Abstracts

Abstracts are grouped under the following main headings: Reports of Experimental Research, Comparative Oncology, Clinical and Pathological Reports, Statistics, and Cancer Control and Public Health. Subheadings are used in accordance with the subjects of papers abstracted.


Reports of Experimental Research

Carcinogenic Compounds


The somatic mutation theory is accepted as the most plausible explanation for cancer, the strongest support for this being the parallelism between the effect of both x-ray and ultraviolet light on mutation and cancer. If a parallelism between mutation and cancer production by carcinogenic hydrocarbons could be established, the mutation theory of cancer production would be strengthened. These experiments were designed to detect any effect of carcinogens on the mutation rate in Drosophila melanogaster. Preliminary experiments in which carcinogens were fed yielded negative results. Adults and larvae were used, the former with greater success. Methylcholanthrene crystals were inserted mid-dorsally, and colloidal solutions of 1,2,5,6-dibenzoanthracene (0.3%) and 9,10-dimethyl-1,2-benzanthracene (0.06%) suspended in Ringer’s solution as given by Ephrussi and Beadle (Am. Nat., 70:218-225. 1936) minus calcium plus 0.5% gelatine were injected mid-dorsally and laterally. The incidence of sex-linked lethals was taken as a criterion of the mutation rate. These were detected by the CIB method in the males. Females injected were heterozygous for sc wu b v and wc bg v od car. They were crossed to v Br males, and the female F1 were individually mated. The absence of av and ad males in the F1 progeny was taken as indicating the presence of a lethal in the treated or control female. No significant increase in mutation rate was found when single or multiple doses were used. The average amount injected was less than 0.27. There was a sex difference in the spontaneous mutation rate in the stocks used. The author accepts Sacharov’s explanation for cancer, the strongest support for this being the parallelism between the effect of both x-ray and ultraviolet light on mutation and cancer. If a parallelism between mutation and cancer production by carcinogenic hydrocarbons could be established, the mutation theory of cancer production would be strengthened. These experiments were designed to detect any effect of carcinogens on the mutation rate in Drosophila melanogaster. Preliminary experiments in which carcinogens were fed yielded negative results. Adults and larvae were used, the former with greater success. Methylcholanthrene crystals were inserted mid-dorsally, and colloidal solutions of 1,2,5,6-dibenzoanthracene (0.3%) and 9,10-dimethyl-1,2-benzanthracene (0.06%) suspended in Ringer’s solution as given by Ephrussi and Beadle (Am. Nat., 70:218-225. 1936) minus calcium plus 0.5% gelatine were injected mid-dorsally and laterally. The incidence of sex-linked lethals was taken as a criterion of the mutation rate. These were detected by the CIB method in the males. Females injected were heterozygous for sc wu b v and wc bg v od car. They were crossed to v Br males, and the female F1 were individually mated. The absence of av and ad males in the F1 progeny was taken as indicating the presence of a lethal in the treated or control female. No significant increase in mutation rate was found when single or multiple doses were used. The average amount injected was less than 0.27. There was a sex difference in the spontaneous mutation rate in the stocks used. The author accepts Sacharov’s results of treating Drosophila eggs with methylcholanthrene as being encouraging but not significant. There are no tables or figures in the paper.—W. J. B.


Tests for carcinogenic activity have been carried out with about 70 compounds, which are mostly new substances synthesized for this purpose and related to known carcinogenic compounds. The compounds tested were derivatives of 1,2-benzanthracene, cholanthenne, 3,4-benzpyrene, 3,4-benzphenanthrene, acridine, and fluorene. These were given by application to the skin, by injection subcutaneously, and in some cases by the mouth. The results support the view that there is a definite association between molecular structure and carcinogenic action. Thus in the 3,4-benzphenanthrene series, which has not hitherto been investigated extensively, positions 1 and 2 seem to be positions for substitution which are more favorable than are 6 and 7. The capacity to produce epithelioma does not always run parallel with the capacity to produce sarcoma.

A preliminary study has been made of the occurrence of tumors of the lung and stomach in mice receiving these compounds. The derivatives of 3,4-benzpyrene, and of acridine and fluorene, appear to produce tumors of the lung more readily than do the compounds derived from 1,2-benzanthracene. Of the derivatives of 1,2-benzanthracene, the 5-n-butyl, 5-n-amy1, and 5-n-hexyl compounds appear to be most active in producing tumors of the lung, while they are deficient in power to produce sarcoma. None of the dibenzfluorenes tested produced sarcoma. Tumors of the stomach occurred most frequently in mice receiving acridines, and these compounds can produce sarcoma. The authors emphasize that much further study of these multiple tumors, and of tumors remote from the site of application, is necessary before any conclusion can be drawn as to their causation. For this investigation strains of mice are required in which the spontaneous incidence of all such tumors is known.—E. L. K.


Series of mice were painted on the skin with benzpyrene (0.3% in benzene) for varying periods and with varying frequency. Fluorescence tests indicated that an application of hydrocarbon persisted for 4 days. Painting every 8th day (i.e. skin free from benzpyrene every alternate 4 days) for 6 months gave as many tumors as did painting biweekly for 3 months, although this 8th day painting lengthened the latent period. Biweekly painting gave in 1 month no tumors; in 2 consecutive months 6 tumors in 17 mice; in 3 consecutive months 18 tumors in 20 mice. Three series were then painted biweekly thus: 3 months’ painting separated by intervals of 1 month; 3 months’ painting separated by intervals of 2 months; 3 months’ painting separated by intervals of 3 months. The yield of tumors was the same in each of the 3 series, 9 tumors in 19 mice, although the latent period lengthened pari passu with the separation period between the painting months.

The authors draw attention to the danger of working with hydrocarbons since contact with the skin initiates changes which are not reversed after the apparent disappearance of the hydrocarbon.—I. H.

