OBSERVATIONS ON THE KVEIM REACTION IN SARCOIDOSIS OF THE AMERICAN NEGRO

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In 1941, Kveim (1) described the production of a cutaneous reaction in patients with sarcoidosis following the intracutaneous injection of heated saline suspensions of lymph glands obtained from active cases of that disease. The response, consisting of a small, brownish-red, indurated papule at the site of injection was remarkable for its slow evolution and its persistence. Characteristically, the reaction required weeks to attain its maximum size and thereafter usually remained visible for many months. Microscopic examinations of tissue from the reaction sites revealed a histological picture similar to that of spontaneously occurring sarcoid. Simultaneous control injections of Old Tuberculin and Frei antigen in the same patients gave no comparable response. Conversely, the sarcoid material yielded negative results when administered intracutaneously to normal individuals and to persons with syphilis or lupus vulgaris. From these findings, Kveim concluded that this was a specific reaction for sarcoidosis, and that it probably was allergic in nature.

Several reports extending and, for the most part, confirming Kveim's initial results have recently been published in the Scandinavian countries (2), (3), (4), (5), (6). In one sense these studies seem to indicate that the specificity of the Kveim reaction is relatively high, since positive results in conditions other than sarcoidosis have been encountered only rarely (2), (4), (5). In another sense, however, the specificity of the Kveim reaction has remained in doubt because complete data on the skin reactivity of sarcoid patients to the intracutaneous administration of different human tissue suspensions are lacking. Indeed, it has been shown that a reaction similar to that described by Kveim may be observed occasionally in cases of sarcoidosis following the intracutaneous injection of such substances as suspensions of leukemic human lymph nodes (5) and killed tubercle bacilli (7), (8). These findings suggest the possibility that the Kveim reaction, rather than being a specific phenomenon, may be a general tissue response on the part of individuals with sarcoidosis to a number of different substances. An opportunity to investigate this phase of the problem in some detail was presented during the course of a recent study of sarcoidosis in the American Negro (9). While there is no conclusive evidence that the disease in the Negro differs essentially from that found in other races, it is true that the cutaneous lesions of sarcoid exhibited by the Negro are consistently of the annular, papular type. The diffuse, plaque-like, lupus pernio skin lesions commonly observed in white individuals are rarely found in Negroes. In its other manifestations, however, the disease does not seem to be significantly

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different in the two groups. Thus far there have been no published investigations of the Kveim reaction in Negroes with sarcoidosis. The purpose of this communication is to summarize in preliminary form some observations on the

**TABLE 1**

Results of the Kveim test in 17 cases of sarcoidosis in American Negroes

<table>
<thead>
<tr>
<th>STATE OF DISEASE</th>
<th>NUMBER OF CASES</th>
<th>NUMBER POSITIVE</th>
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</thead>
<tbody>
<tr>
<td>Active</td>
<td>11</td>
<td>7</td>
</tr>
<tr>
<td>Inactive</td>
<td>6</td>
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<tr>
<td>Totals</td>
<td>17</td>
<td>7</td>
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</tbody>
</table>

**TABLE 2**

Some clinical data and results of the Kveim and other intracutaneous tests in 17 Negroes with sarcoidosis

<table>
<thead>
<tr>
<th>CASE NUMBER</th>
<th>AGE</th>
<th>SEX</th>
<th>MONTHS SINCE ONSET OF DISEASE</th>
<th>ACTIVITY OF DISEASE</th>
<th>SITES OF LESIONS DURING ACTIVE PHASES OF DISEASE</th>
<th>RESULTS OF INTRACUTANEOUS TESTS</th>
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<td>29</td>
<td>+</td>
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</table>

* Including mucous membrane lesions, involvement of tonsils, incidental VII Nerve weakness.
† Results obtained with one or more antigens.
‡ Results obtained with two human spleen suspensions.

Kveim reaction in this race and to record additional data on the characteristics of the test.

**METHODS AND MATERIALS**

The cases of sarcoidosis comprising this study represent an unselected series of Negro out-patient and hospital admissions for this disease. In some instances
the chief manifestations were dermatological, in others the presenting symptoms were mainly those of systemic sarcoidosis, including generalized lymphadenopathy, uveo-parotid fever, pulmonary involvement and bone lesions. The diagnosis of sarcoid in each case was confirmed by microscopic examination of the affected tissues. Supplementary confirmation of the diagnosis was obtained by repeated physical examinations, roentgenographic surveys and blood chemical studies. Tuberculosis was ruled out by microscopic examination and cultural or animal inoculation studies of tissue biopsies.

