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THE ZIRCONIUM DEODORANT GRANULOMA: AN ALLERGIC DISORDER*

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Within the last few years, a new and unusual disorder has been described in the dermatologic literature. This disease showed striking uniformity both clinically and histologically^{1,2,3,4,5,6}, although it was given a variety of names, including axillary granulomas, sarcoid-like eruption of the axillae, granulomatous reaction to deodorant sticks, granulomas of the axillae caused by deodorants, and zirconium granulomas. It was characterized by the presence of persistent painless papules, with minimal acute inflammation and pruritus, appearing in the axillae of persons who had used zirconium-containing deodorants (Figure 1). Histologically, a distinctive granulomatous reaction was seen and was diagnostic (Figure 2). This eruption proved to be virtually refractory to all forms of treatment and its course, following cessation of the deodorant, was one of very gradual, spontaneous involution.



Figure 1

Clinical appearance of axillary zirconium deodorant granulomas.

This patient, a 36-year-old white housewife, developed numerous red-brown papules in the axillae a few months after daily application of a zirconium stick deodorant. Despite cessation of the deodorant the lesions persisted for over two years.

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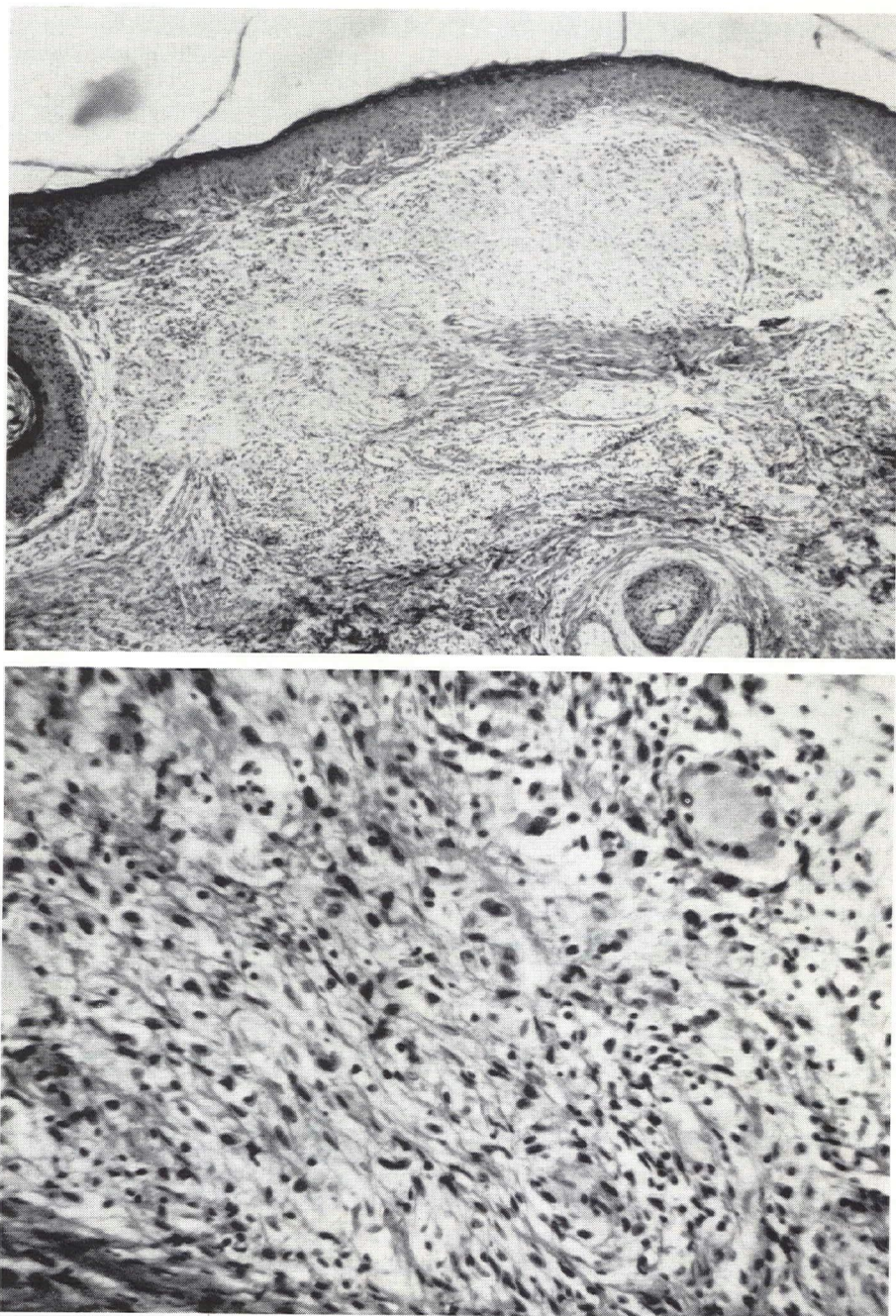