Chemical and biological relationships of cholesterol to carcinogens are discussed. Since conversion of a 4-membered ring structure to a penta-cyclic carcinogen requires two steps: (1) the formation of a new ring by cyclization of the sterol side chain, and (2) the dehydrogenation of the olefinic rings to aromatic rings, Bergmann suggests that it can be assumed that only those steroids with side chains long enough to form a new ring can serve for the biological suggestion of formation of carcinogens. Experimental evidence for step (2) is discussed. The relation of substitution at positions 5,6,9, and 10 in the benzenanthracenes to carcinogenic activity is discussed and it is pointed out that a compound, as yet unknown, worthy of investigation for carcinogenic activity is the 7,9 methyl cyclohexane derivative of methylcholanthrene, named "steranthrene" by Bergmann. Steranthrene is pictured as being readily formed from cholesterol by the 2 steps mentioned. It contains all the carbon atoms of cholesterol except the angular methyl group. Since it is practically all adsorption from benzene solutions on alumina. Tests where the 99% to be accounted for, a large part was eliminated as the fluorescent derivative with substitution at positions 5,6,9, and 10, the compound should prove to have high carcinogenic activity.

Roffo's theory of the conversion of cholesterol into carcinogenic substances by ultraviolet light is discussed. Unpublished results by Bergmann and Strong have shown that cholesterol irradiated with ultraviolet light possesses no carcinogenic properties in mice when applied in benzene solution to the skin, or injected in oil subcutaneously. The high incidence of neoplastic changes in the digestive tract of rats fed irradiated or cooked diets high in cholesterol, reported by Roffo, does not necessarily mean that cholesterol takes on carcinogenic properties after heat or light treatment.-P. P. C.


Data are given on the elimination of benzpyrene, partly unchanged and partly in the form of a fluorescent derivative, in the bile and excreta of the fowl and rat after intravenous or subcutaneous injection. The 2 compounds can be separated by alcohol and acetone extraction followed by chromatographic adsorption from benzene solutions on alumina. Tests where known amounts of benzpyrene were added showed that this method for assaying the unchanged hydrocarbon gave a recovery of 90%. Three rats were given 20 mgm. benzpyrene each in olive oil, subcutaneously, and the pooled excreta collected over 1 month when these no longer gave fluorescent extracts. It was found that 1% of the total benzpyrene injected had been eliminated unchanged, chiefly in the feces. Of the 99% to be accounted for, a large part was eliminated as the fluorescent derivative, and some was still encapsulated at the site of injection, as seen by the fluorescence of the tissues in ultraviolet light.—I. H.


The azonaphthalenes studied in this paper are structurally related to certain dibenzazabases andazo compounds known to be active in producing neoplastic changes in the livers of mice. The following compounds were administered to 444 mice, either by feeding, painting the skin, or by subcutaneous injection: 2,4'-azonaphthalene; 4,2'-azonaphthalene; and 2,4'-diamino-1,1'-dihydathyl. It was found that 2,2'-azonaphthalene and its reduction product 2,4'-diamino-1,1'-dihydathyl induce new growth in the liver either of a cholangiomatosus or hepatomatous character. The other compounds showed little or no activity. Structurally corresponding azonaphthalenes and dibenzazabases corresponded also in their ability or lack of ability to produce neoplastic changes in mouse livers. However, the ability of 3,4,5,6-dibenzazaborole to produce sarcomas at the site of application was not reproduced by the corresponding azonaphthalene. Large members of other organic molecules were tested on mice for their effects on the liver. The only group being active was that containing derivatives of 3,4-benzphenanthrene. Finally, a group of water-soluble azo dyes used extensively in Great Britain for coloring food stuffs was tested, again on mouse livers, without positive result.—I. L. W.


Preliminary observations on the interactions of carcinogenic and related hydrocarbons with various sterols in surface films of the 2 classes of substances on water have been published (Am. J. Cancer, 36:98-109. 1939: 37:453-454. 1939). This paper reports a more intensive investigation of the properties of hydrocarbon-sterol mixed films with special reference to the role of these solutions and molecular associations in the biological effects of carcinogenic hydrocarbons. The apparatus and procedure for making force-area curves were the same as those previously described. A large number of sterols and hydrocarbons, including 1,2,5,6-dibenzanthracene and 20-methylcholanthrene, were studied. In some experiments a kymograph was used to make an automatic permanent record of the force-area relationships. The authors' summary follows:

"From measurements on surface films at the air-water interface, the molecular areas of 9 sterols have been determined. Other data regarding areas of sterols in surface films have been assembled and compared with previously published x-ray measurements on the dimensions of sterol molecules.

As a-A (pressure-area) and A-P (area-pressure) measurements have been made for a series of mixed films containing a sterol and a hydrocarbon in known ratio. Experiments of this type were performed at a number of hydrocarbon-sterol ratios with each of 35 hydrocarbons (chiefly polycyclic compounds including or related to the carcinogenic hydrocarbons) in combination with cholesterol or with cholesterol. Certain representative hydrocarbons were also used with each of the following: epi-cholesterol, coprostanol, ergosterol, neopergsterol, sitosterol, and stearic acid.

"From analysis of data on mixed films obtained in this way it has been found that most of the hydrocarbons studied display sufficient reactivity toward sterol molecules to be held between the sterol ring systems at the air-water surface. The hydrocarbon molecules are apparently held in the mixed films in 2 principal ways: (a) In a 2-dimensional fashion of which the hydrocarbon molecules can enter or leave reversibly; the logarithm of the mole fraction of hydrocarbon held in such solution, at film pressures below 15 dynes, varies linearly with the pressure applied to the film by the movable barrier. At any given pressure the extent of this solubility depends on the structure of both the hydrocarbon and the sterol. (b) In association complexes with sterol molecules, a hydrocarbon molecule apparently is held between 2 appropriately oriented sterol molecules. For such association to occur the hydrocarbon must have a favorable molecular configuration with respect to ring sys-
of Cancer Research, Columbia Univ., New York, N. Y.) The or presence of an improperly packing third film component, de-
cancerization, but that they are made more and more suscep-
tant disease.—L. L. W.

Rats were injected in from 1 to 6 foci.

