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T R A N S L A T I O N

CANCEROGENIC EFFECT OF SYNTHETIC FILMS.

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1. In conformance with Oppenheimer it has been determined that films from regenerated cellulose are cancerogenic when implanted in rats.

2. Crushed glass wool did not produce any cancer in control tests.

3. Films extracted with boiling benzene and pure films of regenerated cellulose produced without any addition, had the same cancerogenic effect as the commercial product.

4. The observed cancerogenic effect of the films is compared with the effect of polymeric silicates which produce "silicosis" and the effect of asbestos causing cancer, of bifunctional methylene diamides, ethyleneimines, epoxides, as well as N-mustard-gas compounds, and related to the fact that functionally important cell proteins are cross-linked with the linear macromolecules by residual valences (hydrogen bonds) and are changed in this way.

5. The cancerogenic activity of polyamide films to be expected according to the above, is determined on rats.

After implanting platelets of the plastic "bakelite" under the skin of rats, Turner (1) observed the local formation of sarcomas. For this reason we have examined, whether also other plastics have a cancer-producing effect. We shall briefly report about the results of the experiments begun in 1949, which were carried out on a total of 281 rats.

Several small discs of the size of a pfenning of commercial film of regenerated cellulose (hydrocellulose) were implanted under the skin or the abdominal cavity of rats of our inbred strains BD I and BDIII, in which since 1937 never spontaneous sarcomas were observed. A total of 13 of the 50 rats which lived longer than one year developed local sarcomas** (Fig. 1-3*).

Before us, Oppenheimer (2), who also observed sarcomas on rats after implantation of cellulose films, obtained the same results. His results, about which we only learned about 2 years ago, agree with ours in all points.

The cancer-producing effect of the cellulose film proved with it, cannot be related to contaminations or additions, since we found extracts, which were produced from the films with boiling benzene, not to be cancerogenic effective. Whereas films previously extracted with benzene propagated cancer (Fig. 2), the same as the initial material and the films, which were manufactured for this purpose from regenerated cellulose without any addition (Fig. 3). Thus, the cancer-producing effect has its origin in the polymeric hydrocellulose itself.

The growths become apparent between the 190 and 600 day after implantation. If the latter was made under the skin, mostly an individual larger cancer gland was produced, in whose necrotic cavity the platelets rested (Fig. 1). The rats, in whose abdominal cavities the platelets were implanted, usually showed numerous smaller sarcomas, which originated at any place where the platelets might have rested (Fig. 2 and 3). On dissection, the platelets usually rested freely in the abdominal cavity and even after 15 months seemed to be unchanged. According to that, the cancerogenic activity of the films must be great. To excite cancer, it seems that a period of direct contact is sufficient, which is considerably shorter than the latent period until the appearance of the growths.

In experiments in which comminuted films had been fed, we observed so far after 2 years a case of lymphatic leukemia (lymphosarcoma) with malignant infiltrates in the lymphatic gland, the liver, spleen and lung.

Control tests, in which we implanted crushed glass wool into the abdominal cavity of 12 rats, produced no growth. Thus, corresponding to the general experimental experiences, the chronical, mechanical irritation in itself is not cancerogenic. Thus, the cancerogenic effect of the films must be related to the substance of the film.

The linear, macromolecular main valence chains of cellulose are linked into a micellar bond by secondary valence forces, whose orientation varies and is not defined. The films swell in water, however, solution in the body fluids is almost inconceivable. At the surfaces of the films, on the other hand, linkage forces are free, by which, for example, dyes may be strongly bound. The fact that fluorescent substances cannot be washed from the films, is even used as distinguishing feature for hydrocellulose films from films of other types (3).

This fact insinuates that also linear cell proteins, which in suitable orientation come into sufficiently close contact with the swollen film surface, may be very firmly bound by the linear macromolecules of synthetic resins, for example by hydrogen bonds, and that in this way the cancerous degeneration of the cells is effected. Also splitting off of individual molecules of the syn-

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thetic substances linked to a cell protein from the surface seems possible. Regeneration of the active surface would simultaneously be in connection with it.

