

Observations on the Effects of Powdered Polymer in the Carcinogenic Process*

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SUMMARY

It has been shown that polymer powders, in contrast to polymer and other films, are noncarcinogenic when imbedded subcutaneously. An important difference in response between films and powders appears to be the fibrous pocket formed around the imbedded film. It is in the lining cells of this pocket that the tumors originate. No such pocket arises with powders.

It was suggested that powder might perhaps induce tumors if presented directly to the cells of a pre-formed pocket.

To test this hypothesis (1) polyethylene powder and (2) glass powder were inserted into pockets produced by imbedding glass films, both with and without the presence of the film.

Results gave no evidence of any significant change in tumor incidence produced by the action of powder on the pocket cells.

This was confirmed by histological observations, which showed a remarkable similarity in response to powder whether imbedded in ordinary connective tissue or introduced into a pocket. A foreign-body reaction, with phagocytic giant cells, was found constantly with imbedded powder.

It has been shown in this laboratory that subcutaneous imbedding of plastic films or metal foils in rodents can cause the appearance of sarcomas and other malignant tumors (7-12). This carcinogenic response has been found with films having a wide range in chemical constitution and has been confirmed by a number of investigators (1, 3-6, 14). On the other hand, imbedding of the same plastics or metals in the form of powders yielded only one tumor out of 387 implants. These facts established that the primary requisite for tumor induction with these substances is that they be in the form of a film. Since a basic difference between imbedding of film and powder is that the former becomes enclosed by a dense

connective tissue pocket whereas the latter does not, it was suggested that this may be a critical factor in the process. This was strengthened by the finding that removal of the pocket precludes tumor production (13).

Although all films tested induced tumors, there was a marked variation in actual tumor incidence with films of different substances. This, in addition to the fact that in some cases a slight degradation of the polymer molecule has been shown to occur after imbedding (8), suggested the possibility that direct chemical action might play some part, perhaps secondary, in the carcinogenic process. It was thought that, although powdered polymer imbedded in normal connective tissue is not carcinogenic if introduced into a pre-formed pocket, it, or its breakdown products, might influence tumor production by a reaction with cells of the pocket wall.

The present report describes experiments de-

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vised to test this supposition. Pockets were formed in rats by imbedding glass coverslips, which in themselves are inorganic and chemically inert but which induce tumors. The effect on tumor production of introducing powders into these pre-formed pockets was then investigated.

MATERIALS AND METHODS

Glass coverslips, approximately 1.8 cm. in diameter, were imbedded subcutaneously in the right and left abdominal walls of 90 Wistar rats by procedures previously described (8). After 4 months, the animals were divided into three groups. In one group, in the right abdominal wall, polyethylene powder was introduced into the pocket against the outer surface of the coverslip, and on the left side glass powder was similarly inserted.

In a second group, the coverslips were removed from both sides, and polyethylene or glass powder was introduced into the empty pocket on the right or left side, respectively.

powder was introduced would be assumed to be due to the powder. Likewise, any significant increase or decrease in the number of tumors, where the powder was added with the film *in situ*, would be directly attributable to the powder. Since polyethylene was previously shown to undergo some degradation after imbedding (8), these experiments were devised to allow for comparison between powders of this material and that of glass. If the degradation products of the polyethylene were carcinogenic, one would expect a higher tumor incidence with polymer powder than with powdered glass.

The results obtained are shown in Table 1. It is seen that glass coverslips by themselves yielded six tumors out of 24 imbeddings, or 25 per cent. As expected, mere removal of the coverslip at 4 months resulted in the complete absence of tumors. Insertion of glass powder into the empty pocket still gave no tumors, whereas polyethylene powder produced one only, more than 2 years after

TABLE 1
EFFECTS OF POWDERS IN PRE-FORMED POCKETS

Group:	1	2	3	4	5	6
Coverslip:	<i>in situ</i>	<i>in situ</i>	Removed	Removed	Removed	<i>in situ</i>
Powder:	Polyeth.	Glass	Polyeth.	Glass	None	None
Imbeddings:	27	27	27	27	25	24
Tumors:	5	6	1	0	0	6
Percentage:	19	22	?	0	0	25
Mean latent period (days):	570 ± 94	547 ± 103	752			303 ± 55

In a third group, the glass coverslips were removed from the pockets on the right side only, remaining *in situ* on the left, and no powder was introduced on either side.

