The Synergism Between Mycotic and Tuberculous Infections of the Lungs

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INTRODUCTION

The idea of a commensal relationship between fungus and tuberculous infections of the lungs has been suggested in the past. It is my impression that the importance of their coexistence has not been fully appreciated by the medical profession. The prevalent knowledge that fungi are ordinarily saprophytic and ubiquitous has, perhaps, led us into the erroneous attitude that all fungi found in the sputum are harmless contaminants, and their importance as a factor in an existing tuberculous process is slight and of no consequence in the consideration of the subsequent course of the tuberculous invalid who is unfortunate enough to be the host to both a tuberculous and a fungus infection. My object in this paper is to refute the impression that these coexisting fungi are harmless, saprophytic invaders, and to advance added data to support the premise that an infection of the lungs with pathogenic fungi in association with a tuberculous infection of the lungs is not harmless and coincidental, but that it definitely increases the activity and virulence of the tuberculous process. An attempt will be made to analyze the possible ways in which this activation or modification takes place. Furthermore, it is hoped that a free discussion at this meeting may add to our knowledge of the underlying reasons for this increased invasiveness of the mycobacterium tuberculosis when a mycotic infection is also present; especially valuable will be observations along the trends of bacteriological, biochemical and immunological analysis.

The Problem of Diagnosis

The detection of a fungus infection with, or without, the presence of pulmonary tuberculosis may be fraught with difficulty. The symptoms and clinical course of pure pulmonary mycoses may be identical with those of pulmonary tuberculosis. Even the roentgenogram may be of no differential value. It is well to remember that fungi found in the expectorated sputa are usually saprophytic; especially is this true of the aspergillus, penicillium,

*Read before the Arizona Chapter, American College of Chest Physicians, Phoenix, Arizona, May 1948.
and the saccharomyces. It has been affirmed that the aspergilli and the penicillia are three times more frequently found than all other species combined. It has been my personal experience that the saccharomyces are found saprophytically in the sputum more commonly than both the aspergillus and the penicillum species. There is only one certain way to guard against the inclusion of saprophytic fungi, and that is by obtaining the specimen for examination by intratracheal aspiration, cultivation on Sabouraud's medium, and animal inoculation to prove the pathogenicity of the fungus. The problem is also enhanced by the relationship of certain fungi, the actinomyces, to the mycobacteria. Most bacteriologists classify both the mycobacteriaceae and the actinomycetaeae under the order actinomycetes, and identify them as bacteria (schizomycetes). There is no doubt that the actinomycetes are phylogenetically very closely related to the mycobacteria tuberculosis. Certain acid-fast forms of actinomycetes bear a close resemblance to the tubercle bacilli in morphology, cultural characteristics, pathogenicity and immunity reactions. The actinomycetes are very labile and prone to change their morphology, and some species may at least temporarily fail to form a mycelium and grow entirely in a bacillus-like form.

**Common Forms of Fungi Observed**

The pathogenic fungi, found in association with pulmonary tuberculosis in our studies of the problems were, the cryptococcus hominis, monilia bronchialis, saccharomyces hominis, aspergillus fumigatus, sterigmatocystis nidulans, and sporotrichum schencki. The penicillium fungus was never encountered even as a probable saprophyte in the expectorated sputum. The fungi, listed above, comprise the results in 12 cases of proved tuberculosis in whom we succeeded in isolating the fungi, by intratracheal aspiration, in pure culture, followed by animal inoculations in which the fungi were recovered from the animals' lung tissues. In 8 other patients, in whose sputum tubercle bacilli were absent, fungi were similarly isolated, and studied with like results. Five of these cases were pure bronchomycoses, including 3 cases of sporotrichosis, one aspergillosis, one cryptococcosis. One bronchiogenic carcinoma was found in association with monoliasis. There were 27 patients, whose expectorated sputa contained fungi, which we were not able to obtain from the trachea. We classified them as saprophytes. They were identified as 2 cases of cryptococcus Kützing, 2 monilia Persoon, 2 sporotrichum Link, 2 acremonium Link, 2 aspergillus Michell and 17 cases of saccharomyces Meyen.

