Restoration of Immunologic Competence to Candida Albicans

C. Orian Truss, M.D.[1]

The existence of Candida albicans in the human body is entirely compatible with a *lifetime of excellent health. It also may at any time, under the influence of various factors, succeed in colonizing tissues, primarily of the intestinal tract and vagina. It then calls attention to its presence by symptoms originating in the infected organs or in remote organs related to immunologic and possibly toxic responses to soluble yeast products, and exerts a paralyzing influence on the capability of the host to mount an effective immunologic response. Restoration of immune competence to its genetically determined maximum should be the goal of treatment, and is the means by which both infectious and allergic manifestations may be terminated.*

INTRODUCTION

Persistence of a foreign organism in human tissues requires the absence of an effective immunologic response to the exposed antigenic determinants of the pathogen. This loss or absence of immunologic competence is variously referred to as tolerance,

[1]- 26)4 Highland Ave.,
Birmingham, Alabama 35205

paralysis, anergy, and unresponsiveness. Disseminated tuberculosis (miliary) and lepromatous leprosy are illustrative of chronic bacterial infections that persist in association with, and possibly because of, an inadequate immune response by the host. Chronic mucocutaneous candidiasis is a fungous infection exhibiting the same phenomenon. The immunologic impairment associated with these infections has been reviewed previously (Truss, 1978).

It follows, then, that a pathogen is eradicated rather than tolerated when the immune system is competent to respond effectively to the antigenic determinants of the organism. Such response embraces both cellular and humoral components of the immune system, even though one may predominate in controlling a particular type of pathogen.

Miliary tuberculosis, lepromatous leprosy, and chronic mucocutaneous candidiasis are advanced chronic infections with widespread dissemination of the organism in the tissues; in all three conditions it is often possible to demonstrate impairment of the immune response. Lymphocytes may fail to respond to the antigenic challenge in vitro, as in the MIF and lymphocyte transformation tests. This defective cellular (T-cell) response

is often expressed in vivo by the failure of these antigens to elicit a delayed (tuberculin-type) skin test response.

Yet in each instance, in the more limited stage of infection, these tests of T-cell response will usually be normal. Indeed, many instances have been documented of actual disappearance of previously positive lepromin or tuberculin skin tests as the antigenic load reaches that critical point beyond which the immune system becomes unresponsive; it is no longer "competent" with respect to the antigenic determinants of the organism in question. A state of "immunologic tolerance", or "paralysis", is said to exist, and may be expected to persist as long as the antigenic load remains undiminished.

The influence of antigenic load on the immune response was demonstrated by Budtz-Jorgensen (1973). In children with chronic mucocutaneous candidiasis, treatment with amphoteracin-B was continued until the skin and mucous membranes were essentially free of the fungus. Before treatment both MIF and lymphocyte transformation responses were absent, indicating marked impairment of the T-cell response to the antigens of this organism. As therapy with amphoteracin-B led to progressive clearing of the yeast from the tissues, competence returned and tests of the T-cell response became normal. Following discontinuation of the drug, tissue involvement with Candida returned and the T-cells again lost their capacity to respond when the antigenic load again overwhelmed the immune defenses.

Thus, loss of immune competence may be associated with chronic infection with Candida albicans, just as with the tubercle and leprosy bacilli. The latter two, however, are also recognized as the cause of chronic illness that may persist for years in a more limited form without measurable loss of immune competence.

With Candida no such chronic systemic disease has been recognized with the exception in children of the congenital disease "chronic mucocutaneous candidiasis". Except for this condition and the occasional patient who develops Candida septicemia in association with leukemia or similar disease characterized by an impaired immune response, it has been viewed as an opportunistic organism characteristically infecting the mucous membranes of the G.I. tract, vagina, skin and nails.

RECOGNITION OF CHRONIC CANDIDIASIS

The concept of candidiasis (non-congenital) as a chronic systemic condition with multiple manifestations was previously presented at the eighth Scientific Symposium, Academy of Orthomolecular Psychiatry, Toronto, Canada, May 1, 1977, and later published (Truss, 1978). It is conceived as analogous to the more limited but chronic forms of leprosy and tuberculosis. The manifestations vary greatly from patient to patient, depending in part upon the location and extent of tissue colonization, but principally upon the patient's immunologic and allergic response to yeast antigens and to possible toxins released by the fungus. Implicit in this concept is that presently available tests of the immunologic response to Candida may be normal, but with impairment of immunologic competence nevertheless clearly indicated by the inability of the immune defenses to rid the host of the organism. It is "tolerated" in the tissues because the immune response is "paralyzed"

If the term "immunologic tolerance" is restricted to conditions with abnormal in vitro tests of the immune response, these patients with chronic infection but normal in vitro tests may be said to be "clinically immunologically tolerant". The eventual development of in vitro tests allowing more subtle quantitation of the immune response should eliminate this distinction.

At the present time the recognition of patients with chronic candidiasis must be based on clinical evidence and confirmed by therapeutic trial; no help is available from the laboratory. Everyone has antibodies, and most have a positive skin test; the yeast may be cultured from many asymptomatic individuals. Many patients with this condition show an immediate (IgE) skin hypersensitivity with a weak or absent delayed response, but there are too many exceptions for this test to be definitive. A careful history that traces the illness from its onset suggests the diagnosis. It invariably includes a story of

ORTHOMOLECULAR PSYCHIATRY, VOLUME 9, NUMBER 4, 1980, Pp. 287-301

futile efforts by many competent specialists to establish an organic basis for the chronic illness, and of the almost irresistible recommendation of psychiatric therapy.

Attention in the history should be directed to the influence of repeated pregnancies, birth-control pills, antibiotics, and cortisone and other immunosuppressants. The onset of local symptoms of yeast infection in relation to the use of these drugs is especially significant and usually precedes the systemic response. Repeated courses of antibiotics and birth-control pills, often punctuated with multiple pregnancies, lead to ever-increasing symptoms of mucosal infections in the vagina and gastrointestinal tract. Accompanying these are manifestations of tissue injury based on immunologic and possibly toxic responses to yeast products released into the systemic circulation. Many infections are secondary to allergic responses of the mucous membranes of the respiratory tract, urethra, and bladder, necessitating increasingly frequent antibiotic therapy that simultaneously aggravates and perpetuates the underlying cause of the allergic membrane that allowed the infection. Depression is common, often associated with difficulty in memory, reasoning and concentration. These symptoms are especially severe in women, who in addition have great difficulty with the explosive irritability, crying, and loss of self-confidence that are so characteristic of abnormal function of the ovarian hormones. Poor end-organ response to these sex hormones is confirmed by the common association of acne, impairment or total loss of libido, and the whole range of abnormalities of menstrual bleeding and cramps, as well as a very high incidence of endometriosis in those who have undergone hysterectomy.

Many of these patients also start developing multiple intolerances to foods and chemicals, making it increasingly difficult for them to live in a normal environment. Many or all of these intolerances disappear as the yeast problem is brought under control.

The purpose of this paper is to outline experiences in the treatment of chronic candidiasis by measures designed to restore immunologic competence to this yeast. Detailed discussion of the manifestations and diagnosis has been presented (Truss, 1978).

