Acceptance of the Howland Award

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Thank you for your kind and generous presentation. I am proud (and also humble) to be considered worthy of this recognition by my professional peers, and to have my name added to those on the plaque that commemorates this event. Awards that come to those who live long enough may have useful purposes. They call the attention of the young in our specialty and of the profession and general public, to the social and scientific developments in our field that represent advances, advances in methods of study and clarification of concepts. At the same time, it must be recognized that many other people help to create an environment that made social and educational changes possible and made these contributions worthy of recognition. A second look at the plaque reminds us of those pediatricians who were on the stage while these contributions to American pediatric progress were consummated. It is a genuine honor to be among them.

It is easy to refer to those of our students and residents who have become chairmen of departments, taking places in academic settings here and abroad. But to them must be added several hundred house officers who now take leadership positions in their communities, on the firing line in the practice of pediatrics. This is my rare opportunity to acknowledge them. They all share in this occasion. Each one left something behind while creating contributions to the community and to our specialty. To each of you men and women, who have contributed to the study of children and their diseases, to the prevention of illness and promotion of health in childhood, and to pediatric education and research, I accept this honor for you; the objectives of the Society have been fulfilled.

In thoughtful heart searching, in preparation for this activity, I tried to record some of the things that I thought had made it all possible. I showed it to Margaret Christie; she was always more successful in explaining where the wind was, when it wasn't blowing. On this current occasion she said, "You haven't captured it yet. The reason why you were continuously successful in attracting a superior group of students to the department, was because you cared. Everyone was part of our family and we cared." I suspect that is what the previous speaker was trying to say.

I decided to give you an abbreviated history of the problem of pulmonary calcification in nonreactors to tuberculin. For over 20 years, I have been associated with this problem.

The history of histoplasmosis has been done admirably by John Schwarz and his colleagues, but it was the suggestion of David Karzon and Jim McKay that you hear it from me. This interesting disease has consumed much of my research time since 1944 and the students are inclined to say "Dr. Christie certainly got a lot of mileage out of that idea." They are correct.

It is well known that only in very exceptional cases will a person who has been previously infected with tuberculosis, fail to react to 1 mg of OT or a second strength PPD. However, some doubt in the validity of this assumption began to appear as early as 1926.

An even more unique situation existed in some sections of the southeastern states and was first reported by Crabtree in 1933. He studied children over 4 yr of age who were negative to tuberculin. Seventeen percent of them were found to have pulmonary calcified lesions by radiographic examination. Bill Nelson and his Chief, Graham Mitchell (1937) from Cincinnati, found calcification in 43% of 27 children who did not react to PPD or OT.

Similarly, it was questioned whether the clinicians in middle Tennessee could recognize calcification. Consequently, chest roentgenograms of 154 children were sent to four independent nationally known specialists in tuberculosis. They were asked to read the films for evidence indicating tuberculosis. They had no knowledge of the tuberculin tests and there was remarkable agreement among them. In 25% of the children who were negative to tuberculin, there was definite evidence of calcification, and therefore the lesions were thought to be tuberculous. These and other studies revealed, with monotonous regularity, that there was, in certain sections of the United States, a prevalence of pulmonary calcification, far beyond that which could be explained on the basis of tuberculosis as revealed by tuberculin testing. It was clear that this discrepancy was most likely in young people living on or adjacent to the western Appalachian plateau or in the eastern half of the Mississippi basin. This prevalence of unexplained pulmonary calcification varied from state to state, within the states, and even in counties within the state. The reasons for these differences remained unexplained. The tuberculin test was therefore thought to be valueless.

By 1944, newly arrived at Vanderbilt, it became clear to me that the accepted interpretation, that pulmonary calcification is usually or generally an evidence of primary (first infection) tuberculosis needed to be completely reevaluated. If it could be shown that this unexplained calcification could be caused by some other organism, the implications, clinical and epidemiologic, were obviously very important. It was totally unacceptable to me that there could be so much anergy to tuberculin, which was an assumption of many authorities. This was the problem I inherited. (Fig. 1) I was assured that the problem had something to do with the limestone in the area, the same limestone which made the blue-grass so green and Jack Daniel's whiskey so pure.

Histoplasmosis was first seen and named by Dr. Samuel Taylor Darling in 1905. He was a pathologist in what is now known as the Panama Canal Zone. His career was tragically ended when he was killed (1925) in an automobile accident near Beirut, Lebanon. Before Darling's report in 1906, the disease was unknown. Thus, the cause of a disease, the definition of the clinical spectrum, the treatment and the natural course have all been developed during my lifetime. In 50 yr, the etiologic agent has been identified, the pathogenesis had been established, and a clinical picture defined in many of its variations. Reliable diagnostic tests have been established and the epidemiology worked out to a considerable degree. Although not always satisfactory, there are acceptable treatments.

