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THE USE OF INERT PLASTIC MATERIAL IN RECONSTRUCTIVE SURGERY

I. A Biological Test for Tissue Acceptance.

II. Tissue Reactions to Commonly Used Materials.

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From the earliest days of the specialty, plastic surgeons have been concerned with inert materials for reconstructive procedures. In spite of half a century of endeavour the use of such material is unsatisfactory. So much so that an authoritative textbook on surgical materials noted: "In spite of all the good results which have been obtained by such means . . . sooner or later the body attempts to reject such foreign material and it therefore can never be considered the ideal substance for the purpose" (Gillis, 1958).

Yet there are clearly occasions when the provision of an implant of foreign materials, acceptable to the tissues, helps both patient and surgeon. This paper attempts to evaluate the need for and uses of inert materials, to present a laboratory method for investigating the biological reactions to them, and to examine experimentally such reactions when materials, in present-day use, are implanted in the rat. It thus forms part of a wider investigation which seeks to lay down standards of quality and technique for implant surgery.

Surgical opinion is divided on the question of the use of foreign material in reconstructive surgery. There are those who hold that such material should be used only as a temporary measure until the time when reconstruction can be completed by living tissue, while others are prepared to consider it permanent. The division of opinion is not limited to plastic surgeons for the subject is very much alive in orthopædic, vascular, and cardiac surgery. The main arguments are summarised below:—

The Case Against Foreign Material.—(1) Reaction of the tissues to a foreign body: This may be immediate, resulting in rejection of the material and usually associated with infection, or delayed for weeks, months, or years. Delayed reaction may occur with infection or collections of sterile fluid, but usually results in eventual extrusion.

(2) Movement of a foreign body is well recognised and many well-placed implants have become less satisfactory for this reason. Where bone has been replaced by the implant, fixation presents its own problems: in orthopædic surgery where such are used to aid ununited fractures of the long bones, stress is a big factor (Scales, 1958). The use of tantalum, much in vogue between the two World Wars, did show that once the material was "on the move," extrusion was the usual finale.

(3) Alteration of physical properties of the implant. Scales *et al.* (1961) have shown that many of the stainless steels used in orthopædic surgery corrode and lead to stress fractures, and have demonstrated crazing in acrylics. Polyethylene

foam, recommended for breast construction, has altered within a year from a soft to a very hard material (the " marble breasts " mentioned by Moran in 1954).

(4) Stimulus to carcinoma: In some experimental animals implant materials do appear to produce malignant disease. This is invariably a sarcoma (Scales, 1958), and never a carcinoma, in the fibrous capsule surrounding the implant. In the rat it takes twelve to eighteen months after implantation for malignancy to appear and this has been found to occur with a wide variety of materials—Polystrene, cellophane, P.V.C. (Northdurft, 1956); Dacron, nylon, Ivalon, Teflon, and silk (Oppenheimer *et al.*, 1955). The very diversity of the nature of these should make one suspect that malignant change is a feature of rat tissue. Scales (1961) has noted that in the guinea-pig malignancy is uncommon. No unequivocal case of malignant change in man has so far been recorded although individual cases where neoplasia was related to metallic implants after thirty to thirty-five years have been published (Siddons and MacArthur, 1952; Penn and Epstein, 1953; McDougall, 1956).

(5) There is a general feeling of disquiet, difficult to put into words, that a material which is not part of the body and has no blood supply is " at risk." Curiously, the same argument does not apply to homograft cartilage.

The Case for Foreign Material.—(1) It makes reconstruction shorter and less traumatic for the patient.

(2) There is an endless supply.

(3) Some natural tissues when transplanted do not behave well: fat " absorbs," tendons become adherent, fascia becomes vascularised and markedly adherent, bone may absorb in certain situations, and cartilage warps.

(4) A special case can be made out for the use of foreign material where the body has an inadequate supply in quantity in children, or in quality such as tendon with paratenon.

(5) It is expendable in a growing child, or where uncertainty of success may retard the progress of reconstruction.

There is, of course, much to be said for both points of view and indeed protagonists and antagonists are much less consistent in clinical practice than in opinion, although the points for and against the use of foreign material are representative. At least one reason for this ambivalence is the uncertainty associated with the lack of precise knowledge of the tissue reaction to foreign material.

Of the thirty-eight papers published on this subject in the past ten years only ten record histology and a mere four produced experimental evidence. In none was there sufficient detail to allow a reader to make an intelligent assessment of the particular material being recommended for clinical use. In this sense, then, most previous publications should be considered pilot trials.

Material and Methods

A pilot scheme for the experimental investigation was set up, using Wistar (white Norwegian) rats. The experimental design was of the most simple kind, rats and material, in sterile (autoclaved) containers, being randomly associated.

TABLE I

Weights of Rats at Time of Implants

Material Implanted	Mean Weight	Standard Deviation
	g.	g.
P.T.F.E. film	172	28·4
P.T.F.E. felt	156	26·3
Polyethylene sponge	184	34·8
Polyethylene sheet	215	19·1
Orlon	161	16·9
Terylene	207	45·3
Nylon	155	29·7
P.V.C.	194	51·3
Estane	183	44·7

to the muscle of the anterior abdominal wall, but others may represent the host's reaction to an irritant. The materials implanted, of 2 by 2 cm. area, were as follows :—

1. Polytetrafluorethylene (P.T.F.E.) sheet, 0·2 mm. thick.
2. P.T.F.E. felt, 3 mm. thick.
3. Polyethylene sponge, 5 mm. thick.
4. Polyethylene sheet, 0·02 mm. thick.
5. Polymethyl methacrylate (Orlon) woven fabric, 0·3 mm. thick.
6. Polyethylene terephthalate (Terylene) woven fabric, 0·15 mm. thick.
7. Polyhexamethylene adipamide (nylon) sheet, 0·07 mm. thick.
8. Polyvinylchloride (P.V.C.) sheet, 0·1 mm. thick.
9. Polyurethrane (Estane) sheet, 1 mm. thick.

RESULTS

Tissue reaction to the various materials was assessed macroscopically and microscopically.

Macroscopic.—Mesentery, playing its part of " policeman " in the abdominal cavity, was frequently found adherent to part or whole of the implant material. Adhesions of bowel, to a marked degree, were commonly found with Orlon, Terylene, nylon, P.V.C., and Estane, and to a milder degree with Polythene. No adhesions of bowel were found when the implants were P.T.F.E.

The results are summarised in Table II.

The Chi square test at the 0·1 per cent. level of significance confirms that P.T.F.E. behaves much more favourably than any other material. The photographs in Fig. 2 show comparable findings at the time of naked-eye inspection.

Microscopic.—Histological notes are given in the legends to the photomicrographs of individual materials (Figs. 3 to 13). The general picture of the findings is described here. The overall microscopic picture of tissue reaction to foreign material concerns round cells, macrophages and giant cells, fibroblasts and fibrous tissue, the vascular supply, and, since these implants were exposed in the peritoneal cavity, the nature of any covering membrane.

