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Tissue Reaction to the "Inert" Plastics

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## Tissue Reaction to the "Inert" Plastics

For many years surgeons have sought a material which could be used as a tissue substitute. A wide range of materials have been tried, but for the most part the results were disappointing. The first foreign substances found which were reasonably well tolerated within the body were the noble metals. These, however, have the obvious disadvantage of being excessively expensive. After long searching a number of useful alloys became available and have subsequently found wide application in orthopedics. But metals, however well tolerated in the body, are too rigid to be used to replace soft tissues. The advent of a group of materials generally known as "inert" plastics appears to answer this need.

The "inert" plastics as a group are all high polymers of a variety of monomeric units. Many such polymers have been made, and many used in surgery, but six have been chosen for discussion here. Because of their usefulness and general availability these particular plastics, polyethylene, Nylon, Orlon, Dacron, Ivalon sponge, and Teflon have found by far the widest use in surgery and documentation in the literature.

Chemically, polyethylene is the simplest member of the group. It is simply a macromolecule constructed of repeating units of ethylene  $\dots\text{-CH}_2\text{-CH}_2\text{-CH}_2\text{-}\dots$ . The other plastics are similar macromolecule polymers differing in the nature of the basic unit.

Nylon is a polyamide; Dacron, Orlon, and Teflon are the du Pont trade names for polyethylene glycol terephthalate, polyacrylonitrile, and polytetrafluoroethylene respectively; and Ivalon sponge is a cross-linked polyvinyl alcohol. (30,47).

This paper is divided into two parts. The first is a discussion and attempted organization of the manner in which tissues respond to the presence of embedded plastic, as these mechanisms are documented in the recent literature. This section is entitled "Inflammation" since tissue response to plastics, at least in the early stages, is primarily a problem of injury and repair. The second part deals with the problem of carcinogenesis by embedded plastics and is a review of the literature on that subject.

There has not been room to discuss the application of plastics to orthopedics with its special problems of stress and weight bearing. Nor has the use of plastics in the presence of infection been included, either where infection is a complication or where the site of the plastic is exposed as, for example, in the case of a plastic esophageal prosthesis. The field of interest in this paper encompasses the response of soft tissues to the presence of reasonably pliable plastic aseptically introduced and without communication to a source of infection.

## Inflammation

The early reaction of tissues to foreign substances placed within them depends upon three fundamental factors. First are the responses due to the division and separation of tissues from their normal state of continuity. Second are the responses to the chemical nature of the substance introduced. Third are the responses due to the physical properties of the substance as it lies in contact with the surrounding tissue. Each of these factors is amenable to experimental variation, and to some extent each may be varied independently of the others. Unfortunately, for our purposes, the literature of the "inert" plastics tends to reflect the demands of surgery for specific prostheses in specific lesions rather than primary interest in the general problem of tissue responses. In addition, experimentation in this field is so demanding in terms of skill, time, and animal material that individual experiments tend to be rather limited in scope. Accordingly it becomes necessary to combine information derived from experiments which in the strict sense are not comparable in an attempt to find order in the conglomeration of reports published in the literature.

### I. Responses due to the division and separation of tissues.

No cavity within the body, in the absence of a communication with the surface, can remain open. Macroscopic physical spaces, whether naturally occurring or artificially induced are promptly obliterated in one of three ways: they collapse, they fill with

blood, or they fill with tissue fluid. A "cavity" in the body is therefor either a potential space or a collection of fluid. In either case, to persist within the body a cavity must be or come to be lined by a specialized limiting membrane. Generally such a membrane has the microscopic appearance of mesothelium or endothelium. In this manner a potential space, to persist, must come to resemble the juxtaposed surfaces of a bursa, and a collection of tissue fluid becomes a cyst. A collection of blood, which must flow if it is not to clot, can persist only if the cavity assumes the function of a vessel and becomes lined with a blood vessel intima. If such a lining does not develop, the cavity is destroyed by cellular growth across the cavity with restoration of tissue continuity. Failure of resolution in one of these ways results in a continuing response known as chronic inflammation.