TREATMENT OF CHRONIC CANDIDIASIS

Chronic antigenemia, occurring naturally or induced experimentally, may result in immunologic unresponsiveness to specific antigens, including those of infectious origin. Antigens that evoke a normal immune response initially may induce immunologic tolerance when antigenic exposure becomes of the quantity and duration critical to its establishment. With its immunologic defenses neutralized, the host becomes incapable of eliminating from its tissues the source of tolerizing antigen, insuring perpetuation of the compromised immune response and persistence in the tissues of the infectious agent.

Total loss of immune capability is suggested by the terms "immunologic paralysis" and "immunologic unresponsiveness"; "immunologic tolerance" may perhaps better describe a continuing but ineffectual immune response that "tolerates" rather than rejects the organism. The "ebb and flow" in the opposing forces of foreign invasion and immune rejection is reflected clinically in the remissions and exacerbations characteristic of many chronic illnesses. The incompleteness of "paralysis" is suggested by fluctuations both in clinical manifestations and in such simple tests of normal immune activity as the white blood cell count, skin test response, body temperature, and antibody titer, as well as by the inconstancy of indicators of abnormal immunologic activity, e.g., immune complex deposition, RA factor, LE cell, ANA. The pattern of the clinical response may undergo constant change as the immune system reacts both normally and abnormally to the qualitative and quantitative variations in antigenic stimulation.

Persistence of Candida albicans in the tissues for prolonged periods typifies these principles. Chronic symptoms representing systemic responses to soluble yeast products accompany manifestations referable to the infected sites. Both fluctuate according to the effectiveness of a weakened immune response that is often influenced by factors directly favorable to yeast growth.

An analysis *of* such factors allows a logical approach to therapy, with each aspect designed either to retard the rate of yeast proliferation or to strengthen the immune response to its presence. Acting together, these measures interrupt the self-perpetuating cycle of tissue invasion and tolerance-inducing antigenemia. In time both local and systemic manifestations cease with eradication of yeast from the tissues—the ultimate goal of therapy.

A program that has proved effective in restoring immunologic competence to Candida albicans is summarized in Table 1 and described in the section following. of carbohydrate, often accompanied by exacerbation of their systemic manifestations.

This preference for carbohydrate has been documented objectively in a strain of Candida albicans reported in Japan; this strain has the unique ability to ferment carbohydrate to ethyl alcohol within the intestinal tract. A rapidly rising level of alcohol is measurable in the bloodstream following the ingestion of a measured amount of glucose or other carbohydrate. Other strains apparently lack the enzymes necessary to complete the conversion to alcohol.

In addition to limiting total carbohydrate intake, avoidance of foods with a high yeast

TABLE 1

TREATMENT OF CHRONIC CANDIDIASIS

I. Non-immunologic measures that retard yeast proliferation
A. Passive: measures of avoidance
1. Diet: low in carbohydrates and in foods with high yeast or mold content
2. Antibiotics
3. Contraceptive hormones
4. Environments characterized by high mold-spore exposure
B. Active: therapy with anti-fungal drugs: nystatin, amphotericin-B, flucytosine, ketoconazole

II. Measures to strengthen the immune response of the host
A. Passive (avoidance): immunosuppressant drugs
B. Active
1. Diet: adequate nutrients for proper immune response
2. Correction of unrelated conditions that impair the immune response, e.g., hypothyroidism
3. Use of extracts of Candida albicans
a. Extracts
b. Testing
c. Treatment

I. Non-immunologic Measures that Retard Yeast Proliferation

A. Passive: Measures of Avoidance

1. Diet

The first component of the "avoidance" aspect of yeast control embodies certain modifications of the diet. Of the three classes of foods, yeasts ferment fat and protein poorly, but thrive on carbohydrate. Limiting the intake of sweets and starches deprives Candida of the nutrient that allows its maximum multiplication. Most patients have observed increased intestinal gas and "bloating" following the intake of large quantities or mold content is helpful. The most important of these include breads and pastries with yeast (which should be avoided in any event as part of the carbohydrate restriction), mushroom (a fungus), aged cheeses, and alcoholic beverages with their high yeast content.

It is difficult to evaluate the benefit from these dietary restrictions when other measures are simultaneously alleviating symptoms. But in theory as well as practice, diet is important, especially early in treatment. Occasional departures seem not to aggravate symptoms noticeably, in contrast to the continuous high intake of these foods.

Additional benefits may derive from carbohydrate restriction. Many patients are allergic to the cereal grains, while others exhibit an abnormal response to carbohydrate in the glucose tolerance test. Carbohydrate restriction may eliminate such food allergens from the diet, and also may correct the excessive insulin response that results in hypoglycemia.

2. Antibiotics

The use of antibiotics should be limited to the fullest possible extent, avoiding in particular the "broad-spectrum" drugs that destroy the gram-negative intestinal and vaginal bacteria. At those times when their use is dictated by culture and sensitivity studies, stimulation of the yeast may be countered with concomitant nystatin therapy, with discontinuation of the antibiotic as soon as possible. For a limited time overt symptoms of increased yeast growth can often be prevented in this way, although they may erupt in fulminant form if the antibiotic therapy is too prolonged. (This was illustrated in a highly sensitive patient who was protected by sixteen nystatin tablets daily during eight days of unavoidable Ampicillin therapy. On the ninth day explosive diarrhea, pruritis ani, and intense vaginitis erupted simultaneously and persisted long after the Ampicillin was discontinued.)

The long-term use of tetracycline for the treatment of acne is particularly insidious and must be discontinued in these patients. Another condition in which antibiotics are often needlessly used is in the treatment of urethritis. Although due to the generalized Candida infection in the vulvo-vaginal area, because of the dysuria and frequency it is often misdiagnosed as cystitis and treated with antibiotics for weeks or months, despite the absence of a clinical response. This serves only to aggravate further the yeast infection that is the actual cause of the discomfort. Finally, viral illnesses are often treated with antibiotics; a great reduction in the use of these drugs would result from the careful differentiation of these from bacterial infections.

3. Contraceptive Hormones

Rivaling antibiotics in impact on the immune containment of Candida have been the “birth control pills", whether used for contraception, prevention of menstrual cramps, or regulation of menstrual irregularity. Avoidance of these hormones is mandatory if chronic candidiasis is to be successfully controlled.

Their use is associated with acute vaginal candidiasis in approximately thirty-five percent of women; it is quite probable that in the remainder, subtle changes occur in those immunologic responses appropriate for control of this yeast. Chronic yeast vaginitis tends to be at its worst when progesterone levels are high, as in pregnancy and the luteal phase of the menstrual cycle; therefore the progesterone component of contraceptive hormones may well be responsible for their adverse effect. The more severe cases of vaginitis often are associated with depression, emotional lability, and an explosive irritability, suggesting that an abnormal vaginal epithelium is but part of a general inadequacy in the response to these hormones.

This association of yeast vaginitis and "emotional" symptoms is worthy of special comment. They frequently appear for the first time in healthy young women soon after their first use of these contraceptive hormones. That they are symptoms of poor hormone function rather than "neurotic" or "psychiatric" in origin is clearly indicated by their absence before the use of these hormones and their disappearance soon after their use is discontinued. In this situation no physician would doubt the relation of these symptoms to improper hormone function. Yet the same symptoms in a young woman not taking hormones are almost always considered "psychoneurotic" in origin, leading to a futile psychiatric approach to therapy. The recognition of these as symptoms resulting from interference with hormone function is vital in recognizing this syndrome.