Implant Technique.—Previous experiments in rats, and in man, demonstrated that insufficient information concerning the tissue reaction to inert materials is obtained by subcutaneous implantation only; intraperitoneal implants on the other hand seemed likely to provide more sensitive tests, and offered the advantage of intermittent inspection and biopsy.

Under ether anæsthesia a midline abdominal incision opened the peritoneal cavity and an area of 2 by 2 cm. on its anterolateral wall was denuded of peritoneum with a thin layer of underlying muscle. The raw surface so produced was covered by the implant material held in place by silk sutures and the abdomen closed (Fig. 1). A gauze dressing over the wound was secured by a couple of turns of adhesive Elastoplast bandage, to be discarded after one week.

Forty to ninety days later the peritoneum was inspected for macroscopic signs of reaction, the animal sacrificed, and the whole implant with its surrounding tissue removed for histology. Specimens were fixed in formol-saline, Bouin, or Zenker. Paraffin sections cut 5 to 7 microns thick were stained by hæmatoxylin and eosin, Mayer's acid hæmatoxylin, Harris's hæmatoxylin, van Gieson, Weigert's elastic, Solochrome cyanin, Alcian blue, Ehrlich's hæmatoxylin. At least ten fields were examined in each slide.

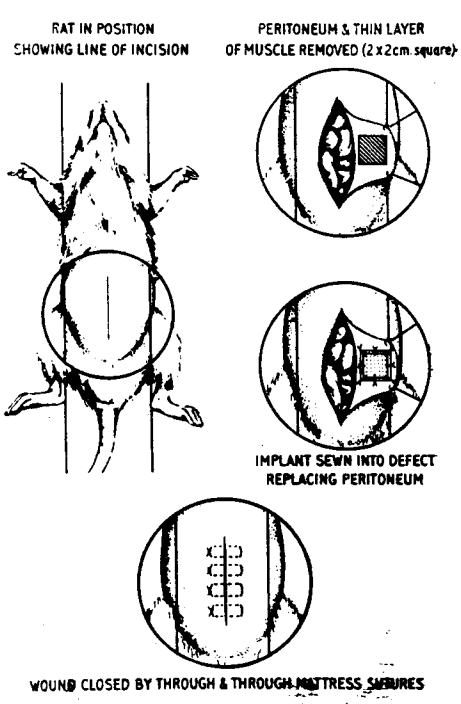

FIG. 1

Implant Materials.—Nine materials in common use were available from the hospital operating theatre. Each rat received a single implant and the experiment was repeated six times, *i.e.*, a total of fifty-four rats, this being considered the minimal number required for statistical assessment. The mean weights and standard deviations of rats used for the various implants are presented in Table I. In each group of six there were an equal number of males and females. One animal died (Estane implant) and eight implants became free in the peritoneum (two nylon sheet, three P.V.C. sheet, three Estane sheet) and could not therefore be assessed histologically. Five became completely enveloped by mesentery (three polyethylene sheet, one nylon sheet, one Estane sheet) and provided little microscopic information of tissue reaction to them. Examination of the remaining forty specimens form the basis for the assessment of the cellular response.

One disadvantage of the technique of peritoneal implantation presented here is the loss of information that can occur when materials fail to remain *in situ*. Some of these were probably due to inadequate suturing of the material

1. *Round Cells.*—Small and large round cells, as part of an inflammatory reaction, were found around all materials examined soon after implantation. After six weeks it was possible to grade the reaction remaining as "slight" or "moderate/severe": P.T.F.E., Orlon, and Terylene (Figs. 3 to 7) appeared to have continued to cause less round-cell infiltration than other materials (Figs. 8, 9, and 10), but the difference was only just significant statistically.

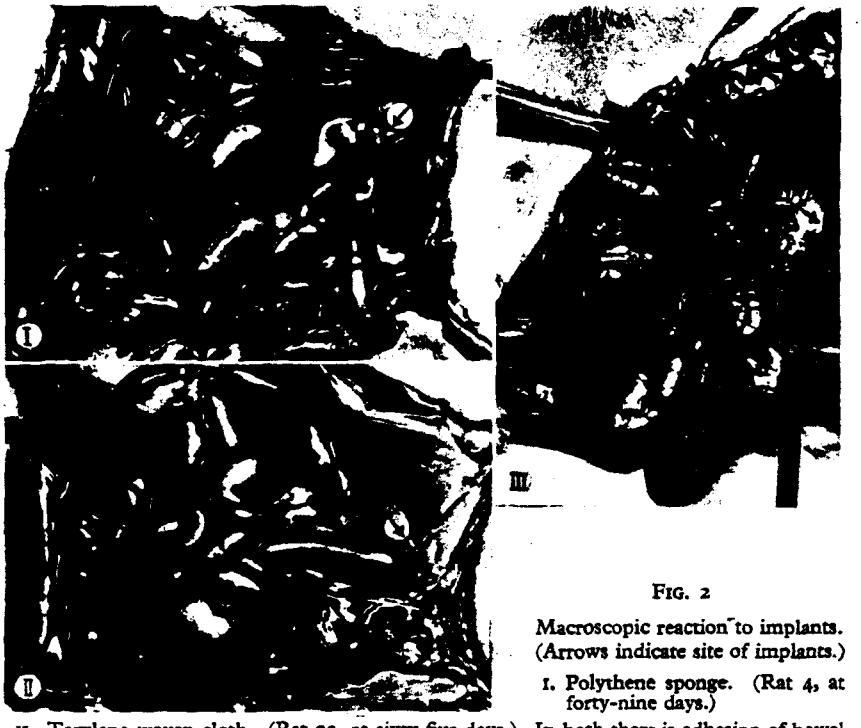

FIG. 2

Macroscopic reaction to implants. (Arrows indicate site of implants.)

I. Polythene sponge. (Rat 4, at forty-nine days.)

II. Terylene woven cloth. (Rat 22, at sixty-five days.) In both there is adhesion of bowel with minor degrees of intestinal obstruction.

III. P.T.F.E. sheet. (Rat 31 at seventy-five days.) No adhesions and material covered by normal peritoneum.

2. *Macrophages and Giant Cells.*—Giant cells, often of bizarre form, were found around and within all those materials of woven or open mesh construction (P.T.F.E. felt, Orlon, Terylene, Polythene sponge). Fig. 11 demonstrates some of these containing fragments of the implant material, while others can be seen in Figs. 3, 6, 7, and 10. Materials of smooth sheet form evoked markedly less giant-cell reaction and with P.T.F.E. sheet giant cells were never found. Presented as a 2 by 2 mm. table, $\chi^2 = 12{\cdot}2$, for one degree of freedom, which is highly significant (Table III).