Numerous observations made recently speak in favor of such a mechanism. Earle (4) found on tissue cultures, which were cultivated on hydrocellulose films, in vitro a "spontaneous" canceration of normal cells, which was proved by retransplanting the cultures on animals of the same species. According to the findings of Oppenheimer (2) and ours, we believe it possible that the observed canceration also in this case must be attributed to the synthetic films.

A similar effective mechanism must be assumed for the silicates which produce "silicosis" (5). Monomeric and amorphous polymeric silicates do not produce any silicosis, whereas crystalline polymers, i.e. the faster and the more so, the higher the orientation in the silicates (5). The charge design ("Ladungsmuster") of the crystallites surprisingly agrees with that in collagen. Also in this case it is assumed as probable that cell proteins are bound at the surface by linear polymeric silicate molecules and that the aggregates formed may split off, the active surface being again regenerated (6). In the mean time, the relatively good solubility of the surface layers of quartz particles was proved (6a). Detecting of silicic acid in the body fluids in itself speaks for a solution. The quartz particles may pass from cell to cell and thereby change the latter, without losing their activity (W. Giese, cited according to Jaeger (5)). The "silicosis"-producing effect pharmacologically agrees with the cancer-producing effect in that both are irreversible and are manifested in man and cause death, often only decades after exposure.

In asbestos, which likewise is insoluble in the body and, in spite of that, in men as well as experimentally in animals produces lung cancer, we find another example for the cancerogenic activity of polymeric substances of linear macromolecules.

According to most recent examinations, the same effective mechanism has become probable also for four other classes of substances, which have a "radiomimetic" effect on cells, and which are cytotoxic as well as mutagenic and cancerogenic, i.e. methylene amide, ethyleneimine, epoxide and the nitrogen-mustard-gas compounds which may be changed in vivo into ethyleneimines or epoxides (Table 1).

Some substances of this kind were used in Germany for a rather long time for finishing textiles. They produced permanent changes in cellulose or protein fibers, i.e. due to the fact that they are bound by residual valences alongside the fibers or produce cross linkages. With these substances, in vitro also changes are observed in nucleic acids (9). When they act on dividing cells, they produce obvious abnormalities on chromosomes (10), which correspond to those after radiation effect ("radiomimetric effect").

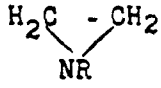
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Table 1. Cancerogenic substances (according to Hendry (14)).

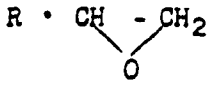
Methylene amide:

$$HOH_2C \cdot NH \cdot R \cdot NH \cdot CH_2OH$$

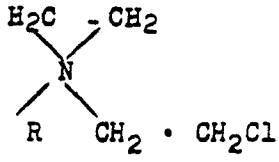
Ethyleneimine:

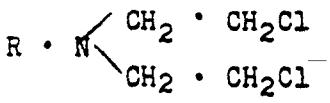


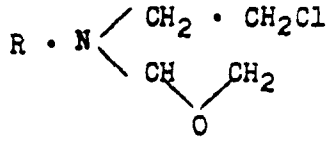
Epoxide:



N-mustard-gas compounds:

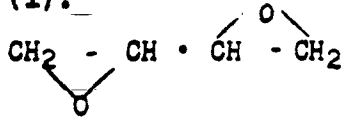






Bifunctional molecules, i.e. the bis-methylene-amides, bis-epoxides, bis-ethyleneimines and bis-(chloroethyl)-alkyl-amines (11) have an especially cancerogenic effect. In vitro, these substances probably give radicals, in any case, they readily form linear polymers.

The cytotoxic, mutagenic and obviously strong cancerogenic effect of this kind of substances is related to the fact that the monomers in the body form linear polymers, which then, as in vitro has been observed with cellulose, proteins and nucleic acids (9), are cross-linked or are longitudinally bound with functionally important proteins or nucleoproteins of the cell, which possess "duplicating" properties, and in this way irreversibly change or block them (11). That such polymerizations can actually take place in the body, i.e. also such which in vitro only take place with catalysts, was recently proved by the example of the acrylic amide (12), i.e. a basic substance for important plastics. So far acrylic amide has not been examined as to its cancerogenic effect. The simplest cancerogenic substance from this series is the butadiene-diepoxide (13) (I).

