

THE IMMINENT (!?)RETURN OF
SKIN TESTING FOR
COCCIDIOIDOMYCOSIS: A
PRIMER

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Outline

- Early Work with Coccidioidin
- Coccidioidin vrs Spherulin
- ST Placement and Interpretation
- Epidemiologic Usefulness of the ST
- Clinical Usefulness of the ST
- Development of a new Cocci ST



Charles E. Smith, MD (1904-1967)

Charles Smith, MD

- Professor of Public Health at Stanford
- 1937-1939 “wandering epidemiologist of Kern and Tulare County”
- Standardized Cocci ST and serological testing
- Consultant to the Secretary of War during WWII
- 1942 Dean of the School of Public Health at UC, Berkeley
- Ref: Stevens, Coccidioidomycosis, A Text, 1980

Coccidioidin- The First Skin Test

- Cooke in 1915 first attempted ST with an emulsion of mycelia and spherules
- Coccidioidin = Culture filtrate of mycelium grown in broth
- Developed and standardized by C. E. Smith and associates in the 1930s
- 1:100 dilution = standard test dose
- 1:10 dilution = optional
- Supplies depleted in approximately 1980

Epidemiologic Studies on Military Personnel in the San Joaquin Valley

- 1940-1941
- Goal: Identify persons who had not been infected before entering the endemic area, determine the extent of illness associated with ST conversion, evaluate the relationship of infection to time of year and climatic conditions
- Provision for the postmortems of persons dying of Cocci

Epidemiologic Studies on Military:

Conclusions

- Previous ST positivity was protective against subsequent infection
- Recruits with negative ST were susceptible to pulmonary Cocci; conversions were often asymptomatic; when symptomatic the disease was rarely fatal
- Black soldiers were more likely to disseminate
- The endemicity of Cocci was spotty even in areas of known risk

Epidemiologic Studies on Military: Conclusions, cont

- There was distinct seasonal variation in the infection rate- highest in late summer
- The more dust, the more ST conversions
- Less construction, more lawns and paving, less outdoor sports = decrease in new infections by 65%
- The infection is was not restricted to San Joaquin Valley
- Ref: Coccidioidomycosis, Drutz, Am Rev Resp Dis, 1978

Spherulin- A Better Skin Test?

- Would a ST antigen prepared from the host-related form provide a superior ST reagent?
- First produced by H.B. Levine 1950s
- Soluble fraction released by spherules produced in vitro then lysed by incubation in sterile water
- Replaced coccidioidin in late 1970s, early 1980s
- 2 strengths:
 - ▣ “Usual strength” equal to the 1:100 coccidioidin (2.8ugm)
 - ▣ “High test strength” equal to the 1:10 coccidioidin (28ugm)

Comparison of Coccidioidin and Spherulin ST

- Spherulin detects approx one third more persons who have experienced Cocci than coccidioidin
- Subjects who react to coccidioidin will always react to spherulin
- Only rare evidence of cross reactivity between Histo and Cocci
- Both ST are non reactive in patients from outside endemic area or with infections other than Cocci

- Ref: Dermal Sensitivity to *Coccidioides immitis*, Levine, Am Rev Resp Dis , 1973

Method of ST Placement

- Intradermal using short beveled 24-26 gauge needle
- Volar surface of the forearm
- At 48 hours, measure visible and palpable induration
- Induration of 5 mm or more is positive
- Avoid ST placement in patients with erythema nodosum- has caused violent reaction, local necrosis, and exacerbation of the EN
- Ref: Drutz, Am Rev Resp Dis, 1978; Sarosi, Am Rev Resp Dis, 1988