There has been a gradual, but progressive, evolution in the conviction among physicians, during the past decade, that pul-
'monary mycoses, associated with pulmonary tuberculosis, must be searched for and seriously considered in every patient with pulmonary tuberculosis. Dodge reviewed the literature up to 1933, and found only 26 cases of pulmonary mycoses, which either simulated pulmonary tuberculosis, or were in association with a tuberculous infection of the lungs. This would indicate, considering my personal experience, that the relationship of the two diseases was not being seriously considered, and the fungus organisms were not being diligently sought for in the sputa of tuberculous patients before that time. Dodge found 19 cases of filamentous fungi, listed as 9 cases of nocardia, 2 oidiuim, 2 sporotrichum, 2 penicillium, 2 aspergillus, and 1 sterigmatocystis. There were found 7 cases of yeast-like fungi, diagnosed as 4 cases of cryptococcus, 2 monilia, and 2 endomyces. It is to be noted that of Dodge's 19 cases there were 13 of the classification of fungi imperfecti, and of our 18 cases of proved pulmonary mycoses, with and without tuberculosis, 10 of the fungi were fungi imperfecti. It would seem logical that we may expect fungi imperfecti to be found in two-thirds of the mycotic infections of the lungs. Other recent reports also indicate this to be true.

Previous Observations

Mary Lapham wrote in 1926, "There are cases of aspergillosis on record which subsequently became tuberculous, and Renon says that this is a dangerous feature of the disease. While it is not generally believed that the development of tuberculosis is in any way associated with a disease so rare that it is a curiosity, how do we know that this disease is so infrequent? Would it be strange if such a disease should seriously complicate, or even inhibit recovery in a case of tuberculosis?" She subsequently stated that when a case of tuberculosis is complicated by aspergillosis, recovery seems more difficult and more unstable because there is a decided tendency to relapses. Also, Castellani reported that some of these mycotic infections resemble tuberculosis clinically, and that the physical and roentgenologic findings will not aid in differentiating them from tuberculosis. Numerous observers have noted the malign effects the presence of a fungus infection has upon the course of pulmonary tuberculosis. This fact seems established firmly in the minds of competent clinicians.

Symbiotic and Synergistic Considerations

A consideration of the symbiotic relationships between mycobacteriae tuberculosis and fungi leads us into the realm of speculation, diverse viewpoints, and lack of definite knowledge. Perhaps one may seem bold, indeed, who essays to piece together the
available knowledge, and add purely theoretical considerations of his own, dealing with the symbiotic and synergistic problems of mycotic and bacterial association as they pertain to the problem before us today. The term “symbiosis” will be used in the same sense as employed in general biology, rather than in the more restricted conception of bacteriologists. In the latter meaning symbiosis refers to the growth of certain bacteria only in the presence of certain other bacteria.

The theories of Professor Wallin⁶ embody clearcut facts of symbiosis in the sense to be used in our discussion. He has proposed the term “prototaxis” to express a principle, defined by him, as “the innate tendency of one organism or cell to react in a definite manner to another organism or cell,” and “positive prototaxis,” as “the affinity of one organism or cell for another organism or cell.” The term “symbiosis,” then, indicates mutual benefit is derived; “parasitism,” on the contrary, presupposes some benefit to the parasite with either a harmful or no response on the part of the host. Wallin further affirms “symbiosis is applied to those cases where mutual benefit is derived. It is evident that there is no sharp distinction between parasitism and symbiosis considered from the point of view of prototaxis; parasitism and symbiosis are merely different end responses in the expression of one and the same biological principle.”

We have no proof that there is any symbiotic relationship between tubercle bacilli and pathogenic fungi when they are subjected to the same cytoplasmic environment in the lung tissues. We know they are subjected to the same encompassing factors—thermal, photic, electrical, chemical, and physical. It may be probable that in combined fungus and tuberculous infections of the lungs that the tuberculous implantation may be the primary one, and that the fungi, attacking the lungs later, produce some change, chemical or physical, which reactivates tubercle bacilli, which have become less virulent because of localizing and focalizing tissue processes and specific immunologic influences. Recently, reports from the Edward J. Meyer Memorial Hospital and the Department of Medicine, and the University of Buffalo School of Medicine,⁷ stated that subcultures of a mold of the penicillium group, obtained from a contaminated culture of tubercle bacilli, showed rapid and luxuriant growth on other cultures of tubercle bacilli at room temperature, that the mold grew faster and sporulated earlier than it did on similar sterile media. Their further experiments indicated the mold inhibited the growth of tubercle bacilli in culture, and, also inactivated tuberculin in two hours. This tendency for molds in inactivate tuberculin, that show bacteriostatic activity against tubercle bacilli in the test tube, had
been previously observed by others. In these test tube experiments, although no growth of tubercle bacilli was observed, acid-fast bacilli were still present in smears after several months incubation of the tubes. Could these findings suggest the mold, when in association with tubercle bacilli in the lungs, inhibits the building up of specific immunity, local and systemic, on the part of the tubercle bacilli? The conditions within the tissues of the lungs are vastly different than in the laboratory test tube. In the former it is quite unlikely the implantation of tubercle bacilli and fungi occur at the same, identical time, as was the case with the inoculation of the test tubes. One or the other, tubercle bacilli or fungi, would be expected to have had prior existence for weeks, months, or years, in the lung tissues, and to have become firmly engrafted with their pathological processes before the other one infected the individual.