Seven inbred and interbred strains of rats were injected with carcinogens (3,4-benzpyrene, methyl-
cholanthrene) were made during the long latent period preceding cancer development. Although a progression of proliferative changes was noted in the tissues leading up to the neo-
plasms, morphological study of individual cells failed to reveal just when the neoplastic change took place. It was noted that after a certain period of specific irritation by carcinogens, tis-

DES LIGNERIS, M. J. A. (The South African Inst. for Med. Research, Johannesburg.) Precancer and carcinogenesis. Am. J. Cancer. 40:1-46. 1940. The author re-emphasizes the importance of studying the "stage of preparation" or precancerous state of tissues later de-
veloping true neoplasms. He feels that not only will such studies lead to the institution of earlier, and so more successful therapy, but also that they may throw light upon the mecha-
nism of the neoplastic process itself. Following a brief review of the pertinent literature, he reports the following experimental studies:

Histological examination of tissues from mice and rats injected or painted with carcinogens (3,4-benzpyrene, methyl-
cholanthrene) were made during the long latent period preceding cancer development. Although a progression of proliferative changes was noted in the tissues leading up to the neo-
plasms, morphological study of individual cells failed to reveal just when the neoplastic change took place. It was noted that after a certain period of specific irritation by carcinogens, tis-

In his concluding section the author states his belief that most cells show a lack of susceptibility towards spontaneous cancerization, but that they are made more and more suscep-
tible to this change by the action of specific carcinogens through-
out the precancerous period. Hence the need for recognition and eradication of this stage in the treatment of human malign-
ant disease.—L. L. W.

DUNNING, W. F., M. R. CURTIS, and M. J. EISEN. (Dept. of Cancer Research, Columbia Univ., New York, N. Y.) The carcinogenic activity of methylcholanthrene in rats. Am. J. Cancer. 40:88-127. 1940. Seven inbred and interbred strains of rats were injected with either 0.5 or 1.0% of methylicholanthrene in paraffin wax. Rats were injected in from 1 to 6 foci. It was found that a total dosage of 12 mgm. of methylcholanthrene divided in 6 foci was sufficiently toxic to cause death of a majority of the animals within 90 days. With this maximum dosage, no tumors were observed in less than 60 days. From data accumulated, it was further found that the animals' age at time of injection was not a factor in initiating the malignancy or in determining the length of its latent period. Although rats definitely under-

The weaker solution of methylcholanthrene (0.5%) produced a larger proportion of tumors than the stronger (1.0%). By comparing a previous experiment with benzpyrene the data indi-
cate that 0.5% methylcholanthrene is approximately equal in carcinogetic potency to 1.0% benzpyrene, and that 1.0% methylcholanthrene induces tumors in a shorter average time than similar doses of benzpyrene. The tumors induced by the 2 concentrations of methylcholanthrene were chiefly fibrosar-
comas. The average diameter of those induced by 0.5% of the chemical was larger than that of those induced by the 1.0% solution after an equal growth period. No difference in the growth rates of tumors in the inbred and interbred strains was found. Hyperplasia of mammary duct epithelium and marked squamous metaplasia of these structures was often observed in the rats with tumors. Occasionally a squamous carcinoma or adenosarcoma of the breast resulted.—L. L. W.

ENGELBRETH-HOLM, J. (Cancer Research Lab. of The Danish Anti-Cancer League, Copenhagen, Denmark.) Acceleration of the development of mammary carcinomas in mice by methylcholanthrene. Cancer Research, 1:100-112. 1941. Twenty-seven females and 26 males of Little's dilute brown mice were painted once a week with 0.5% methylcholanthrene in benzene on various parts of the skin. All the 19 surviving females developed mammary carcinoma. Seventeen of the ani-
mals had more than 1 breast cancer. The tumors developed far earlier than is usual in this strain, the animals dying when from 8 to 10 months old as contrasted with the untreated mice which survived 13 to 15 months. No mammary carcinoma occurred in the males, but after the age of 10 or 12 months, there were some cases of papillomas and carcinomas of the skin. Methylcholanthrene thus accelerated the development of mammary carcinoma in the females.—Author's summary.

ENGELBRETH-HOLM, J., and H. LEFFRÈRE. (Cancer Re-
search Lab. of The Danish Anti-Cancer League, Copenhagen, Denmark.) Acceleration of the development of leukemias and mammary carcinomas in mice by 9,10-dimethyl-1,2-benzanthra-
cene. Cancer Research, 1:102-108. 1941. Reports are given of the results of experiments with 9,10-
dimethyl-1,2-benzanthracene administered to 2 inbred strains of mice, a strain with high incidence of mammary carcinoma and low incidence of leukemia, Dlb, and a strain with high inci-
dence of leukemia, Aka. Pronounced acceleration of the tumors characteristic for the strains, evident in increased incidence and especially in distinctly earlier appearance of the particular tumor, has been produced in these strains of mice by both subcutaneous injection of, and painting with 9,10-dimethyl-1,2-benzanthra-
cene.—Authors' summary.

MORTON, J. J., and G. B. MIDER. (Dept. of Surg., Univ. of Rochester Sch. of Med. and Dentistry, Rochester, N. Y.) Some effects of carcinogenic agents on mice subject to spontaneou

The appearance of leukosis in dilute brown mice may be hastened by painting them with: (a) a 0.1% solution of methyl-
cholanthrene in benzene, (b) a 0.25% solution of methyl-
cholanthrene in benzene, (c) a 0.25% solution of methyl-
cholanthrene in acetone, or, (d) a 0.5% solution of 3,4-benz-
pyrene in benzene. Painting with benzene alone does not have

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an effect of the same magnitude. The incidence of leucosis in line 212 of the dilute brown strain is greater after painting with methylcholanthrene than after painting with benzpyrene. Preliminary reports of the alterations in the blood leukocytes that precede the disease are presented.

Leukosis was found in old Buffalo, new Buffalo, and C3H mice after painting with a 6.5% solution of methylcholanthrene in benzene but not in the C3H black or C albinus strains. All of these mice are known to develop spontaneous leucosis although the incidence is not established.—Authors' summary.


In the course of a review of the cytological processes involved in wound healing, the author mentions that he carried out the following experiment. Mice (actual number not stated) were painted with one of the carcinogenic hydrocarbons for a period of time short of producing tumors. Wounds of a standard size were then made in the areas of depilation. One-third of the animals were kept as controls, 1/3 of the wounds were treated with fresh embryo extract, and the rest were dressed with heparin ("as used in delayed-culture methods in vitro"). "Although one or two tumours arose in the controls, by far the greater number appeared in the heparinized—i.e., inhibited—wounds, and none at all in those treated with embryo extract."

This experiment is quoted in support of Haddow's view that inhibition of mitosis is responsible for the induction of tumors. The author therefore cautions against attempts to stimulate epithelization of wounds by inhibiting fibroblastic growth.—R. J. L.


