UNITED STATES ATOMIC ENERGY COMMISSION

A STUDY OF THE TISSUE RESPONSE TO
STERILE DEPOSITS OF PARTICULATE
MATERIAL

By
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October 1957

Lovelace Foundation for Medical Education
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ABSTRACT

Thirty-seven sterile materials of common construction usage, common lubricants, and samples of wearing apparel were injected as finely divided particles into the subcutaneous soft tissues of guinea pigs, each in six different sites. At intervals of 3, 7, 14, 21, 30, and 60 or 90 days, an inoculation site of each material was excised, in toto, fixed, and examined microscopically. In addition, ten selected materials were injected into the liver and spleen and deposited on the omentum and mesentery of four guinea pigs for each material type. At intervals of 7, 14, 21, and 30 days, one of each group of four animals was sacrificed and a block of tissue containing the inoculum was removed from the tissues and organs, fixed, and examined histologically. The majority of materials induced only a mild and delayed inflammatory response followed by encapsulation at the end of 14 days and a relatively inert fibrous nodule produced by the 21st or 30th day. Copper particles incited a marked inflammatory response with abscess formation which persisted until the 90th day, although showing signs of subsiding at this time. Cadmium lesions were characterized by a peculiar zone of necrosis about the particle aggregate which persisted until the 60th day. Duraluminum of one type incited a pseudoneoplastic fibrous response. Axle grease, in the early stages, induced one of the most intense acute inflammations, in contrast to that produced by motor oil and ordinary lubricating grease, but the process had subsided and was fibrosed by the end of 30 days.

The factors of chemical and physical properties of particles, the piezo-electric and galvanic effects, particle size and surface area, role of bacterial contaminations, and possible effects of adrenal stress were discussed.

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Chapter 1

INTRODUCTION

1.1 GENERAL

This is the second and final report of the results of an investigation into the natural tissue response to sterile foreign-body implants of selected material expected to occur in injuries resulting from an explosive event. The material presented is an expansion of a previously submitted report.¹ This work represents one phase of a relatively broad study of the pathological and physiological effects of blast, and constitutes one aspect of the injurious effects on tissue and organs of a variety of secondary and tertiary missiles dislodged and set in motion by blast. Injuries resulting from such missiles would depend upon several factors:

1. The particle size and total mass of the material and its physico-chemical nature.
2. The site of impact and degree of displacement of the body as a whole or of its component parts.
3. The velocity of the missile, the degree of tissue disruption and penetration, and the amount of energy imparted to the tissue upon impact.

The present report deals primarily with studies of the natural behavior of selected sterile foreign-body material, devoid of effects of physical energy, thermal energy, or ionizing radiation. Early in the investigation, it was real-

ized that several factors characteristic of any given material would influence the behavior of tissues in which it was embedded. Such factors were summarized as follows:

1. The physical and chemical nature of the particle.
2. The size of the particles and the extent of surface area presented for absorption or interstitial chemical reaction.
3. The amount and type of bacterial contamination.
4. The modifying effects of thermal energy and/or ionizing radiation.
5. The metabolic status of the host.

From the standpoint of understanding the pathogenesis of such injuries as well as obtaining data which would be of value in surgical treatment and healing of such injuries in civilian or military personnel, information was sought regarding the tissue behavior under controlled conditions outlined above. Concurrently, experiments designed to demonstrate the effects of bacterial agents, singly and with designated foreign particles, as well as effects of external ionizing radiations, were conducted by Clapper and Meade and submitted as separate reports.^{2, 3} Studies of the effects of energy factors on nonpenetrating missiles are currently in progress (Richmond, Goldizen, Shering, Bowen, and White), and will be the subject of a separate report.

1.2 BACKGROUND

Whereas a wealth of descriptive literature was available concerning the clinical and pathological features of embedded insoluble material, there were only a few detailed reports of the progressive natural tissue response to such. No studies of the natural tissue response to embedded, sterile foreign material, of the type used in this experiment, were found.⁴⁻⁸ The general appearance of the foreign-body granuloma is too well known to warrant further de-

scription.⁹ A wide variety of insoluble materials, not necessarily of exogenous origin, may be associated with such a reaction progressing to encapsulated foreign-body reactions. Ayres, Ober and Hamilton¹⁰ recently have pointed out the difficulty, at times, in distinguishing the lesions of systemic disease such as sarcoid, from crystalline foreign-body granulomas. Some materials are known to induce a more intense reaction and promote greater fibrosis than others.^{11, 12} Some of the theoretical reasons for such are presented in the discussion to follow.

Considerable information was available concerning the marked pulmonary tissue responses and progressive fibroplasia resulting from exposure to silica, quartz, and asbestos.^{6, 13-19} A number of investigators have called attention to the chronic pulmonary and upper respiratory tract irritation from wood,^{11, 20} coal,²¹ asbestos,²² mica,^{23, 24} palladium,²⁵ cadmium,^{26, 27} copper,¹⁹ gallium,²⁸ mercury, welding fumes,^{29, 30} tellurium,^{31, 32} selenium,¹⁹ and tin oxide.^{33, 34} In the interest of industrial hazards, particularly the pneumoconiosis, Delephant³⁵ and Schepers et al.³⁶⁻⁴⁹ have produced a series of sequence studies of intrapulmonary lesions induced by glass wool, rare earths, quartz, talc, gypsum, asbestos, carbon, cobalt and tungsten metals, cobaltic and tantalum oxides, and tungsten carbide. Of the series, cobalt metal was particularly interesting because of the severity of tissue reaction and resulting obliterating bronchiolitis. Many classical papers and continued references concern the systemic toxicity of lead poisoning either by ingestion of soluble compounds of lead or by inhalation of lead fumes and oxides.⁵⁰ Attention has been called to the occasional delayed systemic toxic effects of lead left embedded in tissues for long periods of time.^{51, 52} Compounds of chromate, such as lead and arsenic,^{19, 53} lead alloys,⁵⁴ iron salts,⁵⁵ phosphorous containing material,⁵⁶ are well known as cytotoxic poisons after sufficient exposure. Innumerable sub-

stances of industrial or common use have been shown to give rise to severe contact-sensitivity skin reactions.^{12, 57-59} The more common of these are rubber compounds,⁶⁰⁻⁶² plastics and synthetic resins,^{59, 62-66} cements and quick lime,⁶⁷ waxes, and petroleum products, such as cutting oils.⁶⁸