3. *Fibroblasts and Fibrosis.*—A certain degree of fibroblastic reaction was seen around all implants varying from minimal with P.T.F.E. and Estane (Fig. 12) solid sheet, to severe with P.V.C., Orlon, and nylon (Table IV). Polythene, especially in the very open "foam" form, seemed to encourage the formation

TABLE II

Gross Appearances of Implants: the Presence of Adhesions of Mesentery, Bowel

Material	No Adhesions	Adhesions	Totals
P.T.F.E. . . .	9	3	12
All others . . .	3	37	40
Totals .	12	40	52

$\chi^2 = 20{\cdot}5$ d.f. = 1 $P < 0{\cdot}001$

TABLE III

Influence of Physical Form of Implants. The Presence of Giant Cells

Implant	Giant Cells		Totals
	Present	Absent	
Sheet	6	16	22
Woven or open mesh .	18	0	18
Totals .	24	16	40

$\chi^2 = 12{\cdot}2$ d.f. = 1 $P < 0{\cdot}001$

TABLE IV

Reaction by Fibroblasts and Fibrosis

Material	Reaction		Totals
	Slight	Moderate or Severe	
P.T.F.E. . . .	9	3	12
All others . . .	4	24	28
Totals .	13	27	40

$\chi^2 = 9$ d.f. = 1 $P < 0{\cdot}005 > 0{\cdot}001$

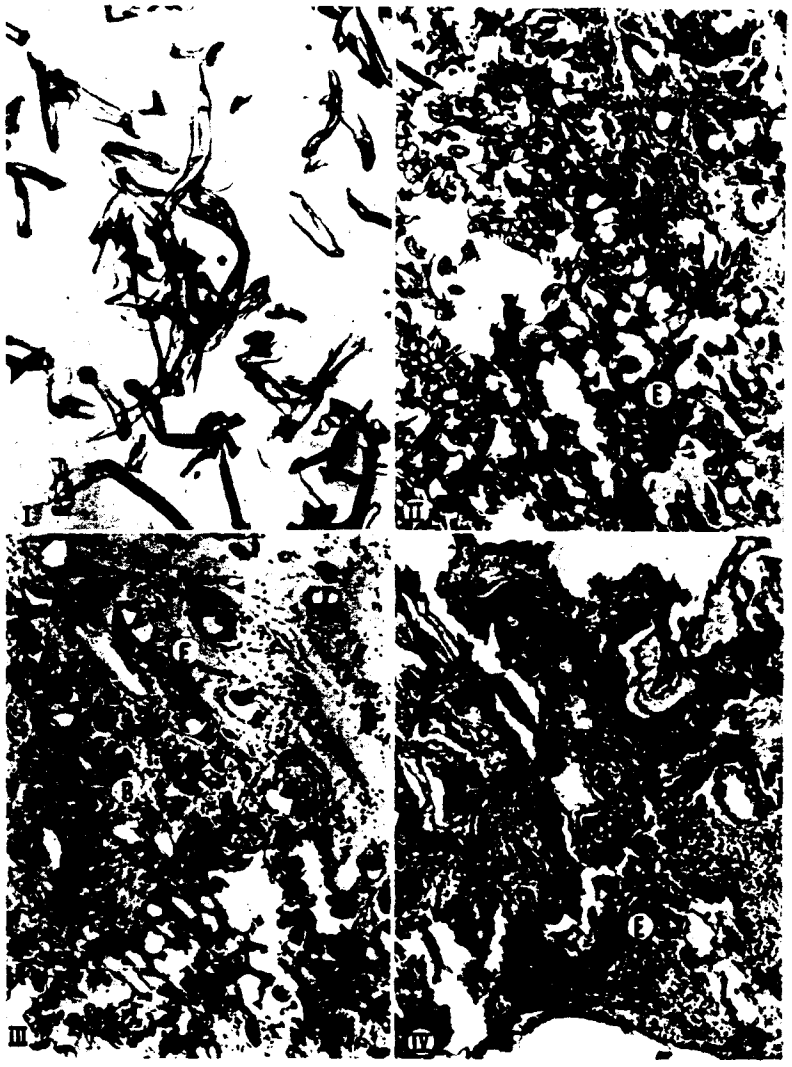

FIG. 3

Polytetrafluorethylene (P.T.F.E.) felt: biological modification of its physical structure.

I. Specimen of P.T.F.E. felt before implantation (×67). Note its fibrous nature and spiked ends. It does not pick up histology stains.

II. P.T.F.E. felt four days after implantation (Rat 58). The material is still spiky and giant cells (E) can be seen at the free edge of the material. (Mayer's acid hæmatoxylin stain. ×67.)

III. A later stage at seventy-six days (Rat 3). There are fewer giant cells (E) but an increase of interstitial fibrosis (B). (Mayer's H. & E. ×67.)

IV. At ninety-four days the P.T.F.E. has become matted and smoothed off. Giant cells are now scanty (E). (Rat 46.) (Ehrlich's H. & E. ×67.)

of fibrous tissue within its interstices to such an extent that the original shape macroscopically was always deformed. Fibroblasts, fibrous plaques, and giant cells were always seen in every field of every specimen of Polythene foam examined (Fig. 10). This perhaps is not surprising when one remembers that Dunphy (1960) has recommended the use of this material as an implant to harvest young fibrous tissue. From the table it will be noted that P.T.F.E. produces less fibrous tissue reaction than other materials, significant at the 0·5 per cent. level of confidence. It is notable that with woven materials (Orlon, Terylene) fibrous penetration of the material was unusual (Figs. 5 and 6).

FIG. 4
P.T.F.E. felt.

I. P.T.F.E. felt to show lack of reaction and covering of mesentery (M). The interstitial reaction is still cellular and the lack of bundles of fibrous tissue is notable (compare Polythene, Fig. 10). (Rat 58 at four days.) (Ehrlich's H. & E. ×67.)

II. P.T.F.E. felt at seventy days to show localised abscess (P) within the material. The clear spaces are artefacts occurring when this tough material is cut on the microtome and the soft tissues are dragged away.

4. *Vascular Connections.*—In the majority of materials it was not possible to show any abnormality of the vessels proceeding to and from the area of the implant, and the fibrous capsules were relatively avascular. With solid materials this was expected except for the unusual phenomenon of "incorporation" of P.T.F.E. sheet which will be described later. With woven materials, as already noted, tissue reaction was confined to the surface and, although there appeared to be an increased number of small vessels at the edges of these implants, the vessels themselves did not appear abnormal. By contrast, in those materials of more open texture (Polythene foam, P.T.F.E. felt) primitive vascular spaces were commonly seen within the implant. These spaces, varying in size from 10 to 100 microns and even larger (Fig. 10) did not appear to be lined by endothelium

in every case. Serial sections confirmed that they were not areas of hæmorrhage within the implant, as at first thought. Although it was not possible to demonstrate their connection with afferent or efferent vessels, their pattern of direction was consistent with such an assumption. Vascular spaces such as these would appear to be unsatisfactory and possibly could produce a hæmolytic anæmia of mechanical origin.