In preliminary notes (Bol. Inst. de med. exper. para el estud. y trat. d. cancer, 50:385-386, 1940) the author described the induction of lung tumors in rats made to breathe mixtures of air and oil or painted on the skin in chloroform solution. A total of 550 breast tumors was diagnosed. In the females there was no significant difference in either the number or time of appearance of the breast tumors in the estrogen treated and untreated controls. However the animals treated with the benzoates of estrone, estradiol, and equinol produced breast tumors on the average 2 months earlier than the estrone treated and control females. Treatment of male animals in a similar manner led to a breast tumor incidence no higher than that of the untreated females. This merely means, according to Butenandt, that the males have been feminized by the estrogen therapy to the point where the hereditary influences in the strain can cause breast tumors.—P. P. C.


A review (Cameron Prize Lecture, University of Edinburgh) of the practical and theoretical significance of the synthetic estrogen analogues, with special reference to the stilbestrol series.—A. H.


Various estrogens were administered to women suffering from an estrogen deficiency. The hormones were given in individual doses ranging from 10,000 I. U. to 150,000 I. U. The total amount administered varied from 90,000 I. U. to 240,000 I. U. The vaginal mucosa resembled that of the adult cyclical female following the administration intramuscularly of 200,000 to 2,000,000 I. U. of estradiol benzoate. When a total of 20,200,000 units of the estrogen were administered, excessive or abnormal proliferation of the vaginal epithelium did not appear. The atrophic endometrium responded more slowly than the vaginal mucosa to estrogenic stimulation. Uterine bleeding usually occurred after the patient had received approximately 3,000,000 to 5,000,000 I. U. during 4 to 6 weeks. Biopsies performed during the period of bleeding showed cystic glands. Following bleeding the endometrium returned to the atrophic state. When the endometrium was stimulated continuously for 6 to 8 months it did not show any greater proliferative activity than after a 4 to 6 week stimulation. The authors feel that within the limits of the dosage used (up to 53,400,000 I. U.) there appears no evidence to justify the fear that carcinoma of the genital tract may result from the therapeutic use of estrogens. It is felt that relatively large doses administered over relatively long periods of time are necessary to produce carcinoma experimentally in rodents.—A. K.

Over 500 intact or ovarietomized female rats (120-125 gm.) received daily subcutaneous injections of 1000 IU. (benzoate units) daily in 0.1 cc. of oil. A mixed diet was fed. Vaginal smears were taken at daily or weekly intervals. Animals were killed at intervals of 10 days, and the uterus, vagina, mammary glands, liver, spleen, bone marrow, gut, bladder, lymph nodes, kidney, and endocrine glands were studied histologically. Some rats were treated more than 1 year. The injected rats gained weight for 50 to 60 days and then stopped growing. The large amount of oil injected accumulated and abscesses formed in the subcutaneous tissue. Scattered areas, or generalized squamous metaplasia of the uterine epithelium appeared. Pyrometra occurred frequently. The mammary glands were well developed and fibrous stroma increased but malignant growths did not appear. Hypophysial chromophob adenomas appeared after prolonged treatment. The tumors contained little thyrotropic or gonadotropic hormone. The ovaries decreased to about 1/8 their normal size. Circulating estrone increased and the thyroid metabolism was reduced to 86% within 13 days. All blood cells decreased with continued treatment. The pathological changes are discussed from their sequence of appearance. A section is devoted to a discussion of the similarity of certain pathological states in man. The paper is illustrated with 37 photomicrographs or charts and 5 tables; 79 references are cited.—W. U. G.


Androgenic hormone tends to transform mammary adenofibroma to pure fibroma in rats. After 25 or more weeks of exposure to physiologic amounts of androgens fibromatous transformation of adenofibromas occurred in 28 of 47 rats (59.6%) and partial transformation took place in the rest. Less than 25 weeks' exposure produced relatively little change in tumor histology. Adenofibroma was never transformed to fibroma in females or in estrogen-injected castrates, and only scarcely so in untreated castrates. The fibromatous transformation produced by androgens does not depend upon inhibition of the growth of the tumor as a whole. Different strains of adenofibroma vary in the degree to which they respond to the fibromatogenic influence of androgens. No adequate explanation based on normal mammary physiology was found for the transformation of adenofibroma to fibroma. Only when the mammary epithelium is a part of a benign mammary tumor does it become sensitive to the inhibitory effect of androgenic hormone.—Author's summary.


In male mice of the Jackson Laboratory dilute brown strain castrated at birth, or at 1 month or 6 months of age, hyperplasia of the adrenal cortex and a decrease in growth of the mammary glands occurred. The changes in the adrenal preceded the mammary gland development and only feminizing effects were observed. Forty males were castrated at birth and 60 at later ages. Thirteen of these castrated at birth were examined when more than 300 days of age. All showed nodular hyperplasia of the adrenals consisting of nonpigmented cells, increasing with the age of the animal. The yellow-brown pigment characteristic of adrenal hyperplasia in older ovarietomized females was almost absent from males of comparable ages, indicating a less advanced hyperplastic condition. Six animals (averaging 644.2 days) showed extensive mammary gland growth (sub-branching and alveoli) not found under 437 days. One male killed at 589 days of age had 2 mammary tumors. Similar adrenal changes and mammary gland growth occurred in males castrated at later ages. The hypophyses contained no castration cells but were enlarged and congested.—C. A. F.

VIRUSES


A dialyzable stabilizing factor for myxoma virus is present in myxoma tissue as well as in normal rabbit muscle and skin and in commercial beef extract. By keeping the virus in contact with a saline solution of the stabilizing factor, it has been possible to concentrate the virus 100 times over that of the original extract by sedimentation in the ultracentrifuge (14,000 g for 2 hours). No sediment was obtained when an extract of normal rabbit muscle was treated in a similar fashion. The suspended particles under the microscope resembled the elementary bodies of vaccinia virus. On a nitrogen basis, 9.4 X 10-6 gm. constituted a fatal dose. About 5/3 of the sediment consisted of a lipid foreign to normal rabbit muscle. It is thought that the lipid consists of a base bearing nitrogen and phosphorus and a steroid that is not cholesterol but possesses some acidic properties.—J. L. M.