Beryllium, because of its use in the manufacture of fluorescent tubes and fatigue resistant copper alloys, has received considerable attention and is known to incite a pronounced fibrocytic tissue reaction, progressive in nature.⁶⁹⁻⁷¹ Many have emphasized its importance in production of extensive pulmonary fibrosis,⁷¹⁻⁷³ and Helwig⁷⁴ has recently discussed the pathological appearance of intradermal and subcutaneous lesions resulting from lacerations by broken fluorescent lamps.^{5, 74-76}

Duraluminum has incited intense foreign-body reactions in the skin of workers subjected to chips and splinters of this alloy.⁷⁷

The reaction and fate of many of the fibers of surgical use in suture material (silk, cotton, catgut, steel and silver wire, nylon) and some metals and alloys used in surgical reconstructive work (steel, stainless steel, vitallium, ticonium, tantalum, zirconium) are well known.^{9, 78-82} Dusting and lycopodium powders have produced relatively inert granulomas,⁸³⁻⁸⁷ as have sulfonamide crystals. A case is on record of granulomatous reaction to an X-ray contrast medium containing carboxymethyl cellulose.⁸⁸

The common inflammatory response to slightly soluble or insoluble materials is of granulomatous character, but not necessarily distinctive as to the type of agent producing the lesion. Similar reactions are commonly observed as a result of endogenous inclusions of lipids (cholesterol and fatty-acid crystals), amyloid, keratin material, hair shafts, bone fragments, and varieties of calculi. The general reaction consists initially of a hyperemia, edema, leucocytic response, occasional necrosis, followed by localizing fibrosing pro-

cesses. The duration and magnitude of the response apparently depend upon the material and other factors mentioned before.

In the light of information obtained from the literature, and for the purpose of the present study, it was assumed that the reactions to the materials employed would fall into one of three groups:

1. The material would be relatively inert, that is, incite little or no reaction.
2. The material would act similar to other more familiar foreign bodies resulting in a moderate inflammation followed by fibrosis and encapsulation.
3. The material would give rise to an inflammatory reaction of varied intensity and be followed by a progressive fibrosis similar in nature to that produced by silica and beryllium.

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Chapter 2

PROCEDURE

2.1 MATERIALS

Since a wide variety of substances could become secondary missiles under explosive situations, the materials tested were restricted to some of those which might be expected to occur under ordinary living conditions. It was obvious that the proportions of such missile types would vary with the particular locale, depending upon the prevalence of one type of building material over another in current use. Emphasis was placed upon common construction materials, disintegrating fragments of which would compose the bulk of penetrating objects. Various types of standard masonry products, woods, glass, metals used in framing, plumbing and electrical work, roofing and insulating materials were tested. Lubricating materials, fabrics, plastics, and a few miscellaneous items were also included. A total of 37 substances were tested as follows:

Metals

1. Copper
2. Cadmium
3. Zinc
4. Duraluminum (Two samples, hereinafter designated I and II)
5. Magnesium alloy
6. Steel
7. Lead
8. Iron Oxide

Hydrocarbons

- 9. Axle grease
- 10. Heavy lubricating grease
- 11. Motor oil
- 12. Road tar

Masonry Products

- 13. Plasticrete
- 14. Finish plaster
- 15. Rough plaster
- 16. Poured concrete
- 17. Hollow construction tile
- 18. Red brick
- 19. Marble chips
- 20. Ceramic tile
- 21. Calcium carbonate

Woods

- 22. Soft pine
- 23. Douglas Fir
- 24. Oak

Fabrics

- 25. Cotton
- 26. Nylon
- 27. Rayon

Plastics

- 28. Rubber
- 29. Bakelite
- 30. Plexiglass
- 31. Micarta

Miscellaneous

- 32. Rockwool
- 33. Fiberglass
- 34. Tar paper
- 35. Window glass
- 36. Safety glass
- 37. Carbon

The materials, where necessary, were reduced to sufficiently small particle size by means of an ordinary mill bastard file, to enable them to be easily introduced as a compact mass into the tissues. Micrometer measure-

ments showed an average particle size of 40-75 micra, with a range of 0.1 micron to 150 micra. Within these limits, no effort was made to control particle size. Masonry materials generally fragmented into a rather wide variety of size, whereas particles of metals, woods, and plastics tended to be quite uniform in dimensions. Fabrics and insulating materials were cut with small shears into as fine filaments as possible, and iron oxide was already finely divided as obtained. The materials were placed in capped storage tubes and sterilized in a dry oven at a temperature of 375°F for a period of two hours.

2.2 METHODS

2.2.1 Subcutaneous Implantations

(a) Animals. Adult guinea pigs, ranging in weight from 400-900 g were used as test animals because of the close similarity of tissue reactions to those seen in the human. They were maintained separately or in pairs in metal cages and fed standard laboratory pellets supplemented with fresh vegetables and approximately 25 mg per day of ascorbic acid in drinking water. For the subcutaneous implantations, two to three animals were used with each test material. The animals were anesthetized with veterinary Nembutal (Abbott), 60 mg per cm³, in a dosage of 0.04 cm³ per 100 g body weight. During the actual operation, this was supplemented by a small amount of ether by inhalation. The skin of the entire back was shaved, cleansed thoroughly with Gamophen soap and water, and prepared with surgical Zepharin-chloride solution. By means of a small scalpel, three small incisions were made on either side of the spine, spaced approximately 2 cm apart. The incisions were of sufficient size to permit the easy introduction of a Vim-Silverman needle into the subcutaneous tissues for a distance of approximately 8-10 mm. This procedure allowed a total of six separate implantations on each animal in an area readily

accessible for biopsy and yet too remote to be readily disturbed by the animal. The test material was packed into the end of a sterile Vim-Silverman needle to a depth of 15 mm, controlled by the trochar. The tip of the needle was inserted through the incision into the soft tissues and the material expelled at a distance from the wound. With a slight twisting motion to aid the deposition of the material, the needle was withdrawn. In general, no suture material was required and the wounds closed spontaneously and healed rapidly. In the case of fluid motor oil, the injection of 0.25 cm^3 was made with a small syringe and hypodermic needle.