The patient that Darling described was a Negro from Martinique who, at autopsy, showed generalized visceral involvement with hepatosplenomegaly and anemia. Darling believed that what he saw in the tissues was similar to if not the same as the findings of Leishman and Donovan. He, therefore, assumed that he was dealing with a protozoal disease. It is interesting that the name *Histoplasma capsulatum* was coined by Darling, who observed in the swollen "histio" cytes, the "plasmo" or "plasmodie" drumlike organisms. His equipment and methods of study were relatively crude by modern standards, but the excellence of his observations both clinically and pathologically was remarkable. The title of Darling's first paper was, "A Protozoan General Infection Pro-

Fig. 1. Healed "military tuberculosis" of yesteryear. Histoplasmin-positive, tuberculin-negative.

ducing Pseudotubercles in the Lungs and Focal Necroses in the Liver, Spleen and Lymphnodes."

Dr. William A. Demonbreun, Tennessean by birth and a graduate of Vanderbilt University had no formal training in mycology, but had learned much about the morphology of inclusion bodies from Dr. Ernest Goodpasture. It was Demonbreun who (1933) presented a paper at the 29th annual meeting of the American Society of Tropical Medicine, which is a masterpiece. He described how he cultured the organisms from the spleen of an infant who had histoplasmosis. His description of the growth characteristics, morphology, and nutritional requirements of *H. capsulatum* remains so accurate that practically nothing has since been added. He fulfilled all of Koch's postulates. He injected the cultures into animals during their life and then cultured the organism again from the organs after the animals died. He demonstrated clearly that a medium containing protein kept at 37° would allow the growth of the yeast forms of the organisms. He was dealing with a slow growing biphasic fungus occurring in yeast form in tissue and forming tuberculate chlamydospores in culture media, and he called these chlamydospores by the picturesque and descriptive term: teutonic war clubs.

I had not been at Vanderbilt very long before a child was admitted to our ward with a large liver, tremendous splenomegaly, and anemia with pancytopenia. The child died and proved to have disseminated histoplasmosis. With my medical school background and my work in the San Joaquin Valley, it was inevitable that I knew about coccidioidomycosis. It occurred to me that it was unprecedented for an infectious disease to be uniformly fatal. There must be a benign form. Could benign cases of histoplasmosis be responsible for the presence of pulmonary calcification and the absence of positive tuberculin tests? I wrote my old friend, Chuck Smith, in California wondering whether histoplasmosis might be responsible for the calcifications in persons who reacted negatively to tuberculin and to coccidioidin. A letter from Chuck

Smith dated December 30, 1943, contained the following postscript: "Old histoplasma holds a soft spot, probably because I know so little about it; but Demonbreun did do his epochal transmission studies at Vanderbilt and the status of histoplasmosis now is like that of coccidioidal granuloma before Gifford and Dickson showed mild infections occurred."

I am most pleased now to acknowledge my associate, Dr. J. C. Peterson. Without his microbiologic skill and meticulous clinical ability, the observations to be summarized could never have been completed. With Dr. Peterson's skill, we brewed a culture of *H. capsulatum* on broth, filtered it, and standardized it; we had developed our own histoplasmin skin testing material.

We tested 180 children during 1944, many of whom reacted positively to histoplasmin, particularly those who had pulmonary calcification, and did not react to tuberculin. As a matter of fact, so many reacted to this antigen that colleagues, locally and nationally, said that we were dealing with a nonspecific agent, and that individuals were sensitive to the broth. I was excited enough to pay a visit to an old friend, Dr. Arnold Rich, whose monumental studies and textbook on tuberculosis contained excellent reviews of anergy, particularly in the southeastern United States. He was not impressed but did not turn off my enthusiasm. Nevertheless, I still thought after learning about disseminated histoplasmosis and its similarity to tuberculosis and coccidioidomycosis that the proper way to explain this phenomenon was to try to find a benign form of the infection, and in that way, explain the pulmonary calcification in the tuberculin negative people. With the circumstantial evidence, I wrote to my old chief, Dr. Edwards Park, and it was he who suggested that I discuss the matter with Dr. Carol Palmer, an officer in the United States Public Health Service, whose epidemiologic studies had already shown pronounced geographic variations in pulmonary calcification in tuberculin reactors. We were devoted to our friend and chief, Dr. Edwards Park, and it was natural that we should share these interests in the problem of pulmonary calcification in nontuberculin reactors.

In March of 1945, Drs. Palmer and Furcolow visited us and became enthusiastic about what Dr. Peterson and I had already shown about this subject. Dr. Palmer obtained histoplasmin which he used in his nationwide project of skin testing of student nurses, reported in 1945. This study was nationwide, and showed enormous differences in the prevalence of skin test sensitivity to histoplasmin among persons from different regions of the United States and a high degree of correlation between histoplasmin sensitivity and evidence of pulmonary calcification in tuberculin negative persons.

In the meantime, we had conducted further epidemiologic studies. These defined the geographic distribution and the early age at which children acquired sensitivity to histoplasmosis and pulmonary calcification not related to tuberculin sensitivity. This was evidence of a relationship, but admittedly circumstantial.