Mice, aged about 2 months, were vaccinated by peripheral injections of virus vaccine which produced no symptoms. This was followed by intranasal instillation of live virus. The survivors, about 3 months old, were exposed for about 10 minutes once an hour to a cloud of dust; in all, 6 times a day on 5 days every week over a total period of a year. Of 23 mice thus treated only 13 survived 10 months or longer. Only 2 of these, aged 605 and 877 days, developed malignant tumors of the lungs; i.e., 15.4%. The average incidence of lung cancer in 593 control mice, and 727 dusted mice of similar ages was 11.5% and 31.5%, respectively. Thus the influenza virus had, if anything, an inhibitory effect on the development of lung carcinoma.—R. J. L.


This article reviews work in which radiation experiments have been used for determining the particle size of viruses and genes, and indicates possible extensions of the method. The inactivation of viruses and phages by ionizing radiations appears to be a simple process, in which a single ionization or cluster of ionizations is responsible for the inactivation of 1 particle. The lines of evidence leading to this conclusion are given, and a simple formula is elaborated connecting the inactivation dose (ions per cm.2) with the particle volume. Experiments of the method are given for phage 16 and the tobacco necrosis virus, the results being in good agreement with the sizes estimated from ultracentrifugation and ultrafiltration experiments. The production of sex-linked recessive lethal mutations in Drosophila by irradiation can be used to calculate the diameter of the gene. In this case a modification is introduced by which the ratio of the doses of 2 different radiations required to produce the same percentage of lethals is estimated. The experimental results with x-rays, neutrons, and a-rays are in agreement with the assumption that the x-chromosome contains 1,860 genes of average diameter 3.78 m/zu. Other biologi-
cal actions of radiation which have been interpreted in terms of regions of special sensitivity in the organism are discussed, and calculations are given to justify the assumption that the lethal effect of radiation on bacteria can best be interpreted as the production of lethal mutation.—H. G. C.

Genetics


This study is based on over 600 fostered mice of the Ak, Rf, and Afl strains observed from birth until natural death. The incidence of leukemia is low in stocks Rf and Afl, and high in stock Ak. Mammary carcinoma is common in both virgin and bred mice of stock Afl, while in stock Rf lung tumors are numerous. Mice of the stock studied having a low incidence of leukemia were not rendered leukemic by nursing with mice of a stock (Ak) having a high incidence of leukemia. Mice of a highly leukemic stock (Ak) fostered by mice of relatively nonleukemic stocks (Rf and Afl) developed leukemia in lower percentage than their nonfostered relatives. Mice of stock Afl having a high incidence of breast tumors failed to develop tumors, with a single exception, when nursed by mice of stocks having a very few breast tumors. Breast tumors did not develop in mice of these stocks with a low incidence of breast tumors when nursed by Afl mice. The incidence of lung tumors was not significantly altered by fostering.—S. H.-J.


Mammary carcinoma in strains of mice having a high incidence of this tumor may be reduced to a minimum by foster nursing. A line of mice with a low incidence of mammary carcinoma, but susceptible to the development of mammary carcinoma, may, without fostering by or association with mice of a strain with high incidence, acquire an active milk influence producing mammary carcinoma. Thus the line may change, in any generation, to a strain with high incidence of mammary carcinoma. It is possible, but has not been demonstrated, for mice of a strain with low incidence of mammary carcinoma, nonsusceptible to development of breast cancer, to acquire, without fostering, an active milk influence and still not develop mammary carcinoma. The active milk influence may arise de novo or by changes in the inactive milk influence. The most consistent explanation for these observations and the data on foster nursing is that the active milk influence is an agent or virus.—Author's summary.


Observations on inbred strains of mice and on single sublines have shown that variation occurs both in the incidence of spontaneous mammary carcinoma and in the average age at which this tumor of the breast occurs. This indicates that inbred strains of mice or sublines of the same inbred stock are subject to mutational changes. In investigations involving comparisons of inbred strains and sublines, the mice to be used as controls should be bred and reared under the same conditions as the experimental animals.—Author's summary.


Considerable variation in the incidence of mammary carcinoma developed in several lines of Little's Dbal strain of mice maintained since 1935 by inbreeding through brother-sister matings at this laboratory in London. All offspring were nursed by their own mothers. The percentage incidence of mammary carcinoma in 5 lines, A, B, C, D, and E, was respectively 63.4, 57.5, 57.4, 56.5, and 10.1. The average age at which tumors developed in the E line mice was no greater than that at which they developed in the A, B, C, and D lines. No cause of the divergence of the E mice from the biological behavior of the rest of the Dba stock has yet been found.—S. H.-J.


Investigations attempting to put the occurrence of spontaneous mammary carcinoma in mice upon a genetic basis have led to controversy. The author discusses the difficulties and records observations on 3 stocks of mice. His conclusions are: "An influence which is transmitted by the mother but not carried in the chromosomes is instrumental in causing her young to have mammary carcinoma. The inbred stocks used apparently transmit this influence in degrees or concentrations which are characteristic of each stock. Physiological stability, as measured by the length of life or ability to survive, is apparently transmitted through the chroatin. The amount of spontaneous mammary cancer in hybrids of these 3 stocks seems to be dependent upon 2 factors: (a) the concentration of the extra-chromosomal influence transmitted by the mother; (b) the physiological resistance of mice of various genetic constitutions to this stimulus."

The paper includes 2 tables and 7 graphs.—S. H.-J.


The authors report on the bone tumors found in 300 mice of the Simpson strain. Seventy-four % of the animals with tumors were females. The mean age for tumor development was 16.6 months for females and 18.1 months for males. Tumors involving multiple bones were very common. Isolated tumors involving 1 bone were found most frequently in the spine, femur, tibia, and jaw. Metastases were frequent, appearing in the lungs, liver, kidneys, spleen, and peritoneum most often. The lesions varied from the earliest neoplastic changes, visible in the bones as an alteration of color (due to an abnormal proliferation of osteoblasts), to diffuse cancellous enlargement, or circumscripted osteoma, or spindle cell sarcoma, and cartilagenous tumors. Excellent photographs of the tumors are included.—L. W.


The histology of the various types of spontaneous bone tumors found in the Simpson strain of mice is described. The main classes of tumors are solid and cancellous osteoma, osteosarcoma with or without giant cells, and chondro-osteosarcoma. Tumors in which bone and osteoid tissue predominate are the most frequent. Photomicrographs of the various types of tumors are included.—L. W.

