Carcinogenic Effect of Metals in Rodents*

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In connection with our experiments on the induction of tumors by imbedding plastic films subcutaneously in rodents, we have also conducted some investigations on the effect of similar imbedding of metal foils. This has included silver, tin, tantalum, vitallium (an alloy of chromium, cobalt, and molybdenum), and stainless steel. The experiments with the first two metals are complete, and final results can be recorded. Although the experiments with vitallium, tantalum, and stainless steel are not yet complete, the fact that positive results have been obtained justifies their being recorded, since they may be of practical significance—particularly since these metals are now being used so extensively in various forms of surgical and dental repair work.

METHODS AND RESULTS

Circles or squares, approximately 1.5 cm. wide, of silver, tin, tantalum, vitallium, and stainless steel foils were sterilized in Zephiran (1:1000 dilution) and washed in sterile saline. These were then imbedded subcutaneously in the abdominal wall of rats just ventral to the fascia. Fifty imbeddings were made with each metal in 25 male Wistar rats, two pieces of foil being imbedded in each animal, one on either side of the abdominal wall. The rats were kept under observation until the incisions were completely healed, and were subsequently examined at weekly intervals for tumor formation. All the animals were kept on a diet of Purina Laboratory Chow, with fresh carrots once a week, and with free access to water.

Table 1 shows the results of these studies. The experiments with silver and tin are complete. Although positive results have been found in the other experiments, no final percentages can as yet be given, since a few of the animals are still alive. Percentage production of tumors is calculated on the basis of the number of animals surviving beyond the minimum latent period found to be necessary for tumor production. As a general rule, 300 days is taken as the minimum latent period, and animals dying earlier than 300 days from the date of imbedding are omitted as incomplete. The tests for malignancy are:

1. The microscopic identification of the type of tumor obtained.
2. Its transplantability.
3. Frequent local recurrence after removal of a primary tumor. Metastases did not occur since the tumors were all removed a week or two after their first appearance.

The tumors obtained were all fibrosarcomas, except for one osteogenic sarcoma induced by vitallium.

TABLE 1

Results of Imbedding Metals in Rats*

Material	Latent period (days)	No. malignant tumors	No. days since imbedding†	No. rats still alive
Silver	275–625	14 (32 per cent)	(Completed)	None
Steel	364–	5	596	4
Tantalum	714–	2	844	2
Tin		0	(Completed)	None
Vitallium	453–	5	725	2

* Based on 50 imbeddings with each metal, two in each of 25 rats.

† Up to Jan. 17, 1956.

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DISCUSSION

As can be seen, all except tin foil induced tumors, with silver foil producing several times as many as any other. The results of the tin foil experiment are different from the others, perhaps because the material was friable and was found in every case to have broken up and crumbled into a fragmentary mass. Whether this change in physical condition is responsible in any way for the nonproduction of tumors cannot be decided at present, but it is an interesting speculation in view of the fact that with plastics the physical form appears to play an important role. We have found (7) that with plastic materials many more tumors are obtained with plain than with perforated film or with fibers (textiles) or powders. We have in progress several experiments on the imbedding of metals in powder form, but they have not proceeded far enough to justify any conclusion at present.

Other experimenters, however, have obtained malignant tumors by implantation or inhalation of powdered metals. Schinz (8) in 1942, noting the occurrence of cancers—especially of the lung—in workers in chromium, cobalt, and nickel ores, laid down "metal depots" in the bones of rabbits and obtained sarcomas of the bones as well as of the lungs. Gardner and Heslington (2) in 1946 and Barnes and co-workers (1) in 1950 obtained osteosarcomas by intravenous injection of beryllium powder and beryllium salts in rabbits. Hueper (4, 5) reported that sarcomas with a frequency ranging up to 28 per cent developed in rats by parenteral, intrafemoral, and subcutaneous introduction of nickel powder, but the sarcomas obtained with beryllium and chromium were very few and of uncertain origin. Heath (3) obtained local sarcomas with cobalt powder introduced intramuscularly into rats. Early in 1955, Nothdurft (6) of Heidelberg reported sarcomas in rats obtained by the subcutaneous implantation of gold, silver, and platinum foil, but he made no mention of powdered metals.

For our studies the chief point of interest in this tumor induction by metal foils and powders is the question of the mechanism involved. Although these experiments were done in conjunction with our studies with plastics, it is quite probable that a completely different mechanism is at work in the case of metals. The inherent difficulty in explaining the carcinogenic activity of plastics, viz., their chemical inertness, does not obtain in the case of metals. These may react by oxidation or reduction processes or by formation of chelates. Silver and tantalum react with sulfur, oxygen, and nitrogen compounds, and interaction of these metals with the sulfur or amino radicals of proteins is very possible. Formation of silver complexes is quite common, and the carcinogenic activity of the latter may be a result of this type of reaction. Various metals are also known to be enzymic poisons, and their biologic activity may stem from this characteristic.

Since nickel, chromium, and beryllium have been shown to have some carcinogenic properties, it is possible that the production of tumors by vitallium and stainless steel may be due to some similar reaction. Indeed, both of these contain chromium, which may perhaps be the important factor in the tumor incidence in these cases.

As all our results have thus far involved only foils, we cannot yet compare the action of foils and powders. Our work with plastics, however, suggests that the influence of the physical form of materials cannot be completely excluded. When our results with powders are completed, we may be able to judge whether the physical form plays any role with metals—as we are convinced it does with plastics.

Since the chemical activity of the metals is so much greater than that of the inert plastics, there is little reason to expect that their carcinogenic activity is primarily a function of their physical form. The fact that powders produce tumors in many cases is evidence of this. However, because of the fact that, with plastics, the physical state does appear to be an important factor, one cannot completely exclude this possibility in the case of the metal foils which we have studied. It is hoped that by our further investigations we will be able to ascertain whether anything like the physicochemical mechanism tentatively formulated by us for plastics may obtain in a limited degree for metals.

SUMMARY

1. A 32 per cent incidence of tumors was induced in rats by the subcutaneous imbedding of silver foil. Sarcomas were induced in lower incidence by vitallium, tantalum, and stainless steel foils.

2. The tumors produced were fibrosarcomas, with one osteogenic sarcoma.

3. Tin foil did not cause any tumor induction.

4. Possible mechanisms are tentatively discussed.

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