accepted as not being due to quantitative storage. The recent report(7) of increased glycosuria in phlorizinized starved dogs after dextran administration indicates that metabolism to glucose is one avenue of disposal. There is evidence in mice of transfer to exhaled CO_2(8). Partial degradation to smaller molecules capable of passing the renal glomerulus constitutes another possibility.

Summary. Except for a decrease in hematocrit volume, intravenous administration of dextran continued for 13 weeks produced in 3 normal, nonshocked dogs no demonstrable harmful effects. Blood viscosity was maintained at or above control levels when the injections were 15 to 20 ml/kg body weight. The dog receiving 10 ml/kg exhibited a tendency to adjust to the foreign polysaccharide as evidenced by a return towards normal hematocrit values and sedimentation rates in spite of continued dextran.

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Sarcomas Induced in Rodents by Imbedding Various Plastic Films.* (19380)

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In 1948 we reported that sarcomas of various types could be induced in albino rats in a significant percentage of cases by imbedding cellophane film subcutaneously in the anterior abdominal wall, or by wrapping it around one kidney(1). Since then the experiments have been extended by imbedding cellophane film in albino and black mice, by testing alcohol-extracted cellophane, and by employing various other plastic films unrelated chemically to cellophane. In addition several other materials were imbedded in an effort to learn the nature of the carcinogenic agent or mechanism involved in the procedure. The results of these new experiments are herewith reported.

Method. The method previously described (1) was used, except that the film or other material was always inserted in the anterior abdominal wall, and no further experiments were attempted with wrapping the film around the kidney. The experiments were conducted over a period of 4 years. Some overlapped. The food cages, handling and room temperature were essentially the same. The rats were all albinos, of the Wistar strain. Films were usually sterilized by immersion in 80% alcohol and then washed in sterile saline solution before imbedding. Occasionally sterilization of the plastic film was accomplished by autoclaving, or by benzalkonium chloride ("Zephiran") 1:1000 or weaker. As malignant tumors arose after any one of these methods of sterilization, it is improbable that the particular technic of sterilization played a role in the result. The malignancy of the tumors produced was established by histologic examination and usually also by transplantability, as previously described(1). Experiments lasted 1-2 years. In calculating the percentage of positive results, *i.e.,* production of tumors, the figures were based on the number of animals that survived the minimum period neces-

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sary for tumor production. In a few instances the imbedded film could not be found at post-mortem examination, probably because it had ulcerated out; such cases were not included in the totals. The imbedded plastic film was almost invariably enveloped by a thin membranous sac from which it could be readily removed. This sac was often found one week after imbedding the film. The sarcoma, if present, was adherent to the outer surface of this sac, and not to the film itself.

Results with cellophane film imbedded in mice. The cellophane film was regenerated cellulose seamless tubing of .0039" thickness, as in previous experiments on rats(1). Squares of cellophane film, 1 cm in diameter, were imbedded in 50 albino mice of the Longacre strain. The results were as follows:

Shortest time of appearance of a malignant tumor	245 days
No. of mice surviving over 244 days	35
No. of malignant tumors	8
Tumors	22.8%

The tumors consisted of 7 fibrosarcomas and one rhabdomyosarcoma. All the tumors except one were transplantable, sometimes to the 4th tumor generation.

Cellophane imbedded in black mice (C57) yielded only one tumor in 23 effective imbeddings. This tumor was, however, a typical fibrosarcoma and was transplantable to the 3rd tumor generation. (It is known that this strain of black mice is unusually resistant to artificial tumor production.)

Experiments with linters in rats. Dry wads of cotton fiber, known as linters, from which this cellophane was manufactured, were imbedded in 50 Wistar albino rats. The linters were sterilized by autoclaving. No tumors resulted. In all instances in which histologic examination was carried out, a foreign-body reaction, never a sarcoma, was found. These experiments show that the carcinogenic agent was probably not the original linters from which the cellophane was manufactured.