The mechanism of healing of tissue defects by inflammation and fibrosis with restoration of tissue continuity is well documented in the literature, and adequate resumes may be found in any standard textbook of surgery (1). It is sufficient here to point out that cellular exudate and granulation may be expected whenever a wound is healing by obliteration of a tissue defect. Necrotic cells and clotted blood are removed by inflammation and granulation bridges the gap (50). The presence in the wound, for example, of an "ideal" plastic mesh whose substance was absolutely chemically inert and whose filaments were too small to constitute a physical barrier to granulation would not by its presence alone be expected to alter the processes of inflammation.

Any reaction of tissue to the presence of a foreign body is superimposed upon the reaction to an unhealed cavity. The literature contains numerous reports of histological evidence of inflammation surrounding embedded plastics, but it is the exceptional report which takes cognizance of the fact that such a reaction may only partially be due to the foreign body.

## II. Responses due to the physical form of the foreign substance.

It is obvious that even an ideally inert plastic, if it is present in the tissues as an impenetrable film, will prevent obliteration of the cavity through its action as a physical barrier to granulation. In this event inflammation will certainly remove any exudated blood and other debris in the area and granulation will repair such damage as may have occurred to the walls of the cavity. It may be hypothesized, however, that in the presence of an "ideally" inert barrier of plastic, granulation will cease at this point and the wound will heal with the production of a smooth, "mesothelial" appearing membrane juxtaposed to the surface of the plastic. Continued inflammatory response, either as an "acute" cellular exudate or as a "chronic" or progressive proliferation of fibrous tissue, may be presumed to be due to chemical (non-inert) effects of the plastic or to mechanical trauma to the surrounding cells. Such a hypothesis, of course, is impossible to prove owing to the lack of a plastic guaranteed to be inert. The plastics in current use, however, do act to a greater or lesser extent as such an ideal plastic when embedded

as a film. Bing (7) showed that smooth balls of polyethylene film embedded intraperitoneally and removed after four months are surrounded by a capsule of connective tissue which is lined by what resembles "a single layer of vascular endothelium". In the same study, Ivalon sponge was flattened and heat molded at 100 degrees between glass plates in such a manner that the sponge retained, in part, a smooth impervious surface. This preparation was then embedded both subcutaneously and intraperitoneally in rats and subcutaneously in rabbits. Histological study after four months revealed that where the surface in contact with tissue was spongy in character, connective tissue had penetrated the spaces; but where the surface was smooth, the tissue response was characteristic of a film. Oppenheimer (48), working with a wide variety of plastics, found that plastic film embedded subcutaneously is encapsulated, within two to four weeks, in a "sheath of connective tissue" which varied in thickness depending on the chemical nature of the substance. He states that "the inner surface of the sheath wall was always smooth, often shiny, and nonadherent to the film, forming a definite pocket from which the film was easily removable". It is significant that once fully formed the pocket persisted even after removal of the plastic film.

Pocket formation around a film constitutes, from the surgical point of view, a failure of the plastic to be incorporated in the surrounding tissue. This is a severe limitation in most of the uses to which plastics are currently put within the body (22). Accordingly, "tissue incorporation" has become one of the criteria

of the ideal tissue substitute (39). When perforations are placed in the film, or when the plastic is embedded as a textile, pocket formation does not occur (26,39,48). Clearly there must be a dividing line, in terms of the diameter of the perforations or holes and their number per unit area, beyond which the plastic acts sufficiently like a film to present a barrier to cellular proliferation. Oppenheimer (48) found that films perforated by 625 holes per square inch did not induce pocket formation but were "'anchored" by connective tissue fibers penetrating \*\*\* through the perforations". Knox (35) found that Dacron mesh of "low porosity" used as an abdominal aortic graft showed neither gross nor microscopic evidence of penetration by connective tissue. In all cases tried in this study, the graft separated easily from surrounding tissue after embedding as long as twelve months. The exact "dividing line" of minimum porosity has not been established (30), and is doubtlessly modified, as are all tissue responses to plastics, by the chemical nature of the material, the site of implantation, and a variety of other considerations important in actual practice such as wound infection, abnormalities of local blood supply, and other host pathology. It is reasonably clear, however, that a sufficiently "inert" plastic, which is sufficiently porous, does not constitute a barrier to granulation. The cavity created in the tissue by its operative placement is healed by obliteration, that is, by restoration of tissue continuity across the defect.