Physical Factors

FULLER, R. H., E. BROWN, and C. A. MILLS. (Lab. for Exper. Med. and Dept. of Path., Coll. of Med., Univ. of Clin-
Virgin female Dba mice kept under conditions of moist warmth (90-91°F) and 60-70%/o relative humidity showed a striking decrease in spontaneous tumor incidence. Tumors that did appear under these conditions grew more slowly and took over twice as long to kill their hosts as tumors in animals kept at cooler, more stimulating temperatures (65°F). Tumor incidence at 70-75°F was practically the same as at 65°F, but the masses grew more slowly. The time interval from discovery of the tumor to the death of the animal was 28 days at 65°F, 47 days at 70-75°F, and 260 days at 90-91°F. That the lowered tumor incidence observed in warm environments represents a real suppression rather than merely a delay to a later age is indicated by a comparison of human cancer death rates by age groups in northern and southern states. Northern rates rise much more rapidly with advancing age than do those in the South. From these findings it would seem that cancer should be classed as a metabolic disease, closely linked to tissue combustion level, as are diabetes, pernicious anemia, hyperthyroidism, and Addison's disease.—Authors' summary.

**Radiation**


Tissue cultures (from choroid and sclerotic of chick embryos) were exposed to a standard dose of x-rays (96.7 r) and the resultant changes studied over a period of 24 hours. The radiation caused a decline in mitosis, followed by an attempt at recovery. This was accompanied by a degenerative process due mainly to the breakdown of cells which had completed prophase. Since the results closely resembled those obtained in experiments in vivo, it is concluded that the effects of radiation in these dosages is independent of any effect on blood circulation.—A. H.


For this research a modification of Caspersson's ultra-violet microphotographic technic was employed, which permitted of a quantitative estimation of nucleic acid, or other known absorbing compounds in sections of tissues. Biopsy specimens were examined from cancer cases before and 80 minutes after x- and gamma-irradiation. There was found a significant increase in the ultraviolet absorption of the cytoplasm after treatment. This was detectable after small doses of irradiation, such as 248 and 388 r but of 6 specimens examined after relatively high dosages (9.1-9.7 r/min.) there was increased cytoplasmic absorption. The magnitude of the absorption is consistent with the possibility that purine and pyrimidine derivatives may be responsible. Microchemical tests have demonstrated in some cases an accompanying positive pentose reaction in the cytoplasm. The absorbing substances can be removed from the cytoplasm in fixed tissues by acid hydrolysis followed by alcohol extraction. Clinically there was no obvious correlation between the response to treatment and the absorption change reported.—R. J. L.


When a dose of x-rays approximating 1,200 r was delivered to the tumor-bed of the Jensen rat carcinoma, the rate of growth of the tumor was considerably slowed and 30 of 82 tumors regressed completely. The number of untreated control tumors which disappeared spontaneously was 13 out of 190.—A. H.


Since the discovery of artificial radioactivity by Curie and Joliot in 1934 its production and use in chemistry, physics, biology, and medicine has increased enormously. This review of advances is written from the point of view of the chemist and physicist. It is divided into the following sections: I. Introduction; II. General considerations; III. Methods of chemical identification and concentration; IV. Methods for detection of radiations; V. Types of reactions and methods of production; VI. Table of artificial radionuclides (a complete list up to July 15, 1940, giving type of radiation, half-life, energy of radiation, and nuclear reactions by which the radioactive isotopes are formed); VII. Applications to chemistry. The review includes an extensive bibliography.—S. B-J.
Guerrin rat carcinoma. Animals bearing these tumors were injected intravenously with aqueous solutions of Chicago blue 68. The results confirm those reported by Ludford and Duran-Reynals in demonstrating that no dyestuff was segregated by the malignant cells. In addition to phagocytes there are always present, in tumors, degenerating cells which constitute an important factor in the localization of acid vital dyes.


Analyses for d(-) form of glutamic acid were made on the hydrochloric acid hydrolysates of 7 malignant tumors from human beings, normal ox heart, and normal calf liver. The amount of d(-) glutamic acid found in tumor tissue was small, 0.5 to 0.91%, in yields of 55 to 81 mgm. of total glutamic acid. Only a slightly smaller amount, 0.33 to 0.8%, was found in normal tissue. The observations of Kögel and Erleben were not confirmed. —S. B. J.


The percentage of water in the livers of rats (young males, Wistar strain) bearing carcinosarcoma 256 was found to be significantly higher than that in the livers of normal rats. This increase in liver water occurred independently of the diets used and is not accounted for by a decrease in dry residue. —Authors' summary.


After reviewing his numerous papers on the subject since 1929, the author records in 34 tables the results obtained when rats are given a single injection of 0.5 cc. of blood or urine from pregnant women or women with cancer of the uterus. Several hundred animals were used. These injections cause hyper trophy of the spleen, with enlargement to 2 or 3 times its normal size. The effect becomes apparent 24 hours after the injection, and lasts for 900 hours. The active principle seems to be linked with the lipid fraction. Normal blood and urine are devoid of any effect on the spleen. In the opinion of the author the increase in tissue cholesterol such as is present in processes of growth is responsible for this effect. —M. D. R.


A comparison of the protein fractions of tumor and normal tissues is dealt with. Employing the belief that one should compare a tumor only with the tissue from which it arose, the author has compared a benzpyrene sarcoma of the rat with the normal cutaneous and subcutaneous tissue of the same animal. The tissues were extracted with a 10% NaCl solution, and then the residues were further extracted with a 0.25% NaOH solution. From 50 to 60% of the total tissue protein is dissolved in this manner. The partition of N and P was then determined in the soluble fractions. Seventeen sarcomas and 7 cutaneous-subcutaneous tissue controls were examined.

The protein in tumor appears to be less firmly bound to the insoluble material of the cell than is that of the normal tissue. However the values are greatly scattered, and overlap considerably. Whereas approximately equal amounts of P are extracted with saline from tumor and normal tissues, about 40 to 80% more P is extracted from the tumor in the subsequent alkali treatment. The ratio of P to N in saline extracts is of the same order for normal cutaneous-subcutaneous tissue (0.124) and for the sarcomas (0.112), but in alkaline extracts it is significantly higher for the tumor tissue (0.125 as compared to 0.093 for the normal tissue). The author contends from these results that sarcoma contains a higher content of P-containing alkali soluble proteins than cutaneous-subcutaneous tissue. —J. L. M.