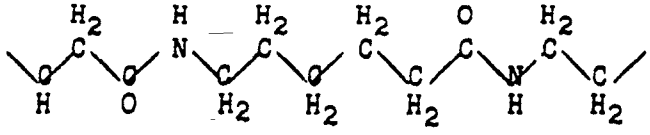


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The polymers of the most active substances of these series show distances of 3.7 to 7.5 Å between the atoms capable of forming bridge rings, which correspond to those between the purine or pyrimidine nuclei in nucleic acids (14). However, this is not strictly so, also substances with deviating distances are still effective. On the other hand, substances whose polymers do not have any capability to form bridge rings, are inactive. Thus, it is probable that not only the presence of free residual valences, more exact: of π -electron or proton donors is essential for said pharmacological effect, but also its spatial orientation, for example their linear distance from each other in the polymers.

Hendry and collaborators discuss such an effective mechanism also for the cancerogenic aromatic hydrocarbons and amines (11). We have showed at another place (15) that the properties of aromatic amines, which define their cancerogenic activity, in many points correspond to the properties of dyes, which stipulate their "substantivity", i.e. their capability to be "directly" absorbed by linear cellulose fibers (16). Such viewpoints seem to be important for pharmacology, because the essential functionaries in the cell probably are above all the linear macromolecules with "duplicating" property.

The presence of residual valence forces in the synthetic substances must be assumed as prerequisite for the binding of the cell to linear macromolecules. Therefore, we have examined a polyamide film, which according to the above should be active, as to its cancerogenic effect, i.e. ε-caprolactam films (II).

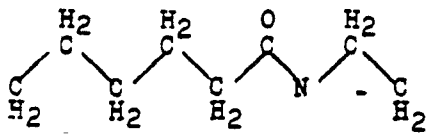


Structure of ε-caprolactam polymer.

5 pieces each of film of the size of a pfennig were implanted into the abdominal cavities of 9 rats. After 360 days, 6 animals were still alive. Four of them have since developed multiple and verymalignant sarcomas, which were distributed over the entire abdominal space (Fig. 4*). The effect corresponds entirely to that of cellulose films and seems to be even greater than that one.

Hendry (11) reports in a supplement to his last article, that the caproyl-ethyleneimine (III) closely related to the ε-caprolactam polymer is strongly cancerogenic. Orientation experiments with some synthetic textiles, such as Orlon, nylon and Perlon fabrics were negative so far, although the observation time was more than 16 months. Since these fabrics differ only in their structure and hardly chemically from the corresponding films, it

Caproyl-ethyleneimine (III)



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must be assumed as possible that also the mechanical injury of the cells by the sharp edge of the film plays a part in its cancerogenic effect and possibly initiates it. By itself, however, the chronical, mechanical irritation cannot produce cancer, as was proved again by the negative results from our control tests, in which crushed glass wool had been implanted. Therefore, the substantial effect of the films must be the essential factor. Thus, the mechanism of this cancerogenic effect of linear polymers may be similar to that in the infection with Rous-sarcome virus, which likewise assumes injury of the cells (18). The mentioned problems may be examined experimentally.

Based on the present findings, it must be requested that polymeric synthetic substances must be used as plastic masses in surgery only after thorough examination in endurance tests on animals. The plastics which are found to be cancerogenic must not be used for this purpose.

Supplement by the correspondent: Recently Oppenheimer and collaborators (19) reported about further findings with plastics on rats and mice. Genuine cellophane films produced in about 36% of the cases sarcomas, films previously extracted with alcohol even in 45%. On the other hand, the alcohol extract was ineffective. Control tests, in which glass platelets or cotton were implanted did not produce cancer. These results are in conformance with ours. Vinyl-chloride films were about as effective as cellophane films, polyethylene films, on the other hand, distinctly weaker (13%), as had to be expected according to the conceptions developed about the importance of groups capable of binding bridges for the activity.

Notes.

* Fig. 1-3, see Table (illegible).

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The work was made possible by the Deutsche Forschungsgemeinschaft.
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