5. *The Covering.*—As already mentioned under macroscopic findings, mesentery was the commonest covering found on the peritoneal aspect of the

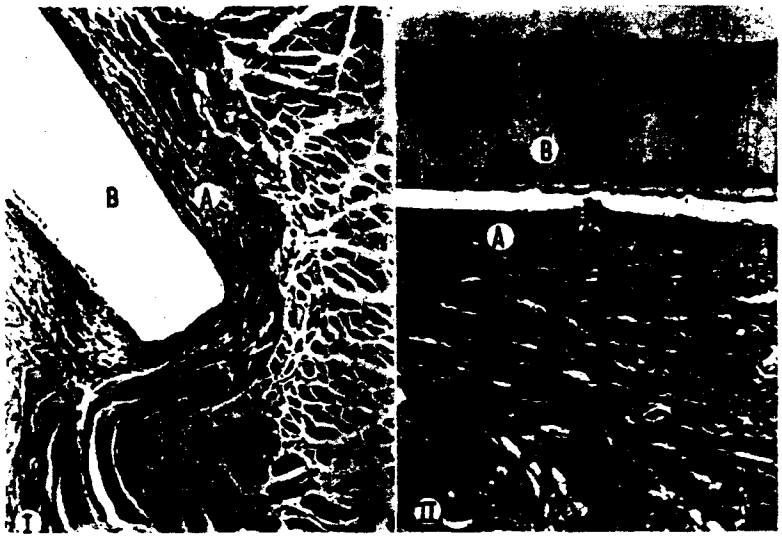

FIG. 5

P.T.F.E. sheet.

I. General view of encapsulated implant. (Rat 25 at sixty-four days.) Note thin capsule of very cellular fibrous tissue (A) surrounding the implant (B), the relative absence of round cell infiltration or giant cells. (E. H. E. ×67.)

II. Junction of implant (B) and capsule (A) where a cellular element with vascular spaces is notable. (Rat 40 at sixty-five days.) (Mayer's H. & E. ×67.)

(*See also* Fig. 13 of incorporated P.T.F.E. sheet.)

implants. From the clinical point of view the most satisfactory implant is one which has become completely covered by a fibrous tissue envelope and is thus virtually extracorporeal. It is known that this of itself carries the risk that any blood-borne infection which settles within the fibrous envelope will also exclude the natural body mechanisms for its defence. Hence abscess formation requiring removal of an implant many years later has become well recognised. The fibrous tissue envelope or capsule does, however, ensure that at the cellular level all is quiet. While sheet (solid) materials were usually encapsulated in this way, open mesh materials never were completely. At one or more areas giant cells and round cells were always found, indicating that biological activity was still continuing (Table V, p. 17). Such histological findings must indicate their unsatisfactory nature for use in reconstructive surgery.

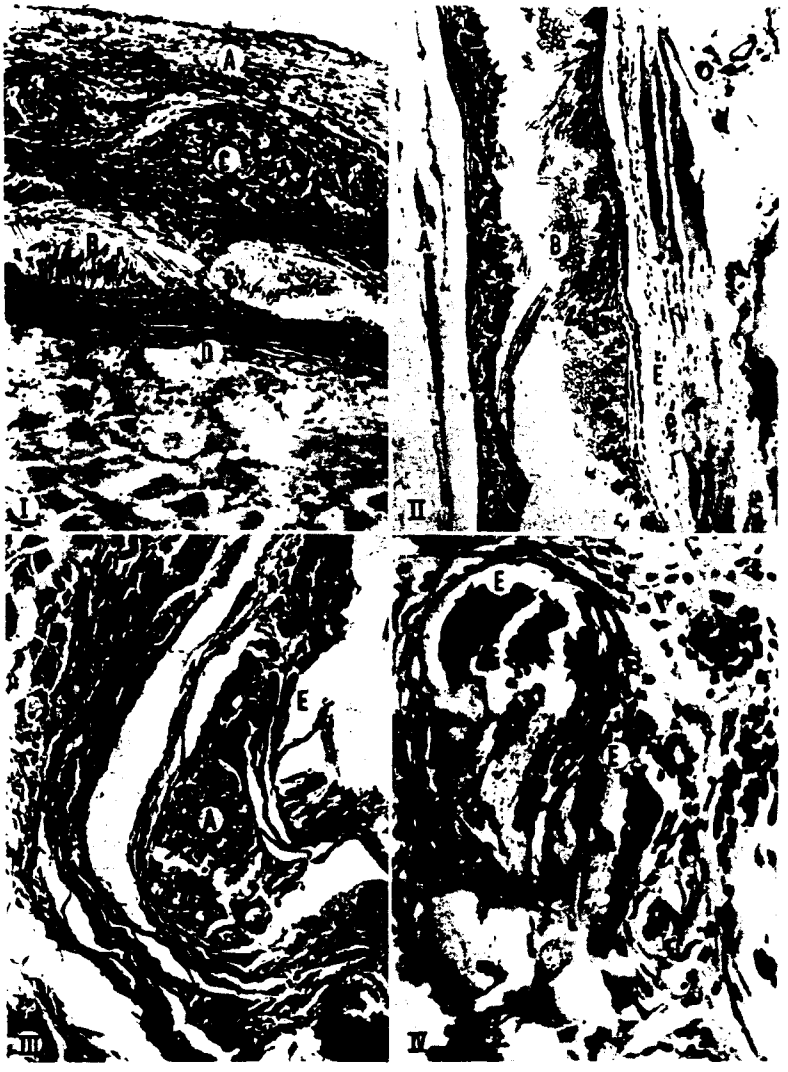

FIG. 6

Orlon woven cloth.

I. General view. (A) Thick fibrous covering of implant. (B) Woven cloth with no tissue permeation. (C) Individual loose fibres surrounded by fibrous tissue, containing giant cells. (D) Deep portion of fibrous capsule and normal muscle of abdominal wall. (Rat 88 at forty-nine days.) (H. & E. (transverse section). ×67.)

II. Longitudinal section to show fibrous capsule (A), lack of tissue permeating the woven cloth (B) and multiple giant cells (E). Beyond the fibrous capsule there is little cellular reaction. (Rat 88 at forty-nine days.) (Mayer's H. & E. ×67.)

III. Local encapsulation of frayed ends of implant (A) within the main fibrous capsule. Note giant cells (E). (Rat 24 at sixty-four days.) (Mayer's H. & E. ×67.)

IV. Bizarre-looking giant cells (E) ingesting Orlon fibres. (Rat 90 at forty-four days.) (Mayer's hæmatoxylin-van Gieson. ×250.)