(b) Control. For comparison, control animals were prepared in the same manner and injected with the Vim-Silverman needle, but no foreign particles were injected. Each site was biopsied on the designated day along with the test animals. Each block of tissue, representing a site of implantation, was fixed and prepared for histologic study in the manner of the test material.

(c) Sampling. At intervals of 3, 7, 14, 21, 30, and 60 or 90 days, one of the inoculated sites on each animal was excised in toto, the animals being anesthetized and prepared as before. The sites of foreign-body deposits were identified by palpation and a 1.0-1.5 cm incision made adjacent to each. The separate entire inflammatory lesions were excised and immediately fixed in buffered-formalin. The incisions were closed with skin clips. Following adequate fixation, the tissues were trimmed and processed to paraffin blocks by customary methods. Histologic sections were cut at 5-8 micra, depending upon the difficulties encountered with denser embedded material, and stained with Harris' hematoxylin and eosin. In many instances, several serial sections could be mounted on each slide, but frequently it was extremely difficult to retain the foreign material in the original location without resorting to unusually thick sections.

2.2.2 Abdominal Implantations

Four guinea pigs, fed and maintained in a manner similar to that employed with the other animals, were used with each specific material tested for the purpose of studying the effects of abdominal implantation. Following anesthesia with Nembutal, the skin of the abdomen was shaved and prepared as usual. A transverse upper abdominal incision was made, approximately 5 cm in length, which permitted ready access to both the liver and spleen. With a Vim-Silverman needle, test materials were injected directly into the parenchyma of the liver and spleen. Bleeding, which was sometimes profuse, was controlled by manual pressure with a pad of Gelfoam for a period of 2-3 minutes, after which the Gelfoam was removed. Particles of the foreign material were then sprinkled in the peritoneal cavity and about the omentum and mesentery. The peritoneum and muscle layers of the abdominal wall were closed with 4-0 silk suture material and the skin closed with metal clips. Attempts to implant foreign particles into the renal tissue did not meet with success and excessive hemorrhage nearly always resulted. All animals so treated expired shortly afterwards of hemorrhage or pneumonitis, before any significant results could be obtained. Control animals were treated in a similar manner, although no foreign material was injected.

Samples of tissue containing the foreign material from the liver, spleen, and peritoneal cavity were obtained at intervals of 7, 14, 21, and 30 days by sacrificing one of each group of four animals. The animals were killed with an overdose of ether, and examined thoroughly. Nodules of tissue containing the particulate material were excised and fixed in buffered-formalin. After proper fixation, the tissue was trimmed and processed in the previously described manner.

Chapter 3

RESULTS

3.1 GENERAL

All sections of tissues biopsied at the various intervals were compared and evaluated with respect to the following:

1. The initial response: 3-7 days
 - a. degree of edema, hyperemia, and vascular change
 - b. degree and character of leucocyte response
 - c. presence or absence of necrosis
 - d. duration
2. The intermediate reaction: localization
 - a. vascular change
 - b. persistence of leucocyte response
 - c. degree of phagocytosis and formation of foreign-body type granulomas
 - d. presence or absence of necrosis
 - e. fibrocytic response and development
3. The terminal status
 - a. degree of fibrocytic encapsulation and penetration into the foreign-body mass
 - b. presence or absence of continued leucocyte response
 - c. stage of relative inertness

3.2 SUBCUTANEOUS IMPLANTATIONS

A general survey of the test material showed that injections were deposited in the loose areolar tissue adjacent to the aponeurosis of the deep back muscles.

Beneath the epidermis there was, in succession, a dense collagenous derma 1.8 mm in thickness, a thin but vascular fat layer (0.4 mm thickness), a layer of striated muscle of 0.8 mm thickness, and finally an underlying layer of loose areolar tissue of variable depth. Injections were implanted in this latter layer, overlying the deep back muscles.

Material from the control animals showed only a very slight reaction in the first specimens, excised on the third day, characterized by the presence of a few scattered polymorphonuclear leucocytes, lymphocytes, and occasional monocytes. The reaction was confined to an area just beneath the surgical incision and was not seen in the more distant subcutaneous fat tissue. All subsequent samples were entirely devoid of inflammation.

The initial reaction of three days duration was characterized by a narrow zone of local edema and separation of collagen strands about the foreign aggregates. The capillary endothelium was universally swollen, with some attempt at proliferation. A delicate net of fibrin was present in the edematous spaces, and moderate numbers of leucocytes, chiefly of the polymorphonuclear type, had made their appearance. The infiltrate also contained lymphocytes and large monocytes. The degree of vascular stasis was variable, and rarely was there any evidence of extravasated red cells or of large vessel injury. Occasionally, there was focal injury or destruction of the thin muscle layer, presumably as a result of injection trauma, and rare degenerated fat cells were noted. The presence or absence of early fibrocytic response depended upon the material as did the degree of inflammation. There was a moderate reaction to most metals and iron oxide (Fig. 20),* but cadmium and copper, and the hydrocar-

*The illustrations are arranged by type of material, the particular material, and the biopsy sequence in time.

bons (Figs. 23 and 28) elicited a moderately severe reaction. Most of the masonry materials gave a relatively mild initial reaction (Fig. 35), although indoor wall plaster and hollow construction tile gave a more pronounced, or moderate reaction. Woods and fabrics (Figs. 47, 50 and 43) produced moderate reactions, as judged by the extent of edema and leucocytic reaction. There was practically no reaction to lead, marble chips, or calcium carbonate. All other substances gave mild reactions (Fig. 62, glass).