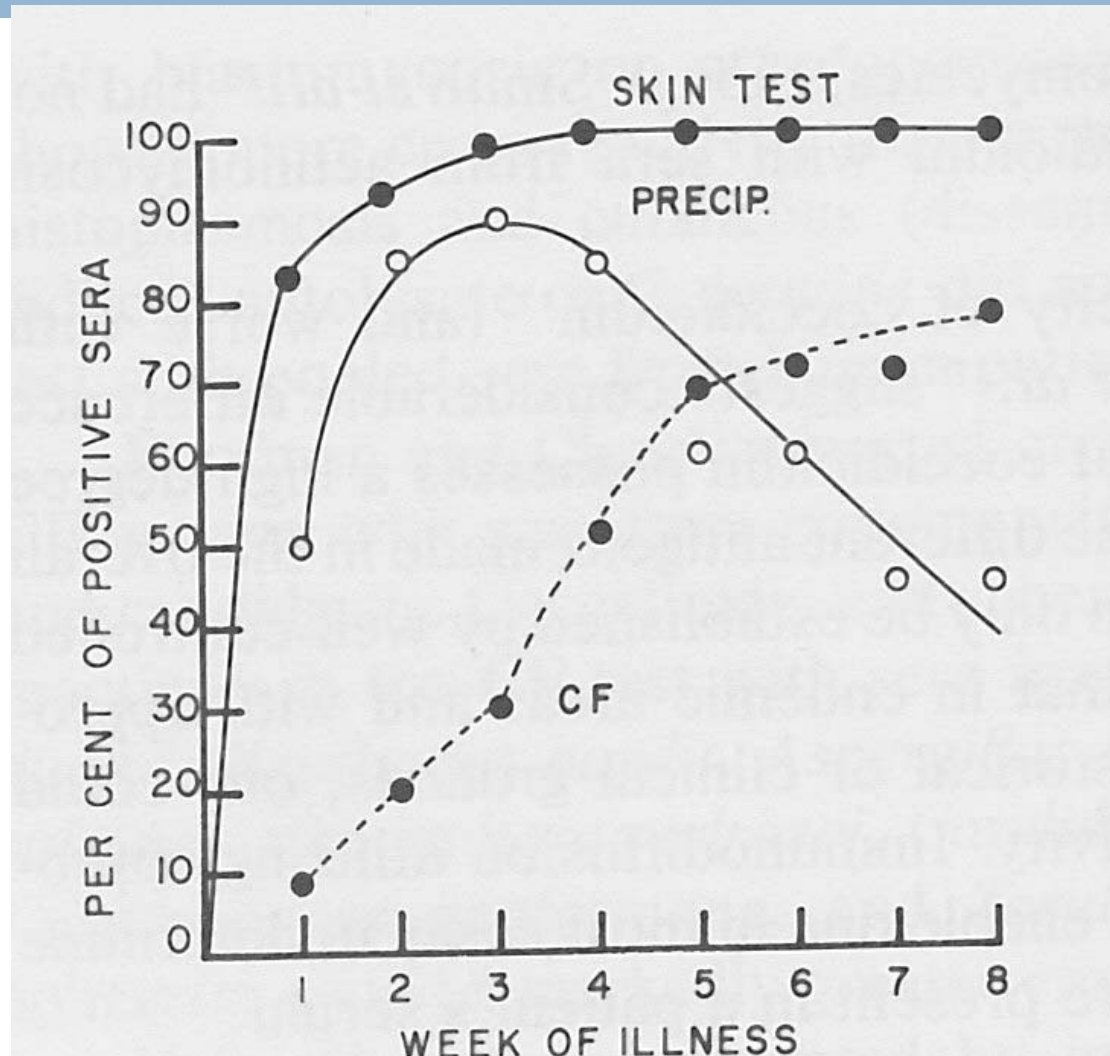
Interpreting Immediate “Wheal and Flare” Reactions

- 7.5% of 1 647 “Anglowhite” subjects exhibited an immediate wheal and flare reaction
- Immediate wheal and flare reaction associated with a higher rate of pos ST reading at 48h
- Reading at 24 hours may lead to a false positive due to immediate hypersensitivity reaction

- Refs: Dodge, Proc of the 4th Internat Conf, 1984; Buckley, Proc of the 4th Internat Conf, 1984