FIG. 7

Terylene woven cloth.

I. General view. (Rat 23 at forty days.) As for Orlon (A), (B), (C). Note giant cells (E) at cut edge of implant. (Ehrlich's H. & E. ×67.)

II. To show fibrous capsule (A) dissected free from surrounding tissue and subsidiary fibrous tissue enveloping individual terylene fibres at cut end of implant (G). (Rat 22 at sixty-five days.) (Mayer's hæmatoxylin–van Gieson. ×67.)

III. Giant cells (E) enveloping free ends of woven cloth. Oblique section. (Rat 4 at seventy-six days.) (Ehrlich's H. & E. ×67.)

Where mesentery or bowel did not cover the implant, a layer of condensed fibrous tissue with occasional fibroblasts was found. Over only two implants of solid P.T.F.E. sheet were endothelial cells found microscopically.

6. *Incorporation.*—It has been stated by several writers (Yeager and Cowley, 1948; Grindlay and Waugh, 1951) that normal tissue has been found permeating polyethylene sponge and the impression given that this state of affairs is ideal. While concurring with the latter, it must be pointed out that the findings from

FIG. 8

Nylon sheet.

Rat 36 at sixty-five days. (A) Fibrous capsule. (B) Fragmented portions of nylon associated with giant cells. Note the general disorganisation of the cellular elements. (Mayer's hæmatoxylin–van Gieson. ×67.)

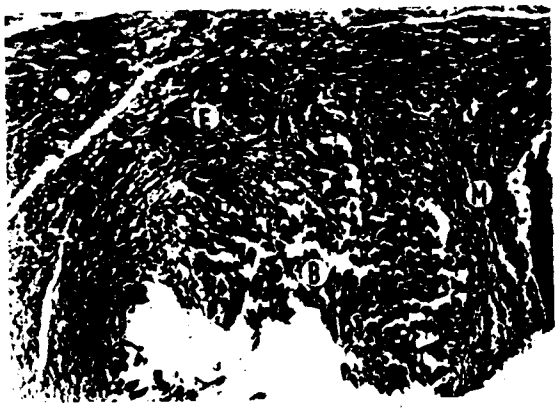

FIG. 9

P.V.C. sheet.

Rat 38 at fifty-nine days. Note the fragmented material (B), giant cells (E), and highly cellular reaction (M) composed of round cells and histiocytes. (E. H. E. ×67.)

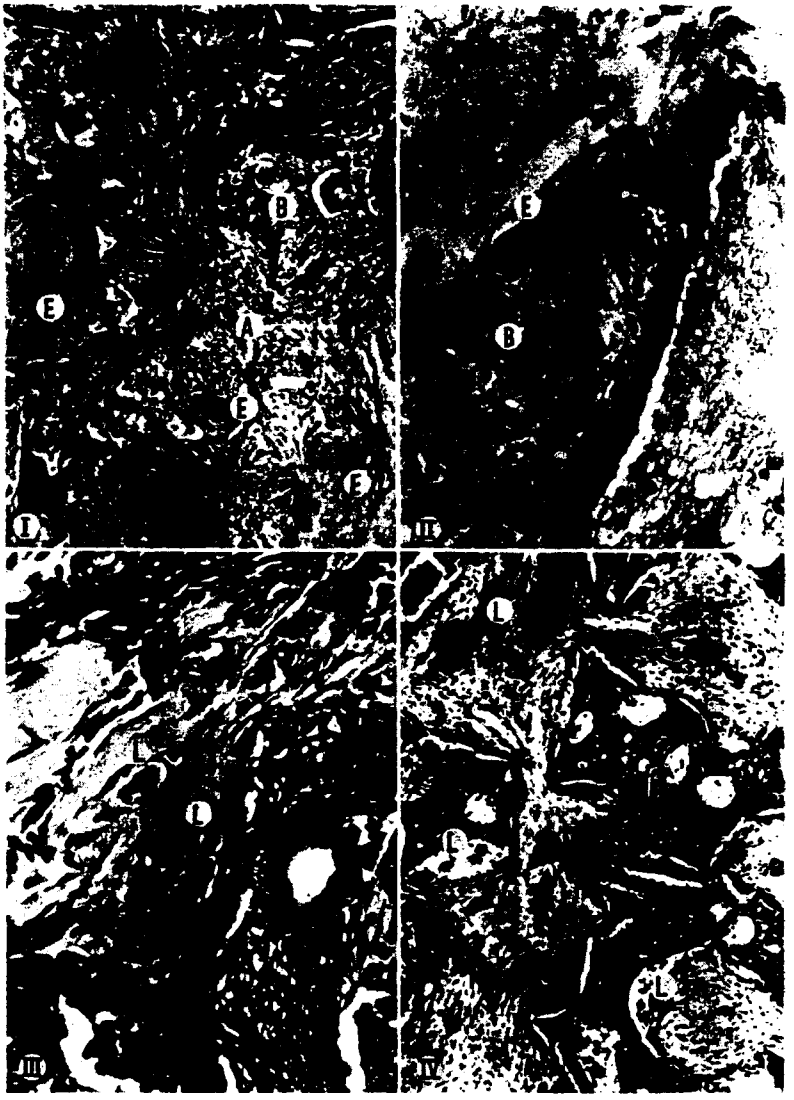

FIG. 10

Polythene sponge.

I. General view. (Rat 18 at seventy-seven days.) Relatively avascular fibrous tissue (A) permeating the interstices of the sponge (B). Note frequent giant cells (E). (Mayer's H. & E. ×67.)

II. Giant cells (E) invading the Polythene (B). Note accompanying histiocytes and fibroblasts. (Rat 80 at fifty days.) (Mayer's H. & E. ×250.)

III. Small vascular spaces (L) within the Polythene sponge—some lined by endothelium, the majority unlined. (Rat 81 at fifty days.) (H. & E. ×250.)

IV. Large vascular spaces (L). As III above. (×100.)

FIG. 11

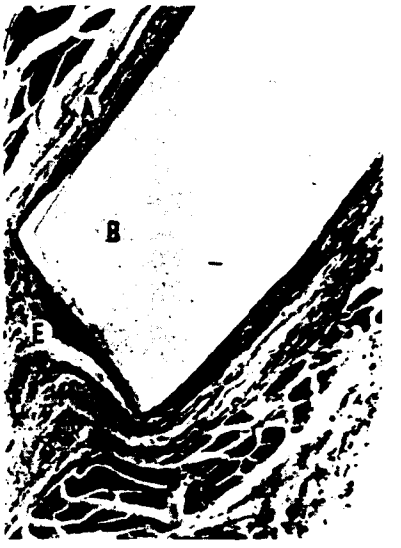

FIG. 12

Fig. 11. — Giant cells containing material. (Arrows indicate giant cells containing portion of material within cytoplasm.)

