severe damage to occur 4 or 5 miles away from the site of ground applications. There have also been cases where insecticides have been contaminated with minute amounts of 2,4-D. In one such case an insecticide manufacturer paid damages of $50,000 to a large cotton plantation owner for such alleged damage.

In many cases the manner by which the herbicide drifted onto the susceptible crop is almost inexplicable. There have been cases where severe damage occurred to cotton that was up-wind from the site of 2,4-D application. The only explanation is that later air currents picked up the herbicide and transported it. Another rather amazing case occurred in the South during 1953. Cotton was damaged by 2,4-D that was applied before the cotton was planted. What appears to have happened is that the herbicide was applied to control willows. The season was dry, and the chemical collected in the dust and soil. Later, winds picked up the contaminated dust and carried it for many miles to damage cotton.

In order to determine just how much 2,4-D is required to cause damage to cotton, the Mississippi Agricultural Experiment Station ran some tests last year. It was found that less than ½ g/acre was sufficient to cause deformation of the leaves of seedling cotton. This is an infinitesimal amount when it is considered that it is spread over an acre. Some types of 2,4-D are much more volatile than others, but the fact remains that any of them may be carried by air currents for considerable distances and that after leaving the spray nozzle they are no longer under human control.

The result of all of this is that various states have passed regulations in an attempt to reduce the damage caused by 2,4-D, 2,4,5-T, and related hormone-type herbicides. Some states even require that all sales of these compounds be recorded as in the case of narcotics. Texas requires that a $20,000 surety bond be posted before permission may be obtained to apply 2,4-D. Other regulations specify minimum distances from susceptible crops.

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Malignant Tumors and High Polymers

A possible explanation of "Malignant Tumors Resulting from Embedded Plastics in Rodents" (*1*) is that many high polymeric materials contain free radical groups as the result of residual initiator, enclosure of growing chains, or pyrolysis or peroxidation of polymer or plasticizer during calendering or molding. In the case of cellophane, radical-forming groups are introduced in the xanthane stage. By transfer of unpaired electrons to (or capture from) molecules in surrounding tissues, free radical chain reactions would be started identical to those initiated, for example, by x-radiation or radioactivity. Many, if not all, carcinogens are compounds capable of forming free radicals (*2*).

If such be the case, the following predictions may be made as to the relative carcinogenicity of polymers and should serve as a basis for testing this hypothesis.

a. The most actively carcinogenic resins should include proliferous ("popcorn") polymer (*3*), because of its extraordinary reactivity, and products of negative free radical initiation by metallic sodium (*4*), hydroquinone and diazoamino-benzene (*5*), or other reducing agents, because of the reduced probability of termination by initiator or growing chain radicals of like charge.

b. The usual peroxide-initiated addition polymers should possess the same order of magnitude of carcinogenicity regardless of their functional groups or chemical reactivity.

c. Polyvinyl alcohol (*6*) and acetals (*7*) might be expected to contain fewer free radicals than polyvinyl acetate because of the alcoholysis and acetalization steps in their preparation.

d. Ionic polymerization, initiated, for example, by aluminum chloride (*8*), should give resins of low carcinogenicity, as should condensation polymerization of polyesters and polyamides.

It must be pointed out that oxidation and pyrolysis during high-temperature processing could alter the content of polymeric free radicals. Preferably, films for the proposed experiments should be cast from solution in solvents other than ketones or ethers.

It might be questioned whether Dr. Oppenheimer's two principal limitations on the free-radical hypothesis, the problem of transport and carcinogenesis by condensation polymers, might not be explained by chain transfer reactions within the body and by peroxidation at secondary or tertiary carbons during processing, respectively. In the case of nylon, a possible course of the latter would be:

$$-CH_2-CO-NH- \xrightarrow{O_2} -\dot{C}H-CO-NH- \xrightarrow{O_2} -CH(OO\cdot)-CO-NH-$$

$$\xrightarrow[RH]{} -CH(OOH)-CO-NH- \rightarrow -CH(O\cdot)-CO-NH- + HO\cdot, \text{ etc.}$$

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REFERRING to the comment by Andrew F. Fitzhugh dated September 16, 1953, we would like to submit the following: The appearance of tumors of malignant character adjacent to or surrounding embedded synthetic high polymers would seem to indicate the diffusion of carcinogenic agents into neighboring cells,

or the removal of tumor inhibitors by adsorption to the plastic. Thinking along these lines, the possibility presents itself that free radicals or free radical-yielding substances are involved. This is particularly pertinent in view of the prevailing polymerization techniques using radical-delivering catalysts, and in view of the existence of free radical mechanisms in the living cell, as pointed out by Waters (*1*) and others. In this respect we are in full agreement with the views of Col. Fitzhugh; in fact we have initiated and carried out for more than a year an experimental program to test this possibility. The program includes the use of polymers of different degrees of radical or peroxide contamination, and of different tendencies as carriers of long-lived radicals (as shown by their ability to continue to polymerize). We are also using the radioactive tracer technique to follow the path of sources of potential radicals leaving the polymer.

Because of the slow character of the work no conclusive results are as yet available. It does not, however, appear that Col. Fitzhugh's and our own expectations are borne out, since apparently there is no correlation between the carcinogenic effectiveness of synthetic polymers and their tendency to include, carry, or release free radicals. There is, for instance, an appreciable carcinogenic activity with condensation polymers.

The real difficulty in our investigation, not touched upon by Col. Fitzhugh, lies in the problem of transport. If a radical were to cover the distance, substantial in terms of molecular dimensions, from polymer to the site of the cancer, it would be extremely unlikely to survive. Similarly, a chain process, whereby unpaired electrons would be transferred, is difficult to conceive in view of the large number of steps and components involved. The agent must further be conceived to be of low molecular character so as to penetrate cell membranes.

The conclusion remains that the agent, if a free radical, must be a very stable one, possibly an ion radical, or a molecule that is liable to turn into a radical or participate in radical reactions once it reaches the interior of the cell. The agent might be derived from monomer, catalyst, or catalyst derivatives, products of oxidation or interaction with the bathing lymph fluid. The best clue as yet lies in the observation, so far uncontradicted, that only synthetic high polymers seem to be carcinogenic. This limits explanations based on free radical theories to addition polymers. The carcinogenicity of synthetic condensation polymers would demand a different mechanism and might possibly be attributable to an intrinsic activity of some monomeric constituents or their derivatives.

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Fashions in Medicine and Science

H. J. Morowitz (*1*) has illustrated fashion in science by an elegant and impressive method; the number of papers published per year (about the biological effects of radiation) was shown to follow a rapid rise and then an almost exponential decay as a function of time.

Penrose (*2*) a while ago made use of the same method to illustrate fashion in medical therapy. His example dealt with the use of thallium in the treatment of skin diseases.

It is interesting to observe some of the differences between these two mental epidemics. A longer lag time previous to the rapid rise in the number of papers as well as a longer decay period seem to be characteristics of fashion in medical therapy; further features of the latter are the favorable description of the results obtained during the rapid rise period and a preponderance of critical papers coinciding with the slow decline or period of "increasing immunity to the idea of the treatment."

Speculations about the factors contributing to the above observed differences are left to the reader.

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