

It has been known for a long time that tar workers and chimney sweeps are very often victims of cancer. Many cases of industrial cancer can be traced to tar. In 1915 two Japanese workers demonstrated that on application of tar to the skin of rabbits for from 9 to 12 months symptoms of cancer were produced. Through the work of Kennaway in 1924 and 1925 and Mayneord in 1927 the carcinogenic compounds in tar were identified as belonging to the condensed ring systems, the similar type which was later shown to have estrogenic activity. Cook and Dodds actually found that many of the compounds which had estrogenic activity also had carcinogenic activity. As pointed out by Dodds the same criterion of structure for estrogenic activities seems to hold for carcinogenic activity. There are, however, compounds having carcinogenic activity which do not have estrogenic activity and *vice versa*. A very interesting example is calciferol, which possesses estrogenic activity but not carcinogenic activity. A very potent carcinogenic compound isolated from coal tar is 1, 2-benzpyrene. In a paper last year Rofo showed that rats subjected to ultra-violet irradiation over a period of from 7 to 8 months developed tumors (carcinomas and sarcomas). Accompanying the malignancy there was a local increase in cholesterol in the same regions.

The phenanthrene nucleus is found in the opium alkaloids, morphine and codeine and their derivatives. Work on these compounds is going on in the laboratory of Eddy. The recent investigations of Jacobs and Elderfield have shown the cholane nucleus in the digitalis aglucones.

Among the principles isolated from toad poisons are compounds which have been shown in the laboratories of Wieland and of Chen and Chen to belong to the cholane ring system. Bufotoxin gives on hydrolysis suberyl arginine and bufotalin. The latter on hydrolysis and reduction gives cholic acid.

HAROLD P. LUNDGREN

MEDICAL SCHOOL

UNIVERSITY OF MINNESOTA

THE PRESENCE IN SELF-BLANCHING CELERY OF UNSATURATED COMPOUNDS WITH PHYSIOLOGICAL ACTION SIMILAR TO ETHYLENE¹

THE characteristic petiolar curvature of the leaves of tomato plants that is produced in the presence of low concentrations of certain substances having carbon-to-carbon double linkages may be used as a highly sensitive qualitative test for the presence of these compounds. Crocker² states that the test is sensitive to

one part in ten million of ethylene. This test was used in an attempt to ascertain whether or not an unsaturated compound is present in the blanched areas of celery.

The celery used was of the Golden Self-Blanching variety grown in the greenhouse in eight-inch pots. Harvey³ has pointed out that the appearance of the leaves of this variety is frequently such as to indicate the presence of mosaic virus in the self-blanching leaves. Stalks and leaves were used when in such condition that the stalks were white and the leaves yellow, mottled with green. The tests were conducted in a building in which there were no illuminating gas connections in order to exclude an external source of unsaturated hydrocarbon. In some cases potted tomato plants were used; in others, the severed top of a tomato plant was placed in water and used. Suitable curvatures were obtained by either procedure.

Fifteen to twenty grams of stalks and leaves of Golden Self-Blanching celery were cut into pieces about an inch long without bruising and placed in a desiccator. The desiccator was evacuated at once to a pressure of about thirty millimeters of mercury with a vacuum pump and placed for two hours in an icebox kept at 12° to 14° C. At the end of this time it was connected by means of a one-inch section of rubber tubing to a bell jar containing a tomato plant. The pressure in the bell jar was reduced to half an atmosphere, and the gases contained in the desiccator were forced into the bell jar by filling the desiccator with tap water. Atmospheric pressure was restored in the bell jar, all connections were sealed, and it was allowed to stand for two and one half hours in a warm (25° to 30° C.) place out of direct sunlight. At the end of this time observation was made to determine whether any curvature of the leaves was produced.

In eight out of ten tests made upon celery which was strongly blanched, a marked curvature of the top-most leaf of the tomato plant was produced, with the lower leaves showing progressively less curvature.

The same procedure was carried through with the same apparatus but without the blanching celery. In no case was the characteristic curvature observed. In another series of experiments grass-green Winter Queen celery was used in place of the naturally blanching celery, with the result that no curvature was produced. This indicates that only celery which is in the blanching condition produced detectable amounts of the substance responsible for the curvature.

Since little was known as to the specificity of this test for unsaturation, a number of compounds were tested to determine whether or not they would produce the reaction. Propylene, butylene and

¹ Published by permission of the director of the Agricultural Experiment Station as Journal Series Paper No. 1337.

² Wm. Crocker, *SCIENCE*, 75: 1948, Suppl., p. 11. 1932.

³ R. B. Harvey, *Minn. Agr. Expt. Sta. Bul.* 222, 1925.

amylene, homologues of ethylene; mesityl oxide, $(\text{CH}_3)_2\text{C}:\text{CHCOCH}_3$, an unsaturated ketone; and vinyl acetate, $\text{CH}_3\text{COOCH}:\text{CH}_2$, an ester of an unsaturated alcohol, all gave positive reactions.

