The Importance of the Portal of Entry in Certain Microbial Infections

The Primary Cutaneous "Chancriform" Syndrome*

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Primary cutaneous (chancriform) coccidioidomycosis was delineated as a distinct entity in 1953 by Wilson, C. E. Smith and Plunkett. This collaboration began six years earlier when the patient first came under observation, but the report was withheld until we could be certain that the passage of time would not negate our opinion that the case was unique.

Subsequently this "chancriform" stage has been amply confirmed for coccidioidomycosis and has been shown to occur also in some other potentially systemic fungal infections. For this form to develop, the causative organisms must be inoculated percutaneously in persons not previously infected in any tissue by the same microbe and who are sufficiently normal immunologically to be capable of developing locally a significant degree of resistance.

Nature usually does not take the trouble to invent multiple methods or mechanisms where one serves adequately. It seems logical, therefore, to believe that the processes by which animals resist different microbial diseases are fundamentally closely similar if not identical. In many respects they do not appear to be so to us at present, but probably this is because there are still great gaps in our understanding of the pathogenesis of these diseases, both individually as well as when compared with each other. I believe there is much to be gained through making careful comparisons, not always searching for differences to emphasize, as has been done so often in the past, but for immunologic similarities followed by all, which may eventually lead to revelation of a fundamental pattern.

I believe the systemic fungous diseases have much to offer in the study of immunology, because the pattern seems to be less complicated than in viral or bacterial infections which have heretofore received the greater attention.

In this report, directed as it is to those interested especially in pulmonary diseases, the significance of an extrapulmonary portal of entry will be discussed for tuberculosis as well as for systemic fungous diseases, revealing considerable similarity in the pathogenesis.

In all of these diseases proved cases of this type are very rare, and would not in themselves be of much importance. The real value of the concept is that it indicates that cutaneous lesions of these mycoses much more often arise by dissemination from primary visceral foci than by direct primary cutaneous inoculation. This must be kept in mind, in spite of the fact that skin lesions are often the first indication of the presence of the disease, in order to avoid the selection of medical or surgical treatment of a type entirely inadequate because of its being directed toward the elimination of a disease wrongly considered to be sharply localized.

Schenck in 1898 firmly established one fungous disease, sporotrichosis, to be due usually to primary cutaneous inoculation. Subsequently, several thousand instances of this infection have been recorded, most of which have revealed a clinical picture so closely resembling the primary lesion of syphilis with its satellite lymph nodes as to deserve the term "chancriform." Very prominent has been lymphangitis, often with ulcerative nodules superimposed intermittently along the lymph channels, and a significant lymphadenopathy limited to the area drained. Some cases of sporotrichosis have presented skin lesions of different types, and there have been occasional instances involving visera, with only vague evidence to indicate the portal of entry. However, apparently none has been observed to have been preceded by a well-developed chancriform primary cutaneous syndrome, indicating that this form can occur only in previously uninfected persons.

Not until Ghon in 1921 described the primary lung focus of tuberculosis in children which became known as the "Ghon complex," and Bruusgaard in 1926 pointed out its equivalent in the skin, was the chancriform stage of tuberculosis separated from other types. Stokes probably should have priority, but he included in his report some cases which were almost certainly not primary in the

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known to be reaching the skin by way of blood or lymphatic channels, it was obviously secondary to a primary visceral focus. In many cases the portal of entry of the bacilli was not designated. However, in several instances of each, the infection was attributed to intracutaneous inoculation, such as occurred during piercing of earlobes (Wild\textsuperscript{18}), vaccination, or various accidental wounds. Even more impressive were cases infected through the process of tattooing with needles moistened in the mouth of a tuberculous operator.\textsuperscript{14-16}

It was never pointed out, however, that these recipients must have had visceral tuberculosis previously, or the chancriform type of clinical picture would have developed. (Of course the incriminated traumas might not have always actually furnished the “original inoculation,” but might have served only to furnish loci minoris resistentiae for secondarily disseminating bacilli to attack).