It is of interest, at this point, to consider the effect of

the volume of plastic material embedded. With an ideally inert plastic, the volume of material is significant only in terms of the width of separation of surrounding living cells. Although increased bulk may alter the situation by virtue of increased trauma or pressure on surrounding tissues, by the same token a thin rigid implant might cause more trauma than a thick pliable one. Accordingly, this aspect of the problem is not considered germane to the present discussion.

Reasoning, a priori, the volume of an implant which has an impenetrable surface would not be expected to alter the tissue response at all, since healing of the wound cavity does not involve bridging the defect. Unfortunately there is no report in the literature dealing specifically with this problem although Oppenheimer (48) in a study involving films of various thicknesses and chemical types notes that variations in the wall of the pocket around the material depend on the chemical nature of the implant. This study, which concerned the development of tumors in the walls of pockets, also revealed that the incidence of tumor development was unrelated to the thickness of the implanted film.

The problem of thickness in the case of porous materials primarily involves sponges. The spaces within a sponge are linked together; channels may be described which, although devious, are continuous from one part or surface of the sponge to another. This property is readily apparent from the easy penetration of sponges by liquids and the fact that sponges may be wrung out, thereby expressing any liquid present in the spaces deep within

the sponge. Such a material, embedded in tissue, maintains a wide separation of the walls of the cavity but does not act as a barrier to granulation. Grindlay (22) has shown that given sufficient time, fibrous tissue grows through the sponge channels, filling the spaces, and establishing continuity with tissue from the opposite wall of the cavity. He notes that a "piece of sponge which is implanted will become a piece of fibrous tissue of the same size and shape". The effect of thickness, in the case of porous material, is upon the time required for complete penetration by tissue, not upon the final result. It is of interest to note that in the same study Grindlay found that the walls of the sponge spaces, which are impervious although the sponge as a whole is not, were "lined by what resembled a single layer of vascular endothelium". It is apparent that the behavior of tissue toward a sponge is no different than its behavior toward any unhealed cavity. Tissue elements grow wherever their growth is unobstructed until tissue continuity is established. Where an obstruction is encountered a pocket is formed and lined with a layer of "specialized" appearing cells.

The interaction of the processes of inflammation and repair with the physical form of implanted plastics is particularly well revealed in the tissue responses to synthetic blood vessel grafts. The application of plastic grafts to the surgical treatment of a wide variety of aortic and major artery lesions has occupied an important segment of the literature of inert plastics for several years. Grafts of many different materials, constructed

in many different ways, have been tried with varying degrees of success. In examining the reports in the literature it must again be emphasized that physical and chemical properties of the implant act together in determining any individual result, although an attempt is made here to consider them separately.

Plastic grafts may be knitted, braided, woven, double or single layered, crimped or smooth, branched or straight, and of greater or lesser porosity in addition to being made of a variety of plastic materials. Essentially, however, the overwhelming majority of reports concern grafts which are all reasonably pliable tubes with porous walls. Variations in detail of construction are principally concerned with technical problems such as suturing, fraying of cut ends, initial blood loss, or "weeping", through the porous wall, and the maintenance of lumen diameter through bends in the graft. The sequence of events leading to healing of the graft is basically the same in all cases, except for some modification due to the chemical nature of the plastic involved, and has been described by Edwards (18), Herrmann (32), Martinez (40), Poth (49), Wesolowski (62), and others. The processes involved may be summarized as follows:

As soon as the graft is in place and blood flow established, there is immediate hemorrhage of blood into and through the porous wall. Clotting occurs within and on both sides of the mesh. The column of blood in the lumen is thus surrounded by an annular clot, containing the graft within it, and flowing blood never again is in contact with the plastic. The luminal surface of the

clot is covered by a layer of white blood cells, principally polymorphonuclear leukocytes. Organization of the clot then takes place by proliferation and growth of fibroblasts and capillaries from the surrounding tissue between the plastic fibers to the luminal surface. Phagocytes enter and remove thrombus debris. The thickness of the clot is progressively reduced; the fibroblasts become more compact and orient themselves with their long axis parallel to the lumen. In this manner the fibrous tissue surrounding the outer surface of the graft becomes continuous with the adventitia of the host vessel above and below the graft, while that on the luminal surface becomes continuous with host intima. Endothelium proliferates from the host vessel at both ends of the graft and spreads toward the center. At the same time islands of identical appearing, smooth, glistening, pearly-white "endothelium", which must be of fibroblastic origin, appear on the luminal surface in the central portions of the graft. These gradually coalesce into an unbroken "neointima" continuous at both ends with the endothelium of the host vessel.

