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Foreign Body Reactions to Plastic Implants

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SUMMARY

There are three types of foreign body reactions to plastic implants: 1) reactions due to physical characteristics of the implant, 2) reactions due directly to chemical properties of the implant, and 3) immune reactions. Responses which vary with the physical properties of the implant are epithelial encapsulation of the plastic, epithelial keratinization in cutaneous implants, thickening of the connective tissue fibrous capsule, formation of ground substance, and the presence of giant cells. Responses related directly to chemical toxicity of the plastic are epithelial hypertrophy (with mild irritants), inhibition of epithelial growth (with more toxic irritants), connective tissue inflammation, accumulation of acellular glycoproteins, and vacuolization of host tissue. Finally, reactions due to infection or the presence of other antigens are characterized by inhibition of epithelial growth, invasion of epithelium by leukocytes, and proliferation of inflammatory tissue with a large population of plasma and other round cells.

There is always a tissue response to a plastic implant, even when the material is chemically inert. However, with use of a suitable design and a chemically inert material, and with sterile conditions, plastic implants with only minimal host tissue response may be achieved. Infection, not physical (design) or chemical properties, remains the primary problem with current implantation procedures.

INTRODUCTION

A foreign body reaction may be defined as any response of the host tissue that results from the introduction of an alien material. The importance of the foreign body response to medicine has increased as a result of the accelerated use of plastic and other artificial prostheses in clinical practice. It is apparent that there is an immediate need in biomedical engineering for a systematic examination of the whole spectrum of foreign body responses that may be encountered. The present study was initiated as a partial fulfillment of this need. The study was limited to the skin epithelium and underlying connective tissue.

Since our primary purpose was to examine kinds of foreign body response, little space is provided in the current report to the solution of problems involved during implantation of artificial materials.

Various devices were implanted in both the epithelium and connective tissue of monkeys, dogs, pigs, and one human volunteer. A number of histochemical techniques were employed in order to follow the biological events that characterize foreign body reactions.

METHODS AND MATERIALS

Plastic devices were implanted in monkeys, dogs, pigs, and one human volunteer. Two types of implants were employed: devices that penetrated through the skin and are usually termed "percutaneous," and devices placed beneath the skin (Fig. 1).

The percutaneous implant consisted of a disc-shaped flange or skirt that was inserted just beneath the skin of the animal and a conduit that projected from this flange through the skin. In most cases, the projecting shaft was topped by an external flange or cap (Figs. 1 and 2). The skirt was 2.54 cm in diameter in monkeys, 3.75 to 5.0 cm in dogs and pigs, and was usually fenestrated with holes 0.10 cm in diameter with 0.10 cm spacing. Eighteen of these devices were implanted in five monkeys, 73 in 32 dogs, and 10 leads in four pigs. A similar device was placed in one human volunteer (see Acknowledgments) except that the subcutaneous skirt or flange was shaped like a collar button instead of a disc.

For monkey implants, 16 devices were fabricated entirely from graphite whereas two were made with epoxy conduits and polyurethane skirts. For dogs, 40 of the conduits were made from polyurethane and 13 from Teflon. Thirty skirts were made from Teflon and 23 from polyurethane. Etched, annealed, and untreated Teflon was used. Eight devices were formed

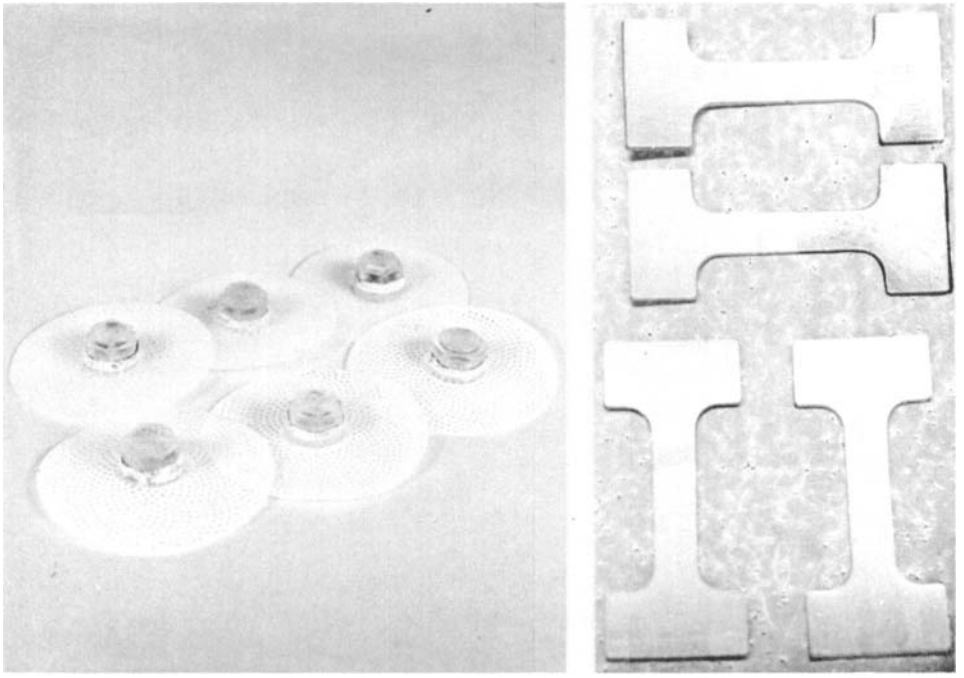

Fig. 1. Photograph of plastic implants employed in the present investigation. Several through-the-skin (percutaneous) devices are shown at left; dogbone-shaped devices implanted only subcutaneously are shown at right.

entirely from polypropylene; the skirts in these implants had no fenestrations in the skirt or only a single row of holes. Twelve additional devices were coated with neutral or anionic polyelectrolyte (Amicon).