Holt\textsuperscript{17} in 1913 assembled a group of cases of tuberculosis acquired by newborn infants during ritual circumcision performed by tuberculous rabbis. Although these were undoubtedly percutaneous inoculations into previously nontuberculous individuals, the chancriform syndrome was not produced. As Sulzberger and Goodman\textsuperscript{18} later confirmed these must be placed in a separate group because large numbers of virulent organisms were implanted in persons too young to have well-developed immunologic defense mechanisms. Instead of the relatively benign, well-resisted chancriform syndrome, these patients exhibited massive dissemination, 39 per cent dying of miliary tuberculosis within two years.

Interspersed in the multitude of reports of tuberculosis of the skin during the first half century after its bacillary cause was revealed, there are hidden some instances of primary cutaneous chancriform infection. Some cases described very early were undoubtedly of this type, such as those reported by Knickenberg,\textsuperscript{19} Hallopeau,\textsuperscript{20} and Guizette.\textsuperscript{21} However, they were then classed as verruca necrogenica, tuberculosis verrucosa cutis or lupus vulgaris. The usual victims were persons brought into manual contact with tuberculous animal tissues such as physicians, dissecting room and mortuary attendants, and butchers.

It is also evident that some patients can exhibit both lupus vulgaris and tuberculosis verrucosa cutis in typical form simultaneously, indicating that the difference in the clinical pictures is due to a different degree or type of local tissue resistance. In these cases, the lymph vessels and regional nodes are not involved unless some other bacterial infection is also present in an acute phase. It is obvious

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that attempts to separate these various forms by dividing lines cannot have mathematical precision. There will be much overlapping, and transitional forms. Many cases cannot be classified, and some will seem to violate all “rules” until many gaps in our present knowledge are filled. Nevertheless, most cases can be reasonably well understood.

Students of tuberculosis may be excused for a 50-year delay in delineating the primary cutaneous complex, for it occurred only occasionally. Schuman28 reported 0.44 per cent in 889 cases. In Wichman’s series29 of 2,000 cases of skin tuberculosis there were only 2 per cent of this type.

However, it is surprising that it required so long for medical mycologists to recognize the chancriform syndrome in the systemic mycoses other than sporotrichosis. It would seem that Schenck’s definitive report on that disease would have pointed the way. The delay was probably due to the comparative rarity with which this stage occurs. It has been estimated that 10,000,000 persons have been infected with coccidioidomycosis, while the total of primary cutaneous cases reported to date is less than 20. The rate is even lower in other deep mycoses.

The various systemic fungous diseases seem at first glance to present more differences than similarities, while actually the converse is true. The discrepancies have been emphasized principally because of two factors. First, we have not yet learned easy methods of separating the clinical consequences of tissue preferences which the individual species of fungi exhibit from those due to the host response. For example, we may recall that Coccidioides immitis tends to invade lungs, and to disseminate preferably to bones and skin; Histoplasma capsulatum prefers to live and grow intracellularly, and even intranuclearly, within the cells of the reticuloendothelial system; while Cryptococcus neoformans is equally desirous of selecting an extracellular location within the nervous system. Thus, we could not expect the clinical pictures resulting from their infections to be the same. However, whatever portions of the syndromes are produced by the immunologic response of the animal host should probably be closely similar in all three diseases.

The second confusing factor is that we have not always been certain that we were comparing these diseases in similar stages. It is here that the delineation of the chancriform syndrome in coccidioidomycosis has been particularly helpful. For example, until about 15 years ago it was accepted as fact that the inoculation into the skin of three different species of pathogenic fungi regularly caused three different clinical pictures. It was thought that Sporotrichum schenckii produced the chancriform syndrome already described, that Coccidioides immitis caused a subcutaneous abscess, from which the infection spread by hematogenous dissemination throughout the body, and that Blastomyces dermatitidis induced an extremely chronic, verrucous skin disorder, slowly spreading superficially for many years, but almost never disseminating internally.