I. Nylon sheet. (Rat 36 at sixty-five days.) (H. & E. ×250.)

II. Orlon woven cloth. (Rat 88 at forty-nine days.) (Ehrlich's H. & E. ×250.)

III. Polythene sponge. (Rat 40 at sixty-one days.) (Ehrlich's H. & E. ×250.)

Fig. 12.—Estane sheet. Complete encapsulation of material (B) which does not accept histological stains. Note (A) fine fibrous tissue capsule, (E) two marginal giant cells. (Rat 13 at fifty days.) (Ehrlich's H. & E. ×67.)

our experiment indicate that scar tissue infiltrates polyethylene, and can hardly be called " normal tissue."

Two specimens out of six, of P.T.F.E. sheet 0·3 mm. thick, were found to be covered by normal peritoneal endothelium (Fig. 13). Microscopically the endothelial cells stained normally with basophilic dyes and clearly received

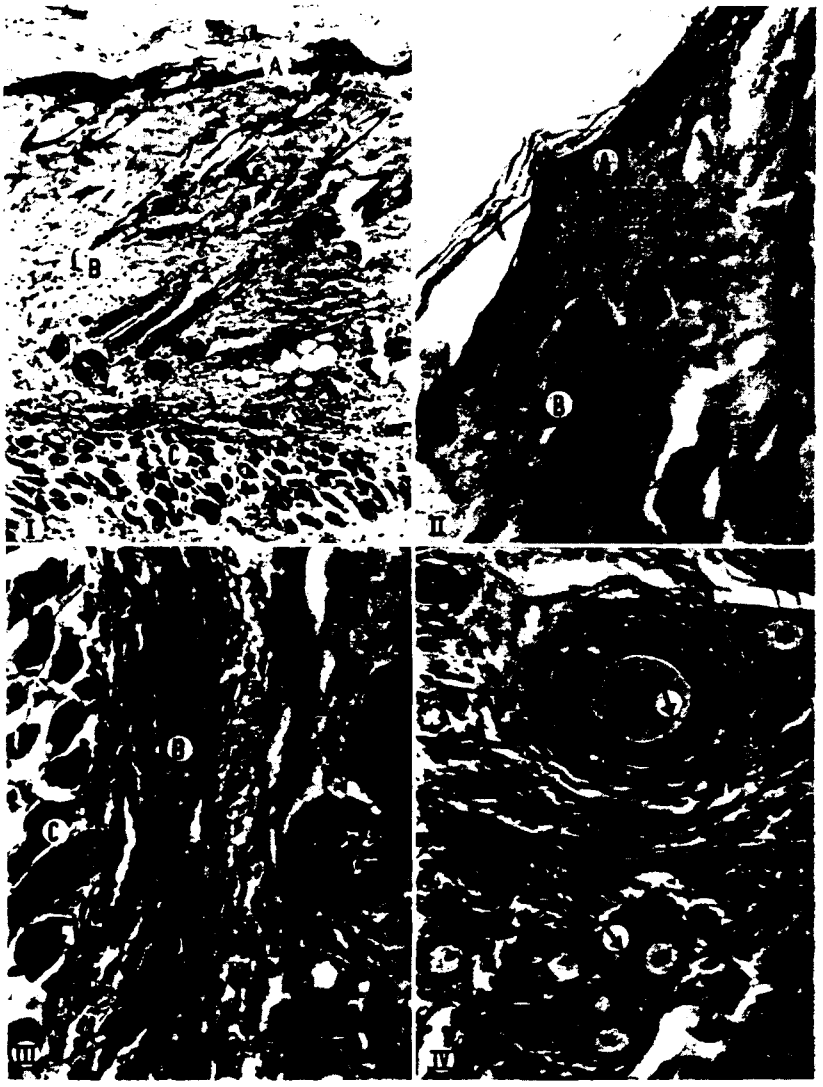

FIG. 13

Incorporation of implant. (P.T.F.E. sheet, 0·2 mm. thick.) (Rat 2, biopsy at sixty-three days.)

I. Whole section. (H. & E. × 100.) (A) Peritoneal covering of previously exposed implant. (B) P.T.F.E. sheet permeated by vessels and occasional cells. (C) Normal muscle of abdominal wall.

II. Normal peritoneal cells (A) covering implant (B). (× 255.)

III. Junction of P.T.F.E. (B) and muscle (C). Note the lack of tissue reaction; the vessel stuffed with cells is probably infarcted and this is the usual biological method for reducing the number of unwanted vessels in tissue. (× 255.)

IV. Normal-looking vessels within the sheet of P.T.F.E. The larger arteriole has well-marked intimal and medial coat. (× 255.)

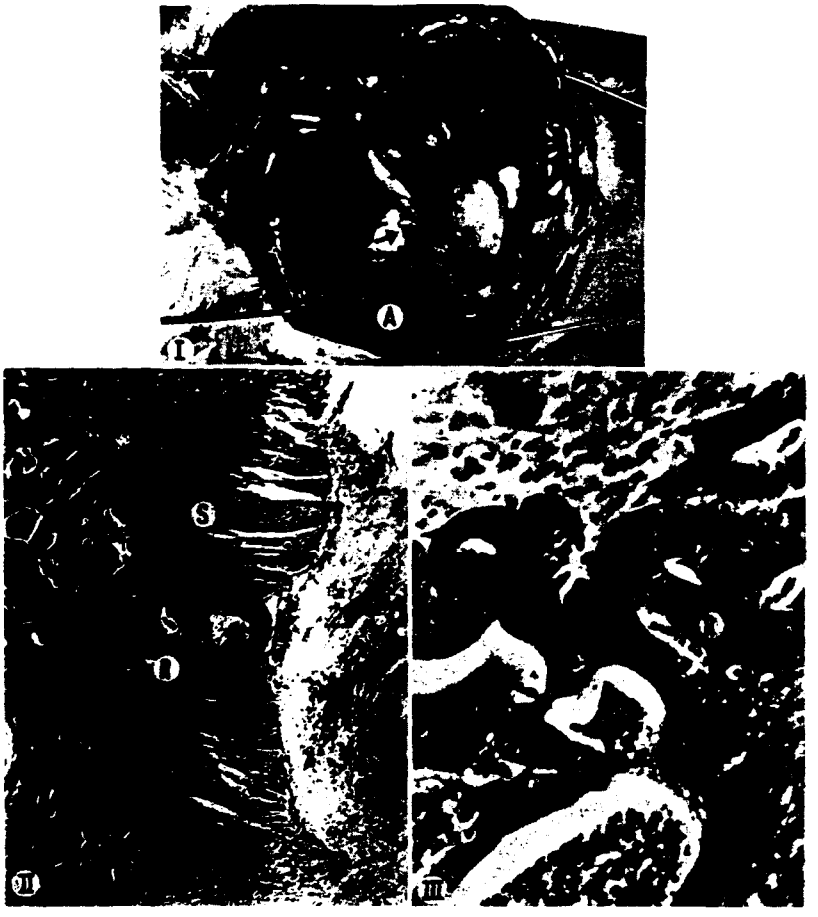

FIG. 14

Adenocarcinoma of large bowel: no relation to implants.