Most implants placed beneath the skin were "dogbone" shaped bars (Fig. 1) 1.9 cm long, 0.25 cm in width, and 0.10 cm in thickness. Only dogs received these devices. Four were fabricated from etched Teflon, 16 from unetched Teflon, and four from annealed Teflon and 19 from polyurethane. Eight discs made of rigid epoxy, of which four contained a non-reactive diluent, were also implanted subcutaneously in dogs. The discs were 1.9 cm in diameter and 30 mm in thickness.

With one exception, all plastics were cured before implant. With one material, however, the polymer, an experimental epoxy adhesive, was allowed to cure in vivo. Four samples, 5.0 cm in length, 2 cm wide, and 1.5 cm thick, were placed subcutaneously in two dogs.

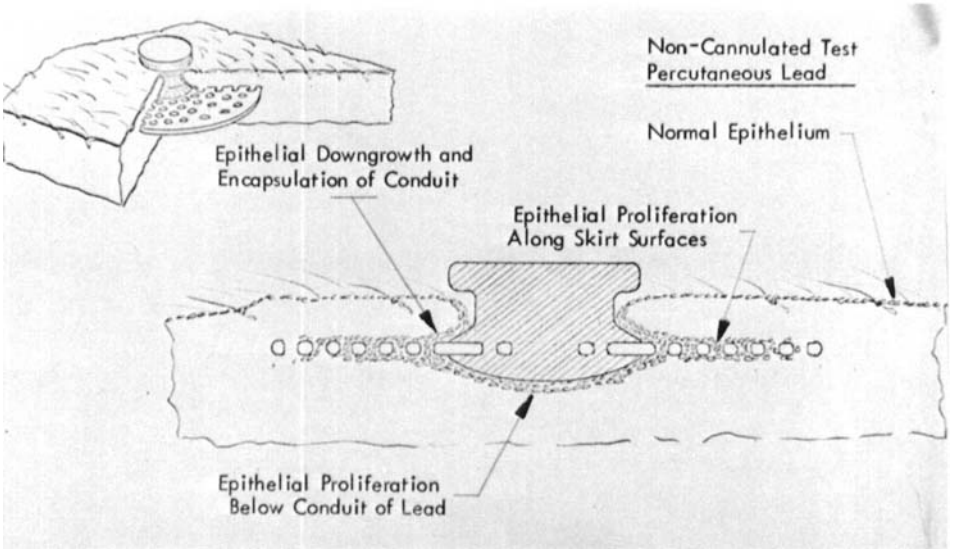

Fig. 2. Drawings of devices having a subcutaneous skirt with fenestrations and an attached conduit projecting through the skin or "percutaneously."

Operative Procedures

The animals were anesthetized with Metofane (Pitman-Moore Co.) endotracheally and Surital (Parke, Davis and Co.) intravenously. The implant devices were sterilized at 250°F steam heat for 15 min. A transverse incision was made in the skin, then a subcutaneous pocket. With devices having a projecting conduit (Fig. 1) a hole was trephined in the skin and the conduit brought through it. Stainless steel sutures were used to close the transverse incision.

Postoperative Care

The animals were under Thorazine (Pitman-Moore Co.) for 4 days. They were injected with 200,000 units of penicillin and 250 units of streptomycin immediately and 250 mg tetracycline three times daily for 4 days. The monkeys were held in restraining chairs for 3 weeks, then transferred to individual cages whereas dogs and pigs were allowed free movement in individual cages when they recovered from the anesthetic.

The implants were examined twice weekly for evidence of infection, including swelling (edema), weeping, and pus formation.

Histology

The plastic implants were excised at intervals of 2, 6, 12, and 32 weeks, and fixed in 10% neutral formalin. The tissues were embedded in paraffin and processed for staining. The following stains were used: hematoxylin and eosin, the periodic-acid-Schiff (PAS) stain for glycoprotein [1], Mowry's alcian blue and colloidal iron procedures for acid mucopolysaccharides [2, 3], van Gieson's stain for collagen [4], and the silver impregnation technique for reticular fibers [5].

RESULTS

Examination of host tissue around the implants revealed that foreign body responses could be separated into three distinct categories, here designated Types A, B, and C.

Type A Foreign Body Reaction

With implants fabricated from Teflon, polyurethane, or the nonplastic material, graphite, the reaction appeared to be determined by the design of the implant.

a. Epithelial Responses. The skin epithelium grew down the projecting conduit and over the subcutaneous skirt (Fig. 3). At first the epithelium was thick and lacked keratin and keratohyalin granules at the surface and pigment granules (melanin) in deeper cell layers. After 3 months the epithelium acquired the appearance of normal skin epithelial tissue: it became thin and formed keratin and keratohyalin granules at the surface and melanin in the deeper strata. Excessive keratin was formed at the angle between the conduit and the subcutaneous skirt (Figs. 3 and 4). No hair follicles or other epithelial derivatives were seen beneath the new epithelium proliferating over the skirt.