Figure 2

Biopsy of one of the axillary lesions shown in Figure 1 revealed characteristic sarcoid-type of granulomatous patterning. In the upper photograph a low power (x70) microscopic view of the lesion shows nests of epithelioid cells replacing much of the normal dermis. In the lower photograph under higher power (x250) the cytologic appearance of the granulomatous infiltrate is visualized. A giant cell of the so-called Langhans' variety is evident in the upper right hand corner.

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Great interest was evinced in this disorder and, in less than two years (1956 to 1958), some 70 cases were described in the literature and a variety of speculations made as to its etiology. Prominent among these were foreign body reactions to zirconium^{1,3}, to contaminant metals such as beryllium⁷ or hafnium⁸, to the lipid^{9,10}, or other inert ingredients of the deodorant vehicle¹¹, and secondary apocrine sweat extravasation¹² or follicular wall degeneration¹³. However, there was little or no experimental support for any of these possibilities, and neither the incitant or incitants nor the mechanism by which the disease was produced were identified.

In this paper we should like to review our experimental and clinical studies of this distinctive new dermatosis. We have elected to call this new condition the zirconium deodorant granuloma. As a result of these observations, we have concluded that the axillary granulomas that develop incident to the use of zirconium deodorants are the result of a specific allergic hypersensitivity to the metal zirconium which manifests itself as a stable, sarcoid-like granuloma.

The Zirconium Deodorant Stick

It should be emphasized that no single deodorant preparation had been used by all of the patients described in the literature. However, the vast majority had applied a new stick-type deodorant containing sodium zirconium lactate. This stick was essentially a soap-alcohol-gel composed of sodium stearate, ethyl alcohol, carbitol and water with approximately 10% of an aqueous solution of sodium zirconium lactate, and small amounts of hexachlorophene and a perfume incorporated into the basic gel.

Each of the components of this stick alone or in combination was suspect in the production of this granulomatous disorder. However, it was difficult to predict which of these substances was causal. The sodium stearate seemed a quite unlikely candidate since the daily use of soap for years by many millions of people on broken and unbroken skin has never produced a single granuloma. Similarly the ethyl alcohol, while at times capable of producing transient irritation, has never been known to induce such chronic change despite its ubiquity in cosmetic and topical medicinal products. Carbitol/diethylene glycol mono-ethyl (ether) as a congener of glycerine is miscible with water and extensive studies have indicated that it is essentially non-irritating to rabbit skin¹⁴. However, absorption of large amounts of carbitol can prove fatal to these animals. Hexachlorophene has been used for many years as a germicide for surgical scrubs. It has also been employed topically in creams and lotions on adult and infant skin without ill effect. The very small quantities of perfume that were present in the stick would seem to make it an unlikely possibility also.

Of all the ingredients of the stick deodorant, zirconium loomed as the most logical candidate for the granulomagenic agent. Indeed, the majority of observers were of the opinion that it was in some way responsible, since the appearance of this new granuloma coincided with the introduction of zirconium in deodorants. Zirconium, a metallic element in group IV period V of the periodic table, is normally found in the earth's crust as an oxide or silicate in a concentration of about 0.22%. It is not radio-active and is closely related to hafnium chemically. Actually, as much as

2% hafnium has been found in the purest zirconium preparations. Sodium zirconium lactate is a recently synthesized salt. It is used as a 40-45% aqueous solution (Ph-7.5-8.2) which is compatible with soap. In the axilla its primary action is as a deodorant and it produces this effect apparently by reducing the surface bacterial flora and probably also by forming a complex with the malodorous fatty acids. Any antiperspirant effect it may achieve is the result of eccrine poral closure in a manner similar to that of the aluminum salts. However, in the axilla this effect is not remarkable.