I. *Clinically obvious ring carcinoma of descending colon (arrow) with subsequent spread.* (Rat 56, male, 255 g. weight.) (A = site of P.T.F.E. sheet implant.)

II. General view of section of bowel, showing well-differentiated adenocarcinoma (R) invading muscle layer (S). (H. & E. ×25.)

III. General features of adenocarcinoma. This rat was one of two in which carcinoma of bowel was found out of 100 in which the viscera were examined at laparotomy. In this rat a peritoneal implant of P.T.F.E. sheet had been placed on the left anterior abdominal wall one month ago. A diagnosis of bowel neoplasm was made on clinical examination: cachexia and a palpable abdominal mass were present. (H. & E. ×250.)

nourishment through the implant material. Many vessels of normal appearance were seen within the sheet of P.T.F.E. and only occasional round cells. At the junction of P.T.F.E. and underlying abdominal muscle the cellular reaction is minimal and in some areas muscle and P.T.F.E. abut without any intervening layer. The P.T.F.E. sheet, which before implantation refused to accept any of the common histology dyes, was readily stained an even bluish-grey with

TABLE V

Influence of Physical Nature of Implant on the Total Biological Reaction

Material	Incorporated or completely Encysted	Partially Encysted and Giant Cells, etc.	Totals
Sheet . . .	10	8	18
Others . . . (woven, felt, sponge)	0	24	24
Totals .	10	32	42

$\chi^2 = 9{\cdot}52$ d.f. = 1 $P < 0{\cdot}005 > 0{\cdot}001$

hæmatoxylin. This indicated that some biological transformation had occurred in the material which microscopically now measured 0·6 mm. thick. Increased water retention (normally 0·1 per cent.) due to separation of the fibrous elements of the sheet would explain the post-implantation stainability and apparent increase in thickness of the sheet. The P.T.F.E. used was made from granular polymer and no explanation can be offered for the elongated fibres seen in the histological sections. They do bear some resemblance to collagen fibres and it is intriguing to believe that they have been accepted biologically as such. The term "incorporation" is suggested for this particular tissue reaction (Calnan, 1961).

DISCUSSION

There are several facets of this work worthy of further exploration.

1. **On the Technique Presented.**—Barr (1953) called attention to the need for laboratory testing of implant materials used in orthopædic surgery. The requirement is no less urgent in plastic or any other branch of surgery. Barr went further and condemned the present order whereby materials are used clinically and investigated only when things go wrong (cf. Gibson and Davis, 1953). "Scientific testing methods are available which are much more accurate than clinical trial, and the human guinea-pig technique is to a large extent outmoded and indefensible." While no biological study can give a complete guarantee that failures will not occur, the risk will be so reduced as to justify the cost and time of the research. The negative attitude, whereby laboratory

investigations disclose which materials are unsuitable for use in man, is perhaps of even greater benefit.

The technique of the testing *in vivo* of materials in the rat differs from that offered by others (LeVeen and Barberio, 1949; Grindlay and Waugh, 1951; Moore and Brown, 1952; Brown *et al.*, 1954; Harrison *et al.*, 1957). By placing the test material in the peritoneum a macroscopic assessment which does not disturb the implant may be added to the microscopic examination and so increase the precision of observation. By choosing a suitable experimental design and statistical test of significance, it becomes possible to compare accurately and validly the biological reactions between different materials. The combination of macroscopic, microscopic, and statistical analysis ensures that a sufficient number of animals will be used in the test and that the results will be applicable to the animal population concerned. While the *exceptional* response will be noted it will not become confused with the *usual* and faith can be distinguished from fact.

While it is not claimed that the technique presented cannot be improved upon, the information so derived from it does allow a valid comparison to be made between the biological reactions to the various implant materials.

2. **Macroscopic Findings.**—Gross observation of the peritoneum and its contents at varying periods revealed evidence of the intensity of the inflammatory reaction to the implanted material (LeVeen and Barberio, 1949). With P.V.C. and nylon, multiple adhesions of bowel, producing kinking and minor degrees of intestinal obstruction, were invariably found. Rough-surfaced materials (Polythene foam, woven Orlon, and Terylene) usually had a thick covering of mesentery but P.T.F.E. felt implants had only a thin film of mesentery covering them. This suggested that there were two factors involved—the physical nature of an open mesh and a chemical difference in this biological situation. When the gross appearances of P.T.F.E. in both sheet and felt form are compared with those of other materials (Table VI) it is clear that there is a highly significant

TABLE VI

Cellular Reaction to Physical Form of Implant Materials

Materials	Cellularity		Totals
	Slight	Moderate or Gross	
Smooth sheet . . . . (P.T.F.E. and Polythene)	5	4	9
Rough . . . . (P.T.F.E. and Polythene)	2	10	12
Totals .	7	14	21

$\chi^2 = 1{\cdot}84$ d.f. = 1 $P < 0{\cdot}2 > 0{\cdot}1$

difference in the gross appearances, indicating that of the two factors the chemical is probably more important to the tissue reaction than the physical. The influence of physical form should not be neglected, however. From Table III it is clear that smooth-surfaced materials are less commonly associated with giant cells microscopically.

3. **Microscopic Findings.**—Clearly the microscopic findings are of the greatest interest because it is possible only in this way to appreciate the reaction to implant material at the cellular level. Yet new materials are recommended for use in reconstructive surgery in man either without any microscopic observations (Blaine, 1946; Farmer, 1947; Rubin *et al.*, 1948; Jeremiah, 1950; Aldunate, 1957; Edwards and Lyons, 1958; Gordon, 1958; Neuman, 1958) or with inadequate observation and description of the histological changes that have occurred around such materials (Frantz, 1943; Brown *et al.*, 1948, 1954, 1960). Others draw conclusions more favourable towards the new material under examination than could possibly be accepted by others not equally biased. This is an understandable attitude in clinical practice where the urgent need is to find materials to help our patients. Unfortunately, history does not support the good intentions. A pertinent example is the use of polyethylene sponge. In 1951 Grindlay and Waugh reported favourably on its use following implantation for eighteen months in twenty-eight dogs. Much support followed in the literature (Moore and Brown, 1952; Johnson and Grindlay, 1954; Struthers, 1955) which ceased when clinical failures obtruded themselves, to be followed by a new wave of enthusiasm when polyurethane sponge became available. It is only very recently that Gilmer and his colleagues (1961) have pointed out that the "living tissue" which grows into the sponges (in dogs) is "*in situ* fibrogenesis developing an avascular connective tissue which cannot be likened to granulation tissue." Nor can it be fairly called "normal tissue" for, although the individual elements are not abnormal, the total composition of the tissue is abnormal and unwanted. Sponge has been advocated as a framework for bone formation (Struthers, 1955), and again Gilmer *et al.* (1961) point out that any bone found within the sponge is formed by a process of metaplasia within the collagen at the periphery: they also noted that while the sponge might form a useful framework for bone, it did in fact cause a distinct delay in bone formation in dogs which prevented healing for as long as one year.