It may be pointed out that the healing of a synthetic blood vessel graft is no different, with respect to the plastic, than the healing of porous plastic embedded elsewhere. Strictly speaking, a column of blood within a healed graft is "outside" the plastic in the same sense that intestinal contents are "outside" the body. Healing in the immediate vicinity of the plastic occurs by obliteration with establishment of continuity between connective tissue on both sides of the plastic mesh. Only after

penetrating and "incorporating" the plastic does proliferating connective tissue encounter a "barrier" of moving blood. Thereupon proliferation ceases and a pocket is formed, the lumen, which possesses a specialized lining.

Comparison of the neointima of synthetic aortic grafts with the normal intima of host aorta has yielded some surprising results. Not only is neointima, once completely healed, fully as capable as normal intima of resisting intravascular clotting of stagnant blood (18), but neointima appears to be much more resistant than normal intima to the development of atheroma in the presence of hypercholesterolemia (14,51).

### III. Responses due to the chemical nature of the foreign substance.

From the point of view of the surgeon, any tissue reaction to the chemical nature of embedded plastics constitutes a liability. Although absorbable sutures are deliberately designed to evoke inflammation so that they will be broken down and removed by digestive enzymes and phagocytes, "inert" plastic implants are generally designed for more or less permanent placement within tissues and are therefor made as inert as possible. Desirable tissue response is primarily that due to the physical nature of the graft and the presence of an unhealed wound as previously discussed. Incorporation of the graft in living healed tissue is desired; continued inflammatory response and excessive fibrosis around the graft are not (39). Exceptions to this rule are rare, but one exception is worthy of some

discussion.

During and for a few years after World War II, a number of workers used polyethylene to wrap aortic aneurysms in the hope that the fibrosis which had been observed to occur about this substance would strengthen the wall of the aneurysm and, by constriction, reduce its size. In 1948, Yeager (64), noting wide discrepancies in reports of the efficacy of this procedure, compared the effect of a specially prepared pure polyethylene with the commercial brand of du Pont polyethylene then in current use. In this way he was able to show that only minimal and, for this purpose, inadequate fibrosis occurred around pure polyethylene, but that the presence of Dicetyl phosphate used in the manufacture of the commercial material evoked extensive fibrous tissue response. He concluded that since the basic substance was relatively inactive, conflicting reports in the literature probably resulted from use of different batches of material containing varying amounts of impurities and manufacturing additives. Further study has confirmed these results (12,16,53).

Additional evidence for the importance of impurities in tissue response to synthetic high-polymer plastics as a class may be found by examination of workers engaged in the manufacture of these substances and therefor "heavily exposed" to them for protracted periods of time. Cranch (13) in a careful study of disease in this industry, especially contact dermatitis, found that toxicity was important only with regard to secondary materials compounded with or involved in the manufacture of the primary

substance, the basic synthetic resin being essentially inert.

The foregoing is not to say that the "inert" plastics themselves are without chemical effect on tissues. What is indicated, however, is that these materials, viewed as a group, incite minimal inflammatory reaction compared with wood, ivory, rubber, paraffin, cotton, silk, catgut, or a host of other materials that have for one reason or another been placed within body tissues. It must be remembered that the various impurities and additives present in the "inert" plastics as they are obtained commercially may severely complicate the study of these materials by producing inflammatory reaction far in excess of that due to the basic substance under scrutiny. Currently most workers in the field are well aware of this problem and take careful precautions to remove these impurities as completely as possible (3,15,27,31).

The chemical effect of plastics on tissue response has been studied by a variety of methods; various sites and types of implants having different advantages. In general, the chemical properties of the various plastics appear to evoke an interaction between host and implant in which the plastic itself is altered to a greater or lesser extent. This interaction should be borne in mind during the following discussion.