A generally more pronounced reaction to all materials appeared on the seventh day. Vascular congestion and proliferation were marked. The zone of edema was broadened, and leucocyte response was usually fairly intense with infiltration into the foreign aggregates. The distinctive feature was the marked fibrous development characterizing this interval. The entire lesion was surrounded by large numbers of proliferating, swollen fibrocytes in depths varying from 30 to over 100 micra. Phagocytosis of small particles by histiocytic cells was evident at this time but the degree varied widely and seemed to be related to the number of minute particles present in the aggregate. The formation of multinucleated giant cells of foreign-body type also occurred at this time. Fibrous response was pronounced with copper (Fig. 1), cadmium (Fig. 7), zinc (Fig. 11), and duraluminum I, approaching neoplastic proportions with the latter material. During this period, small foci of necrosis were frequently encountered and their presence, as expected, paralleled the intensity of inflammation. Necrosis was seen in the inflammatory areas about copper, cadmium, iron oxide, duraluminum I, axle grease (Figs. 24 and 25), and road tar. The leucocyte reaction to lubricating grease (Fig. 29) had subsided considerably, although the fibrous reaction was intense. Multinucleated giant cells were present about large grease globules, but foam histiocytes were not seen. Masonry materials reacted typically, although cinder block material

(Fig. 36) showed a lesser fibrous reaction than poured concrete and wall plaster (Fig. 39), and there was a relatively mild fibrous response to marble, ceramic tile, and calcium carbonate. The fibrous response about the remaining material was mild (duraluminum II, Fig. 17). Occasionally, at this stage, the earliest attempts at vascular and fibrous proliferation into the interior of the aggregate was seen (oak, Fig. 46; cotton, Fig. 48; nylon, Fig. 51; Bakelite, Fig. 58).

For the great majority of the materials, the stage of active acute inflammation had generally subsided by the 14th day and distinct fibrous condensation with capsule formation enveloped the outer margins of the deposit. Vascular congestion and edema had notably subsided, although few leucocytes were still scattered about, generally in the interior of the aggregate. Small mononuclear leucocytes and histiocytes were present in variable numbers, and sometimes the latter cells exhibited phagocytic properties by completely engulfing very fine particles. From the capsular margins, thin vascular connective tissue septa extended into the center of the aggregate dividing it into small compartments. Large, oddly shaped, multinucleated foreign-body giant cells were quite variable and seemed to depend considerably upon the material used.

For a few of the substances (copper, cadmium, zinc, duraluminum I, axle grease, and road tar), active acute inflammation persisted, in spite of the fibrous encapsulation. This was especially true of axle grease deposits (Fig. 26), which exceeded any of the others in intensity of inflammatory cell response, although the reaction to copper particles (Figs. 2 and 3) followed close behind, with lubricating grease (Fig. 30) and motor oil (Fig. 32) being relatively inactive. It was interesting to note that while the acute inflammation persisted, there was no attempt to form foreign-body giant cells. The degree of marginal fibrogenesis was occasionally quite pronounced and broad sheets

of hyperchromic fibrocytes were found. The magnitude of this response always appeared to parallel the severity of inflammation.

Cadmium particles appeared to exert an unusual effect not only on the adjacent tissue but also upon the infiltrating leucocytes. A marginal and very distinct zone of necrosis persisted about the particles through the fourteenth day, into which leucocytes failed to infiltrate (Fig. 8). The outer rim of the necrotic zone contained only pyknotic remnants of leucocytes. The appearance of this peculiar zone suggested the presence of a substance liberated by cadmium particles causing the death of the adjacent structural elements as well as the approaching leucocytes. At the same time, cadmium did not seem to incite a particularly marked fibrogenesis during the period of observation. The remaining metals produced well localized reactions (Fig. 18, magnesium alloy, and Fig. 19, steel).

The masonry products were characterized by a moderate but typical reaction (Figs. 37 and 41). The reaction to indoor plaster was more intense with a greater number of giant cells per unit area. One singular feature of this material was the abrupt change, at this interval, of the tinctorial qualities of the plaster fragments, which up to this time were acidophilic, but beyond this point were characteristically basophilic. Polymorphonuclear leucocytes were persistent in hollow tile lesions (Fig. 42), with small foci of necrosis, and the fibrocytic response appeared greater. Ordinary red brick appeared to produce only a mild fibrous reaction, as did glass particles, which were well localized at this time. The previously delayed but mild reaction of marble chips was well localized but still exhibited marginal hyperemia; few giant cells were present.

Foreign-body giant cells were far more common about the wood particles (Fig. 44) and fabric fibrils (Figs. 49, 52 and 54) than any other substance.

They were somewhat less frequent about particles of iron oxide (Fig. 21) and rockwool insulation. The remaining substances were well localized (Fig. 60, rubber), with little or no leucocytic reaction and few multinucleated giant cells.

At the end of three weeks, most of the lesser reactive materials had reached a stage of relative inertness, beyond which the histological appearance of the lesions changed but little; except for becoming somewhat more compact and showing hyalinization of the connective tissue capsule and dividing septa. The inflammatory reaction to copper, cadmium (Figs. 9 and 10), zinc (Fig. 12), and axle grease persisted, and traces of inflammatory cells were found in the centers of aggregates of road tar and rockwool (Fig. 56). Fibrous encapsulation, even where inflammation persisted, seemed complete. Duraluminum I (Fig. 14), was still characterized by extraordinary fibrous proliferation. The formation of foreign-body giant cells had attained a maximum and no further development of this type of structure was found. Examples of essentially inert materials are lubricating grease (Fig. 31), nylon (Fig. 53), rayon (Fig. 55), plexiglass (Fig. 59), and tar paper (Fig. 61).