4. Environments Characterized by High Mold-Spore Exposure

Many molds that do not exist within the body have some degree of cross-antigen-icity with Candida albicans. Patients often

notice aggravation of their symptoms in environments characterized by a high content of mold spores; basement apartments and homes with a chronic moisture problem are frequently seen examples. Homes near poorly-drained areas or bodies of water are likely to have a high count of mold spores. Correction of drainage problems is helpful, as is proper control of the level of humidity in the home. Occasionally it is necessary to change homes.

B. Active: Therapy with Anti-fungal Drugs

Drugs that kill or suppress the growth of Candida albicans in vivo are of great benefit; only nystatin will be considered in detail. Other drugs are available but heretofore their toxicity has limited their use to life threatening Candida infections. Indications for their use should widen with increased understanding of the relation of yeast to systemic illness, both physical and mental. Drugs not presently available may serve better than nystatin to eradicate yeast from deeper sites within the tissues; ketocona-zole is a promising example.

Nystatin is valuable both diagnostically and therapeutically in human candidiasis. It is absorbed poorly from the intestinal tract, and is generally considered ineffective for other than yeast infections of mucosal and skin surfaces, where it may be brought into contact with the organism. As a suspension, it contacts yeast on the oral and esophageal mucous membranes; in tablet form it reaches the remainder of the intestinal mucosa. Suppositories are necessary for vaginal yeast suppression, and occasionally the cream or ointment is helpful for yeast infections of the vulva, skin, or nails.

Nystatin is fixed in the wall of yeast cells; this leads to increased permeability with efflux of vital cellular components and ultimate cell death. Absorption from the gastrointestinal tract is poor; a dose of approximately eight million units (sixteen tablets) results in low plasma levels in the range of 1 to 2.5 micrograms per mililiter (Goodman and Gilman, 1975). Even this low level may be of some benefit, however, since in vitro concentrations between 1.5 and 6.5 micrograms per milliliter may be toxic to Candida albicans (Goodman and Gilman, 1975). This is an important point. Electron microscopy has demonstrated that Candida albicans penetrates the epithelial cells of the mucous membranes, to persist therein as an intracellular organism. Thus even this limited absorption into the bloodstream may extend the effectiveness of nystatin to the more protected intra-epithelial cell sites and may account for the additional benefit noted in certain patients with higher doses. Even without penetration of the epithelial cell itself, the drug should encounter yeast cells in transit to this ultimate intra-epithelial destination. Also theoretically it is possible that yeast cell destruction in these deeper tissues is accomplished by lower doses in that this drug is fixed by the yeast cell wall, and perhaps could accumulate slowly therein until of sufficient concentration to initiate cell leakage and death.

Immunologic tolerance results from long-term exposure to an antigen either in low or high amounts. Interruption or reduction of such chronic antigenemia is essential in the restoration of the capacity of the immune system to respond competently to the antigen. To achieve maximum reduction in the antigenic load, nystatin must be brought into contact with the greatest possible number of yeast cells, hence the necessity for these various preparations. Candida lives predominantly in the gastrointestinal tract and vagina. A negative culture for yeast does not establish its absence in a given location. For reasons that at present are obscure, it frequently fails to grow with present culture methods, even though it may do so after stimulation with tetracycline for two to three days.

For these reasons nystatin in several forms simultaneously is used even if cultures are not positive from each site. This is particularly important initially when attempting to confirm the diagnosis by therapeutic trial. The combination may subsequently be modified in each patient according to the location of mucosal symptoms. The preparations and dosages that have proved useful may be summarized as follows:

(a) Oral suspension: Since the tablet passes immediately into the stomachy the liquid must be used to coat the mucous

membrane from mouth through esophagus. One teaspoon four times daily is adequate. The patient is instructed to use it as a mouthwash for one to two minutes, attempting to achieve contact with the maximum area of mucous membrane. As it is then swallowed, the esophageal mucosa becomes coated with the drug. The patient is advised to avoid food or drink for one to two hours after each dose in order to obtain maximum benefit. Use of the liquid is important since the lower part of the esophagus is a favorite site of yeast growth. In addition to reducing the release of yeast antigens from this area, nystatin administered in this way will often relieve symptoms of "heartburn," "indigestion," etc. that may have been present for years.

(b) Nystatin tablets are less expensive than the liquid and are used in its place to the fullest possible extent, although both are used initially. One tablet four times daily is a suitable starting dose. An increase to two tablets four times daily is recommended after three to six weeks except when the initial dose proves adequate for effective control of symptoms. After three to six weeks at this level, further increases to twelve or sixteen tablets in divided doses may be tried. If no additional benefit is derived; the dose is reduced to the least number that achieves maximum symptomatic relief. Nystatin is well-tolerated by most patients. Nausea or mild diarrhea may occur with higher doses. One patient complained of leg cramps accociated with nystatin therapy. Slight skin rash has been seen twice after long-term use. All such intolerances have cleared within several days after reduction of the dose or discontinuation of the drug; no serious toxicity has ever been encountered.

A special problem may occur when initiating therapy in the patient with multiple food and chemical intolerances. The different preparations may be tried individually in small initial doses. For example, the liquid may be tolerated by a patient who reacts to excipients in the tablet. Once a starting point is achieved, increased tolerance to these preparations will coincide with general improvement in the intolerances to foods, drugs, and chemicals.

(c) Vaginal suppositories are important in the initial treatment and are required intermittently in most women. This is especially true from puberty to menopause; the high progesterone levels following ovulation and during pregnancy often are associated with an increase in yeast symptoms. The use of vaginal suppositories should be continued during the menstrual period, blood being an excellent nutrient for yeast.

(d) Nystatin as a cream or ointment is prescribed when there are symptoms or signs of external yeast growth. In practical terms this is usually limited to the vulvar area, although occasionally infection may be noted on nails, at the corners of the mouth, or as a "diaper rash."

These, then, are the various preparations of nystatin that have been so valuable both in therapeutic trials and in the ultimate restoration of immune competence to Candida albicans. Other more toxic drugs are available, but the indication for their use must be weighed against their greater toxicity. Additional drugs of low toxicity are available for vaginal yeast infections and they can be tried if vaginal symptoms respond poorly to nystatin. Development of Candida albicans resistance to nystatin is said to be rare, but this should be reevaluated.

One phenomenon deserving emphasis is seen occasionally when therapy is initiated. It suggests the Herxheimer reaction, originally described when syphilis was treated with the arsenicals, and consisting of a febrile reaction thought to result from the massive absorption of dead spirochetes as well as to activation of foci of syphilitic infection (Herxheimer and Martin, 1926). It is important to recognize and distinguish this transient occurrence; otherwise it will appear to be allergy or intolerance to nystatin and the patient will be deprived of the benefit of this valuable drug. The reaction is usually limited to a flu-like syndrome of mild generalized aching and low-grade fever, but may also encompass an exacerbation of the patient's allergic manifestations. This was exemplified by a patient who developed a temperature of 101 degrees orally with associated generalized aching, beginning the first twenty-four

hours of nystatin therapy. Within three days he exhibited a recurrence of the acute agitation typical of his long-standing mental illness considered to be "schizophrenia." If indeed this was an example of the Herxheimer phenomenon, it established the relation of yeast products to this patient's chronic mental symptoms. The simultaneous diminution of multiple "mush/' stools in this patient indicates their relation to yeast infection of the bowel and further strengthens the concept that Candida is etiologically related to his symptoms.