Zirconium has long been regarded as a very innocuous substance. Careful toxicologic studies support this^{15,16,17}. As a metal it has been employed successfully in surgery as bone screws, cranial plates, intramedullary pins, sutures, and bone clips¹⁸. In animals its introduction in both soluble and insoluble forms parenterally, by ingestion and by inhalation for as long as two years has not produced significant acute or chronic change^{19,20,21,22}. Granulomas have not been reported in men working with zirconium in industry nor have pulmonary changes been observed. Its use topically (4% zirconium dioxide ointment) in patients with poison ivy dermatitis has not proved harmful^{23,24}. Even intravenous administration of zirconium salts has been safely employed in patients with pyodermas²⁵. The consensus of opinion was that zirconium in any form seemed to be a safe and essentially harmless compound for man. Thus, despite the circumstantial evidence incriminating zirconium as the granulomagenic substance, there was little in the literature to support such suspicion. Moreover, it should be pointed out that the new stick-type vehicle used in these deodorants was of very recent vintage also, and this lent credence to the view that one of the components of this stick or a contaminant was responsible. It thus became apparent that only through careful experimental study could one identify the substance or substances responsible for this new dermatosis.

Experimental Studies

It was stated earlier that as a result of extensive experimental investigation we concluded that the zirconium deodorant granulomas were the result of an allergic hypersensitivity of these patients to the metal zirconium. These studies have been carefully detailed in another report¹¹. They were carried out under controlled conditions in healthy adult male volunteers. They may be summarized briefly as follows:

(1) Experimental production of histologically proved axillary granulomas identical with those of clinical cases was achieved in two (subject No. 2 and subject No. 35) of fifty subjects by the daily intensive (5 minutes) application to the axillae of deodorant sticks containing sodium zirconium lactate in both 5 and 10% concentrations. Sticks containing zirconium in 1% concentration produced no such reaction. These granulomas were typically chronic persisting for as long as six months following cessation of the zirconium deodorant sticks. Several other subjects developed transitory acute inflammatory changes to the 5 and 10% zirconium sticks, but these reactions were clearly non-granulomatous histologically. Control sticks, identical except for the absence of zirconium, failed to produce any acute inflammation or granuloma in any of the fifty subjects.

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(2) Zirconium deodorant sticks deleted of the hexachlorophene, carbitol, and perfume regularly found in the commercially available sticks, were equally capable of inducing the granulomatous reaction.

(3) Substitution of 5% aluminum chloride for the sodium zirconium lactate in the deodorant sticks failed to result in the development of axillary granulomas.

(4) There was no epidermal (contact) sensitivity to zirconium or any of the other ingredients of the deodorant stick as evidenced by routinely negative patch tests to the deodorant sticks in all of the experimental subjects.

(5) Intradermal injections of dilutions of aqueous solutions of zirconium salts reproduced the granulomatous reaction in the two subjects (No. 2 and No. 35) in whom the axillary granulomas were seen to develop. Injection of these zirconium salts in many normal control subjects and injection of all other ingredients of the deodorant stick, as well as other representative metals (beryllium and silicon) in subjects No. 2 and No. 35, and in the control subjects, failed to produce any such response. Table I depicts the results of these studies.

(6) In a concentration of 1:10,000 aqueous solutions of soluble salts of fifty-seven elements of the periodic table also were injected intradermally in the subjects No. 2 and No. 35, and in the twenty control subjects. In all of the men so treated there were no granulomatous reactions at any of the injection sites except at that of zirconium in subjects No. 35. It is to be recalled that he responded similarly to 1:10,000 zirconium in the previous series of injections (Table I). The elements that were included in this second series of intradermal tests included:

Aluminum	Europium	Manganese	Silicon
Antimony	Fluorine	Mercury	Silver
Arsenic	Gadolinium	Molybdenum	Strontium
Barium	Gallium	Neobium	Tantalum
Beryllium	Germanium	Neodymium	Tellurium
Boron	Hafnium	Nickel	Terbium
Bromine	Holmium	Palladium	Thulium
Cadmium	Indium	Praesodymium	Tin
Cerium	Iodine	Rhenium	Titanium
Cesium	Iridium	Rhodium	Tungsten
Chromium	Lanthanum	Rubidium	Vanadium
Cobalt	Lead	Ruthenium	Ytterbium
Dysprosium	Lithium	Samarium	Yttrium
Erbium	Lutetium	Scandium	Zinc
			Zirconium

These experimental studies indicated that zirconium and zirconium alone was the critical substance responsible for the development of the granulomatous reactions seen in this disorder. Furthermore, the pathogenesis of these granulomas was shown to be the result of a specific hypersensitivity, probably allergic in nature, to the metal zirconium.

Our next step was to confirm these findings in clinical patients with the zirconium deodorant granulomas.