At the end of thirty days, with the exception of copper (Fig. 4), cadmium, duraluminum I (Figs. 15 and 16), axle grease (Fig. 27), and road tar (Fig. 34) deposits, most of the lesions had become completely inert. Leucocytes were absent and fibrous activity had ceased. Except for the morphological differences in the particle aggregates, the lesions were generally quite similar in appearance (Figs. 33, 38, 40, 45 and 57). Although well encapsulated, the abscess formation in response to copper particles persisted. In this particular case, although the inflammation was subsiding, areas of necrosis and leucocyte infiltration existed in the samples examined at ninety days (Figs. 5 and 6). The intensive fibrocytic granulomatous reaction of duraluminum I and zinc (Fig. 13) had subsided, but leucocytes were still present and marginal hyper-

emia still existed. Cadmium lesions showed a persistent zone of necrosis around the aggregate up to the time of the final biopsies, although the area was encapsulated. The previously intense reaction to axle grease had subsided at this interval and the inoculation site was replaced by an irregular fibrous zone containing many clear vacuoles of marked variation in size. Otherwise, the appearance of the tissue response to other material at sixty or ninety days was essentially similar to the thirty-day period (Fig. 22, iron oxide).

3.3 VISCERAL IMPLANTATIONS

The following materials were selected from the main list for implantation directly into the parenchyma of the liver and spleen, as well as deposition on the surfaces of the peritoneum, mesentery, and omentum:

1. Concrete masonry
2. Red brick
3. Construction tile
4. Wood (pine)
5. Glass (window)
6. Duraluminum II
7. Lead
8. Steel
9. Zinc
10. Copper

As originally planned, each type of material was embedded in four animals and one of each group was to be sacrificed on the 7th, 14th, 21st, and 30th day. Technical difficulties associated with the surgical procedure proved to be far more formidable than expected and operative and postoperative mortality among the animals was extraordinarily high. Death was usually due to uncontrolled hemorrhage or the development of pneumonia. These events substantially reduced the number of animals in each group such that complete sampling over the intended period was not possible. Examination of the available material further showed that the reactions in and about the site of inocu-

lation were quite variable in appearance and much of it appeared unrelated to the presence of the foreign material itself.

With rare exceptions, the intrahepatic injections were accompanied by considerable traumatic necrosis of liver tissue, frequently taking the form of wedge-shaped areas of infarction. The resulting inflammatory response to such necrotic zones virtually obliterated the response to the particle deposits. In many instances, it was impossible to accurately distinguish the particle reaction per se. The few random sections of material taken at later intervals showed no significant difference or variation from the subcutaneous deposits. Samples of these are illustrated in Figs. 63 to 67, inclusive.

The intrasplenic inoculations were fraught with similar difficulties. The particle implantations were necessarily accompanied by tearing of the splenic parenchyma and considerable hemorrhage in the injection tract. The resulting inflammation to the hemorrhagic areas all but obscured the early reaction to the particles, and generally only late stages could be evaluated. Here, again, the tissue reaction did not appear essentially different from the subcutaneous implant. As was expected, peritoneal and mesenteric deposits induced tissue responses similar to those seen in the subcutaneous fatty tissue. The particles generally induced a moderate inflammatory response followed by fibrous encapsulation and the formation of foreign-body type granulomas. However incomplete the obtained data appear, it seems singularly significant that the parenchymal injury associated with the introduction of the foreign particles into a visceral organ was a far greater hazard than the presence of the particle itself, from the standpoint of inflammation and repair.

Chapter 4

DISCUSSION

It is apparent that the general tissue reaction induced by the presence of these sterile foreign particles differs from an ordinary wound, contaminated by dirt and bacteria, by the delay in leucocyte and cellular response. The common injury is notable for the rapid development of edema, hyperemia, and the infiltration of leucocytes resulting in swelling and induration of tissues developing within a few hours. In the sterile and essentially nontraumatic particle deposition, these changes developed gradually over a period of 3 days and leucocyte infiltration was seldom very marked.

At the end of 3 days, most of the implant sites exhibited a mild to moderate degree of edema, variable hyperemia, and an early but relatively slight leucocyte response, frequently of mixed cell types (polymorphonuclear cells predominating). The number of leucocytes reached a maximum intensity during the interval of 7-14 days, subsiding thereafter, with certain exceptions. Rarely was fibrogenesis notable as early as the 3rd day, but was quite prominent by the 7th day. The individual fibrocytes were swollen, hyperchromic, and often contained mitotic figures. At the 14-day interval, the fibrous elements became compressed or condensed to form a distinct capsule serving to more rigidly localize the particles. Phagocytosis was not generally noted until this time and appeared to be related to the number of very fine particles present. At the end of the 3rd week, vascular fibrous septa extended from the

capsule margin into the center of the foreign aggregate separating the particles into small compartments. This was associated with the disappearance of leucocytes and the formation of multinucleated giant cells of bizarre sizes and shapes. The latter embraced, either partially or completely, the larger foreign particles. Most frequently, the process had attained an inert stage by the end of the 30-day period with the ultimate formation of a circumscribed fibrous nodule. Material removed at the 60- and 90-day periods differed but little from the 30-day period except for further condensation of connective tissue, hyalinization, and compression of the nodule into a more compact mass. Progressive fibrogenic lesions, such as those induced by silica and talc, were not observed in this study, although the marginal fibroplasia was quite marked in the lesions induced by copper, duraluminum I, zinc, axle grease, and road tar. The degree of fibrous response appeared to parallel the intensity of inflammation and its relative duration.

The masonry products generally reacted typically and yielded a mild to moderate inflammatory tissue response similar to that described above. The construction tile and indoor wall plaster induced a marked inflammatory response with some delay in the organizing or fibrosing process. In the tile lesions, leucocyte activity was very intense at the 14th day, resulting in microabscess formation, and continued into the 30th day. Even at 60 days a few polymorphonuclear leucocytes were still present. The fibrocytic proliferation, however, was not delayed but was greater than seen with other masonries, and the fibrous and vascular infiltration into the particle mass was deferred until the 30th day by the still active inflammation. At the end of the test interval (60 days), the lesion was well circumscribed, but appeared still active, with continued fibrous response. In the plaster induced lesions, there was an earlier and more pronounced inflammation which quickly subsided, and vascular and

fibrous invasion took place earlier than usual (14th day). At 21 days the lesion appeared relatively inert. There was no discernible difference between the rough and finish plasters. Marble chips, calcium carbonate, window and safety glass, and ceramic tile induced only a mild response with rapid encapsulation. The lesions appeared nearly inert at 14 days.