Thus, when symptoms follow **immediately** the institution of nystatin therapy, it is. unlikely that a drug allergy is the cause. If such a reaction aggravates or reproduces the patient's previous chronic symptoms, it is confirmatory of their relation to Candida. This type of reaction to treatment will only be seen initially, and is not at all common. The possibility of this occurrence, however, suggests the wisdom of initiating therapy with a low dose of nystatin in patients whose symptoms would be particularly unpleasant if aggravated.

II. Measures to Strengthen the Immune Response A. Passive: avoidance

Immunosuppressants comprise a third class of drugs associated with a breakdown in the immune response to yeast. By definition these are certain to enhance yeast growth by their non-specific suppression of the immune response.

The most widely used drugs in this category are the adrenocorticosteroids. Their. effectiveness in suppressing the immune response has led to their extensive use in allergic and autoimmune disorders. Suppression of an abnormal immunologic phenomenon is beneficial with respect to the patient's symptoms as long as therapy is continued. But if the abnormal immunological response in question represents a response to Candida antigens, as suggested previously, (Truss, 1978), the immunosuppression induced by the steroid allows increased growth of yeast, even as the patient's condition is temporarily improved by these valuable drugs. Symptoms in such autoimmune
and allergic conditions result largely from inflammation induced by some type of abnormal immune response. Suppression of these abnormal immune responses cannot be achieved without at once suppressing normal immune mechanisms vital to the containment of yeast. With the etiologic agent in these cases an organism living within the body, steroid therapy actually constitutes an obstacle to the ultimate goal of clearing the tissues of the source of the incriminated antigen.

Judicious use of this type therapy is essential in many situations. Minimal doses with strict indications, perhaps in short courses rather than continuously, should minimize the impact of these drugs on immune competence to Candida. Meanwhile more specific measures for control of yeast should gradually obviate the need for the continued use of these drugs in conditions caused by Candida.

Similar reasoning is applicable to other forms of immunosuppressive therapy. When used in conjunction with organ transplantation, treatment of autoimmune disorders, etc., the underlying indication for immunosuppression will almost always override all other considerations. When Candida albicans is not etiologically related to the condition requiring this type therapy, induced exacerbation of candidiasis is of little consequence other than for increasing the risk of fatal septicemic spread in patients often already debilitated and often immunocompromised.

B. Active 1. Diet

Malnutrition may prohibit the normal immune response; therefore it is mandatory to detect and correct deficiencies in those nutrients essential for the proper function of cells of the immune system.

2. Correction of Unrelated Conditions

Similarly, endocrine or other metabolic abnormalities may impair the immune response, hypothyroidism being a common example. These should be identified and corrected when possible.

3. Use of Extracts of Candida Albicans

A rational approach to the use of antigenic stimulation (vaccine therapy) in the restoration of immunologic competence to Candida albicans in humans must be based primarily upon experiments in animals in the induction and termination of immunologic tolerance, supplemented by observations in humans of the natural history of diseases that eventuate in the state of tolerance.

Immunologic mechanisms responsible for "unresponsiveness" to "foreign" antigens appear to be similar to those involved in the maintenance of tolerance to "self" antigens. Evidence suggests that both depend upon the continued presence of thymus-derived suppressor cells which specifically prevent an immunologic response that in their absence would otherwise occur. Thus tolerance, even to "self antigens, seems to be an active rather than passive process.

Consideration of the experimental manipulations that first cause loss of and then restoration of responsiveness to an antigen suggests that the basic requirements for tolerance induction are met by chronic exposure to Candida antigens when clinical conditions are suitable for its continued presence in the tissues.

Similarly, experimental techniques for the "breaking" of tolerance illustrate principles applicable in the use of vaccines as an aid in the restoration of immunologic competence to Candida albicans in the human.

(a) Extracts: Because of the marked variation and irreproducability in the complement of antigens among strains of Candida, each new batch (lot number) should be tested for skin reactivity on known reactors. This applies equally to successive batches whether from the same or different companies. The importance of this "bio-assay" was illustrated recently when fresh extracts obtained from four different suppliers were tested simultaneously in a number of patients with previously demonstrated reactivity. Immediate hypersensitivity reactions ranged from 0 to ++++. This same inconsistency applied as well to the delayed skin test, considered indicative of the cellular immune response. Thus, depending upon the batch used, the same patient will, according to skin test, vary from non-allergic to highly allergic, with an immune response ranging from strongly positive to totally absent. The fact that these two types of skin response may vary independently suggests the possibility that different antigens are involved.

(b) Testing: Testing normally begins with .1 cc intracutaneously of the 1:1,000 dilution of the 1:10 concentrate. This is observed for immediate hypersensitivity, Arthus, and twenty-four and forty-eight hour delayed immune responses. If the immediate hypersensitivity reaction is negative and the delayed no more than moderately positive, the test is repeated using the 1:100 dilution, again to evaluate the patient for an allergic response. However, if the twenty-four or forty-eight hour delayed response is strongly positive to the 1:1,000 dilution, testing with the 1:100 strength is omitted because of the probability of an excessively large and painful delayed reaction. In any event, a positive test for immediate hypersensitivity is not essential for the diagnosis. A negative test reflects only a lack of response to the antigens in the particular extract.

A word of caution is in order regarding testing. The 1:10 undiluted concentrate should not be used. Too large an amount of antigen may lead to immune-complex deposition. A severe Arthus reaction beginning at two to four hours, consisting of a diffuse, indurated, itching, erythematous area several inches in diameter, may evolve into ulceration. This may be accompanied by a systemic allergic reaction such as occurred in one patient tested in this way by her physician; a very large Arthus reaction occurred, and within forty-eight hours she developed severe tinnitus and vertigo which required fully two years to subside completely.

Using this protocol, there have been no problems testing in this manner. Many allergists use different techniques for testing. Three patients described severe systemic responses to sub-lingual testing, and two patients told of similar reactions when tested by the serial-dilution "neutralizing" technique. These cases may be exceptions, and it would be helpful to know the experience of allergists who use these techniques in the

diagnosis of Candida albicans sensitivity.

Interpretation of test results: Despite the inconsistencies in extracts and the large number of healthy individuals exhibiting positive tests, efforts are continuing to find correlations of test results to aid both diagnosis and treatment. At the present time, however, tests do not distinguish between the symptomatic and asymptomatic individual with respect to Candida; neither are they of help in the choice of extract strength with which to treat; and they offer no clue as to the speed or degree of response to therapy. Thus, at the present time they are of no help in the diagnosis, treatment, or prognosis.

(c) Treatment: The injection of an extract of Candida albicans constitutes an attempt to strengthen the immune response to the yeast in a patient who is actively infected by the organism. Symptoms, both infectious and allergic in nature, exist in a setting of an impaired immunologic capability. Marked variation is exhibited among patients in the pattern of their allergic responses. It is not surprising, therefore, that in this unique situation it has proved impossible to standardize a program of injection therapy. The strength of the extract and the interval between injections varies not only among patients, but also in the same patient at different stages of recovery; it is as though the strength of antigenic stimulus must be matched roughly to the status of the immune response. Immunologic techniques may someday aid in explaining these variations and in establishing for each patient the optimal protocol for immunization; at present this must necessarily be based on empirical observations. The presentation to follow summarizes experiences and present methods of applying immuno-therapy in an overall program aimed at restoring to its maximum the immune capability with which an individual is genetically endowed.