Dichloroethylene, $\text{CHCl}:\text{CHCl}$; trichloroethylene and tetrachloroethylene failed to give the reaction. This is undoubtedly accounted for by the fact that a substituent on a double bond carbon affects the reactivity of the double bond, which seems to be necessary to produce the reaction.

Acetone, acetaldehyde, diethyl ether and chloroform failed to give the reaction.

From these facts it seems likely that some gaseous or volatile unsaturated hydrocarbon or similar compound is present in Golden Self-Blanching celery during natural blanching of the leaves. The celery, Winter Queen, which is not self-blanching, does not produce such substances. It seems indicated therefore that the disappearance of chlorophyll from self-blanching celery is accomplished by some process similar to that by which celery is commonly blanched artificially by application of ethylene in low concentrations.⁴

R. C. NELSON

R. B. HARVEY

MINNESOTA AGRICULTURAL EXPERIMENT
STATION

NEW CANCER-PRODUCING HYDROCARBONS

Two hydrocarbons, belonging to series not hitherto known to be active as agents for cancer production, have been found to cause malignant growths in mice. These two compounds are sym.-triphenylbenzene and tetraphenylmethane. Their action is slower than that of the substances discovered by Cook¹ and coworkers. A specific strain of mice was treated to weekly injections amounting to 1 cc of a 5 per cent. solution of triphenylbenzene in sesame oil. In a year's time 12 out of 60 mice had well-developed tumors of a highly malignant type. In the case of tetraphenylmethane 25 mice were painted twice weekly with a 0.5 per cent. solution in benzene. After the same period well-developed epitheliomata were present in 8 cases. It is interesting to note that the percentage of positive results is relatively high in spite of the long time necessary to induce the growth.

The interest which these results arouse is chiefly in the complete lack of resemblance of these new compounds to the hydrocarbons discovered by Cook. The

⁴ Since the work described was completed for publication, it came to the authors' attention that R. Gane had published in *Nature*, December 29, 1934, Vol. 134, p. 1008, a paper entitled "The Presence of Ethylene in Some Ripening Fruits."

¹ Cook, Hieger, Kennaway and Mayneord, *Proc. Roy. Soc.*, B, 111: 455, 1932; Cook, 485.

compounds² investigated by him had condensed ring systems containing 4 to 5 aromatic rings in the molecule and possessed a phenanthrene nucleus. He found that the ring system of 1, 2-benzanthracene³ is present in many cases, although not absolutely necessary. He also observed a possible relationship⁴ with the dehydrogenation products of the sex hormones and bile acids. Triphenylbenzene and tetraphenylmethane possess nothing in common with the properties listed above, except that each contains 4 benzene rings. The significance, if any, of this point is not evident at present. Any other structural similarity is lacking, for there is a complete absence of condensed ring systems or a phenanthrene nucleus in the two new agents. Neither may they be derived from the sex hormones or the bile acids.

In triphenylbenzene a single ring holds three other benzene rings attached in the 1, 3, 5 positions, but in tetraphenylmethane no benzene ring is attached to another. The linkages in this last instance are through a central carbon atom. In an effort to find a common ground on which these widely different classes of carcinogenically active agents can stand we may make the tentative assumption that in the hydrocarbons so far discovered the property of producing cancer resides in the benzene nucleus as modified or affected by substituents attached in either the condensed or open manner. Work is now in progress to limit more exactly the nature and position of the substituents. We are also investigating the higher phenyl homologues of the above-named series in the expectation that they may be more active still in causing tumorous growths.

The work is being conducted under a joint program of research of the Evans Memorial Hospital of Boston and the Massachusetts Institute of Technology at Cambridge.

AVERY A. MORTON

DANIEL B. CLAPP

MASSACHUSETTS INSTITUTE OF
TECHNOLOGY

CHARLES F. BRANCH

EVANS MEMORIAL HOSPITAL

THE FORMATION OF CARBOHYDRATE FROM GLYCEROPHOSPHATE IN THE LIVER OF THE RAT

GEMMILL and Holmes¹ reported recently that the carbohydrate content of liver slices from butter-fed rats increases during 3 hours' incubation in bicar-

² Cook, *Proc. Roy. Soc.*, B 113: 273, 1933.

³ Cook, *Jour. Chem. Soc.*, 1592, 1933.

⁴ Cook, *Proc. Roy. Soc.*, B 113: 273, 1933; Cook and Haslewood, *Jour. Chem. Soc.*, 428, 1934.

¹ C. L. Gemmill and E. G. Holmes, *Biochem. Jour.*, 29: 338, 1935.