When the skirt-conduit junction formed a sharp 90° angle, the epithelium was thickened and growth was slowed (Fig. 4). It required 2 months to grow on to the skirt. In devices where this angle was graded, the epithelium grew down the conduit and on to the skirt in several weeks. Epithelium also managed to grow over the conduit whenever a prominent cap was absent, completely burying the implant.

b. Connective Tissue Responses. Following the operation, numerous white blood cells, most neutrophils, surrounded the implant. Delicate fibers,

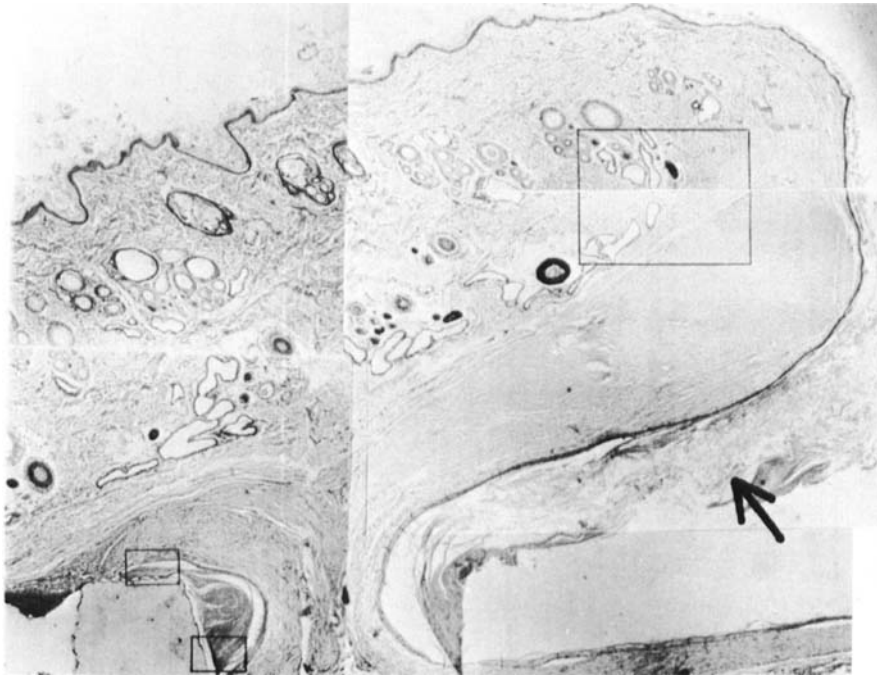

Fig. 3. Composite photomicrograph of dog skin surrounding a percutaneous implant for 9 months prior to excision. The space at the right was occupied by the conduit which projected through the skin and the space at the bottom of the photograph was occupied by the subcutaneous skirt or flange. The arrow points to keratin formed at the conduit-skirt junction. The upper square marks the boundary between normal skin (above) and the fibrous capsule which thickened over the 9-month implant period. The lower squares mark the site of keratinization at the skirt-epithelial interface. Hematoxylin-eosin. 40X

demonstrated by the silver impregnation method for reticular fibers, formed the connective tissue matrix. Macrophages and some giant cells appeared at early intervals. This "granulation" tissue was gradually replaced by fibroblasts and mature collagen fibers embedded in a mucoid ground substance. The ground substance stained strongly with Mowry's colloidal iron and alcian blue stains for acid mucopolysaccharides and the PAS stain for glycoproteins (Fig. 5). Collagen fibers were arranged somewhat parallel to

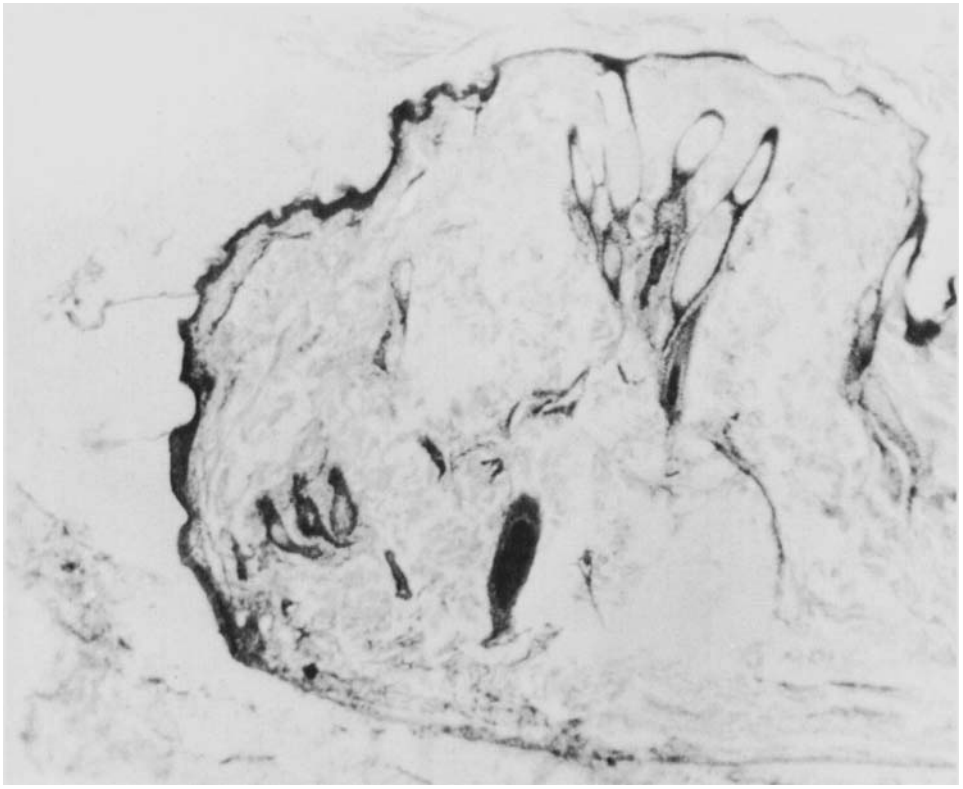

Fig. 4. Photomicrograph of skin tissue surrounding a percutaneous implant in a rhesus monkey. Space at left was occupied by a conduit projecting through the skin. The epithelium (staining darkly) has proliferated down to the skirt but growth has been slowed by the sharp 90° angle between skirt and conduit. Hematoxylin-eosin. 40X

the surface of the implant. These fibers stained weakly but positively with van Gieson's stain for collagen.