Perhaps the best way to begin is to emphasize several principles that have not proved useful. It has already been pointed out that the choice of extract strength cannot be established by skin reactions, and that no combination of immediate and delayed skin tests indicates whether to treat, or predicts in any way the response of the patient to treatment.

Likewise thus far unsuccessful has been the attempt to choose, based on skin test, the particular batch of vaccine to which an individual patient might best respond. Efforts along this line are continuing, because in theory a patient should respond differently therapeutically to two vaccines that elicit sharply differing immediate and/or delayed skin reactions.

Also unrewarding has been the steady increase in extract strength that is often successful with conventional injection therapy for inhalant allergy. Although the patient may improve with each increment in dose, symptoms soon return and a further increase is required; eventually the maximum available concentration is reached and no further increase is possible. The immune system seems to adjust to each level of stimulation if given time. In most patients, therefore, changes in extract strength are made infrequently, and only when no response is apparent at the previous level.

Extensive experience with concentrations from 10^{-2} to 10-30 has led to the choice of extracts in the 10^{-5} to 10⁻15 range, although occasionally concentrations outside of this range are employed. One-tenth milliliter (.1 ml) subcutaneously twice weekly is a suitable starting point, but the interval may be varied in either direction. One departure from this basic schedule has frequently proved useful, often affording dramatic relief of acute symptoms. This consists of dividing the dose into several injections given at thirty to forty-five-minute intervals. Although the total dose may be virtually unchanged, the patient's response may be quite different. For example, ten doses of .1 ml each of the 10~15 strength contain the same total amount of antigen as .1 ml of the 10¯14 strength—still an extremely small amount. Administration of two to four injections spaced this way will often afford relief not provided by a single injection of either of the two adjacent dilutions. This technique has proved very valuable diagnostically as well as in conjunction with efforts to alleviate such acute problems *as* migraine headache, bladder or urethral

spasm, or joint manifestations.

A tendency to overdo this departure from the regular schedule should be resisted because of its effect on the long-range immune response. Patience is essential to allow the immune system time to adapt to and begin its response to antigenic stimulation at the chosen concentration and interval.

One pattern of response occurs sufficiently often to merit special discussion. Marked, often dramatic improvement may occur in the first few weeks of treatment using the same dilution of antigen. Then the patient may report a symptom occurring as a result of the injection, often within thirty minutes or so; it may be a "stopped-up nose," or "extreme sleepiness." Such a symptom will clear almost immediately if the identical dose is repeated as soon as the symptom occurs. Thus the dose to which the patient has responded with steady improvement suddenly results in a symptom that is relieved by giving more antigen. At that point the amount of antigen given routinely should be increased until this minor side effect ceases. A change to the next stronger concentration is usually effective. (Example: .1 ml of $10\sim1^{5}$ twice weekly leads to steady improvement. After eight to ten weeks the above phenomenon occurs and the symptom is cleared by repeating the .1 ml of 10^{-15}. Thereafter treat with .1 ml of the $10\sim1^{4}$ strength twice weekly.) This unusual reaction is never serious, and usually occurs only once in a given patient, most often after the first few weeks of treatment. Since it is seen in the clinical setting of a much improved patient, it seem logical that it is occurring in a setting of an improving immunologic response to the vaccine. Speculation concerning the responsible immunologic mechanism is futile. Since more antigen relieves the symptom, it is useful to think in terms of the balance between antigens and antibodies in the serum; as the antibody response becomes stronger, symptoms result because an imbalance in the direction of antibody excess perhaps leads to immune-complex deposition. The injection of more antigen returns the antigen-antibody balance to the zone of equivalence. Experimentally immune complexes are much more damaging if given in the zones of either antigen or antibody excess. (The immune response comprises much more than the antigen-antibody relationship, and it is highly improbable that this explanation is more than a useful framework for necessary adjustments in response to a changing immunologic picture.)

In certain patients an additional modification of the basic schedule is occasionally necessary, and again, an explanation based on immunologic evidence is not possible. Certain patients will notice complete relief of symptoms following the antigen injection. However, if they are still asymptomatic at the time of the next injection, symptoms may recur within a few minutes of the injection. Such cases are better managed by delaying their injection until symptoms have started to return, at which point relief rather than aggravation will occur. (Using the same immune-complex hypothesis, the asymptomatic state represents the absence of significant antigen or antibody excess, at which point antigen administration results in antigen excess and onset of symptoms. On the other hand, the return of symptoms signals the beginning of antibody excess and injection of antigen, if delayed until this time, again restores antigen-antibody balance.)

In summary, immune therapy with Candida albicans extracts consists of arbitrarily choosing a starting dilution and observing the patient's response over a period of a few weeks, adjusting the strength and interval of extract accordingly. It is important to explain to the patient that symptoms will recur frequently, but that with patience and time, as the resistance to yeast gradually increases, relapses will become less frequent and less severe. The situation is unique. An effort is being made to rekindle the immune response to an organism that is actively infecting the patient. It is both an infection and a systemic allergic and/or toxic response to metabolites of an organism that has been able to perpetuate its presence in the tissues by effectively neutralizing host defenses.

DISCUSSION

One method for the experimental induction

of immunologic tolerance is to expose an animal repeatedly to soluble protein antigen below the threshold dose that is immunogenic (Benacerraf and Unanue, 1979). This "low zone" tolerance is usually restricted to the T-cell, the B-cell retaining or recovering the ability to respond with antibody production.

Colonization of tissues by Candida albicans provides in the human the counterpart of this experimental protocol for the induction of T-cell tolerance. The presence in human sera of 79 immunologically distinct antibodies to Candida indicates the chronic release of a complex mixture of soluble proteins, thus simulating the conditions for experimental tolerance induction by chronic exposure to low doses of antigen. Studies reported by Budtz-Jorgensen in children with advanced chronic mucocutaneous candidiasis demonstrated that in this condition tolerance is primarily in the T-cell. When the fungus was suppressed by am-photeracin-B therapy, the ensuing reduction in antigenic load led to conversion from negative to positive of in vitro tests of the T-cell response without detectable change in antibody titers. Upon withdrawal of amphot-eracin-B, these in vitro tests reverted to negative with relapse and spread of the fungous infection, again with no detectable change in antibody levels. Further confirmation that B-cells may remain functional in the presence of tolerized T-cells is suggested by experiments in monkeys with induced Candida infections of the palate (Budtz-Jorgensen, 1973). Without suppression of the T-cells by azothiaprine, an early T-cell response preceded by several weeks the onset of detectable antibody. Prior treatment with this immunosuppressant prevented the T-cell response and resulted in a stronger and much earlier antibody response, suggesting that T-suppressor cells were more susceptible than T-helper cells to inhibition by azothiaprine.