Dry wads of sterile surgical cotton were inserted into 5 albino rats. After 468 to 634 days, no tumors resulted; only foreign-body reactions around the cotton fibers were found.

Results with alcohol-extracted cellophane in rats. As the nature of the carcinogen in the original cellophane was unknown, an endeavor was made to remove impurities by extracting the film as thoroughly as possible with hot methanol for 24 hours in a Soxhlet apparatus, kindly done by Dr. Hans T. Clarke. The extract itself when injected subcutaneously into rats, produced no tumors. On the other hand, sarcomas were produced in a high percentage of rats by imbedding the extracted film (called by us "cellophane B".) Results of imbedding alcohol-extracted cellophane ("cellophane B"):

No. of rats used		50
Shortest time of appearance of tumor		263 days
No. of rats surviving over 260 days		44
Total No. of malignant tumors		20
Fibrosarcomas	12	
Incipient sarcomas	3	
Liposarcomas	1	
Osteogenic sarcomas	2	
Myxoma (malignant)	2	
Tumors		45.4%

On removal from the rat the alcohol-extracted cellophane film usually showed opaque patches and was less flexible and more brittle than on insertion. In contrast, other plastic films appeared as transparent and almost as glossy after imbedding as on insertion.

Results with polyethylene film in rats and mice. A commercial polyethylene film, 0.002 mm thick, was first tested, as this was being used by surgeons; subsequently a specially prepared pure polyethylene was employed. Results with the commercial polyethylene were as follows:

No. of rats imbedded		98
Shortest time of appearance of tumor		392 days
No. of rats surviving 392 days		80
No. of malignant tumors		10
Fibrosarcoma	8	
Rhabdomyosarcoma	1	
Osteogenic sarcoma	1	
Tumors		12.5%

Polyethylene is not always a pure product. For example, it may contain dicetyl phosphate which is a violent irritant to tissues. Since it seemed possible that the carcinogenic action might be due to the presence of such additives or impurities, a very pure polyethylene was prepared with no additive of any kind. We have reason to believe that this polyethylene film is as pure as can be manufactured. The film on insertion was glossy and transparent,

TABLE I. Results of Imbedding Plastic Films, etc. in Rodents.

Material imbedded	Animals used	No. imbedded and surviving‡	Malignant tumors produced No.	Malignant tumors produced %	Transplants made	No. animals still alive
Cellophane (A) (original)*	Albino rats	42	15	35.7	To 5th tumor generation	0
"	" mice	35	8	22.8	4th	0
"	Black mice	23	1	4.3	3rd	0
Cellophane (B) after extraction with alcohol	Albino rats	44	20	45.4	2nd	0
Commercial polyethylene	" "	80	10	12.5	3rd	0
Pure polyethylene	" "	40	5†	12.5	1st	15
"	" mice	28	3	10.7	1st	1
Vinyl film	" rats	44	14†	31.8	2nd	5
Cotton linters	" "	50	0	0	—	0
Surgical cotton	" "	5	0	0	—	0
Glass cover-slips	" "	50	0†	0	—	23

* The experiments with this original Cellophane (A) appeared in our previous publication, and are included here for completeness.

† Incomplete.

‡ Surviving minimal time for tumor production.

and when removed from the animal after prolonged imbedding, showed little or no change.

Results of imbedding pure polyethylene film in rats and mice. To the present, this film on imbedding in rats produced 12.5% fibrosarcomas. Fifteen rats are still alive, about 20 months after imbedding the film. In another series of experiments with albino mice (Paris strain) 10% of fibrosarcomas were produced. Only one mouse is still alive 19 months after imbedding. It is possible, but improbable, after such long intervals that more sarcomas will appear in these animals.