The tissue reaction to wood particles was rather characteristic and imitated that seen with fabric materials. At 3 days, a moderate degree of edema was present, but very few leucocytes were found. The oak hardwood reaction seemed slightly less intense than that of the soft woods. The distinguishing feature was the large number of multinucleated giant cells appearing on the 14th day, followed by conversion into an inert fibrous nodule. However, none of the samples exerted any unusual fibrogenic stimulus other than that necessary for encapsulation.

Of the metal products used, lead was nearly inert. The reactions to duraluminum I and magnesium alloy were essentially mild with complete encapsulation and formation of an inert nodule by 21 days. This was in contrast to the pronounced fibrous reaction to duraluminum I. However, the material used in the two series was derived from different sources, and, judging from the complexity of alloy manufacture, was probably of slightly different composition, although offered as basic duraluminum. Zinc particles produced a reaction similar to duraluminum I, but of lesser magnitude.

One of the most severe inflammatory reactions was induced by copper particles resulting in abscess formation which essentially continued until the 90th day, although it was evident that the process was subsiding at this time. As expected, the later stages were associated with considerable fibrosis.

Cadmium lesions were unique and distinguished by the presence of a prominent zone of tissue necrosis about the aggregate which greatly inhibited the ap-

proach of leucocytes. Although the area was encapsulated and isolated, the necrosis persisted until the latest stages, and the ultimate fate was not determined.

Iron oxide induced only a minimal reaction of inflammation although the multinucleated giant cells were quite numerous.

All of the fabric fibrils were characterized by the formation of the most numerous multinucleated giant cells of the foreign-body type. The early inflammatory process was relatively mild and rapidly subsided with minimal fibrosis. The reactions induced by rockwool and fiberglass were essentially similar.

Of the hydrocarbon group, the intense reaction associated with the presence of axle grease was most interesting, in contrast to the rather mild inflammatory reaction to motor oil and lubricating grease. The early stages were characterized by considerable fibrin deposition, central necrosis, and finally abscess formation. At the 21-day interval, the intense inflammation was subsiding and at 30 days the area was replaced by fibrous tissue in which numerous large globular spaces existed. The lesion was not considered inert until the 60-day interval. The inoculation sites of motor oil and lubricating grease had reached an inert stage by 21-30 days.

The remaining substances yielded only mild to moderate typical reactions, becoming well localized, encapsulated, and inert at the end of 30 days.

The phagocytosis of small particles, in most instances, appeared proportional to the amount of finely divided material in the implants. Transportation of such particles to a more distant site was not observed in this material. However, the presence of the particles in the cytoplasm of enveloping fibrocytes was a common observation, similar to the manner in which silica is seen in human pulmonary fibrous lesions. There were two exceptions noted,

in the cases of duraluminum I and zinc. In the initial implants, no fine particles of such size as to induce phagocytosis by individual cells was noted. However, as early as the 7th day, there were many mononuclear cells and some fibrocytes containing intracytoplasmic tiny particles of fairly uniform size. This phenomenon continued throughout the test period. It seemed most likely that these particles represented a fine oxide removed from the surface of the larger fragments. Such oxide may have been present at implantation or could possibly have been formed in situ by the action of tissue fluids. No attempt was made to measure quantitatively the mass of the foreign body before and at the end of the test period, in order to ascertain the amounts of solubility or possible rate of disappearance of the material from the site.

The qualitative differences in reactivity between certain foreign substances introduced into tissues has long been recognized, but no satisfactory explanation for the differences has been found. Most insoluble particulate matter incites some form of leucocytic reaction in the very early stages and will induce phagocytosis -- if in small enough form -- or fibrous encapsulation, after which the lesion is reduced to an inert status. Investigations concerned with industrial hazards have shown that some compounds, such as silicon dioxide, have the property of inducing an excessive fibrous proliferation, whereas others, such as carborundum, hematite, carbon, and diamond dust, do not. Evans¹ and Evans and Zeit,^{2, 3} in search of a common denominator, have expressed the view that a piezoelectric effect, defined as the appearance of electrical charges upon the surfaces of certain crystals when the crystals have been subjected to mechanical stress, may furnish an explanation to this fibrogenesis. Most asymmetric crystals exhibit a piezoelectric effect whereas symmetric crystals do not. Intraperitoneal injections of several powdered substances of known piezoelectric characteristics and some which had none, were given to

rats. Half of each group of animals were kept in an electromagnetic field of 1200 megacycles for periods ranging from 8 to 40 days. The piezoelectric substances, Wulfenite (lead molybdate), barium titanate, tourmaline (aluminum-boron silicate), Berlinite (aluminum orthophosphate), and cholesterol crystals, all induced a marked fibrogenic response, whereas the non-piezoelectric substances, silicon carbide, white mica, fused quartz, and pyrex glass induced only a mild reaction of simple foreign-body type in the electromagnetic field. Further, the fibrogenic reaction in the electromagnetic field was greatly enhanced, whereas the control group was not. However, this has not explained the unusual fibrogenic activity of talc, asbestos, opal, aluminum phosphate, etc., which are not piezoelectric, and induce progressive fibrosis.

Additional work of Evans and Zeit^{2, 3} pointed out that when two dissimilar metals were embedded in tissue as an electrolyte, the resulting galvanic currents stimulated fibrous proliferation proportional to the electromotive dissimilarity between the metals used. This is in essential agreement with the work of Bates, Reiners and Horn,⁴ who have shown the existence of galvanic currents in such alloys as vitallium (alloy of cobalt, chromium, and molybdenum), and stainless steel (18% nickel, 8% chromium, 2-3% molybdenum, remainder iron, manganese, and carbon). These alloys were suitable for use in tissues but did incite a mild reaction. Tantalum and zirconium, basic elements without galvanic currents, induced much milder tissue response. Venable,⁵ in 1942, demonstrated the effects of dissimilar metals by the intense tissue reaction resulting with vitallium plates fastened with steel screws, necessitating eventual removal of the steel.