The importance of retained B-cell function in association with T-cell tolerance to Candida antigens relates to experimental techniques for the termination of specific immunologic unresponsiveness. Provided that B-cells remain functional, T-cell tolerance may be "broken" by the injection of a cross-reacting antigen, which may be defined as a protein with determinants that are shared with the tolerated protein as well as others that are specific to itself. For maximum effectiveness the degree of antigenic identity should be at least 15 percent but not more than 75 percent. Current theoretical explanations for this phenomenon have been presented in a recent concise review (Benacerraf and Unanue, 1979). T-helper cells that are tolerant and unresponsive to shared determinants will respond to those determinants specific to the cross-reacting protein. If there are B-cells capable of cooperating with these stimulated T-helper cells, they will produce antibodies that are effective in terminating tolerance.

An exception that has been described to this general principle could well be important in the clinical setting of candidiasis. If the tolerated protein is injected simultaneously, the cross-reacting protein fails to terminate tolerance, the theory being that the shared determinants temporarily toler-ize the B-cells, rendering them incapable of responding to the new T-helper cells. In patients the various factors that stimulate yeast growth should result in the increased release or "injection" of the tolerated protein. By analogy, this should decrease or prevent the desired response to the cross-reacting protein, which in this case has been extracted from Candida albicans and administered as a "vaccine." The clinician endeavoring to restore a patient's competence to respond to the antigens of this yeast is not so fortunate as the experimentor, who may arbitrarily withhold further exposure to the tolerated protein. Surges of yeast growth associated with high carbohydrate availability, contraceptive hormones, antibiotics and immunosuppressant drugs, and characteristic of the luteal phase of the menstrual cycle and pregnancy may account in large measure for inconsistencies in the response of patients, particularly in the early months of treatment. The pre-menstrual period is characteristically the time of greatest intensity of yeast vaginitis for most women; the sudden return of symptoms at this time is the most frequent example of this fluctuation in response.

Recovery from immunologic tolerance may also occur spontaneously, i.e., without **the** influence of cross-reacting antigens. Since this is greatly influenced by the presence of residual antigen capable of tol-erizing new cells arising from the stem cell pool (Benacerraf and Unanue, 1979), all aspects of therapy other than active immunization with extracts are designed to minimize the "tolerogenic" load. If total elimination were possible, presumably spontaneous recovery from the tolerant state would co-' incide with the emergence of young competent cells in the absence of tolerogen.

Of the greatest importance to many patients with chronic candidiasis is the development of intolerance to foods, drugs, and chemicals. A careful history often reveals the earliest of these intolerances occurring in the first several years after the symptoms of chronic yeast infection. Thereafter occurs a rapidly accelerating inability to tolerate environmental chemicals, whether they be known as "foods," "drugs," or "chemicals." These patients may literally become unable to live in normal environments, resorting for relief to the most dramatic measures of environmental control. They are unable to work, and may even move to remote areas in their attempt to minimize the total load of chemicals contacted in their daily lives.

Dr. Theron Randolph (1962) called attention to this developing problem beginning in the early 1950's and discussed the problem at length in 1962. His pioneering efforts have enabled many patients to be helped by a program of maximum avoidance of the offending chemicals, including contaminants in both food and air. It is of great interest and potential significance that his observations and publications in this field coincided with the tremendous proliferation of articles delineating the increasing prevalence of chronic yeast problems in the population, attributable to the advent and wide-spread use of the broad-spectrum antibiotics.

Disappearance of such chemical intolerances often occurs when the candidiasis clears. Patients may begin to note improvement in the first few weeks of treatment; within six to twelve months, most or all of the intolerances will be gone in many cases. The rapidity and degree of recovery may well reflect the speed of recovery from the yeast antigenemia which in turn is influenced by the sensitivity of the specific strain of yeast to nystatin, by the degree and speed of response to yeast vaccine by the immune system, and by the extent to which the patient is able to avoid those factors that favor yeast proliferation.

The suggestion is made that one of the adverse effects of chronic candidiasis is to alter the adaptability to environmental contacts. Probably everyone would react to any chemical if exposed to a sufficiently high concentration. Therefore it appears to be the threshold at which an individual reacts that is altered by the chronic exposure to yeast products. When this alteration is minimal, environmental intolerances are minimal. But in a patient who is highly susceptible to this particular effect of Candida, the number and severity of intolerances may be completely incapacitating. Even the slightest exposure to cosmetics, foods, drugs, and almost any other class of "chemicals" may lead to severe physical symptoms, including those arising from the central nervous system and so frequently er-roneously considered "psychoneurotic" in origin.

The relation of Candida albicans to the de-velopment of drug allergies is of particular importance. Intolerance develops to a rapidly expanding number of drugs. This often is one of the earlier manifestations of chemical intolerance. It suggests the possibility that either Candida antigens, or antibodies directed at these antigens, are acting as carrier proteins, combining with the drug ("hapten") to form an allergic complex.

Finally, it cannot be emphasized too strongly that the treatment of this condition is unique. Each patient requires close attention and ready access to the physician. When symptoms recur, the associated depression and anxiety may be severe, accompanied by a destructive loss of self-confidence and nope. Together with the lethargy and excessive sleepiness that often coincide with the physical manifestations characterized for each patient, these "emotional" symptoms, actually referable to the

effect of yeast on the central nervous system and on hormone function, may render a patient unable to cope with the simplest daily problem. This may be devastating in women during the child-bearing years, almost certainly due to interference in the response to hormones so characteristic of this condition.

Marital problems are often acute. If most physicians are so quick to relegate these patients to the psychoneurotic category, one can only imagine how difficult it is for a husband to accept that this is not willful behavior, and absolutely cannot be controlled voluntarily any more than other conditions that adversely affect brain physiology. His interpretation of his wife's behavior is profoundly reinforced by her often total loss of libido and aversion to marital relations. The patient herself feels hopelessly isolated, with no place to turn as she sees her life disintegrating. Faithful adherence to medical recommendations (including psychiatric treatment) by many specialists for many years has not stopped the deterioration of her health and her life. In fact, often the combined undesirable effects of many well-intentioned medications have only served to depress further the involved physiologic processes, with minimum benefit symptomatica! ly. Careful explanation to a husband is of great value to him, to the marital status, and to the woman struggling to escape from this disaster during the time necessary for her to begin to improve. Once improvement begins, it becomes easier for all concerned to accept that all along this has been a physiological and not a psychiatric problem, and to believe that finally there is a justifiable basis for renewed hope.

When these patients have the sudden recurrence of symptoms, it has proved most valuable to have them stay in the office and receive the yeast extract at twenty to thirty-minute intervals for one and a half to two hours. This is almost always effective in alleviating the acute symptoms, both physical and mental. Of even greater value is the benefit to patient and family of seeing this reversal of these unbearable symptoms. Even though cautioned that relief by this method lasts only a few hours to a few days, they now have evidence from their own experience that there truly is a physical reason for what to both family and physician had seemed so surely to be psychiatric in cause.

SUMMARY AND CONCLUSIONS

Chronic infection with Candida albicans results when a state of impaired immunity prevents the normal immunologic responses necessary for eradication of the yeast from the tissues. Symptoms usually occur at the sites of fungous colonization. More importantly, symptoms frequently result from responses in uninfected tissues to yeast metabolites released systemically; these may represent an allergic or other abnormal immunologic response, but theoretically could also result from toxins acting through non-immunologic mechanisms.

A program has been described that is designed to achieve the maximal possible reduction in the quantity of yeast products entering the bloodstream, together with a program of active therapy with extracts of Candida albicans designed to terminate the state of immunologic tolerance. The rationale presented is based on current theory of mechanisms involved in the induction and termination of tolerance.