The capsule of collagen fibers and ground substance thickened with time around all surfaces forming sharp angles. Continually thickening capsules were noted at the angular tips of implanted bars at the junction of skirt and conduit (Fig. 3) and around the right-angled corners of skirt fenestrations (Fig. 5). A relatively large fibrous capsule also occurred around skirts with few or no fenestrations. Adjacent to rounded surfaces, including the rim of the skirt (Fig. 5), almost no capsule was noted even 9 months after

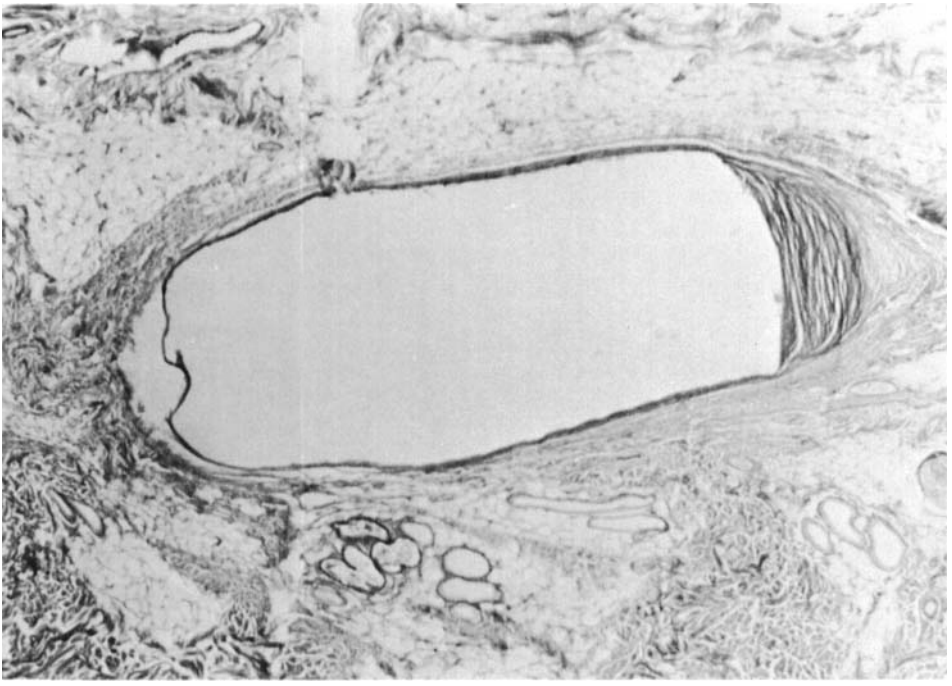

Fig. 5. Photomicrograph of subcutaneous tissue enveloping plastic implant in dog. Fibrous capsule seen on the right is a tissue response to the sharp edge of the skirt fenestration. Note that there is little capsular formation (at left side of photograph) adjacent to the smooth rounded rim of the skirt. PAS stain. 40X

implant. Staining reactions for mucopolysaccharides and glycoproteins were weak. There was also little development of the capsule at the flat surfaces of the implants, and little evidence of polysaccharide and glycoprotein formation (Fig. 5).

In the presence of proliferating epithelium, the connective tissue capsule was modified. It lost its peculiar staining properties and assumed the appearance of healthy skin and subcutaneous connective tissue.

Giant, multinucleated cells (Fig. 6) were most frequently found at irregular surfaces of the implants in monkeys. They were prevalent in the skirt fenestrations and at frayed edges of the skirt. Macrophages and giant cells were more abundant in dogs around skirts with no fenestrations and adjacent to the ball-shaped implant from the human volunteer. In all cases