Table I

Intradermal Injections (0.02 cc)	Sodium Zirconium Lactate				Zirconium Chloride		Zirconium Nitrate		Beryllium Sulphate	Colloidal Silica	Other Compon- ents of Deodorant Stick*
	1:100	1:1000	1:10,000	1:100,000	1:1000	1:10,000	1:1000	1:10,000	1:1000	1:1000	1:1000
Subject No. 2	+	+	0	0	+	0	+	0	0	0	0
Subject No. 35	+	+	+	0	+	+	+	+	0	0	0
Controls (20)	0	0	0	0	0	0	0	0	0	0	0

*The various ingredients of the stick were injected alone and in combination in the above concentrations. They included sodium stearate, hexachlorophene, ethyl alcohol, carbitol, and perfume.

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Clinical Studies

Four patients with zirconium deodorant granulomas were available for study. All had the typical histologically proved granulomatous lesions in the axillae and all were in good health. A battery of general medical studies were within normal limits on all of these patients. These patients were women, ranging in age from 23 to 42 years. Three of the four women had used the zirconium stick deodorant for at least two months prior to the appearance of the eruption. However, one patient states that the lesions appeared after only two applications of the stick. In each case all forms of treatment, including topical steroids, were ineffective. The chronicity of the lesions was an outstanding feature in these patients, and in one patient residual papules were still visible over two years after cessation of the zirconium stick and other deodorant applications.

Special studies performed on these patients included:

(1) Intradermal injection (0.02 cc.) of 1:1000 and 1:10,000 dilutions of aqueous sodium zirconium lactate solution produced a papule in 10 days in three of the four patients. On biopsy these papules showed the characteristic granulomatous picture. The fourth patient responded similarly only to the 1:1000 dilution of the zirconium solution. None of the four patients showed any visible response to 1:100,000 sodium zirconium lactate.

(2) Intradermal injections (0.02 cc.) of 1:1000 beryllium sulfate and 1:1000 silicon dioxide were negative in all four patients. Patch tests to zirconium deodorant stick (full strength) were negative at 72 hours in all four subjects. However, in one subject, a small papule (Figure 3) appeared at about one month. Although involuting



Figure 3

Granulomatous reaction appearing at site of patch test to zirconium stick deodorant. Four to five weeks after a negative response (72 hours) to a closed patch test to a standard zirconium stick deodorant, a papule (shown above) appeared in the patch test site in one of our clinical patients. Histologically this papule showed granulomatous change comparable to that seen in the axillary granulomas.

gradually, it was still evident six months later. This lesion was similar clinically to the axillary granulomas and proved to be granulomatous histologically also.

Discussion

The metals, silicon and beryllium, have long been known to be capable of inducing cutaneous granulomas in some individuals after accidental inoculation^{27,28}. In order to determine the presence or absence of these metals as contaminants, we had spectrographic analyses performed on the commercial sodium zirconium lactate solution used in our studies. Many elements were tested for and several were found to be present, in addition to the major constituent, zirconium. Silicon was detected in a concentration of about 0.008%, but beryllium was not found. All of the other elements found were in similarly low concentration and included aluminum, boron, calcium, chromium, iron, magnesium, nickel, and strontium. These were included in the test series of injections made on the experimental subjects, it should be recalled, and were found to be incapable of eliciting a granulomatous reaction.

Although a perusal of these studies leaves little doubt that these patients manifested a hypersensitivity to zirconium, that this hypersensitivity was allergic in nature requires further amplification.

Allergic states are *acquired*, not inherited. Although we have no skin tests or other information indicating the lack of allergic hypersensitivity of these individuals prior to their exposure to the zirconium deodorant sticks, we may presume that they had no such prior hypersensitivity. This hypersensitivity developed some time during the period of application of the deodorant sticks. More compelling evidence that this zirconium hypersensitivity is acquired is available in another experimental subject (not recorded here and not a part of these studies) in whom initially negative intradermal injections of zirconium became granulomatous several months later. Careful study of this subject verified the specific hypersensitivity to zirconium.

Allergic states are *specific*. The specificity of the reactivity of these subjects to zirconium should be apparent after a review of the data outlined above. Moreover, the ability to respond to great *dilutions* of the zirconium points to the allergic nature of this *unusual* reaction.