Because we were in the middle of an endemic area, never without the problem of unexplained pulmonary infiltration and because we were urged by Dr. Goodpasture to demonstrate the

Table 1. A disease spectrum of human histoplasmosis
Clinical forms

1. Primary
2. Postprimary complication
 - (a) Intrathoracic
 - (1) Miliary, "atypical pneumonitis"
 - (2) Mediastinal adenopathy
 - (b) Extrathoracic
 - (1) Which may affect any tissue of the body and reinvolve many medical subspecialties. *i.e.*, regional adenopathy, meningitis, lytic bone lesions, Addison's disease, eye, skin, mucous membrane, ulceration, myocarditis and endocarditis, mesenteric adenitis, and ulcerative colitis.
 - (c) Disseminated, progressive varieties of histoplasmosis. Experienced house officers will frequently admit these cases with a diagnosis of aleukemic leukemia.

organisms morphologically in tissue, we set up some prospective studies. We had already been able to culture *H. capsulatum* from biopsy of various tissues but being the outstanding morphologist that he was, he wanted to see the organisms in tissue. Consequently, Dr. Peterson and I began, in our well baby clinic, to skin test in a prospective fashion. We put histoplasmin tests on well babies every 3 months until the children had converted. Then we studied them for evidence of systemic disease. We were amazed, in these converters, to find otherwise unexplained and frequently relatively asymptomatic lesions in the roentgenograms of the chest. During this time, several children died, either by accident or unexpectedly. Autopsies in these cases, revealed granulomatous lesions, some with calcification in the pulmonary and other tissues. These were reported by us in 1947. Thus, when we documented by cultural and microscopic demonstration studies that *H. Capsulatum* was present, this satisfied Dr. Goodpasture.

After this, the clinical spectrum of human histoplasmosis began to clarify and cases involving almost every organ and tissue in the body emerged. Every specialty and subspecialty of medicine became involved in this interesting spectrum which, even now, enlarges and broadens. In the meantime, by serologic methods, our laboratory aided in the clarification of certain epidemics of pneumonitis, unexplained pulmonary infiltration, and certain other chronic cases of tuberculin negative, sputum negative, cavitory disease in tuberculosis hospitals.

Chuck Smith, during the war, had been called to study an epidemic of pneumonitis at Camp Gruber. By that time, the epidemic should have been clarified because most of the patients reacted positively to histoplasmin that we supplied. However, the specificity of histoplasmin was not universally accepted. Many epidemics, because of Drs. Furcolow and Grayson, have now been correctly interpreted. Cave disease has been elucidated, and many epidemics have been studied. Patterns are recurrent—exposure to spore containing dust, bird droppings, mild to severe pulmonary disease, and general recovery are followed by calcification of the pulmonary lesions. Significant serologic complement fixation titers during the acute phase can be demonstrated. Cavitory disease was demonstrated by Drs. Batson and Johnson. Dr. Furcolow has contributed in many fields of histoplasmosis research, including clinical, and he has helped greatly in bringing information about histoplasmosis to the attention of the medical profession at large.

The clinical manifestations of human histoplasmosis are of protean nature. In many (most) of its manifestations, a single primary lesion may be entirely asymptomatic and appear only as a positive histoplasmin skin test. On the other hand, the acquisition of an infection may produce fever (101–103°F), malaise, fatigue with desire to rest rather than to play after school, cough, and night sweats.

Depending on the resistance of the host, and the presence of overwhelming infection with reexposure, there may be postpri-

mary complications (Table 1). Nevertheless, it is a strangely benign disease with many individuals who have acquired primary or even postprimary infection and have spontaneous recovery without ever knowing what the “flu”-like symptomatology represented.

To summarize and reemphasize, the clinical manifestations of histoplasmosis are so variable that it would be wise and helpful to remember everything known about tuberculosis. The generalized reticuloendotheliosis of histoplasmosis accounts for the disease in acute, subacute, and chronic forms with many systemic manifestations. The disseminated progressive varieties, much as in miliary tuberculosis, are postprimary complications.

When we entered the scene, thousands of individuals, particularly in this geographic area, but more widely distributed, even world wide, had pulmonary calcification and therefore, “tuberculosis.” The absence of tuberculin sensitivity was an enigma. The tuberculin skin test became useless as a case finding tool and roentgen examination of the chest became the accepted method of diagnosis. It has been fun, therefore, to see the pieces of the jigsaw puzzle of the 30's fall into place. Besides aiding in the elucidation of the clinical spectrum of human histoplasmosis which, in itself, has been important, I am personally satisfied to have contributed to the definition of the benign form of histoplasmosis and in that way see the tuberculin and histoplasmin tests come to their rightful places as a case finding tools. Their proper use and interpretation has become the epidemiologic index that is deserved.

The story of medicine is dynamic and inspiring no matter from which angle it is approached. It is closely interwoven with the story of peoples, civilization and most of all, of human minds. On one hand, it springs from folklore and superstitions and, on the other hand, from intelligent minds, culture, labor and a constant search for the truth. Whatever else it is or may be, I hope the story of medicine and histoplasmosis is never a dry repository of names and formulas.

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