One might reasonably expect biochemical interchanges to be produced when pathogenic fungi and tubercle bacilli both infect the pulmonary tissues. Tubercle bacilli usually become less virulent, and assume a less active and invasive state after residing within the lung tissues for varying periods of time. This lessened activity is dependent upon such factors as the initial virulence of the tubercle bacillus and its reaction to general bodily resistance, the acquired localizing tissue defense mechanisms and systemic immunologic developments, as well as the lessened nutrition for the bacilli within the tissues, which may partly or wholly encapsulate them. Such bacilli, deprived of an adequate, or balanced nutrition are less capable of multiplying because their limited intracellular reserve foodstuffs are thereby diminished. As a consequence there will be a marked reduction in the metabolic activities of the tubercle bacilli. It has been proved that inactive, or resting, bacteria regain their catabolic activities when any substance, normally utilized in their catabolism, is rendered available to them. The possibility that the mycelial fungi, especially, may supply nitrogen, at least, is suggested by our knowledge of the effects of certain mycelial fungi in the metabolism, life history, and successful development of higher plants. Mycelial fungi grow in and on the roots of many of these plants; the legumes, for example, are furnished available nitrogen by this means. The fungus mycelium may also serve to increase the decomposition of the infected tissues, thereby the cytoplasmic resistance to the inroads of the tuberculous infection is decreased. The highly speculative nature of these remarks is apparent to me. They are advanced as ideas of no definite value, perhaps, and solely for their importance in bringing about a more plausible explanation from your discussion of this problem.
In some cases of pulmonary mycoses the pathology closely resembles tuberculosis. Surrounding the fungus infection there is usually tissue destruction and softening, an accumulation of leucocytes, and the formation of pus. The abscesses become surrounded with a dense layer of new fibrous tissue, infiltrated with mononuclear leucocytes, and sometimes containing giant cells. This is interesting to note, even though no relationship is suggested, when we remember the frequently observed similarity in the clinical courses of chronic pulmonary tuberculosis and pulmonary mycoses.

Previous Personal Observations

In a former paper, written with Dr. H. N. Gemoets, our findings were reviewed of an investigation of 301 consecutive admissions to the Houston Tuberculosis Hospital. The object of the survey was to determine the degree, if any, of association of mycotic infections in tuberculous patients. Two hundred and ninety-five of the patients were definitely tuberculous; the remaining 6 cases were repeatedly sputum negative for acid-fast bacilli. In 45 patients of the total number (301) we isolated fungi from the expectorated sputum, but in only 18 cases did we obtain the fungi by means of an intratracheal aspiration. The remaining 27 cases, comprising the group in which we were unable to recover the fungi from the trachea, were excluded from our study because of the likelihood of the fungi, obtained from the mouth, being saprophytic. The fungi from the 18 patients were subjected to intensive studies, including injection into the lungs of rabbits. In every one of the cases pathological changes were noted in the lung tissues of the inoculated rabbits, and the identical fungus was recovered, again, by culture. We believe we were justified in deciding that these fungi were pathogenic. The larger number of these fungi were filamentous in type. We were greatly surprised at the remarkably short period of time elapsing between the inception of clinical symptoms in these patients and the development of advanced pulmonary disease. In 8 (77 per cent) of our 12 proved tuberculous patients the average time since the onset of their primary clinical symptoms was just 9.6 months. However, in this short period the lung changes had become far advanced. We suspected there was some cooperative influence at work to bring about such devastating changes in less than 10 months duration of known symptoms of sickness.