Fig. 1. Case No. 8. Sarcoid-like response seven months after the intracutaneous injection of Kveim antigen. The cells infiltrating the lesion are lymphocytes, epithelioid cells and occasionally a giant cell. Hematoxylin and eosin stain. × 100

From time to time during the period of observation, efforts were made in each case to estimate the activity of the disease. Sarcoidosis was arbitrarily classified as active when new lesions of the skin or mucous membranes developed or when there was evidence of progression or persistence of uveitis, hilar adenopathy, parenchymal lung infiltrations, bone lesions or peripheral glandular enlargement. All patients in this series were tested intracutaneously with 0.1 cc. of various dilutions of Old Tuberculin, as well as with Kveim antigen and control suspensions of normal human spleen in 0.15 cc. amounts. Some pa-
patients also received intracutaneous injections of a number of other organic and inorganic substances as additional controls.

The Kveim antigens employed in this study were prepared from sarcoid tissue obtained from three Negro patients with active and apparently progressive forms of the disease. Two of the antigens were prepared from enlarged posterior cervical lymph nodes, the other from skin lesions in an individual with generalized systemic involvement. In each case, examination of the tissues showed the histological characteristics of sarcoidosis. Appropriate cultures and animal inoculations for *M. tuberculosis* were negative. The sarcoid material was weighed and then ground with physiological saline in a sterile mortar. Sufficient saline was added to give a final dilution of approximately 1:10 by wet weight of tissue and the resulting suspension was allowed to stand for three minutes before decanting. This permitted the largest shreds of tissue to settle out and be dis-

1 One of these patients exhibited widespread manifestations of sarcoidosis in the skin, bones, lungs and lymph glands. The other showed only generalized peripheral lymphadenopathy without other signs of the disease.
carded before the relatively opaque suspension was sterilized. The material was then heated in a water bath at 56°C for two hours on two successive days. Aerobic and anaerobic cultures were made to insure sterility. If no growth was obtained, phenol was added as a preservative in a final concentration of 0.25 percent and the tissue suspension stored in rubber-capped vials at 4°C. For testing, the antigen was shaken well and 0.15 cc injected intracutaneously through a 22-gauge needle into the flexor surface of the forearm. Injections were made with needles of relatively large bore because one of the outstanding peculiarities of the Kveim reaction is that the antigen is quite ineffective unless injected in grossly particulate form. The test was considered to be positive if a papule or an area of induration of any size occurred at the injection site and remained palpable for at least 60 days from the date of its appearance. All individuals included in this report were observed at one to two week intervals for the first 90 days and then more irregularly for a minimum of nine months thereafter. Each patient was tested with at least two Kveim antigens before the final results

Fig. 3. Case No. 8. Cutaneous reaction seven months after the intradermal administration of normal human spleen suspension. Extensive formation of "naked tuberculoid" structures with some giant cells. Hematoxylin and eosin stain. X 100
were recorded. The amount of antigen available did not permit the administra-
tion of all three preparations to every patient.

Simultaneous control injections were carried out with suspensions of normal
human spleen tissue, obtained from two individuals at autopsy. Both of these
patients were males who had died of cardiovascular disease. They suffered
from no obvious infections and showed no evidence of sarcoidosis. The human
spleen control suspensions were prepared and administered in the same manner

![Image](image-url)

**Fig. 4.** Case No. 8. Higher magnification of section shown in figure 3. Hematoxylin and eosin stain. X 430

as the test material. Criteria for reading and recording the results of the control
injections were the same as those for the test.

It should also be mentioned that the sarcoid antigens and normal human spleen
suspensions used in this work did not give characteristic skin reactions when
injected intracutaneously into twelve normal individuals and eight patients with
such varied conditions as leprosy, granuloma annulare, lymphogranuloma
venereum, systemic tuberculosis and metastatic carcinoma. When cutaneous
reactions occurred in these instances they were always evanescent and disap-
peared completely within two or three weeks.
RESULTS

The results of the Kveim tests in seventeen cases of sarcoidosis in Negroes are summarized in table 1. The data recorded in this table show that the Kveim reaction was positive in seven of the eleven patients with active sarcoidosis. None of the healed or inactive cases included in this series yielded positive Kveim reactions. These findings are somewhat at variance with those obtained in the Scandinavian countries where the incidence of positive Kveim tests in patients with sarcoidosis has been found to be higher (6). Whether or not this may be explained by assuming that the disease in Negroes is different from that in other racial groups is open to question. In any event, these results suggest that the Kveim test may have only limited value in the diagnosis of sarcoidosis in the Negro. On the other hand, it is possible that the reaction may be of some prognostic help in following the course of the disease since the patients who were in remission when studied all gave negative tests.
Further clinical data obtained in this series of patients are shown in table 2. The finding of interest here is that the patients who showed a positive skin reaction to the injection of sarcoid material also gave a typical Kveim response to the intracutaneous injection of suspensions of normal human spleen tissue. In such cases, biopsy specimens taken from the sites of the positive tests and control injections after a period of six or seven months showed a histological picture analogous to that of spontaneous sarcoid (fig. 1-8). It should be noted that characteristic skin reactions following the injection of either Kveim antigens or normal human spleen suspensions were obtained, with one exception (Case 4), only in patients showing active cutaneous manifestations of sarcoidosis at the time of testing.