Essentially, this procedure resulted in four experimental and two control categories. The experimental groups included:

1. Polyethylene powder with coverslip in pocket
2. Glass powder with coverslip in pocket
3. Polyethylene powder in pocket, no coverslip
4. Glass powder in pocket, no coverslip

The controls included:

5. Coverslip removed from pocket—no powder
6. Coverslip in pocket—untouched

RESULTS AND DISCUSSION

In these investigations the powders were introduced between 4 and 5 months after imbedding of the original film because previous experiments, with polystyrene (19), had shown that, if the films are removed within this period, no tumors occur. Thus, any sarcomas which might appear in the cases where the film was removed and the

imbedding. The significance of a single tumor in this category is difficult to evaluate. Introduction of polyethylene or glass powder into the pocket without removal of the film gave 19 per cent and 22 per cent of tumors, respectively. Thus, these additions had no significant effect on the number of tumors as compared with the film alone, and certainly produced no increase. The time elapsing before the appearance of tumors (latent period) shows little difference whether powder was inserted or not, but the longest latent period shown (752 days) was with the single tumor appearing when polyethylene powder was placed in the pocket with no coverslip.

These results lead to the conclusion that powders are ineffective in producing tumors even though a pocket has already been formed, and they corroborate the previous proposition (2) that there is no direct chemical action involved in carcinogenesis by plastics. If there were such an action, a higher incidence of tumors would be expected upon introduction of polyethylene powder into the pocket because of the increased sur-

face available for chemical reaction. The slight degradation of the polyethylene is probably not involved in the carcinogenic process but is merely a coincidental occurrence as far as tumor induction is concerned.

The reason for the difference in carcinogenic activity between powder and film is still somewhat obscure, but one important factor may be that films produce an enveloping pocket and powders do not. Histological examination shows that a film becomes enclosed by a thick continuous wall of collagen fibers packed closely together, with a few flattened inactive fibroblasts between (Fig. 1), while the tissue reaction to powders shows a much looser, more open, and less regular arrangement of fibers around the individual powder masses, fibroblasts with large rounded nuclei which remain continuously active, as well as many phagocytic multinuclear giant cells (Fig. 2). This active foreign-body reaction continues apparently indefinitely.

When the powder was inserted into a pre-formed pocket with the film still *in situ*, the powder appeared to stimulate the adjacent inactive pocket wall to a foreign-body reaction very similar to that found in ordinary loose connective tissue (Fig. 3). Removal of the film from its surrounding pocket has been found to result in the slow regression and ultimate disappearance of the pocket wall. When powder was introduced into a pocket upon removal of the film, this regression was accompanied by the usual tissue reaction to powder, and after many months the surrounding tissue resembled that in which powder alone had been imbedded. The reaction of powder with pocket cells, whether with a film or without, appears very similar to that with ordinary connective tissue. No histological evidence of carcinogenic action by the powder was observed in this investigation.

Owing to the difficulty of cutting microscopic sections of tissues containing insoluble powders of glass and polyethylene, we have been unable in this experiment to follow every stage of the reactions to powder imbeddings. Experiments are in progress, however, with a polymer which can be dissolved out, and we hope to present a more

detailed histological study in a subsequent report. Comparative studies of the chemistry of the tissue surrounding powders and films are also under way in this laboratory.

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FIG. 1.—Inactive, fibrous, thick-walled pocket formed around glass coverslip; 21 months after subcutaneous imbedding. H. & E. X810.

FIG. 2.—Tissue surrounding polyethylene powder, showing foreign-body reaction with marked fibroblastic activity and many phagocytic giant cells; 40 days after subcutaneous imbedding. H. & E. X400.



FIG. 3.—Result of inserting polyethylene powder in pre-formed pocket showing similar intense fibroblastic activity in the wall, with numerous giant cells; 7 months after insertion of powder. H. & E. $\times 425$.

FIG. 4.—Regressing pocket wall 14 months after insertion of polyethylene powder and removal of glass coverslip. Wall is markedly reduced in thickening, but fibroblastic activity with giant cells is still present around the powder. H. & E. $\times 650$.



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