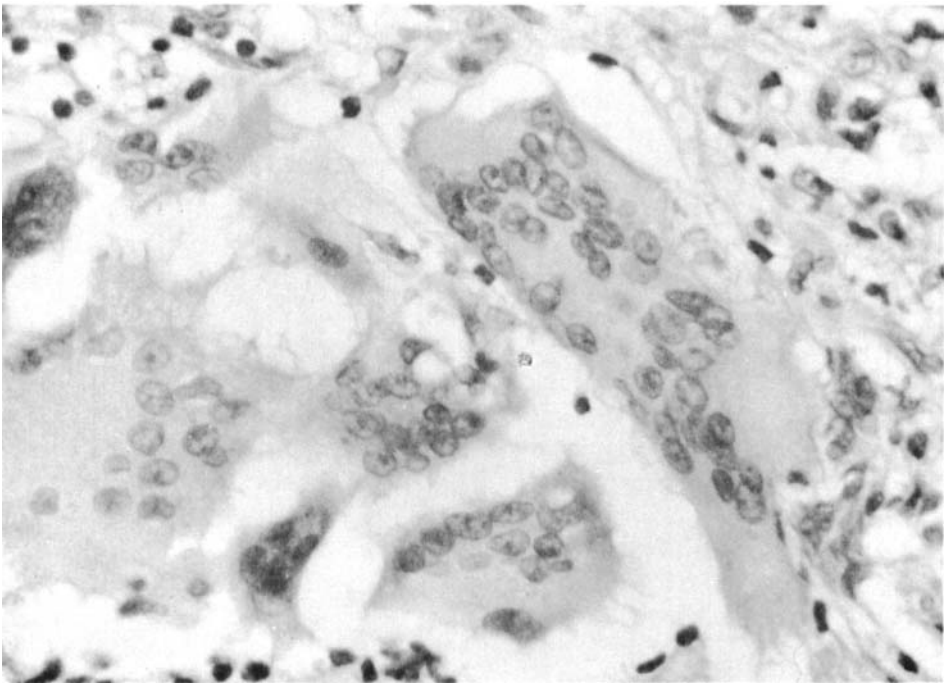

Fig. 6. Photomicrograph of multinucleated giant cells beneath human implant. Surface of the device was concave and was without fenestrations. Giant cells apparently form in response to irregular or uninterrupted surfaces. Hematoxylin-eosin. 500X

both multinucleated giant cells and macrophages were situated inside the fibrous capsule and appeared to be attached to the implant surface.

Type B Foreign Body Reaction

With implants fabricated from polyelectrolyte-coated plastics and from certain epoxy resins, a reaction ascribable only to toxicity of the material occurred.

a. Epithelial Responses. There was very rapid growth of epithelium and formation of keratotic cysts adjacent to the conduit (Fig. 7) with implants coated with polyelectrolytes.

b. Connective Tissue Responses. Inflammatory (granulation) tissue

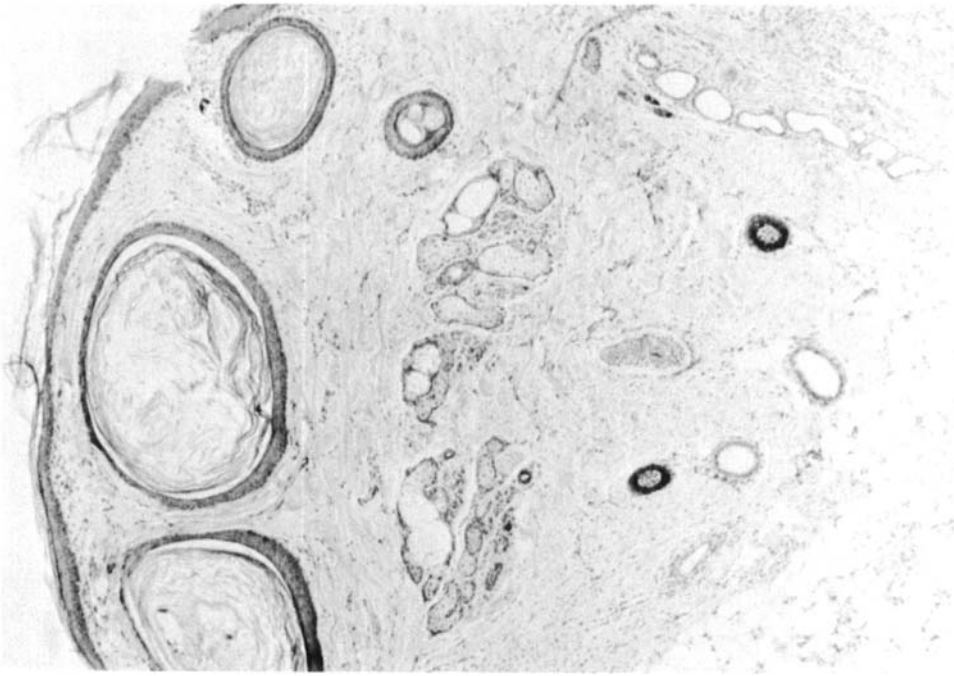

Fig. 7. Photomicrograph of enormous cysts in dog skin formed in response to polyelectrolyte-coated conduit. Space at left was occupied by conduit projecting through the skin. Hematoxylin-eosin. 40X

surrounded the implant in this type of reaction. The tissue was not replaced by fibrous encapsulation as in the previous type of response. There was, however, a variably developed capsule outside of the ring of inflammatory cells. The granulation tissue consisted of neutrophils, small and large lymphocytes, macrophages, and a few giant cells in a meshwork of reticular fibers. It was sometimes vascularized. Plasma cells, however, were generally absent.

This connective tissue response, in order of increased severity, was seen associated with the following: polyelectrolyte coated implants, epoxy resins, epoxy resins with a hydrophobic, nonreactive diluent, and the experimental adhesive cured in vivo. With resins which contained the diluent, an acellular mucoid material, staining strongly with the PAS technique for demonstration of glycoprotein, but weakly with eosin, was found at the tissue-implant interface (Fig. 8). There was a large amount of acellular