The intradermal administration of lymphogranuloma venereum antigen (chick embryo origin) and saline suspensions of calcium sulfate, collodion particles, coagulated egg white, *Pityrosporum ovale*, defatted human skeletal muscle, normal human lymph nodes, and oil-free soy bean phosphatides2 did not induce com-

2 The soy bean phosphatides were supplied through the courtesy of Dr. Albert Scharf, Associated Concentrates, Inc., Woodside, Long Island, N. Y.
parable reactions in these patients. In two of the positive cases, however, skin reactions clinically similar to the Kveim response were observed following the intracutaneous injection of saline suspensions of mixtures of heat-killed tubercle bacilli (BCG and H$_{37}$ strains). Unfortunately, the sites of these reactions have not yet been examined histologically so that their structure remains uncertain.

![Figure 7](image)

**Fig. 7.** Case No. 12. Widespread production of sarcoid-like tissue six months after the intracutaneous injection of normal human spleen suspension. Hematoxylin and eosin stain. × 100

**DISCUSSION**

Kveim (1) and Danbolt (2) have postulated that the Kveim reaction is an allergic cutaneous phenomenon, specific for sarcoidosis. This may be so, but the acceptance of this explanation in the light of present knowledge encounters certain difficulties. For example, if the nature of the Kveim reaction is allergic in the ordinary sense of the term, it is not easy to explain why the cutaneous response appears from several days to many months after the administration of the antigen. It is conceivable that the prolonged latent period is only a manifestation of a delayed response *in situ*, caused by the reaction of sensitized tissue with an immobilized depot of residual antigen. Once the reaction has taken
place, however, the similarity between the artificially induced skin lesions and those of the naturally occurring disease is striking. But the Kveim reaction itself, whatever its mechanism, does not explain and is not necessarily explained by the etiology of sarcoidosis. One would not be justified, therefore, in pursuing the analogy unduly. Nevertheless, electrophoretic studies of the serum proteins in cases of active sarcoidosis show a large increase in gamma globulin, suggesting the possibility that antibody formation occurs in this disease in response to some as yet unidentified antigen or antigens \((10), (11)\). Although the nature

![Figure 8. Case No. 12. Higher magnification of section shown in figure 7. Hematoxylin and eosin stain. \(\times 430\)](image_url)
injection of normal human spleen tissue, leukemic lymph nodes, and perhaps occasionally to tubercle bacilli, does not suggest that Kveim antigens prepared from sarcoid tissue possess any inherent specificity \textit{per se}. Instead, such evidence indicates that the Kveim reaction possibly may be explained as an unusual type of isomorphic response on the part of sarcoid patients to one or more chemical complexes (haptens?) contained in certain human tissues and other sources. The fact that Kveim antigens can withstand heating to 100°C for 20 minutes without loss of reactivity (5) immediately suggests that such chemical complexes may be largely of a lipoid or lipoid-carbohydrate nature.

It is well known that local histological changes entirely comparable to those seen in sarcoidosis may be found in such chronic conditions as tuberculoid leprosy, syphilis, tuberculosis, leishmaniasis, brucellosis, and certain fungus infections. It has also been established that sarcoid-like lesions can occasionally be produced experimentally by the injection of lipoid-containing extracts of various microorganisms, as well as by certain oils. While the full-blown clinical picture of sarcoid does not occur in these circumstances, the findings suggest that the syndrome we recognize as sarcoidosis may merely be a generalized tissue reaction to a number of related or unrelated substances. Possibly the condition represents an unusual reticulo-endothelial response to various antigenic stimuli. Not only might the antigenic insults be exogenous in origin but they also might be derived endogenously from tissues within the body of the host which have been altered in some manner by the exogenous factors. Direct experimental proof of this is lacking and the limitations of this type of reasoning are obvious. At the same time, a mechanism of this sort may partially explain why certain individuals with active sarcoidosis give characteristic cutaneous reactions to some component of normal human spleen tissue as well as to Kveim antigen prepared from sarcoid material.

**SUMMARY AND CONCLUSIONS**

1. The results of a study of the Kveim reaction in seventeen cases of sarcoidosis in American Negroes have been presented.

2. The Kveim reaction was positive in seven of eleven patients with active sarcoidosis but none of the healed or inactive cases in this series gave a positive Kveim response.

3. All individuals who exhibited a positive skin reaction to the injection of sarcoid material also gave a completely characteristic Kveim response to the intracutaneous injection of suspensions of normal human spleen tissue.

Grateful acknowledgment is made to Dr. Gerald F. Machacek, Dr. Harry M. Rose, Miriam C. Wallace, and Marjorie J. Ruttan for their assistance in this work.

**REFERENCES**

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