Results of imbedding vinyl chloride film in rats. This is an opaque film. After imbedding the only obvious change was less flexibility. The results were as follows:

No. of rats imbedded with film		45
Earliest time of appearance of tumor		189 days
No. of rats surviving for over 189 days		44
No. of malignant tumors		14
Fibrosarcoma	12	
Liposarcoma	1	
Unclassified malignant sarcoma	1	
Five rats are still alive, about 22 months after operation.		
Tumors—to date		31.8%

Results of imbedding glass cover-slips in anterior abdominal wall of rats. Since cellophane, polyethylene, and vinyl chloride film all produce sarcomas in a variable percentage, and yet appear to have no common chemical factor to explain their carcinogenic effect, the question of chronic mechanical irritation arose. Therefore chemically-clean round glass cover-slips, approximately 0.2 mm thick and 18 mm in diameter, were imbedded subcutaneously in the anterior abdominal wall of 50 rats. At post-mortem examination these cover-glasses were occasionally found to be cracked or splintered. Up to the present, 12 to 14 months after insertion, no tumors have been produced, but 23 rats are still alive. These negative results, combined with those of experiments with linters and surgical cotton, afford avidence that the chronic irritation alone of these foreign bodies does not produce tumors. They also serve, in a measure, as controls for our positive results with plastic films.

A summary of the results of all our experiments is given in Table I. For the sake of completeness we have included the results of our previously published experiments on the original cellophane (called by us "cellophane A".) Throughout this series, tumors reported as artificially induced all arose at the site of imbedding of the plastic films. Among the 636 autopsies performed on these rodents, 13 spontaneous tumors were found, but these could not be confused with the artificially induced tumors, since they arose at sites other than the place of imbedding.

Discussion. The results of these experi-

ments are of both theoretical interest and possibly of some practical importance. At present we have no explanation of the mechanism by which the imbedding of these particular plastic films results in sarcomas of various types. Histologically these tumors resemble those obtained in rodents by the injection of benzpyrene; but the plastic films used here are all polymers, not aromatic hydrocarbons. One should recall that Turner(2) found accidentally that bakelite disks implanted for long periods in albino rats produced fibrosarcomas. As yet we have not found a plastic film which did not produce sarcomas, but other materials are now being tested with our technic.

The question of mechanical irritation and carcinogenesis is an old and broad one, and is still open. Our evidence does not favor mechanical irritation as the cause by itself of tumor production. In endeavoring to find an explanation for the carcinogenic effect of these films, differing as they do from one another in chemical composition and with no apparent common chemical factor, one obvious suggestion is that the tumor is caused by some impurity, such as an additive or plasticizer used in their manufacture. This explanation is rendered less likely by the finding that cellophane thoroughly extracted with alcohol, whereby most of such impurities would be removed, is at least as carcinogenic as the original film. Moreover, the pure polyethylene, without additives, produces about the same percentage of tumors as the commercial film. As to possible practical implications of these experimental results, it is known that plastics are now being used for a great variety of very useful purposes by surgeons. It must be emphasized again that so far there is no reported instance in which the imbedding of a plastic film in a human being has resulted in a malignant tumor.

Summary. 1. Sarcomas have been produced in rats by imbedding subcutaneously various plastic films, namely cellophane, an alcohol-extracted cellophane, a commercial polyethylene, a very pure polyethylene and vinyl chloride film. 2. Sarcomas have been produced in mice, but in a lesser percentage of cases, by imbedding cellophane and pure polyethylene film. 3. Apparently impurities and additives in the films do not account for the production of these malignant tumors. 4. So far every plastic film tested has produced sarcomas in a certain percentage of instances. 5. Other foreign bodies, such as linters, surgical cotton and glass cover-slips similarly imbedded in the anterior wall of rats have not produced malignant tumors. 6. No adequate explanation of the mechanism of this carcinogenic effect of imbedded plastic films has been found. 7. The experiments have been limited to rats and mice.

Conclusion. A group of agents, all polymers, and differing from previously known carcinogens, has been found to be carcinogenic for rats and mice.

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