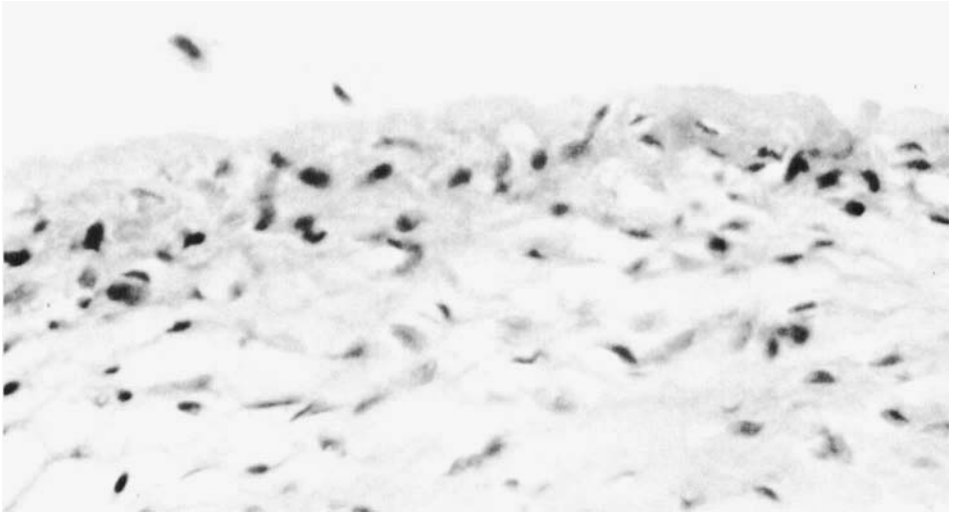

Fig. 8. Acellular mucoid material seen on surface of tissue in this photomicrograph was a response to a mildly toxic plastic material. PAS and hematoxylin counterstain. 1000X

material which was strongly eosinophilic surrounding the adhesive implants. Large vacuoles were present in the granulation tissue (Fig. 9).

Type C Foreign Body Responses

This type of reaction was associated with 50 dogs and all ten pig implants having a projecting conduit (Figs. 1 and 2). It was not seen in monkey implants, the single human implant, or in dog implants which were purely subcutaneous and lacked a through-the-skin conduit. It was associated with implants fabricated from all plastics employed in the study.

In gross examination, percutaneous implants which belonged to this group of reactions showed signs of infection, including weeping, edema, pus formation, and chronic scabs.

a. **Epithelial Responses.** The skin epithelium seldom managed to grow down over the conduit to the skirt. It never continued over the skirt to encapsulate the implant. It was frequently invaded by granulation tissue.

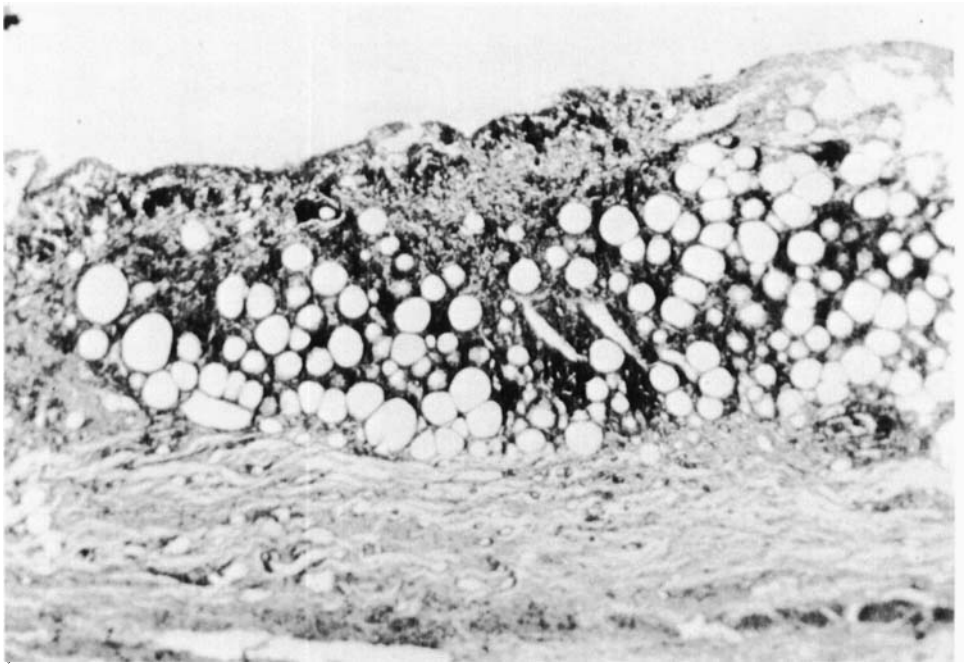

Fig. 9. Photomicrograph showing numerous vacuoles and inflammatory tissue surrounding very toxic adhesive implanted subcutaneously in the dog. Hematoxylin-eosin. 100X

b. Connective Tissue Responses. An inflammatory reaction was seen, similar in some aspects to that described in the previous reaction. Granulation tissue surrounded the implant. A fibrous capsule was found outside of this inflammatory mass. Neutrophils, small and large lymphocytes, macrophages, and giant cells were present. There was a large population of plasma cells (Fig. 10). The tissue was well-vascularized. Empty spaces and deposits of acellular material were generally absent.

DISCUSSION

Three distinct types of tissue responses were seen in the presence of plastic and nonplastic implants. All were apparently foreign body reactions because they were not observable in adjacent normal tissue where alien materials were absent. On the basis of evidence cited below, these three reactions