Demonstration of an antigen-antibody reaction is an important and ultimately requisite step in the confirmation of allergic reactions. We are studying this problem at the moment. Classical serological tests and serum passive transfer techniques for the demonstration of antibody have not been of value possibly because the antibody concerned with this form of allergy may well be cellular. Modified cell transfer methods and other *in vivo* and *in vitro* methods are being employed at present.

The failure to identify the antibody concerned with the hypersensitivity reaction to zirconium in the cases described herein does not invalidate our thesis that this reaction is truly allergic in nature. It should be recalled that other forms of allergy were well accepted as such many years before any antibody was ever demonstrated. Tuberculin allergy and contact allergy are excellent examples in point. It is only within recent years by means of specialized cell transfer techniques that these forms of allergy have realized antibody demonstration.

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In the axillary zirconium deodorant granulomas which are seen clinically, the possible route or routes of entry of the zirconium have caused much discussion. In women, in whom this disease has occurred predominantly, shaving of the axillary hair is such a common practice that it was regarded as an important factor in the development of this dermatosis. Indeed, in one of our experimental subjects in whom we produced the deodorant granulomas, the lesions could be clearly seen to develop in a linear shaving cut. However, they have also been observed beneath focal areas of miliaria. Actual streaming of microparticulate material through the miliarial vesicles and down into the dermis could be observed histologically. It is our feeling that any process, dermatitic or traumatic, which destroys the integrity of the epidermis or its impermeable barrier will allow for ready absorption of the essential granulomagenic substance, zirconium. Actually, in these hypersensitive individuals, it is likely that enough zirconium is absorbed through the major normal route of absorption, the pilosebaceous apparatus.

Further consideration of the natural history of the zirconium deodorant granuloma as it relates to the allergic process is in order. The affected patients almost uniformly give a history of having used a zirconium-containing product for weeks to months prior to the appearance of their papular eruption. This, then, is the period in which the patients are non-allergic and will not react in this fashion to zirconium. In the latter part of this period they become sensitized to the zirconium. Once this sensitivity arises, residual or additional zirconium in the skin results in a delayed allergic granuloma formation. This latter phase, the development of the granuloma following exposure to the zirconium in the sensitized individuals, represents the *reaction time*. For this form of allergy the reaction time is about two to three weeks for the development of a mature, fully-formed granuloma, although in more sensitive individuals, it may be shorter. In a few patients, the granulomatous reaction developed after what was believed to be the initial contact with zirconium. In these instances, which must be quite uncommon, we can assume that the patient had had prior exposure to zirconium, possibly as an inhalant, with prior sensitization. The concentration of zirconium in the deodorant sticks which will elicit the granulomatous response after topical application was shown to be 4% or above. However, it is possible that in more sensitive subjects one might expect even trace amounts of zirconium in any deodorant or other topical preparation to produce this response. We have no evidence as to the critical concentration necessary to induce sensitization to zirconium, but would feel that as with other forms of allergy, higher concentrations would more readily produce this effect.

Treatment of the zirconium deodorant granuloma has been generally disappointing. Systemic steroid therapy may produce temporary improvement and local injection of hydrocortisone may induce resolution of the lesions. This is quite in keeping with the allergic nature of the disorder. Topical treatment is ineffective in reducing or clearing the basic granulomatous process and is usually unnecessary for the management of any secondary acute inflammatory changes or pruritus since the latter are not prominent features of the condition. Cessation of zirconium deodorants and avoidance of all zirconium-containing products is necessary, of course, and eventually within 1-3 years the granulomatous lesions will involute spontaneously. It is quite probable that this clinical entity, the zirconium deodorant granuloma, will rarely be seen in the future

since zirconium has been removed from the market as a deodorant. However, individuals who have developed such sensitivity should be advised to avoid further contact with zirconium. This allergic sensitivity is not localized to any area of the skin nor to the skin alone. It is generalized in nature and it is conceivable that a granulomatous "zirconiosis" of the lungs could ensue after inhalation of the element in industry or accidentally in dust in a given area of the country. Furthermore, it would seem judicious to re-examine the use of zirconium in surgical plates, intramedullary pins, sutures and the like in certain patients.