Graph of Cocci Serology and ST Conversion

- Smith, Ped Clinic N Am, 1955



ST in Primary Pulmonary Cocci

- Positive ST develops within 3 days to 3 weeks after onset of symptoms
 - 83% within the first week
 - 99% by the third week
 - ST does not adversely effect illness, serological testing
-
- Ref: Coccidioidomycosis, Drutz, Am Rev Resp Dis, 1978

Interpretation of a Negative ST

- A negative test suggests the patient has not been infected –as long as the patient does not have a chronic underlying condition that suppresses delayed cutaneous hypersensitivity
- However, there is a 2-4 week delay between infection and skin positivity
- ST reactivity may wane with time- Clinical significance not clear

ST in Disseminated Cocci – a Special Situation

- Usually ST reactivity never develops or wanes coincident with CF increasing
- A ST may be negative in a patient with severe Cocci infection
- Establishment or re establishment of reactivity during treatment or convalescence may be a good prognostic sign

- Ref: Drutz, Am Rev Resp Dis, 1978

Interpretation of a Positive ST

- A robust cellular immune response indicates that Cocci infection has occurred and that the host has developed long lived immunity
- Some cross reactivity between Cocci ST and histoplasmosis – though endemic areas are almost exclusive - overlapping only in Texas

Epidemiologic Uses of ST

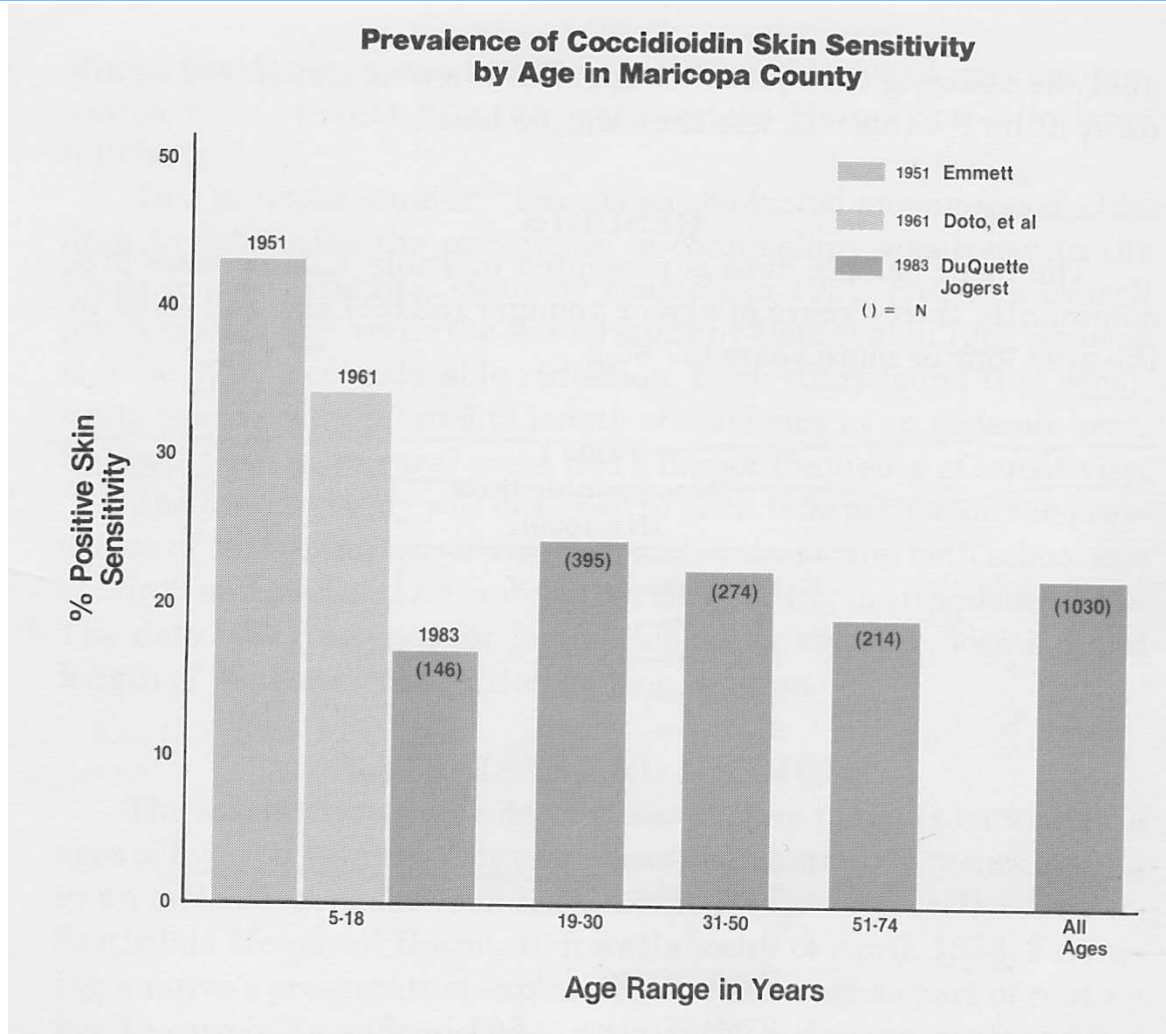
- ST data provides prevalence data in certain geographic areas
- Knowing the current prevalence of infection in a population helps estimate the number of persons susceptible
- Together with recognition of proven cases and ecologic studies, ST data is used to establish the distribution of C. Immitis in nature