Protein-like substances were concentrated from the urines of 6 men and 8 women by precipitation with 10% sodium tungstate, followed by precipitation in a mixture containing 60% acetic acid and 4% ammonium hydroxide, and precipitation of the desired fraction from this solution by increasing the concentration of the acetone to about 80% and adding a few drops of acetic acid. These concentrates were tested for abortifacient action by subcutaneous injection in pregnant albino mice. The urine-concentrates of each of the 7 patients with cancer exerted some abortifacient action. Concentrates of urine from normal men gave no abortifacient action. In the urine of 1 normal man there was some evidence of the abortifacient. The urine of all 3 of the noncancerous but otherwise ill women showed as much evidence of abortifacient material as did that of the cancer patients. Egg albumin and proctalin had no abortifacient action. Peptonate, injected in doses of 8 to 10 mgm. caused resorption and expulsion of fetuses. Gonatropic substances in doses ranging from 3.75 to 25.0 rat units per day for 3 days tended to produce death of fetuses and their retention in the uterus, but differed considerably from the abortifacient effect of the extracts of urine. —S. B. J.


The sera of cancerous and noncancerous patients and of dogs with Brown-Pearce tumors were found to contain small amounts of d-di peptidase. d-Leucyl-glycine served as the substrate. The enzymatic reaction had to run for exceedingly long periods of time (6 days) in order to demonstrate even this small activity. —J. L. M.


The growth of tumor 15501a was studied in pure strain mice in correlation with the histology. The tumor grew well in the ABC ALB and ABC-AC strains, but the Dba strain was relatively resistant, and no takes at all were observed in C57 BLK mice. Individuals of the Dba strain in which the tumor failed to grow or regress were resistant to reinoculation. In the susceptible animals the tumor became necrotic at the center but grew at the periphery. Vasculatization became evident on the 4th day. Failure of the tumor to grow was associated with the development of a vascular fibrous capsule accompanied by mononuclear phagocytes about the pyknotic tumor cells. Ultimately a scar resulted. The more slowly growing tumors in the
susceptible strains also possessed thick fibrous capsules. There was no evidence that the capsule in itself is responsible for failure of the tumor to grow.—A. A. L.


Intra-uterine implantation of a rapidly growing sarcoma into Swiss, Longacare, and AKA mice was successful in 75% of cases, 20% less than upon subcutaneous inoculation. The number of takes was least if implantation was made at estrus (59%), and best at proestrus (82%), or in 4 to 6 day pregnant, pseudopregnant, or lactating animals (79%). Growth was poorest at estrus and metestrus and best at diestrus and in pseudopregnant animals. It may be significant that the uterine fluid is less alkaline as decidual reaction develops, than at estrus or metestrus. Histological studies of implantation and growth of the tumor implants showed that even minute injuries with the trocar are sufficient to permit the implantation of the sarcoma cells. Tumor masses in the lumen rapidly underwent necrosis. With the development of the decidual reaction, sarcoma cells rapidly invaded the entire wall of the uterus. Both estrus and copulation were observed in mice with large uterine tumors. Decidua induced by placing tumor masses in sensitized uterus developed and differentiated much like those induced by embryos.

Invasion of lymph channels resulted in metastases in the lymph glands within 5 days after implantation of the tumor in the uterus.—A. A. L.


Endometrioma of large rabbits previously treated with estrone was minced in saline and injected into the ear veins of the donors. Eight of 12 rabbits had endometrial tissue in their lungs 1 to 3 months later. Some of the pulmonary implants obliterated vessels and penetrated the walls of blood vessels. Thirteen other rabbits similarly received endometrial tissue and were mated or injected with stilbestrol. The endometrial tissue in the lungs showed decided changes in the pregnant rabbits and responded characteristically in rabbits receiving stilbestrol. The observations were discussed from the standpoint of vicarious menstruation and origin of benign and malignant tumors in women. The paper is illustrated with 11 photomicrographs.—W. U. G.

Tissue Culture


The virus cultivated was the hemocytoblastosis strain T1 of Englebreth-Holm; the technic employed the Carrel flask method. Two types of experiments were carried out. Bone marrow and fragments of heart muscle were cultivated separately in the plasma of leukotic fowls, and also colonies of fibroblasts were bathed for 1 hour in cell-free ultrafiltrates of heart and spleen extracts of leukotic fowls, and then cultivated in a mixture of 1 part of normal plasma to 2 parts of the ultrafiltrate. Both types of cultures were washed at intervals and re-fed with normal plasma (method of Parker and Fischer). Growth of virus infected cultures has been maintained for 86 days. Incubation in fowls of ultrafiltrates of the fluid used for washing these cultures, and of the cultures themselves, gave positive results. It is thus demonstrated that cultivation of the virus of fowl leukosis in vitro does not necessitate the presence of primitive blood cells, since it can be cultivated in the presence of fibroblasts.—R. J. L.


The roller tube culture technic appeared to furnish a practical method for the maintenance in vitro of the specific cells of the Brown-Pearce carcinoma. After 44 days in tissue culture the carcinoma cells still retained their ability to produce malignant growths in susceptible animals. Definite evidence that these carcinoma cells proliferated in vitro was not obtained. The round tumor cells retained their characteristic morphology throughout the course of the experiments and no transition to a spindle-shaped fibroblast was observed. Serum and tissue extracts from animals immunized against the tumor showed no definite capacity to exert a cytotoxic action on the tumor cells in vitro.—Authors' summary.


A pure strain of malignant cells derived from a spindle cell sarcoma induced in a mouse by 1,3,5,6-dibenzanthracene has been grown in flasks on a fowl plasma coagulum and with either heparinized fowl plasma, or a mixture of fowl serum and a little chick embryo extract. The cells tended to grow in close association with one another forming branching ribbon-like strands or broad sheets, which resembled the epithelial type of growth in vitro. It is suggested that this type of growth results from the inability of the sarcoma cells to liquify heterologous plasma in the absence of chick embryo extract, or when it is present in a low concentration. This pure strain of sarcoma cells has been cultivated in vitro for 215 days. After 134 and 181 days in vitro cultures were inoculated into mice, and although they had been grown in completely heterologous media, they gave rise to typical spindle cellled sarcomas.—R. J. L.