In an earlier part of our study we learned that a granuloma develops when appreciable quantities of sodium stearate were introduced into the dermis. Initially we were convinced that this substance was responsible for the deodorant stick granulomas. However, we later came to realize that this was not the case, and that sodium stearate was producing a simple, non-allergic granuloma of the foreign-body type. In another paper we have recorded our findings with this non-allergic granuloma²⁹. Sodium stearate is not responsible for the clinical axillary granulomas seen since: (1) large quantities of sodium stearate are required to produce the granulomatous response, (2) stearate granulomas resolve within a few weeks, (3) stearate will elicit granulomas regularly in every individual, and (4) patients with clinical deodorant granulomas show the normal response to stearate. However, the most spectacular distinction between the allergic and non-allergic granulomas relates to the quantity which one must inject in order to produce the two responses. In the zirconium granuloma, it is necessary to inject only a fraction of a microgram. With the stearate, in order to produce a comparable but non-allergic lesion, there must be a thousandfold increase in the quantity introduced.

The zirconium deodorant granuloma is a prototype of the allergic granulomas seen in man. Histologically it is composed of nests of epithelioid cells, without central necrosis or caseation and with minimal associated inflammatory reaction. The development of this pattern and its immutability for months to years, once its peak has been reached, are outstanding features of this type of granuloma. There is no piecemeal destruction of a central mass of insoluble or particulate matter as is seen in various *foreign body granulomas*. There is no palisading of the epithelioid cells peripherally about a central caseous or necrotic mass with an outside rim of monocytes as is seen in the tuberculoid granulomas such as tuberculosis, syphilis, and mycotic infections. There is simply gradual growth and transformation of reticulo-endothelial cells into stable epithelioid cells apparently as a result of antigen-antibody reaction. This is a focal process at first, perivascular in the main, but ultimately the picture is quite diffuse with replacement of most or all of the normal tissue. This type of granulomatous patterning has been referred to as "epithelioid" or "sarcoid" and is seen classically in such conditions as sarcoidosis and tuberculoid leprosy. It is not possible at this time to state that these diseases, which resemble the allergic zirconium deodorant granuloma histologically, are necessarily totally allergic in nature themselves. However, with the knowledge that a simple chemical, zirconium, can of itself produce the diffuse, sarcoid-type granuloma as described herein, we should critically evaluate these and other granulomatous diseases with this possibility in mind. There is some evidence to indicate that both sarcoidosis and tuberculoid leprosy do represent allergic granulomas

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in the strict sense. Support for such a view is found in the Kveim test, in which the intradermal injection of a 10% saline suspension of sarcoid tissue produces a granulomatous papule at three to five weeks in most cases of sarcoidosis. The allergen or granulomagenic material in the Kveim antigen has not yet been identified. Similarly, intradermal inoculation of a phenolized, ground-up suspension of lepra bacilli will produce, in patients with tuberculoid leprosy (but not in those with lepromatous leprosy), a granulomatous papule at three weeks. This reaction, known as the Mitsuda reaction, is an aid in the diagnosis of tuberculoid leprosy and indicates a hypersensitivity of these patients to some fraction of the mycobacteria. Beryllium and silicon granulomas also may represent allergic granulomas and should be investigated from this standpoint. Intradermal testing with dilutions of beryllium or silicon salts might well indicate that these patients have a hypersensitivity to these metals which could be responsible for their granulomas.

It is not necessary to postulate an allergic mechanism to explain the pathogenesis of foreign body granulomas since the process seems to be simply one of phagocytosis of the foreign material by the reticulo-endothelial cells. Extensive discussion of the possible importance of an allergic process in the development of the tuberculoid granulomas is not within the scope of this paper. Patients with tuberculosis, deep fungous infections, syphilis, do have an associated allergic hypersensitivity, as indicated by a tuberculin-type (48 hours) response to skin test antigen preparations of the various organisms. However, this allergic response is *not* granulomatous in nature and, unlike the Kveim or Mitsuda reactions, does not necessarily indicate that a granulomatous stage of the disease is present. As exemplified by the Mantoux tuberculin test, a positive skin test merely indicates previous exposure and sensitization (with the tuberculin-type allergy) to the purified protein derivative of the tubercle bacillus. The pathogenesis of the tuberculoid granulomas does not seem to have been satisfactorily explained on the basis of secondary reaction to the organisms themselves, their products, or as a result of tissue destruction³⁰. Its elucidation awaits further study.

Summary

A new dermatologic entity, the zirconium deodorant granuloma, has been described and experimental and clinical studies regarding its pathogenesis reviewed. It has been shown that the zirconium deodorant granuloma is the result of an allergic hypersensitivity on the part of the affected individuals to the metal, zirconium, which manifests itself as a granuloma. This, to our knowledge, is the first demonstration in man, that an allergic process can be responsible for the development of a granuloma. The significance of this new form of allergy in relation to other granulomatous disorders in medicine is discussed.

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