Prevalence of Cocci ST in Ambulatory Population- Maricopa County, 1983

- 1020 patients aged 5-74
- Jan to April 1983
- Over all prevalence rate for all ages = 21.5%
- Rate directly related to length of residence in an endemic area
- Marked increase when residence was 5 or greater years

- DuQuetee, Coccidioidomycosis, Proceedings of the 4th International Conference, 1984

Prevalence of Cocci ST Sensitivity by Age in Maricopa County, 1983



Clinical Use of Cocci ST

- Documented conversion from negative to positive can be used to help diagnose primary pulmonary Cocci
- A positive ST is protective against second infection
- Therefore, in a host known to be previously ST positive, a new pneumonia is not likely to be Cocci

Clinical Uses of ST, Cont.

- Development of a positive ST in a patient with known pulmonary Cocci is a good prognostic sign
- Failure to develop a positive ST in a patient with known pulmonary Cocci is a bad prognostic sign and is associated with a higher frequency of relapse when therapy is discontinued.

Development of a new Cocci ST

- Spherulin was originally produced and marketed by Berkley Biologicals.
- Subsequently the product was sold twice and marketing was discontinued in 1990s.
- Since then, the product was purchased by Allermed and a reformulation and testing project was undertaken.

Spherule Derived Coccidioidin (SDC) (Spherusol)

- Newly formatted phenolic preserved spherule derived coccidioidin (SDC) – Studies over the last ten years.
- Ref: Delayed Hypersensitivity Skin Testing for Coccidioidomycosis: The Re-evaluation of Four Studies on the road to a Marketable Test Antigen; R. Johnson, N. M. Ampel, S. Nielsen, S. Kernerman, B. Sawtelle

SDC Specificity Studies

- In individuals with no history of or likely exposure to coccidioidal infections in Spokane, Washington on 59 evaluable patients:
 - ▣ Only one individual had a 5 mm response.
- In a study in Blair, Nebraska, an area endemic for histoplasmosis, on 12 patients:
 - ▣ All twelve were negative.

SDC Sensitivity Study

- In a phase III sensitivity study undertaken in Bakersfield, California and Tucson, Arizona:
 - ▣ 52/53 reacted positively.
 - ▣ The adverse event rate was low.

SDC Conclusion

- SDC was demonstrated to have sensitivity, specificity and safety such that it should be available for use in evaluating individuals for Coccidioidomycosis.
- Currently in the hands of the FDA.....(!?)

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- ***Discussion?***