From our own observations on polyethylene sponge implanted in rats, giant cells were always seen, and usually in every microscopic field examined, while the fibrosis within its interstices was considerable. These two findings alone should be sufficient to deter anyone from using the material in man except under experimental conditions. It is difficult to understand why they were not noted by early investigators for they would certainly have prevented the wholesale use of moulded implants in breast reconstruction and the subsequent misery of the recipients.

It would seem worth while to consider four features of the histological reaction—the intensity of the round cell infiltration, the presence of giant cells, the amount of fibrosis, and the condition of vascular spaces. The technique advocated here allows one to observe whether living tissue will grow over the implant either to seal it off or become a part of it. The main differences between the histological features associated with the various implants have already been

pointed out. The presence of clusters of round cells, commonly called chronic inflammation, near foreign material at any time later than say three weeks after implantation, must always be viewed with suspicion. Clinically, one knows that such foci can erupt into an acute inflammation with little warning. Giant cells always indicate instability of tissues at the cellular level and materials which evoke this response are unlikely to give satisfaction. In our own investigation, a giant cell response seemed to be associated more with the physical form of an implant than with its chemical nature, and such has been noted with silica in man. Silica in the lung produces no giant cell reaction and is by necessity of small particle size, whereas silica under the skin is invariably associated with giant cells. It would be naïve to believe that no reaction occurs around any one material, but the superiority of P.T.F.E. in this respect should be noted (LeVeen and Barberio, 1949), for it is only in comparative experiments that a greater or lesser biological reaction to foreign material may be demonstrated with certainty, and this has been the error of many previous investigations. Harrison *et al.* (1957), investigating the tissue reactions to Dacron, Ivalon sponge, nylon, Orlon, and Teflon (P.T.F.E.) implanted into the subcutaneous tissue of the anterior abdominal wall in dogs, reached the same conclusions concerning P.T.F.E. Indeed, the photomicrographs of the tissue reaction in their paper bear striking resemblances to those found in our rats. The order in which they ranked materials by the tissue response, in decreasing magnitude, were nylon, Dacron, polyvinyl sponge, Orlon, Teflon—a ranking which differs little from that reported here. The paper by Harrison *et al.* (1957) offers strong support that the biological reaction to implants is similar in dog and rat. While comparative studies in man have not yet been published, individual reports (Teplitsky and Rubin, 1949; Rubin, 1949, 1951) would seem to imply that extrapolation of these findings to man are likely to be accurate.

4. **Implications for Clinical Practice.**—It is clear from what has already been written, both here and in other publications, that implants of foreign material may initiate six different biological reactions :—

1. Immediate inflammation, either chemical or bacterial, with immediate rejection of the implant.
2. Delayed rejection of the implant, of the order of weeks, months, or years, and probably due to an " uneasy " acceptance of the material by the host ; round cell infiltration, giant cells, and unorganised vascular patterns are seen histologically many weeks after implantation.
3. Encystment without reaction—*i.e.*, a fibrous tissue envelope.
4. Encystment, with an incomplete fibrous capsule where cellular reaction is continuing.
5. Slow absorption, where giant cells dominate the histological picture.
6. Incorporation or complete acceptance of the material.

At the clinical level one has to define what is meant by an " inert " material. Chemical inertness is evidently not sufficient. Physical inertness would appear to be of equal importance, for we have shown that the biological reaction to smooth, solid implants differs materially from that to porous, woven, or spongy implants. It is hoped to publish more detailed experimental evidence concerning the influence of physical form in the near future.

On present evidence it would seem reasonable to recommend that materials

other than P.T.F.E. should be abandoned and that, where possible, smooth-surfaced implants are preferable to those of open structure.

5. **The Risk of Neoplasia.**—Neoplasms, and invariably sarcomas, have been noted arising from the fibrous capsule surrounding implants in rats (Oppenheimer *et al.*, 1948, 1955; Druckrey and Schmahl, 1952; Laskin *et al.*, 1954), but the great variety of materials which may cause them should make one suspect that this may largely be a species reaction (Scales, 1958, 1961). Northdurft (1956) suggests that neoplasia is related to the physical form of the implant and not to its chemical nature, and he believes that malignant change occurs in the cells of the avascular capsule. Leighton *et al.* (1956) support this and suggest "anaerobiosis could have contributed to the formation of a morphologically malignant variant."

It is not generally known that carcinoma can occur spontaneously in rats. In the execution of the present and other experiments, two well differentiated carcinomas of the colon were found during laparotomy of 100 rats. One had received an implant of P.T.F.E. sheet thirty days earlier, the other not. It would seem unlikely that P.T.F.E. in this instance had contributed to the carcinoma of the bowel. Neoplasms do not appear to develop in less than one year after implantation (Turner, 1942; Oppenheimer *et al.*, 1948) and hence none in our series was expected.

In man, other than in association with very obvious chronic irritation, malignant changes have not been reported. The risk that it could occur would seem to be slight although Scales (1958) suggests that one may have to wait thirty to forty years before reaching a firm decision. The story of the treatment of thyrotoxicosis by irradiation and the subsequent development of skin carcinomas would support Scales' guarded prognosis.

CONCLUSIONS

1. Arguments for and against the use of inert foreign materials in reconstructive surgery have been considered. It is unrealistic to believe that their use should, or can be, abandoned entirely.

2. A technique for the biological testing of materials in rats is presented and particular features discussed. With a laboratory test of some precision available, the "clinical trial" of new materials in man without prior investigation in animals is indefensible and outmoded.

3. The macroscopic and microscopic tissue reactions to materials commonly used in reconstructive surgery (nylon, Polythene, Orlon, Terylene, P.V.C., Estane, and P.T.F.E.) have been examined by this laboratory technique and the findings assessed statistically.

4. Tissue reaction to P.T.F.E. is less than with any other material and for this reason it is recommended that the use of all less satisfactory materials should be discontinued.

5. The influence on the biological reaction of the physical form of an implant has been demonstrated and this will be amplified in a further publication.

6. Although consideration of the biological tissue reaction to implant materials in man is beyond the scope of the present paper, certain resemblances indicate that experimental results may be extrapolated with fair accuracy. It is hoped to publish at a later date experimental and clinical support for this.

7. Incorporation of an implant as opposed to encapsulation is a new phenomenon which would appear to be the ideal.

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