The goal set forth in the title of this paper is at once ambitious and unattainable except in a relative sense. Its universal presence in humans indicates an inherent weakness of the immune response to this yeast.

More properly stated, the goal of therapy becomes the restoration of the maximal immune capability with which each individual is genetically endowed, whereby is achieved the maximum possible reduction in the chronic exposure to this organism and its metabolites.

References

BENACERRAF, B. and UNANUE, E.: Textbook of Immunology. "Tolerance." Baltimore: Williams and Wilkins Co.; 166-177,1979.

BUDTZ-JORGENSEN, E.: Cellular Immunity in Acquired Candidiasis of the Palate. Scand. J. Dent. Res. 81; 372-383.1973.

BUDTZ-JORGENSEN. E.: Immune Response to Candida Albicans in Monkeys with Experimental Candidiasis in the Palate. Scan. J. Dent. Res. 81;360-371,1973.

GOODMAN, S. and GILMAN, A.: The Pharmaceutical Basis of therapeutics, 5th ed. New York: MacMillan; 1235-1236.1975.

HERXHEIMER, K. and MARTIN, H.: Dermatology and Syphilis. Arch. Derm, and Syph. 13; 115,1926.

RANDOLPH, T.: Human Biology and Susceptibility to the Chemical Environment Springfield, Illinois: Charles C. Thomas, pub., 1962.

TRUSS, C: Tissue Injury Induced by Candida Albicans: Mental and Neurologic Manifestations. Journal of Orthomolecular Psychiatry 7,1, 17-37,1978.

BOOK REVIEWS

PSYCHOBATTERY:
A CHRONICAL OF
PSYCHOTHERAPEUTIC
ABUSE
Theresa Spitzer
Humana Press Inc.,
Clifton, N.J., 1980

Everyone who contemplates psychotherapy, every family physician who recommends it to his/her patients, every psychiatrist who is unaware of what it does, must read this book. Psychotherapy is one of the martial arts which must be entered into with great care and trepidation.

I hesitate to use the word 'psychotherapy' for I define psychotherapy within the medical model as a relationship between patient and physician where the physician supports the patient, encourages him/her to follow treatment, to deal with current problems, to discourage aggression, to avoid invading his/her privacy. It follows the ancient and wise rule "above all do not harm the patient."

After reading **Psychobattery** I was left with a feeling of guilt and despair, with a sense of collective guilt as if I were personally responsible for the brutal psychiatry described in this book. Nearly 30 years ago I had assumed group therapy would play a very insignificant role in the future.

In 1950, group therapy was new and appeared to be promising. For over a year I was group leader to two groups of my patients. As a resident I was responsible for thirteen patients. We were then preoccupied with the holy therapeutic hour (50 minutes after Freud) which each patient received three hours per week. Had I tried to follow this prescription I would have spent 39 hours each week, but we all had other responsibilities as well. This meant putting in a 70 hour week. Instead I saw each patient one hour per week in individual therapy and in two group sessions. Thus everyone was seen the holy three hours.

Those days we must have been naive for we did not encourage aggression and hostility. I hoped my patients would gain comfort and support from the group. As group leader I did not allow any attack upon any patient, nor were they forced to speak up, emote, cry, scream or speak in tongues.

Within a year I had concluded group therapy was no better than individual therapy, which in turn was no better than chance in producing recovery. But by then I was busy with our double blind experiments testing Vitamin B3 as a treatment for schizophrenia.

From then on I paid little attention to group therapy until I began to practice in British Columbia four years ago. I was amazed at the wide popularity of groups, especially among psychiatrists. I began to see patients, refugees from groups, but was too disinterested in this to obtain the details. I still find it hard to understand how so many psychiatrists can be so interested in such a large number of therapies (over 200 and growing) which yield so few positive results.

I feel guilty for we have failed to alert our colleagues to the dangers of group therapy run wild, therapy which is no longer restrained by the humane principles of the medical model.

Theresa Spitzer describes a number of patients who suffered and were damaged by one of the encounter therapies. Several later came to me. It is a litany of horrors and could be made into a current horror movie. Patients were assaulted, brutalized, abused, their privacy invaded, experimented upon without their consent, let alone informed consent. The fortunate escaped to recover after receiving biological treatment. Patients were subjected to a variety of encounters such as primal scream, reality therapy. They received ridicule, insult. A constant theme was aggression. These therapists believed all patients suffered from unexpressed hostility. This is not a new idea. Several decades ago a well known psychoanalytic institute made depressed patients polish floors. Their "hostility" "directed against self was directed outward and sublimated into a clean, shiny floor. I like this better than hitting patients with soft bats; at least cleaning floors could reduce costs of hospital treatment.

These encounter therapists create paranoia in their patients by directing anger against their family, preferably against mothers. One social worker accepted this literally by talking about 'parentectomy.'

What is even more bizarre is that these patients were referred to these therapists by a department of psychiatry of a Canadian medical school. This medical school considers that vitamin therapy is much too dangerous and bizarre to be used. But they have given no thought to the toxicity of psychotherapy. Perhaps this book will alert them.

This book can protect patients from the toxicity of non medical psychotherapy. If you are normal, tough, resilient and merely want a bizarre experience by all means try encounter therapy, but have a close friend standing by to pull you out if you are not as normal as you thought you were. If you are anxious, depressed, uncertain, harassed or have any problem, avoid these groups like you would the plague.

If you are already receiving these paranoid encounter therapies please read this book and then discuss it with your encounter therapist.

A. Hoffer, M.D., Ph.D.

AMERICAN PSYCHIATRIC ASSOCIATION TASK FORCE REPORT # 14 (Sept. 1978) ON "ELECTROCONVULSIVE THERAPY"

We would not normally review a report on electroconvulsive therapy in this journal. It is a long established, useful treatment which must be used carefully as part of a comprehensive treatment program. When properly employed it can be lifesaving, can shorten serious illnesses, and occasionally it can prevent a lifetime of chronic psychosis, which many consider to be a fate worse than death itself.

This report, which concludes that ECT is a useful treatment, interests us for another reason. It was produced by an APA Task Force because this long-used treatment had recently become a matter of controversy. A small number of physicians had published a few hostile reports in which they claimed that ECT was a violation of patients' rights. We shall compare the way in which this task force was conducted with that other one dealing with megavitamins and Orthomolecular psychiatry whose report was published five years earlier.

The ECT task force was chaired by Dr. Fred H. Frankel. It consisted of nine members in all. A brief examination of the literature cited shows that every member had published at least one paper on ECT, some more than ten. This shows that they had expert knowledge of the subject and were

properly assigned to the committee. It also indicates there was no bias against the use of ECT. The nine members came from eight different institutions located in places as far apart as New York and California. No one institution could exert an inordinate influence on the committee.

The megavitamin committee was constituted differently. Its Chairman, Dr. Morris Lipton, frequently stated he had never used megavitamins himself; indeed, it seemed he rarely treated schizophrenics. He did not include in his committee one member who was recognized as being an Orthomolecular psychiatrist. One member had indeed done some poorly conceived comparison studies in Montreal. He used chronic patients for brief periods of time. He did not follow published protocols and did no follow up studies. He was known as an opponent of Orthomolecular studies and was considered to be biased, as we later discovered, by his own staff. All that can be said in his favor is that he did not conceal his dislike of the treatment. All five of Dr. Lipton's committee came from three institutions, NIMH in Washington, D.C., the university where the Chairman was located, and a mental hospital in Montreal. The Chairman himself and his university colleague and two other members had openly admitted their bias against the use of vitamins in both public lectures and critical reports before the task force completed its work.