One characteristic property common to all the "inert" plastics, and one which perhaps might be used to define them as a group, is the lack of a systemic or "toxic" response in the host even when relatively large amounts of material are embedded. This "inertness" stands in contrast to the relatively pronounced

systemic response occasionally encountered from foreign implants such as cellulose and neoprene which found some use before the newer materials became generally available (37). Any chemical reaction that does occur is apparently confined locally to the tissues close to the plastic.

Acute inflammatory response, as manifested by the well known and characteristic inflammatory cellular exudate (50), may be studied in any site of implantation. A great many reports in the literature, which are primarily concerned with the use of a single one or another of these plastics, include descriptions of the microscopic appearance of tissue in the neighborhood of the implant. But for each material reports may be found showing no evidence of inflammation (2,10,20,33,52,63) while others describe the presence of varying amounts and types of cellular exudate (26,35,38,40,52,61). These discrepancies probably find their source in variations in technique, preparation of materials, time after implantation, and lack of uniformity in observation. More reliable, although more rare, are studies in which the acute reactions to a number of materials are described in the same experiment with control of these variables.

Harrison, in a recent study of blood vessel grafts (30), notes that Nylon produces marked acute inflammatory reaction not evidenced by Dacron, Orlon, Teflon, or Ivalon sponge. Bing (7) found that subcutaneously implanted Ivalon sponge is "absorbed by macrophages with large cytoplasm filled with droplets and by foreign-body giant cells", while similarly implanted polyethylene mesh showed

an early exudate of polymorphonuclear leukocytes in addition to the "later" response of foreign-body giant cells and monocytes. Several workers have embedded a variety of plastics intraperitoneally. This may well be a particularly advantageous site since introduction may be performed with a minimum of trauma and hemorrhage in the immediate vicinity of the material. Usher (58) and LeVeen (36) have further refined this approach by employing finely divided bits of plastic in an effort to minimize effects due to physical form and also to expose as large a surface as possible for interaction with the tissues. LeVeen found that Nylon was similar to celluloid, lucite, and cellophane in causing marked inflammatory reaction leading to extensive fibrosis and adhesions, whereas Teflon caused no inflammatory reaction that could be grossly observed. Usher found that seven days after embedding, Nylon, Orlon, and Dacron all produced a response of foreign-body cells, while Teflon and Marlex produced very little. Marlex is a recently introduced, highly crystalline derivative of polyethylene which shares with Teflon the property of being extremely non-wettable.

Late or "chronic" inflammatory reaction is characterized by a proliferative tissue response (50). In fact, if healing does not occur, fibrous proliferation may progress indefinitely. The presence of an "inert" plastic appears to evoke such a proliferative fibrous reaction, the extent of which may be judged by the length of time required for healing and the amount of fibrosis in the vicinity of the implant. Presumably, any differences in the extent of this process in the vicinity of implants of different materials

but of similar construction and situation would depend only on their relative chemical effects. Although such differences among the plastics have been noted in a variety of implant sites (36,48), the blood vessel graft has a particular advantage for study. Since the neointima is formed only by proliferation of tissue through the plastic mesh and has a definite boundary on the luminal side, its thickness can be measured quite accurately. In addition, as a further spur to investigation, this thickness is of critical importance since it can seriously compromise patency of the lumen in a graft of small diameter. Harrison, in a carefully executed series of experiments (30) has shown that the thickness of the neointima is unrelated to the diameter of the graft or to its construction, but depends on the chemical nature of the plastic. With Nylon the intima formed was 2-3 mm. in thickness. Healing of Nylon grafts in some animals required up to 76 months and the "fibrosis around the grafts was more extensive than with any of the other materials". With Dacron the lining was 1-2 mm. thick, healing required 4-6 months, and the surrounding fibrosis was less than that observed with Nylon. Both purified and commercial Teflon were used. Purification consisted of aggressive pretreatment by "boiling for twentyfour hours in each of the following solutions: concentrated nitric acid, concentrated sulfuric acid, 50 percent sodium hydroxide, and aqua regia". Teflon thus cleansed of impurities incited the least tissue response of any material tested. The neointima was less than 1 mm. thick, healing occurred in 4-12 weeks, and fibrosis

around the graft was minimal. Commercial Teflon was the next most inert material tested and evoked only slightly greater tissue response than after purification. Ivalon sponge deteriorated to such an extent within the tissues that adequate measurements were not obtainable, and Orlon performed unsatisfactorily, for technical reasons, and could not be evaluated. Harrison concludes: "\*\*\*\* in general the thickness of the fibrin lining deposited on the inner surface can be correlated with the chemical stability, wettability and amount of tissue reaction incited by the graft".

