intellectual functions. It is vital to recognize this problem in early adolescence for reasons discussed earlier.

3. The single largest category of chronic candidiasis seems to be (at least at this time) the older teenage or adult woman with progressively severe illness resulting from repeated pregnancies; birth-control pills before, between, and after pregnancies; antibiotics; immunosuppressants for whatever reason required; and usually much therapy with psychiatric-type drugs. Menstrual disorders and much gynecologic surgery are usual, and depression and agitation are severe.

4. The special category of chemical intolerance: Reactions to inhaled or ingested chemicals, to foods, and to drugs increase relentlessly in number and severity. These may be superimposed upon any of the above problems.

5. Schizophrenia and similar illnesses: I must leave evaluation of Candidiasis in these illnesses to those who can treat the severe cases in a hospital setting. It has been my experience that it is impossible to carry out this treatment program in severe cases living at home. In cases sufficiently mild to allow patient cooperation, results have been most encouraging.

6. I have saved until last a statement regarding the autoimmune diseases. It is impossible not to feel excited about the possibility that Candida albicans is able to release into the bloodstream products that can alter cells of the immune system in a way that prevents it from exerting its normal suppressing effect on immunologic attacks of normal tissues. The laboratory findings of suppression of total T-cells and of gross distortion in the ratios of their various subgroups, and the very recent finding of severe depression of the newly-discovered class of lymphocytes known as "natural killer cells" furnish some degree of objective evidence, embryonic though it is, in support of this concept.

In many of these diseases autoimmune antibody combines with its antigen to form what is known as an "immune complex." These may be found in the blood stream, but also may be deposited in the tissues, resulting in inflammation and symptoms. For many years exhaustive efforts have been largely unsuccessful in identifying the antigen in these antigen-antibody combinations, most efforts having focused on the search for viruses either as the antigen or as the cause of damage that renders previously normal tissue antigenic.

Possibly nowhere is the establishment of cause and effect more difficult than in the search for those factors responsible for the many diseases to which the human body is susceptible. The thought that a number of

diseases of such prominence, differing so markedly in their clinical pictures, could share a common underlying basis, at first seems totally incomprehensible. But perhaps just as difficult to comprehend, if each of these many diseases has its own separate cause, is the failure of even one of these diseases to yield to the massive expenditure of money and energy in research funded by the government, and often by national societies, for the past 35 years.

This thought, together with the knowledge that these diseases share the abnormality of loss of immunologic tolerance to normal tissues, lends some support to the concept of a common etiology based on distortions in the cells of the immune system. That this agent could be Candida albicans is plausible in view of its presence in the body from soon after birth until death, its very universality accounting for its remaining unsuspected in connection with these diseases. Should this prove to be true, it still might be just one among multiple factors capable of causing the type of immune damage that allows what may be a normal immunologic response, except that its expression is directed toward normal cells, or in the case of Candida, toward cells that perhaps have been damaged by yeast antigens or toxins.

It has been said that this fungus is the most complex infectious agent yet studied. This is based on the finding in human sera, thus far, of 79 separately identifiable antibodies, meaning that this yeast is releasing 79 substances sufficiently different chemically that the corresponding differences in the resulting antibodies are recognizable. Each strain is thought to have 30 to 35 of these antigens, meaning that many trillions of strains are possible. Further, it has been shown that one individual may simultaneously harbor more than one strain. And, although I do not know that it has been studied, it would seem likely that different strains could colonize the same person at different stages in life. We also know that an individual strain can be made to change its functional characteristics—for example, can be trained to ferment a particular sugar not normally amenable to its enzymes. Further, it has been shown that a particular antigen may not be expressed until the yeast becomes invasive. This indicates that invasion of the tissues brought on, for example, by an antibiotic leads not just to an increase of the antigens already being released but to the elaboration of new antigens, and quite possibly of substances that are toxic to tissues but have not been discovered because they are not antigenic and have no antibody in the serum to give away their presence in the blood.

Thus emerges the picture of a universally present organism of great complexity and variability, its own physiology and growth characteristics influenced strongly by many factors in our lives—those as simple as diet or the amount of mold in the air we breathe, or as complex as the hormones of the menstrual cycle and pregnancy, or as poorly understood as those that influence the competency of the immune system.

Consideration of such a constantly-changing spectrum, both quantitatively and qualitatively, of substances released by this yeast into hosts of infinite genetic variability makes less implausible the concept that tissue damage induced by metabolic products of this fungus could be represented by abnormal function in the many organs affected in the autoimmune diseases as a group.

It is important to emphasize the preliminary nature of the laboratory studies, and the necessity for more time in which to evaluate these and additional patients with autoimmune diseases, both in their response to anti-yeast therapy and in the laboratory. It would have been preferable to have an additional two or three years for these studies before discussing them, but interest has increased so rapidly recently (based on calls and letters) that 1 felt it better to present the findings up to this point.

As stated earlier, cause and effect are difficult to establish. It is possible theoretically that some cause exists even beyond the Candida, and that the improvement realized by these patients did indeed derive from yeast suppression despite the presence of this theoretical underlying agent of disease that had increased their susceptibility to this fungus. Or, again theoretically, should nystatin prove to have an as yet unsuspected

effect on the body—perhaps, for example, serving as a powerful stimulant of the immune response—then the benefit realized from its use would not be due necessarily to its effect on the fungus, which could instead have been eliminated by the strengthened immune response.

For many reasons, I do not believe these alternate possibilities, but have presented them for one reason. Already a number of patients have benefited greatly from treatment based on suppressing this yeast and endeavoring to restore competence to the immune system. Even should Candida be unrelated etiologically, patients with autoimmune disease deserve to have their yeast problem treated. If it is not the cause of their illness, treating it should do no harm, and if it is the cause, then that is what we are looking for. I presented these alternate theoretical explanations because it is of the greatest importance that we not build false hopes where there have been so many disappointments in the past.

For this reason, in stating these present views of the role of Candida albicans in human disease, I have attempted to choose my words with great care. I hope they have been listened to with the same care and, if quoted, convey the cautious optimism that was their intent.

Addendum: In treating autoimmune diseases, it has not been necessary to use immunotherapy. In multiple sclerosis, immunizations of all types have been suspected of causing exacerbations of the illness. Because of the abnormalities of the immune system in these diseases, the nature of which is at present unclear, it might be expected that the immune response would not be the same as in the ordinary allergy patient.