SUMMARY

An attempt has been made to discuss the commensal relationship between fungus and tuberculous infections of the lungs.
coexistence of these two infections produces a more rapidly fatal issue in tuberculous individuals than one should expect from a consideration of the duration of the disease process in the lungs. Fungi from the expectorated sputum are usually saprophytic. It is safest to obtain the sputum specimens by intratracheal aspiration, and subject the fungus to animal inoculation, if there is any doubt regarding its pathogenicity.

Physicians should search diligently for coexisting pathogenic fungi in every tuberculous patient whose clinical course is unusually rapid or prone to relapse. The fact that 1.6 per cent (5 patients) of our clinically diagnosed tuberculous patients harbored pathogenic fungi in their tracheal excretions, although tubercle bacilli were never recovered from these 5 patients, should be remembered. The mycelial fungi are found more frequently than yeast-like fungi as the etiologic agents of pulmonary mycoses, associated with pulmonary tuberculosis. The close phylogenetical relationship of the mycobacterium tuberculosis to certain fungi, the actinomycetes, and the frequently noted similar pathological changes in mycotic and tuberculous disease of the lungs are of interest. All ideas dealing with the cooperative relationship between the tubercle bacilli and fungi existing together in diseased tissues are highly speculative, as little, if anything, is known regarding such interacting or interplaying processes. Our investigations would suggest, in a limited number of cases, that the association of a fungus infection of the lungs in a patient having pulmonary tuberculosis would augment and accelerate the activity of the tubercle bacilli, either directly, or by lowering the vitality and resistance of the patient to the end that a more unfavorable course of the tuberculous disease, marked by relapses and relatively rapid progression, may be observed. It is suggested that there is some factor present in this interplay of two coexisting infectious diseases, some prototaxic or symbiotic influences, which causes an added infection of the lungs with pathogenic fungi to increase the ravages of pulmonary tuberculosis.

RESUMEN

Se ha intentado discutir las vinculaciones entre las infecciones fúngicas y tuberculosas de los pulmones. La coexistencia de estas dos infecciones en individuos tuberculosos produce un desenlace más rápidamente fatal de lo que uno esperaría tomando por base la duración del proceso morboso en los pulmones. Los hongos obtenidos en el esputo expectorado generalmente son saprofitos. Es mejor obtener los especímenes de esputo mediante la aspiración intratraqueal e inocular los hongos en animales, si existe alguna duda en cuanto a su patogenicidad.
Los médicos deben buscar asiduamente hongos patógenos coexistentes en todo paciente tuberculoso cuyo curso clínico es excepcionalmente rápido o propenso a recaídas. Debe recordarse el hecho de que el 1.6 por ciento (5 pacientes) de nuestros pacientes tuberculosos diagnosticados clínicamente tenían hongos patógenos en sus excreciones traqueales, aunque nunca se pudo encontrar bacilos tuberculosos en estos 5 pacientes. Se encuentran más frecuentemente los hongos micelianos que los hongos parecidos a la levadura, como agentes etiológicos de micosis pulmonares asociadas con tuberculosis pulmonar. La estrecha relación filogenésica entre el microbacterio tuberculosis y ciertos hongos, los actinomicetos, y las alteraciones patológicas semejantes, frecuentemente encontradas en enfermedades micóticas y tuberculosas de los pulmones, son de mucho interés. Todas las ideas tocantes a la relación cooperativa entre el bacilo tuberculoso y los hongos, cuando existen juntos en tejidos patológicos, son altamente especulativas, ya que poco o nada se sabe de la acción recíproca de tales procesos. En un número limitado de casos, nuestra investigación indica que la asociación de una infección fúngica de los pulmones en un paciente con tuberculosis pulmonar aumenta y acelera la actividad del bacilo tuberculoso, ya directamente o reduciendo la vitalidad y resistencia del paciente, de tal manera que se observa un curso más desfavorable de la tuberculosis, caracterizada por recaídas y un progreso relativamente rápido. Se sugiere que en esta acción recíproca de dos enfermedades infecciosas coexistentes existe algún factor, alguna influencia prototáctica o simbólica, que causa que una superimpuesta infección de los pulmones con hongos patógenos aumente los estragos de la tuberculosis pulmonar.

REFERENCES