In modifying the technic of Borger and Zenker, who employed dried chick embryo extract, the authors have shown that a desiccate of chick embryo is equally efficacious. For preparing cultures they add an equal volume of distilled water to their desiccated chick embryo is equally efficacious. For preparing cultures they add an equal volume of distilled water to their desiccated chick embryo extract, or when it is present in a low concentration. This pure strain of sarcoma cells has been cultivated in vitro for 215 days. After 134 and 181 days in vitro cultures were inoculated into mice, and although they had been grown in completely heterologous media, they gave rise to typical spindle cellled sarcomas.—R. J. L.

General Reviews


This is a comprehensive review of the biochemical developments in cancer research discussed under the following headings: A viruses and tumor-producing agents; B carcinogenic compounds were washed and steroid hormones and their relation to the cancer problem; D biological relations between carcinogenic compounds and viruses—mode of action of cancer-producing compounds; E chemistry of tumors. Under A the work on the Rous chicken sarcoma, Shoape rabbit papilloma, and rabbit myxomatosis, and their respective viruses, is discussed. The viruses are considered as a group of carcinogenic compounds characterized by their high molecular weight and protein character. The discussion under B deals
with the various types of carcinogenic compounds of known chemical structure, and includes the aromatic hydrocarbons, the azo dyes, and the quinoline dye, styril 430. The chemical and carcinogenic properties of those compounds are discussed. Section C on the steroids is taken up in more detail. Experiments in collaboration with Dannenberg and Friedrich-Freska which have been going on for 3 years are quoted as failing to support the claims of Schabad. Pathological changes are noted following injection into mice of the non-saponifiable fraction from livers of cancerous patients, but no typical epitheliomas or sarcomas, such as are produced by the known steroid carcinogens, have been observed. Butenandt is emphatic in stating that the naturally occurring follicular hormones and their esters cannot be considered as carcinogenic in the same sense as the known carcinogenic hydrocarbons. Since the so-called carcinogenic action of the estrogens is seen only in males or castrated females of mice strains with a high incidence of spontaneous mammary carcinoma, the effect of the estrogens is that of bringing about proliferation of the mammary gland, which permits the factors responsible for the high spontaneous incidence to operate. The fact that stilbestrol and related compounds act in a similar way as the follicular hormones is taken as further evidence for the view that the follicular hormones themselves cannot be considered carcinogenic. Results of experiments carried out with Kaufmann, Müller, and Kroning on the effect of follicular hormones on tumor production in 3,000 mice are referred to in support of the above view. Under section D the viral infection theory is discussed at length. The suggestion is made that the different carcinogens might be thought of as affecting a virus infected cell in such a way as to upset the balance in favor of the virus which would then act to bring about a malignant change in the cell. The genetic influence in carcinogenesis is emphasized and the problem of somatic mutation is mentioned. With regard to the latter, Butenandt refers to negative results of Piepho who attempted to influence the rate of spontaneous mutation in germ cells of Drosophila pupae by benzyrene. The final section on the chemistry of tumors E, briefly treats the work of Warburg on aerobic glycolysis, that of von Euler on the low cytochrome content of tumors, and the high ratio of dihydrocozymase:cozymase in Jensen sarcoma. Butenandt discusses at some length the work of Kögl on the presence of nonnatural glutamic acid in tumor proteins, and briefly refers to the reports of Waldschmidt-Leitz on the presence of d-peptidases in the blood of cancer patients, and the influence of d-peptides on carcinogenesis. Section F is not reviewed critically by Butenandt. Most of the material presented in this section has not been confirmed, particularly that of Kögl and Waldschmidt-Leitz.—P. P. C.


A survey of difficulties in making available the data of cancer research. Five types of problems which arise in abstracting are discussed: I. "The manifold aspects of the cancer problem cause the relevant papers to be distributed over a very large number of journals." II. The literature of cancer research would be lightened if the subjects of surgical technic and nursing care could be left to other abstracting journals. III. Too many post-mortem reports, especially those including irrelevant details, are published. IV. Papers of importance are often published in journals whose titles do not indicate that such journals contain articles on cancer research. In this way, valuable contributions may escape notice. V. Japanese journals publish an increasing number of articles in Japanese with no summary in any European language.—J. S. L.

COMPARATIVE ONCOLOGY


In 25 female rabbits which were under observation for more than 900 days, adenocarcinoma of the uterus appeared in 15. Cystic mastopathy was noted in 14. Primary uterine and mammary tumors (the latter multicentric and probably malignant) were present simultaneously in 3 instances. Of the 25 rabbits, 15 had been treated in various ways with 1,2,5,6-dibenzoanthracene, and of these 10 had uterine tumors. Of the remaining 10 rabbits which had not received any carcinogenic compound, uterine tumors developed in 5. Hence, it is unlikely that 1,2,5,6-dibenzoanthracene played any part in inducing the neoplasia. The ovaries showed advanced changes (enlargement due to intracellular deposition of lipid) and it is suggested that these may have been concerned in the causation of the tumors. Most of the rabbits had been repeatedly pseudopregnant.—A. H.

CLINICAL AND PATHOLOGICAL REPORTS

DIAGNOSIS—GENERAL


The author emphasises the simplicity and efficiency of this diagnostic procedure. Four photomicrographs and 2 color drawings are appended.—M. D.-R.

THERAPY—GENERAL


Emphasis on the use of nonnarcotic medication in preference to narcotics.—H. G. W.

SKIN AND SUBCUTANEOUS TISSUE


Case report of recurrent leiomyosarcoma arising from the subcutaneous tissue of the mastoid region.—M. D.-R.

NERVOUS SYSTEM


A discussion from the roentgenologic viewpoint.—H. G. W.

BREAST


This paper records the influence of estrogens (estradiol benzoate, stilbestrol) and an androgen (testosterone propionate) on the course of chronic mastitis. The effects were estimated clinically and also by the examination of biopsy specimens, special attention being paid to the number of glandular systems (adenosis), the extent of epithelial proliferation (epitheliosis) and the degree of fibroplastic activity. Certain of the histological features of chronic mastitis appeared to be more advanced.

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