These discrepancies were resolved by the discovery of several cases in which Coccidioides or B. dermatitidis were known beyond a doubt to have been inoculated primarily into the skin and in which the resulting syndrome was chancriform, practically identical with that in the common form of sporotrichosis, indicating that when the portal of entry was the same, the disease produced was similar. The original case of primary cutaneous chancriform coccidioidomycosis reported by Wilson, Smith and Plunkett1 was soon confirmed by another observed by Trimble and Doucette,24 and later by reports by Wright and Newcomer,25 Overholt and Hornick26 and Goodman and Schabarum.27 Winn28 has observed several more, as have Levan and Huntington.29 Experimental intracutaneous inoculations in monkeys have followed this pattern.30,31 The status of primary cutaneous North American blastomycosis tests on the reports of Schwarz and Baum32,33 and of Wilson and colleagues.34 Although few in number, these patients were definitely known to have been intracutaneously inoculated, and the study of them has led to the conclusion, supported by ever-increasing evidence, that many of the rest of the cases of these diseases in which the initial lesion appeared in the skin were nevertheless not due to inoculation at that point, but to dissemination from a previously unrecognized or subclinical primary infection elsewhere in the body, usually the lungs.

Curtis and Cawley35 and Curtis and Grekin36 reported a case of histoplasmosis which followed the same chancriform pattern. Tosh et al37 have reported another.

Baumgarten38 has reported a case which was clinically exactly like the usual form of lymphatic sporotrichosis except that Nocardia asteroides was the organism recovered by culture. Alarcon, Obadia, and Borelli29 have reported a similar case caused by N. brasiliensis; another was described by Rapaport,30 and a third by Moore and Conrad.41 Guy42 had reported a chancriform syndrome caused by Nocardia in 1922; the species was not identified.

Thus, the chancriform syndrome has now been observed (with little variation in the clinical pic-
ture) in infections resulting from four species of pathogenic fungi and two Nocardia species when intracutaneously inoculated. Nevertheless it has not been reported to have occurred in several other systemic infections including cryptococcosis, actinomycosis, maduromycosis, South American blastomycosis and only doubtfully in chromoblastomycosis. In some of these it is likely that the chancriform syndrome never occurs, while it may occasionally do so in others under special circumstances. One reason may be the manner in which the various fungi grow in nature. *Sporotrichum schenckii* lends itself well to being inoculated percutaneously by growing as a closely adherent moist mat on thorny plants or wooden timbers, which can furnish thorns and splinters capable of inflicting wounds and leaving therein fragments of plant material containing many fungal spores. In nature, the spores are not easily released from the moist cultures, and are therefore not often air-borne. It is easy therefore to see why sporotrichosis is almost always acquired by primary cutaneous inoculation.

Conversely, Coccidioides and Histoplasma grow in and on soil as fluffy mats of thread-like hyphae, with spores so lightly attached and fragile that they blow away in the slightest breeze, making it easy to understand why they are seldom inoculated in any large quantity through the skin. The infections are therefore almost always acquired by inhalation. *Blastomyces dermatitidis* has been recovered recently from soil. Most of the systemic fungi not yet known to have a chancriform stage also grow in soil, including *Cryptococcus neoformans*, and the organisms of Mycetoma. The source in nature for *Paracoccidioides brasilienis* is not known as yet, nor has it been proved for the fungi causing chromoblastomycosis, although species closely similar to the latter are known to grow on dead vegetation which could cause intracutaneous inoculation.

Baquero \(^43,44\) reported some evidence that the usual chronic cutaneous form of chromoblastomycosis, formerly assumed to have originated by direct cutaneous inoculation, may in reality occur by dissemination from a previously unrecognized primary pulmonary focus, as is now widely believed to be the case in North American blastomycosis and coccidioidomycosis. He has cultured the pathogen from bronchial washings in four such cases. There are some recorded cases which appear to have been somewhat chancriform, but not typically so. The fungi causing chromoblastomycosis are so closely allied to common air-borne contaminants that it is not always possible to differentiate them and the inhalation of either form might alter the recipient's immunologic reactivity enough to obviate the development of the chancriform syndrome when the pathogenic species is subsequently encountered intracutaneously.

Even if intracutaneous inoculation does occur, for the chancriform syndrome to develop it is also necessary that the organism is resisted rather strenuously by the normal patient's immunologic mechanism. Otherwise, the point of inoculation would be as inapparent as it is, for example, in malaria, trypanosomiasis and yellow fever. In the chancriform cases of coccidioidomycosis, North American blastomycosis and histoplasmosis, the degree of resistance has been high enough to result in spontaneous cure eventually, although months or even years were necessary. It is less perfect in sporotrichosis because most cases do not recover spontaneously; but it is still good enough to cause the infection to remain localized and to be cured easily by any of several drugs, which fail miserably when pitted against other less well resisted forms of that disease.