Fundamentally there are only two ways in which a foreign body may interact chemically with tissues. Either molecular sized bits of the material must fragment off and become available to the surrounding cells through solution, destruction, enzymatic action, or by some other mechanism; or else the surface of the material, in spite of remaining intact, must adsorb surrounding molecules in such a way that a chemically active but somehow "foreign" aspect is presented to the tissues. Surface activity appears to be intimately related to the wettability of the material as shown by LeVeen (36) who found that of a variety of materials tested, only Teflon, which is unwettable, did not acquire a surface adsorption of proteins. The importance of wettability is further attested in many other reports (29,30,39).

Wettability is also directly correlated with loss of tensile strength of the fabric while it is embedded in tissue. Since this loss of strength in tissue far exceeds the "shelf life" of the material, active chemical degradation must occur. Presumably the

breakdown products of this action may reach and influence surrounding tissue. Harrison (31) has carefully measured tensile strength loss and found that Ivalon sponge and Nylon undergo rapid and extensive degeneration. Dacron and Orlon, however, showed loss of only a few percent of their strength after prolonged implantation, and Teflon showed no change whatever. Edwards (19), in a discussion of material for blood vessel grafts, concludes that retention of tensile strength, thinness of the neointima, and speed of healing are all direct functions of the wettability of the material. He lists the degree of water absorption by various plastics as Nylon 4%, Orlon 1.0%, and Dacron 0.1%. Teflon absorbs no water whatever.

Thus far, only one report in the literature deals with an attempt to follow the breakdown products of plastics through the host's metabolism. Oppenheimer, in a study of tumor production (47), embedded extremely pure samples of three plastics, polystyrene, polyethylene, and polymethyl methacrylate, each of which was radioactively tagged with C<sup>14</sup>. After 21, 26, and 54 weeks, respectively, minute traces of radioactivity were detected in the urine. No radioactivity could be detected in the expired air, in the tissues of the animal, or in tumors which occasionally occurred in association with these implants. Nor could the nature of the breakdown products be determined. When the plastic was removed, urinary radioactivity disappeared.

From the evidence published in the literature, it seems clear that the "inert" plastics, although tolerated within tissues to the extent that healing is possible in their presence,

nevertheless do interact chemically with the body. The extent of chemical effects varies among the materials. In general, Nylon, polyethylene, and Ivalon sponge appear to evoke the greatest inflammation of the group, whereas Teflon is the most inert. Indeed Teflon may well approach closely the "ideally" inert plastic sought by surgery. Dacron and Orlon appear to occupy an intermediate position between these extremes. (19,30,31,39). It must be remembered, however, that inertness is only one of the properties a plastic must possess for use in surgery. Physical structure is also of crucial importance, as was discussed earlier, and compromises must frequently be made between the chemical properties desired and the ability of manufacturers to produce the plastics in various physical forms.

### Carcinogenesis

The first report of malignant tumors associated with embedded plastic was published in 1941. Turner (57) while engaged in investigations in quite another field chanced to observe a tumor in a Wister strain rat which had developed in the vicinity of a Bakelite disk after prolonged subcutaneous implantation. To determine whether this was merely a chance association, Bakelite disks were implanted subcutaneously in 13 rats of the same strain. Of nine animals that survived longer than twenty months, four developed tumors. By microscopic diagnosis, all four tumors were fibrosarcomas. None of the animals that died before twenty months developed tumors. Bakelite disks were also embedded in ten male mice, strain dba, at two and a half months of age. None of these animals survived longer than eighteen months, nor did any develop tumors. Turner noted that: "In three tumors a brownish-orange colored fluid was in contact with the bakelite disk. In one instance, the disk was inclosed in a cyst containing this fluid. \*\*\*\* A spectrographic examination of the fluid \*\*\* revealed only components of the hemoglobin spectrum."