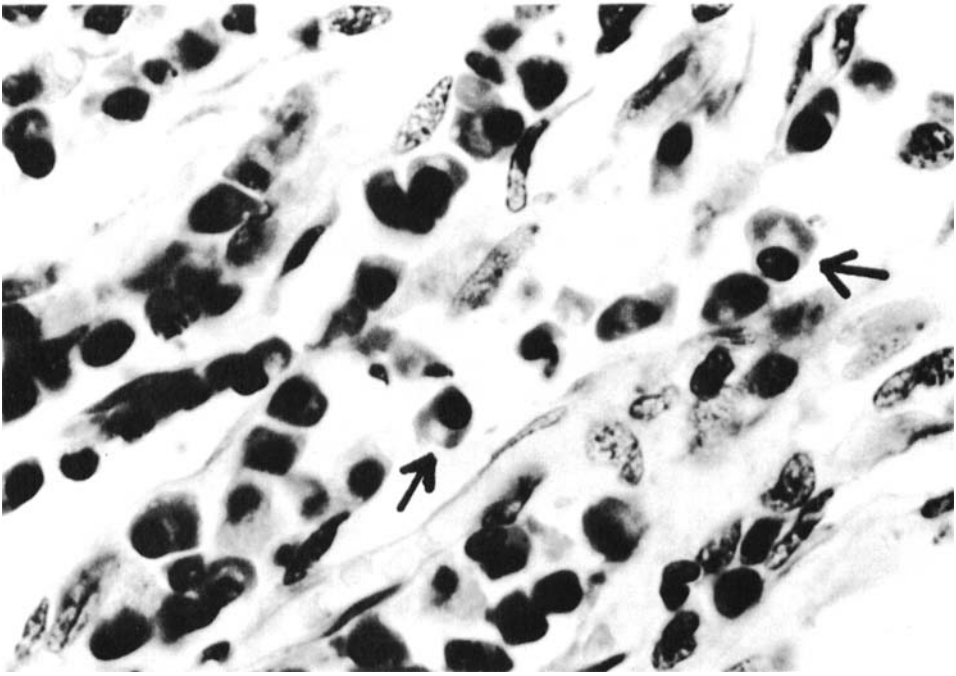

Fig. 10. Plasma cells (arrows) are characterized by a cartwheel nucleus and a whitish or pale staining area in cytoplasm immediately adjacent to nucleus. Plasma cells were always found associated with chronically infected implants. Hematoxylin-eosin. 1000X

may be divided into those due to physical characteristics of the implant (designated Type A in the previous section), chemical characteristics of the implant (Type B), and those resulting from the presence of antigenic elements such as bacteria or foreign protein (Type C).

Reactions Due to the Physical Characteristics of the Implant

There was good evidence that one group of reactions was related to the physical properties of the implant. They were associated with Teflon and polyurethane and with the nonplastic material, graphite.

The most prominent epithelial response that appeared related to the physical properties of the implant was encapsulation of the through-the-skin device (Fig. 3). In some of the implants the conduit and skirt formed a right angle and epithelial growth was stopped or delayed (Fig. 4). When the angle

was less acute, epithelium progressed easily down the skirt and over the skirt surface (Fig. 3). Epithelial encapsulation was observed only in implants which did not have steep angles, were made of relatively inert materials, and were free of infection. Actual rejection by epithelial undergrowth was not seen in this study because of the anchoring action of the skirt. However, extrusion is a common problem with through-the-skin implants when such a fixing device is not incorporated in the design [6].

Another apparently epithelial response related to design of the implant was hyperkeratinization. Excessive formation of keratin was seen at the angle between the conduit and skirt and in the skirt fenestrations (Fig. 3). Presumably, this was a reaction to movement of the tissue against the implant at these critical locations. Hyperkeratinization of epithelium is a notable response to pressure and is exemplified by thickened foot pads of mammals. Overgrowth of the conduit when an inhibiting cap was absent was a still further example of an epithelial response to a particular configuration.

There was also evidence that several connective tissue reactions were based solely on physical features of the implant. There was always a fibrous capsule present around the implant; however, greater thickening of this capsule was seen at the conduit-skirt junction (Fig. 3) than elsewhere. Capsular thickening was also pronounced around sharp angles of skirt fenestrations and subcutaneous bars (Fig. 5) and almost absent at the smooth rounded rims of the skirts (Fig. 5). Fibrous capsule thickening was also greater around skirts without fenestrations than that seen in well-fenestrated skirts.

There was not only more advanced capsular development at sharp, angular surfaces, but also more persistent formation of ground substance that stained intensely with the PAS technique for demonstration of glycoproteins [1] and with Mowry's alcian blue and colloidal iron procedures for detection of acid mucopolysaccharides [2, 3]. Both glycoproteins and acid mucopolysaccharides are large neutral or acidic sugar groups associated with noncollagen protein. They are usually formed in response to trauma and persist through much of the healing process [7]. At sharp angled tips of subcutaneous bars both glycoprotein and mucopolysaccharide ground substance was more prevalent than near other surfaces of the implant (Fig. 5). There was no more demonstrable polysaccharide at the smooth, round skirt edge than in normal subcutaneous tissue (Fig. 5).

The above data suggest that epithelial linear growth, hyperkeratinization, capsular thickening, and excessive polysaccharide formation was due to pressure phenomena and related to the configuration of the implant device.

Moreover, giant cells were found primarily at irregular surfaces of animal implants (Fig. 6) and at the convex surface of the human implant. Such multinucleated cells were also more numerous around large, uninterrupted surfaces, i.e., skirts with no fenestrations, than implants with interrupted surfaces such as skirts with fenestrations. The reason for preferential giant cell formation at irregular or expansive surfaces cannot be explained by current data or by reference to the literature.

Signs of inflammation and necrosis were lacking, which provided evidence that chemical stimuli were not involved in this set of responses.

Further evidence of a negative character that these responses depended primarily on physical or design factors was the absence of infection, as indicated by both gross and histological examination. There was no pus formation or weeping of the wound site and there was no inflammatory tissue present following healing of the wound. In addition, plasma cells were generally absent from tissue sections. Plasma cells are indicators of chronic infection and are believed to produce antibodies to antigenic foreign bodies [8].

