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FIELD TRIAL OF SPHERULIN, A NEW DIAGNOSTIC REAGENT
IN COCCIDIOIDOMYCOSIS

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FIELD TRIAL OF SPHERULIN, A NEW DIAGNOSTIC REAGENT
IN COCCIDIOIDOMYCOSIS*

Introduction

Coccidioidomycosis is a pulmonary fungal disease that is widespread throughout the Americas. An estimated total of 55,000 new symptomatic infections occur yearly. But diagnosis is very difficult and the actual number of symptomatic cases may exceed the figure above many times. In numerous instances the course and pathologic features of coccidioidomycosis parallel tuberculosis, and many documented cases of the former have been initially misdiagnosed as the latter.

A most important means for detecting a subject with Coccidioides immitis is the indurated delayed cutaneous response that develops when coccidioidin is administered intradermally. Coccidioidin, which is derived from the mycelial or saprophytic phase of Coccidioides, plays a prime role also in the diagnosis and even in the prognosis of coccidioidal disease. We showed previously that spherulin, a derivative of the spherule or parasitic growth phase, was a superior skin-test reagent in mice and guinea pigs. Its efficacy in man was unknown.

Spherules ordinarily occur in coccidioidal lesions but they can be produced in a chemically defined medium. Spherulin was prepared from such spherules. In this project, it was tested in residents of Mexico in regions endemic and nonendemic for coccidioidomycosis.

Spherulin was compared directly with coccidioidin in the same subjects. Histoplasmin was also administered for purposes of cross-reactivity control. Two attributes of the reagents relating to their efficacy in man were studied in detail: sensitivity, or the capacity of one of the reagents to elicit reactions either missed or equivocally detected by the other; and specificity, or the property of the reagents

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of not reacting in unrelated infections. The findings showed that spherulin was the reagent of choice.

Method

Spherulin, 2.8 µg per dose, and coccidioidin (lot 64D₄; 1:100), 26 µg per dose, were administered intracutaneously to five groups of people in Mexico. Histoplasmin was administered concurrently in the dose the manufacturer recommended.

The groups included cavalry troops in Esperanza; Yaqui tribesmen in Potam; and prenursing students in Obregon, all in the state of Sonora, which is highly endemic for coccidioidomycosis. As a negative control, selected residents of Mexico City who had never been in a region endemic for coccidioidomycosis were tested. Finally, a small group of persons with culture-proved coccidioidomycosis was studied.

Results

In the endemic regions, spherulin (2.8 µg) detected numerous reactors missed by coccidioidin (26 µg). Thus 61.1 per cent of 113 cavalry troops showed a positive reaction to spherulin compared to 37.2 per cent who reacted to coccidioidin. In 83 Yaqui tribesmen, the positive rate was 63.8 per cent with spherulin compared to 44.5 per cent with coccidioidin. And, among 47 prenursing students, the rate was 74.4 per cent positive with spherulin compared to 46.8 per cent positive with coccidioidin.

In the negative control group, living in the nonendemic Mexico City region, none of 90 residents reacted either to spherulin or to coccidioidin.

No evidence of cross-reactivity between spherulin and histoplasmin reactors was found, nor was evidence that dermatophytosis, tuberculosis, chromomycosis, actinomycosis, Hansen's disease, scabies, impetigo, or acne produced a positive reaction with spherulin. Spherulin appeared to be highly specific. In cases where subjects reacted to both spherulin and

coccidioidin, the reaction was usually stronger to spherulin. Additionally, some persons responded equivocally to coccidioidin but were frankly positive to spherulin.

In Mexico City, three culture-proved disseminated cases of coccidioidomycosis with pulmonary, bone, and cutaneous involvement were studied for their reactions to coccidioidin and spherulin. All had been previously determined to be nonreactive to coccidioidin. This nonreactivity to coccidioidin was confirmed again in the present study. However, in one case, in which the patient had shown striking improvement, the skin sensitivity reaction became very strongly positive to spherulin (55 mm x 40 mm induration) even though it remained negative to coccidioidin.

Discussion

This research has disclosed a new, more sensitive reagent for detecting human experience with Coccidioides immitis. The enhanced sensitivity permitted the detection of such experience in cases where response to coccidioidin was frankly negative or equivocal. Thus, considering the role of the skin test in identifying respiratory disease, spherulin offers an improved diagnostic tool and a more precise reagent for epidemiologic studies. The value of spherulin in prognosis remains as yet unknown, although in one case of disseminated coccidioidomycosis that showed dramatic improvement, spherulin detected cellular reactivity where coccidioidin failed to do so.