In spite of its serious implications, Turner's report appears to have attracted little attention at the time. In 1945, Oppenheimer (43) reported a similar chance observation of tumor production. In an attempt to produce hypertension experimentally in rats, cellophane had been wrapped around the kidneys to stimulate annular fibrosis and scarring. Several tumors were noted to develop near the cellophane after a prolonged

period of implantation. To confirm this observation, a formal experiment was carried out in which cellophane (regenerated Visking 5½ High Stretch cellulose film sausage casing) was embedded both subcutaneously and perinephrically. The shortest time for development of a tumor eight millimeters in diameter in the perinephric site was 362 days, while subcutaneously it was 471 days. The rats were all albinos of the Sherman and Wister strains. Of the animals surviving eleven months or more, tumors were found in 8 out of 23 in the perinephric site, and in 15 out of 42 in the subcutaneous site; this being 35 percent in each case. By microscopic diagnosis, the types of tumor produced were: 17 fibrosarcomas, 2 liposarcomas, 1 rhabdomyosarcoma, 1 undifferentiated sarcoma, 1 osteogenic sarcoma, and 1 plasmacytoma. Since 1945 most of the published reports on the carcinogenic properties of plastic implants have been due to Oppenheimer and his associates.

Following the report just reviewed, a much larger study was carried out and reported in a series of articles in 1952 and 1953 (44,45,46). A large number of plastic films of many types were embedded subcutaneously in rats. The materials included cellophane, Dacron, Nylon, polyethylene, polystyrene, polyvinyl chloride, Teflon, and others. In addition a number of these materials were subjected to a variety of purification procedures to test the effects of impurities. All of the materials tested showed tumor production after prolonged implantation, although the percentage of animals developing tumors varied from 4.5 percent with Teflon to 45.4 percent with cellophane. Although a wide variety of sarcomas

were again found, 81.9 percent of the tumors were fibrosarcomas. Various non-plastic control substances were also embedded including cotton and glass. Only one tumor developed in the control group, a fibrosarcoma associated with a glass cover slip, which developed after 659 days. These results were subsequently confirmed by Bering and others (5,6). It is noteworthy that Bering (6) was able to provoke locally invasive tumors in hamsters with pure polyethylene film embedded subcutaneously for a minimum of 442 days. This is the only report in the literature of tumors developing in relation to plastics in a species other than rats or mice.

In 1955, Oppenheimer (47) published a report of the progress and early results of his next large series of experiments in which he attempted to elucidate the mechanism of tumor production by plastics. In addition to many commercial products, a number of the materials embedded were specially prepared without the use of catalysts, plasticizers, stabilizers, or other additives. Other experiments were designed to test other possibilities: the basic monomers of a number of plastics were painted on the skin of rats and mice; pellets were embedded containing various concentrations of benzoyl peroxide, a catalyst used in the manufacture of a number of plastics; and polymers tagged with  $C^{14}$  were embedded to investigate breakdown and metabolism of the plastic in the tissues. Although the study was primarily oriented toward chemical carcinogenesis, the effects of physical properties of the material were tested by embedding several of the polymers in a variety of physical forms including films of

various thicknesses, textile fabrics, films perforated by 625 holes per square inch, sponges, granules, and powders. Non-plastic control substances which were embedded included glass coverslips, wood, mica, paraffin, cotton "linters", surgical cotton, glass cloth, and various metal foils.

Although most of these experiments were not yet completed, the early results were given in the report. Neither benzoyl peroxide nor any of the monomers tested were observed to produce tumors. With the radioactively tagged polymers, as previously discussed in connection with the early chemical interaction of plastics and tissues, minute traces of radioactivity were detectable in the animal's urine after a latent period of 21 to 54 weeks. This appears to indicate that at least these polymers (polystyrene, polyethylene, and polymethyl methacrylate) do undergo breakdown and metabolism, although at a very low rate. It is especially noteworthy that tumors were noted to occur with each of the polymers embedded, although the number of tumors and the length of the "latent period" varied among the materials. Most of the tumors, however, were found to occur when the plastic was embedded in the form of a film. The incidence of tumor production was much lower with other physical forms. At the time of publication no tumors had yet been obtained with plastics in powder form, although these experiments had not been completed.