Such galvanic action could have been a factor in the marked fibrous response induced by duraluminum, but it remains possible that the magnesium or manganese content of the alloy may have been an inciting factor. Bates⁴

had pointed out, in his discussion of prolonged usage of an alloy, the interesting fact that alloys may undergo a "stress corrosion" in which the elements change their physical relationships, and as a result may convert from a biologically inert form to a potentially dangerous one.

It seems probable that the differences in reaction between the substances used in these experiments were the result of surface chemical effects on the cellular constituents, either directly or indirectly by the formation of chlorides or other salts in an electrolyte medium. The differences in reactivity of iron, zinc, and lead were rather marked and it is difficult to associate the reactions with galvanic currents in the essentially pure basic metals. Nearly all of the masonry products, however, contain silica in varying proportions. The reactions and ultimate fate of the lesions seemed essentially similar, except with the hollow tile. If the effect of the agent were a predominantly chemical one, the particle size and presenting total contact surface area should be an important factor in determining the magnitude of the inflammatory response. However, at this time, no studies were directed to test this latter effect.

Although not a subject of this report, the factor of associated bacterial contamination of the particles appears to present a synergistically enhanced inflammatory process and augmented tissue response. Preliminary studies with the particles have shown in mice that the controlled injection of bacteria and sterile particle, separately, did not result in a tissue reaction of the magnitude of the mixed bacteria-particle inoculum.

The phenomenon of stress and adrenal response is an additional factor which should be considered in evaluating the foreign-body lesion and the tissue response. Certain of these agents may prove to be marked "stressing" agents, as is formaldehyde, when injected into tissues and, as such, may greatly modify

the ensuing reaction, temporarily at least. Cortisone or adrenal stimulation has been shown to effectively alter the fibrogenic response in tissues.

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Fig. 1. Copper, 7 days, subcutaneous lesion. The inflammatory response is extraordinarily intense with central areas of necrosis. X 128

Fig. 2. Copper, 14 days, subcutaneous lesion. The inflammation has progressed to abscess formation, although fibrous encapsulation is now apparent. X 128

Fig. 3. Copper, 14 days, subcutaneous lesion. Illustrating the intensity of fibrous proliferation. X 128

Fig. 4. Copper, 30 days, subcutaneous lesion. Persistent abscess with exceptional leucocyte reaction. Note the sharply defined marginal capsule. X 128

Fig. 5. Copper, 90 days, subcutaneous lesion. Although the inflammation is subsiding, areas of necrosis and leucocyte infiltration still persist. X 128

Fig. 6. Copper, 90 days, subcutaneous lesion. Rare local foreign-body granulomatous response. X 128

Fig. 7. Cadmium, 7 days, subcutaneous lesion. The early inflammatory response with sharply defined zone of necrosis which particularly characterizes the presence of these particles. X 128

Fig. 8. Cadmium, 14 days, subcutaneous lesion. The opaque particles are separated from the organizing inflammatory process by a persistent zone of necrosis. X 44

Fig. 9. Cadmium, 21 days, subcutaneous lesion. Persistent necrotic zone. Particles are not present in the illustration. X 128

Fig. 10. Cadmium, 21 days, subcutaneous lesion. Another field illustrating the peculiar necrotic zone. X 128

Fig. 11. Zinc, 7 days, subcutaneous lesion. A moderately intense, inflammatory reaction. Early fibrous proliferation surrounds the opaque particles. X 71

Fig. 12. Zinc, 21 days, subcutaneous lesion. A marked proliferation of fibrous tissue similar to that of duraluminum I, although of lesser magnitude. X 128

Fig. 13. Zinc, 30 days, subcutaneous lesion. There is a distinct capsule present, but there is residual acute inflammation about the particles. X 128

Fig. 14. Duraluminum I, 21 days, subcutaneous lesion. Foreign material in upper portion of illustration. Note the remarkable pseudoneoplastic fibrocytic response. X 128

Fig. 15. Duraluminum I, 30 days, subcutaneous lesion. Higher magnification of proliferative fibrous reaction and formation of multinucleated giant cells about the particles. The granular cytoplasm is studded with tiny particles. X 490

Fig. 16. Duraluminum I, 30 days, subcutaneous lesion. Another field similar to Fig. 15. X 490

Fig. 17. Duraluminum II, 7 days, subcutaneous lesion. Encapsulation is proceeding with little inflammatory response. X 128

Fig. 18. Magnesium alloy, 14 days, subcutaneous lesion. A relatively inert stage is reached at this interval with moderate foreign-body type response. X 128

Fig. 19. Steel, 14 days, subcutaneous lesion. Moderate leucocytosis associated with the fibrous proliferation. X 128

Fig. 20. Iron oxide, 3 days, subcutaneous lesion. A moderate initial inflammatory response which quickly subsides. X 128

Fig. 21. Iron oxide, 14 days, subcutaneous lesion. Separation of the aggregate into smaller groups by vascular fibrous septa; some phagocytosis. X 128

Fig. 22. Iron oxide, 90 days, subcutaneous lesion. Nodular inert stage.
X 128

Fig. 23. Axle grease, 3 days, subcutaneous lesion. Intense initial inflammation with extensive necrosis. X 71

Fig. 24. Axle grease, 7 days, subcutaneous lesion. The inflammation has progressed to abscess formation. Marked marginal fibrous proliferation. X 128

Fig. 25. Axle grease, 7 days, subcutaneous lesion. Part of the hyperchromic and proliferative fibrous wall. X 128

Fig. 26. Axle grease, 14 days, subcutaneous lesion. Although the entire lesion is encapsulated, the abscess persists. X 128

Fig. 27. Axle grease, 30 days, subcutaneous lesion. The intense inflammation has subsided. The inoculation site is replaced by fibrous tissue containing large vacuolated spaces. X 71