Reactions Due to the Chemical Properties of the Implant

Several reactions were due, evidently, to chemical properties of the implant. These responses, in order of increased severity, were associated with the following: polyelectrolyte coated implants, epoxy resins, epoxy resins with a hydrophobic diluent which does not bind permanently to the resin, and experimental adhesives cured in vivo.

Growth of keratotic cysts and accelerated growth of epithelium occurred contiguous with polyelectrolyte-coated material (Fig. 7). This seemed to be a peculiar response of epithelium to polarized material. Certain materials, particularly mild irritants, have already been shown to stimulate epithelial growth [9]. Preliminary work suggests that some polymers may completely inhibit epithelial downgrowth. Chemicals found in certain classes of plastics are toxic to fully keratinized skin as well as to newly proliferating epithelium.

An inflammatory reaction by connective tissue was seen in polyelectrolyte-coated plastics and with certain epoxy resins. A more acute response, secretions of mucoid substances around the surface of a resin containing a hydrophobic diluent, was demonstrated by the PAS stain for glycoprotein (Fig. 8). The most convincing evidence of connective tissue response to toxic material was the presence of large spaces and abundant extracellular amorphous material in the inflammatory tissue (Fig. 9). These signs of necrosis were associated with the adhesives cured in vivo.

The absence of plasma cells (in most sections) further indicated that chemical irritation, not infection, was the determining factor in this group of responses.

Unlike the group of reactions in which physical factors were the determinants, no fibrous capsule was found encircling the implant. The capsule, when present, was outside the necrotic regions, the mucoid substance, and the thick population of inflammatory cells.

Reactions Based on the Immunologic Response

Evidence for the presence of infection in the third group of reactions was provided both by direct observation and by histological data. Most implants with shafts or conduits projecting through the skin showed gross signs of infection in dogs and pigs: purulent weeping, edema, and chronic scabs at the interface between the skin and the conduit. Histological evidence of infection was the presence of numerous plasma cells and other round cells in proliferating inflammatory tissue (Fig. 10). Plasma cells, as already noted, are invariably present in chronic infection and are believed to produce antibodies to foreign bodies [8]. In addition, epithelial downgrowth was slowed and the neutrophil population of the inflammatory tissue sometimes invaded the new epithelium.

Unlike the group of responses due to chemical poisoning, there was minimal evidence of acellular glycoprotein accumulation and there were no large empty spaces.

The high frequency of infection in dogs and pigs was believed to be due to trauma. Apparently because these animals abused the leads, epithelium failed to grow down and provide a bacterial seal. Microorganisms were therefore able to invade the host connective tissue through the conduit-connective tissue interface.

This form of reaction is seen where antigenic substances are present. Antigenic substances include living organisms and many proteins and carbohydrates extracted from living organisms. Plastics do not contain antigens because they lack protein or carbohydrate moieties which stimulate the immune response. Such a reaction is ordinarily due, therefore, to the absence of sterile conditions and not to the physical or chemical nature of the polymer. A few investigators, however, have recently postulated that toxic plastic materials may denature host proteins which may then become antigenic [10]. In such a case (if it can exist!) the immune group of reactions would be blamed on chemical irritation, not infection.

Physical features of plastic implants are related in an indirect way to infection. Surfaces with many interstices tend to trap bacteria. The body's

normal immune response is not always adequate to remove these buried microorganisms: plasma cells and macrophages cannot gain access to them. Even antibiotics may prove ineffectual for reasons which are not well understood. In such situations, the surgeon must replace the implant.

Infection, based on results of this work, appeared to be the principal problem encountered when plastic implants projected into the body cavity or through the skin. Physical (design) and chemical toxicity problems of the material were overcome far earlier in the investigation.

Importance of Physical-vs-Chemical Characteristics of Plastic Implants

Investigators disagree as to the relative significance of implant design and the chemical properties of the material. Oppenheimer et al. [11] found that plastics with a large, uninterrupted surface area induced more tumor formation in rodents than implants made of identical composition but with less continuous surface. Implants consisting of large sheets produced fibrosarcomas while small granules of the same composition usually appeared almost inert. Giant cell neoplasms, according to Hohman et al. [12], were more numerous in the presence of irregular margins or in the case of implants with large, uninterrupted surface areas. These findings agree, in part, with our own. Capsular thickness was related in part to surface area and giant cell population was related to both surface irregularity and surface area. Tumor formation never occurred in the present investigation, even in poorly designed devices, probably because of the slower metabolism in primates, dogs, and pigs than in rodents. In fact, tumor formation resulting from long-term plastic implants has never definitely been proven in humans (13) or any other primates. This, again, has been ascribed to the slower metabolism of humans as opposed to rodents [13].

In contrast, Hueper [14] found that certain polymers caused more tissue responses in rodents than others. Polymers which were highly polarized, were water soluble, or which contained residual monomers because of inadequate curing were more apt to induce unwanted tissue reactions, including metastasis. This also agrees somewhat with our findings, especially with adhesives cured in vivo. Many removable amines were probably contained in these implants. Although, due to species differences, tumor formation was not induced by chemical irritants in the present work, it was evident that some plastics caused reactions ascribable only to chemical components, not to their physical features.

It appears probable that all plastic implants provoke some foreign body reaction. Both this investigation and past reports indicate that there is no such thing as a totally "inert" implant. However, in the present study,

it was found that a plastic implant with only minimal host tissue reaction could be achieved with a suitable design, a relatively inert material, and sterile conditions.

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