It is evident that the degree of immunity which accompanies this syndrome need not be complete, and should not be relied upon always to achieve spontaneous cure, although it will be helpful. There are good illustrations in tuberculosis, such as a report by Akerberg \(^45\) of the primary cutaneous complex which included a case which disseminated four years later.

One of Winn's cases of coccidioidomycosis \(^28\) disseminated to the central nervous system. Although his patient did develop the lymphatic involvement characteristic of the primary cutaneous chancriform type of infection, she was negative to the intradermal test with coccidioidin 1:100 and had a complement fixation titer with coccidioidin of 1:32 when first tested, which clinicians have learned to interpret as a poor prognostic combination. Winn therefore quite properly instituted early vigorous treatment with amphotericin B.

In fact, most of my recommendations derived from the study of the chancriform type of infection have been intended to warn clinicians that they should not accept cutaneous lesions of nonchancriform types (which are the first evidence of infection) as indicating that the disease is localized enough to be subject to local therapy alone. Even when typically chancriform, I would advocate drug therapy for all such cases, if it were not for the fact that the best drug, amphotericin B, is not as safe nor as reliable as desired. Only if all other signs and symptoms also point toward a benign course should specific drug therapy be withheld.
These immunoallergic considerations may explain the failure of the chancriform syndrome to occur in Cryptococcus neoformans infections, for this organism is apparently not usually pathogenic for immunologically normal persons. Those abnormal ones who do become infected do not respond immunologically sufficiently to produce the chancriform syndrome. Perhaps this also underlies the lack of the chancriform syndrome in individuals with South American blastomycosis (paracoccidioidomycosis).

In conformity with all of the above facts, and directed particularly by what happens when tuberculosis is contracted percutaneously after previous pulmonary involvement, is the speculation that perhaps the usual chronic verrucous forms of chromoblastomycosis, North American blastomycosis and perhaps coccidioidomycosis actually can result from cutaneous inoculation, but only in individuals previously altered in their capacity to react immunologically by having previously inhaled the fungus and acquired the infection in the lungs. Perhaps also it could be predicted which patients would not produce the chancriform picture by revealing them to be sensitive to skin testing with specific antigens derived from such organisms. In only two of the reported cases of chancriform coccidioidomycosis was the previous status of the patient with regard to the specific skin test known, and both of these had failed to react, indicating that they had had no previous infective contact with C. immitis. Previous reactive status was not known in any of the cases of chancriform North American blastomycosis. Perhaps a chronic verrucous form would result from intracutaneous inoculation of these organisms into persons already skin-test-positive to the specific antigens.

In this regard, the case of sporotrichosis reported by Carr, et al\(^4\) is instructive because it lasted 21 years while it duplicated exactly the chronic verrucous slowly spreading infection so typical of North American blastomycosis and chromoblastomycosis and sometimes seen in coccidioidomycosis. Thus, each disease usually takes its favorite course, but with the right set of circumstances can probably duplicate any of several clinical syndromes. In determining the result, the portal of entry of the organisms is one important factor.

**SUMMARY**

The inoculation for the first time of many species of microbes capable of causing systemic infections through the skin of persons capable of developing locally a significant degree of specific immunologic resistance results in what is appropriately termed the primary cutaneous complex or syndrome. The resemblance to primary syphilis is so striking that the word "chancriform" has also been used.

Clinically the initial papule soon becomes a relatively painless ulcer, lymphangitis develops, often with ulcerative nodules distributed along the vessels, and lymphadenopathy where this drainage reaches. There is a strong tendency toward eventual spontaneous healing of this entity, although systemic spread may take place.

Sporotrichosis in its common form was established as chancriform in 1898, tuberculosis in 1926, and coccidioidomycosis in 1953. Since then, this concept has been extended by similar cases in North American blastomycosis, histoplasmosis and infections with *Nocardia asteroides* and *N. brasiliensis*. In some of the remaining deep fungous infections it may occur under special circumstances; in others, it may never occur.

This stage is rare in most of these diseases, principally because the organisms do not exist in nature in a form appropriate to cause infective puncture wounds. This rarity should alert the clinician to realize that in contrast most cutaneous lesions in these disorders result from dissemination from a visceral focus and are therefore not sufficiently localized to be treated by local therapy alone.

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