The methods used by these two committees were also very different. The ECT committee completed a comprehensive literature survey, sampled 20 percent of the membership of the APA, held five two-day meetings where psychiatrists could appear to give their evidence and opinions. There was also one evening session and a two-day open forum during an APA forum.

Because they discovered there are few "well controlled studies" the ECT committee considered it essential to examine empirical evidence. This meant that after nearly 40 years of using ECT there are very few double blind studies, but the committee paid careful attention to clinical studies. The committee invited some highly experienced clinicians to give their opinions. They also sought out the views of the two neurologists most vehemently opposed to ECT. They examined evidence from a few selected psychiatric hospitals which used ECT. This committee tried hard to examine ECT in a fair and comprehensive way. In our opinion the Chairman and his members succeeded.

The megavitamin committee conducted itself very differently. Its members too claimed to find few well controlled studies. They ignored the series of double blind studies begun in Saskatchewan in 1952 under our direction in their conclusions. They did not realize that these were the first of their kind done in psychiatry and among the first of their kind in medicine. This alone made our studies worthy of serious consideration and careful scrutiny. The fact that they misinterpreted our data and misunderstood our conclusions might be due to faults in our presentation, but since we were never invited to appear at their meetings we could not correct their mistakes. (Just how many of these there were can be found in our pamphlet "In Reply", Hoffer and Osmond, 1976.) The only APA committee we were invited to meet, at our insistence, was the committee on ethics. Complaints had been made by unknown members of the APA that publishing papers describing the use of vitamins in psychiatry was against psychiatric ethics; that committee dropped the matter.

However, unlike the ECT committee which sought to supplement the shortage of "controlled studies" (so called), the megavitamin committee ignored all empirical data. It did not invite a single Orthomolecular psychiatrist to appear before it. We have learned that some private consultations were held with professors of psychiatry, none of whom had used Orthomolecular treatment. It held no public meetings to which the Academy of Orthomolecular Psychiatry was invited to present evidence. A few weeks before an evening panel at an APA meeting one of us was invited to a debate sandwiched between two hostile critics and a hostile chairman. This may have been an attempt to give the committee some appearance of fairness. This dubious invitation was declined.

The committee's literature search was defective since the members, never having practised this form of treatment, were un-

familiar with the extensive literature. This too could have easily been remedied. Finally, they made no attempt to inquire from hospitals and clinics of which there were a number then using Orthomolecular therapy.

The method used by this committee showed that they were intending to support conclusions reached well before the study began. The ECT committee members, if their publications are any guide, were biased in favor of that treatment, but were sure enough of their ground to undertake a fair and impartial inquiry. They then let the evidence speak for itself.

There are several possible explanations for the very different ways in which these Task Forces, both appointed by the APA, functioned. The Association may have profited from the criticisms to which it was exposed after the megavitamin report was issued. They may have developed rules for their committees which will prevent such a dismal performance ever being repeated. Perhaps the APA has two sets of guidelines for their committees, one for procedures which appeal to most of their members such as ECT, psychotherapy and drugs, and another for less popular treatments such as mega-vitamins in particular and nutritional therapy in general. In sharp contrast the vast majority of patients who have experienced tranquilizers alone and Orthomolecular therapy later prefer the latter. Most patients treated by Orthomolecular therapists have already failed to respond to standard psychiatric treatment.

Perhaps it was simply the chairmen who imposed their styles and biases on the members. Yet it is also possible that committee members forced their chairmen to behave as they did. Because the megavitamin committee conducted its affairs secretly we may never know about its inner workings.

There is suggestive evidence that this committee did little more than endorse a report prepared by its chairman and his junior professor, also a committee member, well before the committee was appointed. Dr. Morris Lipton gave a preview of this report at a public meeting in Los Angeles in 1971. A copy of this manuscript was sent to us by one of a number of people to whom he had distributed it.

We shall never know what happened unless there is a public inquiry into the workings of his committee, which is unlikely. Meanwhile if the APA wishes to improve its image as an ethical professional body it ought to invite another committee to examine Orthomolecular psychiatry. This time it should follow the rules of the National Academy of Sciences for inquiries into controversial matters. For a good beginning it might copy the methods of its own ECT Task Force Report #14.

While no one deplores the APA Task Force and its inept report more than we do it is a small consolation that this kind of misfortune occurs in the most august quarters. Recently the Food and Nutrition Board of the National Academy of Sciences stated that there should be no concern about fat, cholesterol and heart disease. These conclusions are at wide variance with those expressed by eighteen organizations concerned with nutrition and health. The Food and Nutrition Board is heavily biased by university biochemists and nutrition researchers. Because they can not find a direct metabolic link between fats and heart disease they are unwilling to accept that there is a relationship. The other school represents the epidemiological school who do accept a relationship. We think both schools have neglected a third more important relationship which is that both cardiovascular disease and fat levels are merely symptoms of a more fundamental syndrome, the Saccharine disease. This is caused by an over consumption of refined carbohydrates and an under consumption of fiber. Nevertheless, both camps can not be correct. If prestigious bodies can sometimes blunder it should not be too much for the APA to recognize that it too can make the same kind of mistake.

The APA committee accepted only double blind experiments as evidence (unless they were the ones we did which then were not acceptable). It should be salutory to them to read about the Anturan controversy. This drug was used to reduce post infarct complications. It was tested in a very rigorous double blind experiment which has been

described as one of the best experiments with rigorous supervision. Biostatisticians from Johns Hopkins and from the University of Colorado without notice would examine records in Winnipeg, for example, to make sure protocol was followed. The results were so impressive that an editorial in the **New England Journal of Medicine,** a very careful, prestigious establishment journal, hailed the drug as one the four greatest advances of the decade for post infarct patients. But, recently the FDA made a contrary conclusion; examining the same data a spokesman stated there was "some suggestion of beneficial effect" but, he added, it doesn't come close to statistical significance. This very expensive model double blind controlled experiment appears to have settled nothing. All that remains will be a long acrimonious debate between two important and prestigious groups.

Literature Cited

TASK FORCE REPORT 7 MEGAVITAMIN AND ORTHOMOLECULAR THERAPY IN PSYCHIATRY. July 1973. Chairman Dr. M. Lipton, American Psychiatric Association, 1700 18th Street NW, Washington, DC 20009.

ELECTROCONVULSIVE THERAPY. TASK FORCE REPORT 14. September 1978.<hairman Dr. F. H. Frankel, American Psychiatric Association, 170018th Street NW, Washington, DC 20009.

MEGAVITAMIN THERAPY. IN REPLY TO THE AMERICAN PSYCHIATRIC ASSOCIATION TASK FORCE REPORT ON MEGA VITAMINS AND ORTHOMOLECULAR THERAPY IN PSYCHIATRY. Hoffer, A. and Osmond, H., Canadian Schizophrenia Foundation, 2229 Broad **Street,** Regina, Saskatchewan S4P1Y7,1976.

A. Hoffer, M.D.,Ph.D. H. Osmond, M.D.