Oppenheimer draws the following conclusions from these experiments. The fact that the incidence of tumor formation shows no relationship to the purity of the embedded film, together with the absence of activity of any of the monomers or impurities

tested, makes it "fairly certain that the carcinogenic activity of plastics is inherent in the polymer itself". In addition the particular form of the macromolecule does not appear to be of fundamental importance in view of the fact that tumors were produced by a wide variety of polymers of completely unrelated chemical structure. These various materials have in common only the property of being macromolecules constructed of repeating units. The only good correlate of tumor production in this series was the physical form of the material. Although the thickness and the pliability of films did not alter tumor production, "a plain film appears to induce more tumors than other forms such as perforated films, textiles, or powders".

Although no specific chemical properties of plastics can be directly implicated on the basis of these experiments, Oppenheimer notes that chemical mechanisms can not wholly be eliminated at this time. The fact that isotope tracer studies revealed radioactive breakdown products of the plastic in the urine of the test animals maintains the possibility that these breakdown products may be carcinogenic. The breakdown and loss of tensile strength of some embedded plastics, as noted by Harrison (30), may be cited as confirmation of these results.

The importance of physical form, however, was clearly evident from these results, and Oppenheimer accordingly designed a series of experiments especially to study this effect. The report was published in 1958 (48). Oppenheimer notes in the introduction to this report that the presence of plastic in the

tissue as a film seemed to be of particular importance. Averaging the incidence of tumor formation for all the materials studied in more than one form, the percentages were: "plain film or sheet, 27.4%; perforated film, 11.7%; textiles, 1.5%; and powders, 0.6%". The variation due to form far exceeded the variation due to the chemical type of plastic. Since the embedding of a film produces formation of a "pocket" in the tissues which is not seen with porous materials where connective tissue can grow through the holes and "anchor" the plastic, the formation of tumors might well be related to the formation of or changes in the pocket wall. It was noted, however, that tumors did not develop at the time of pocket formation, but only after a prolonged "latent" period. A long study was carried out in which 900 polystyrene films were embedded in 450 rats in an effort to "ascertain how long the film must remain in contact with the tissues for a tumor to be induced, and whether the pocket wall has any function of importance". By removing, on succeeding months, films from some animals and both films and pockets from others, the animals being maintained alive for continued observation, three experimental groups of animals were effectively followed with monthly observations of the histological changes occurring in the tissues. The incidence of tumor formation in the various groups was ascertained and correlated with times of embedding and removing the film. The results clearly indicate the following conclusions: If plastic films are removed within six months after they are embedded, no tumors will develop even though the pocket is allowed to remain. If the film is removed at any time more than six months after

embedding, but the pocket is allowed to remain, tumors will develop, months or perhaps a year later, in approximately the same percent of animals as when both film and pocket are allowed to remain undisturbed. Finally, if the pocket is removed with the film, no tumors develop thereafter regardless of the time of removal.

The critical time of six months during which the film must remain in the pocket correlates well with the histologic picture of pockets examined at this stage. In the early months after embedding, the initial inflammatory reaction was noted to diminish in all animals to a point of inactivity which might be described as "healed". In most pockets examined, the situation remained this way indefinitely. In a number of pockets, however, focal activity was again noted in local areas of the pocket wall beginning approximately six months after implantation. The activity at this time had the microscopic appearance of fibroblastic proliferation. In pockets examined in succeeding months, there was again only a small proportion showing activity, but among the active pockets a steady transformation could be traced in which atypical cells and nodular growth appeared and, finally, the microscopic picture became that of a sarcoma.

The current status of work on the carcinogenic properties of plastics may therefor be summarized as follows. Although chemical effects cannot definitely be ruled out at this time, the presence in the tissues of a polymer in the physical form of a film seems to be of primary importance. In the early stages

the film is crucial, but after a certain, relatively short, interval the film may be removed and the processes leading to the production of frank malignancy go on in its absence. These processes are localized in the pocket wall which may be removed with the plastic thereby preventing tumor formation. The mechanism by which a plastic film induces these processes and the reason why they occur around some films and not around others remains completely obscure. It is noteworthy that all of the tumors produced thus far in association with plastics have been of mesenchymal origin, the vast majority being fibrosarcomas. And finally it may be pointed out that to date no report has yet appeared in the literature of a malignant tumor arising in a human being in association with any foreign body.

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