Fig. 28. Heavy lubricant grease, 3 days, subcutaneous lesion. Moderate infiltrations of leucocytes. The wide spaces to the left contain the masses of grease. X 128

Fig. 29. Heavy lubricant grease, 7 days, subcutaneous lesion. Beginning fibrous proliferation. X 128

Fig. 30. Heavy lubricant grease, 14 days, subcutaneous lesion. Foreign material is at bottom of illustration. Note the marked fibrous reaction, together with moderate leucocytosis. X 73

Fig. 31. Heavy lubricant grease, 21 days, subcutaneous lesion. Persistent fibrous proliferation similar to that seen in duraluminum I. X 128

Fig. 32. Motor oil, 14 days, subcutaneous lesion. Moderate fibrous proliferation about the oil globules. Inflammatory cells are sparse. X 71

Fig. 33. Motor oil, 30 days, subcutaneous lesion. Except for some increased fibrous tissue, there is little difference from the 14-day lesion.
X 71

Fig. 34. Road tar, 30 days, subcutaneous lesion. The heterogenous particles are rapidly encapsulated. Some inflammation persists. X 128

Fig. 35. Plasticrete cinder block, 3 days, subcutaneous lesion. Foreign material is in the upper left corner. Note the mild edema and relatively few leucocytes. X 128

Fig. 36. Plasticrete, 7 days, subcutaneous lesion. Foreign material in upper left corner. Greater leucocyte infiltration and marked fibroplasia. X 128

Fig. 37. Plasticrete, 14 days, subcutaneous lesion. Fibrous condensation and encapsulation. X 128

Fig. 38. Plasticrete, 30 days, subcutaneous lesion.

Fig. 39. Wall plaster, 7 days, subcutaneous lesion. Fibrous proliferative stage is greater than that of concrete. X 73

Fig. 40. Wall plaster, 30 days, subcutaneous lesion. The foreign particles are enclosed in inert, dense fibrous tissue. X 128

Fig. 41. Poured concrete, 14 days, subcutaneous lesion. The particle masses are embedded in condensing fibrous tissue. X 128

Fig. 42. Construction tile, 14 days, subcutaneous lesion. Leucocyte reaction is more intense than concrete or plaster, and fibrous proliferation is delayed. X 128

Fig. 43. Pine, 3 days, subcutaneous lesion. The initial reaction is quite mild. X 128

Fig. 44. Pine, 14 days, subcutaneous lesion. An inert, localized granulomatous nodule. Numerous multinucleated giant cells. X 128

Fig. 45. Douglas Fir, 30 days, subcutaneous lesion. An inert, well localized, foreign-body nodule. Numerous giant cells have formed about the spicules. X 128

Fig. 46. Oak, 7 days, subcutaneous lesion. There is slight inflammatory response, but the spicules are encapsulated at an early interval.
X 128

Fig. 47. Cotton fabric, 3 days, subcutaneous lesion. A typical early inflammatory response characterized by edema and slight leukocyte infiltration. X 128

Fig. 48. Cotton fabric, 7 days, subcutaneous lesion. Early and pronounced foreign-body type reaction. X 128

Fig. 49. Cotton fabric, 14 days, subcutaneous lesion. Fibers are embedded in dense fibrous foreign-body granuloma. Note persistent leucocytes. X 128

Fig. 50. Nylon fabric, 3 days, subcutaneous lesion. The initial reaction is quite minimal. X 128

Fig. 51. Nylon fabric, 7 days, subcutaneous lesion. Early and pronounced foreign-body type reaction. X 128

Fig. 52. Nylon fabric, 14 days, subcutaneous lesion. Marginal encapsulation is generally complete and tissue reactivity has subsided. X 128

Fig. 53. Nylon fabric, 21 days, subcutaneous lesion. No essential change from the 14-day lesion. X 128

Fig. 54. Rayon fabric, 14 days, subcutaneous lesion. The process is encapsulated with prominent foreign-body response. X 128

Fig. 55. Rayon fabric, 21 days, subcutaneous lesion. Further condensation of connective tissue, but little change from the 14-day period. X 128

Fig. 56. Rockwool, 21 days, subcutaneous lesion. Particle aggregates enveloped by a thin capsule. A few leucocytes are present in the interior of the nodule. X 128

Fig. 57. Fiberglass, 30 days, subcutaneous lesion. Inert nodule with numerous giant cells. Glass spicules are often difficult to discern since the refractive index is similar to that of the mounting medium.
X 128

Fig. 58. Bakelite, 7 days, subcutaneous lesion. Leucocyte response is moderate, with penetration into the foreign mass. X 128

Fig. 59. Plexiglass, 21 days, subcutaneous lesion. A localized, rapid, fibrous encapsulation with little leucocyte response. X 128

Fig. 60. Rubber wire insulation, 14 days, subcutaneous lesion. Leucocytes are still present but vascular fibrous infiltration is progressing.
X 128

Fig. 61. Tar paper, 21 days, subcutaneous lesion. An inert, fibrosed, and encapsulated mass. X 128

Fig. 62. Glass, 3 days, subcutaneous lesion. Slight to moderate leucocytosis with fibrin deposits. Rapid encapsulation followed. X 128

Fig. 63. Steel, 7 days, intrahepatic lesion. Inflammatory cells are sparse. Large marginal histiocytes have absorbed fine particles. X 128

Fig. 64. Steel, 14 days, intrasplenic lesion. Well localized aggregate with narrow fibrous capsule. No significant inflammatory cell response. X 128

Fig. 65. Concrete, 3 days, intrahepatic lesion. There is a marginal proliferation of fibrous tissue, but inflammatory cells are sparse. X 128

Fig. 66. Lead, 21 days, intrasplenic lesion. The irregular spicules are separated by fibrous septa, with very few inflammatory cells.
X 128

Fig. 67. Lead, 3 days, intrahepatic lesion. The large zones of hepatic necrosis are associated with the inoculation procedure and seem unrelated to the actual presence of lead particles. X 71