Abstracts

Experimental Research, Animal Tumors


An ether solution of a hydrocarbon (e.g., 20-methylcholanthrene or 3,4-benzpyrene) is added to an aqueous solution of ether soap ("1 cc. of the ethereal soap solution used contains 1.8 gm. soap"), diluted with water to obtain the desired percentage of hydrocarbon and of soap, and the ether removed by boiling."Fluorescence spectroscopy reveals identical bands for 3:4-benzpyrene in aqueous soap solution and in acetone." The solution becomes opalescent after a few hours, but "even so the particles are much smaller than those of colloidal suspensions." "Rats show no aversion to drinking 0.01 per cent hydrocarbons in 7.5 per cent aqueous soap solution, and have showed no toxic effects after drinking it daily for six weeks."—I. H.


Strains IF and CBA are completely free from spontaneous mammary cancer. Females of both strains treated intranasally with an oily solution of methylcholanthrene developed about two-thirds of the survivors. Males of the IF strain that had been feminized by an estrogen (triphenylethylene) also developed breast cancer (11 of 16 mice) after methylcholanthrene given intranasally. This second experiment disposes of the objection that the females in the first might have transferred methylcholanthrene to the mammary ducts while cleaning themselves. No mammary ducts were found in estrogen-treated males.

Numerous skin tumors were found. "Within each strain there is no evidence that the frequency of skin tumours is significantly different in mice which developed mammary tumours."—I. H.


Observations are reported and discussed with reference to the experiments of Miller and Baumann. The following points are made:

The chemical classification of a solvent has no relation to the fluorescence intensity of the hydrocarbons dissolved in it.

For the particular case of 3,4-benzpyrene solution in ethanol-water mixtures it can be shown that the differences in fluorescence intensity according to the percentage of solvent composition are entirely due to a quenching effect of dissolved O₂. The differences disappear in N₂. In many other cases the solvent effect on fluorescence intensity can be largely accounted for by the quenching effect of O₂, though there are exceptions where a solvent effect proper persists even in the absence of O₂.

The stability of the fluorescence of benzpyrene solutions also depends on the solvent. No appreciable change occurs in hexane or benzene during a 20 minute irradiation. In acetic acid, and especially in 80% acetic acid—20% water mixture, photo-oxidation takes place in the presence of O₂. In ethanol and in mixtures of 60% ethanol with 40% N/10 HCl, water or N/10 NaOH a fairly slow nonoxidative fall of fluorescence, increasing in the order named, is observed.

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The rapid destruction of fluorescence in chloroform is confirmed and is shown to be a nonoxidative reaction.

Inhibitors of fluorescence in solution belong to one of three categories: (a) substances causing a reversible photochemical reaction ("genuine quenching"); (b) substances causing irreversible changes of the fluorescent material; (c) substances that absorb the exciting wave lengths ("filter effect"). Many solvents in which hydrocarbons do not fluoresce belong to this class.

An unsaponifiable fraction of mouse tissues is less susceptible to the quenching effect of O₂ than carcinogenic hydrocarbons. It is recommended that fluorimetric determinations of hydrocarbons be carried out in N₂,-

Author's summary.


This paper deals with mesenteric tumors that occurred in the course of experiments designed to test Roffo's report that fats become carcinogenic when heated at 350 °C. The experimental animals were male Norwegian hooded rats fed on an adequate diet (N rats) and also male Wistar rats fed on a restricted diet of white bread and milk (W rats). The heated lard consumed averaged 6 gm. weekly per rat.

Fifty N and 20 W rats were fed lard heated for 1 hour at 350 °C. Two N and 1 W rat developed multiple mesenteric sarcoma; 3 other N and 2 other W rats were found to be infested with Cysticercus fasciolaris (1 of the W rats had liver sarcoma due to the worm). Four W rats had multiple ulcerated papillomas in the forestomach.

Thirty-five N and 20 W rats received lard heated for 12 hours at 220 °C. One N rat had mesenteric sarcomas; 2 W rats (1 with liver sarcoma due to the worm) were infested; 2 W rats had stomach papillomas.

Fifty N rats received lard heated for 4 hours at 220 °C. Two W were infested, one of which had a mesenteric sarcoma very close to the intestinal site of the worm.

Twenty-four controls (16 N and 8 W rats) had 6 gm. of unheated lard per rat weekly. One N and 1 W rat were found infested with the worm.

It is concluded that the evidence points to the presence in fats heated to about 350 °C. of some factor capable of inducing malignant mesoblastic tumors along the path of their absorption in addition to the benign gastric lesions previously described.—I. H.


(1) Cholesterol, (2) cholesterol heated at 270-300 °C. (unchangedsterol removed), (3) residue from (2) after removal of cholesterol and dihydroxyether, (4) Δ₃,5-cholestadiene were added separately to the diets of groups of rats for 24 months. Only one papilloma and hyperkeratosis (of forestomach ?) was observed. (5) Heated cholesteryl esters, (6) cholesterol heated at 430 °C, also given by mouth, gave no tumors in 15 months. Oily solutions of the products listed above, injected subcutaneously into 90 rats, gave 2 fibrosarcomas (which products were effective is not stated). Examination of absorption spectra gave no support for Roffo's claim that heated cholesterol contains a polycyclic hydrocarbon very similar to 3,4-benzpyrene.—I. H.


The addition of 2-acetyl-amino-fluorene to the diet of rats produces tumors in different organs. In female rats the majority of the tumors are mammary adenocarcinomas. Glycocyamine added to the acetyl-amino-fluorene containing diet accelerates the appearance of mammary tumors and also increases the number of liver tumors in the females. "These results suggest that the reduction of available labile methyl-groups brought about by the conversion of glycocycamine into creatine enhances the carcinogenic action of 2-acetyl-amino-fluorene."—I. H.


Stock mice receiving an adequate diet with the addition of either 3,4-benzpyrene or 2-methylcholanthrene in solution in olive oil or cod liver oil developed papillomas of the forestomach with a tendency to malignant evolution. Even a small number of positive results in the experimental induction of tumors of the forestomach of mice must be considered significant in view of the extreme rarity of such tumors in this species.

Unlike the diffuse benign gastropapillomatosis associated with dietary deficiencies, papillomas induced with carcinogenic hydrocarbons (a) tend to be localized and invasive, and (b) are not prevented or influenced by the addition to the diet of large amounts of vitamin A.

The relative values of stock mice and inbred lines for investigating the competence of tissues to react to carcinogens are discussed.—Authors' summary.


Rats on an adequate basal diet, fed the residue (left after the removal of dihydroxyether and Δ₄-cholestenone) from cholesterol heated to 300 °C., at a level of 20 mgm. daily for 2 years, showed no tumor of the forestomach nor of the glandular zone.

Other rats fed Δ₃,5-cholestadiene at a level of 25 mgm. daily for 2 years plus an adequate basal diet, showed no tumor in either part of the stomach. It seems unlikely that this diene is concerned in the avitaminosis A induced in rats by feeding heated fats.

A large, inorganic bladder stone is reported in one rat of this series.—Author's summary.

Studies in Esterase (Butyric) Activity. III. The Effect of Foster Nursing on the Esterase Content of Blood Serum and Liver of Strains of Mice Susceptible or Insusceptible to Mammary Cancer.

The effect of foster nursing on the esterase activity of serum and livers of mice, of a high mammary cancer strain (C3H) and a low mammary cancer strain (C57) was studied.

Reciprocal foster nursing resulted in a change in the esterase content of the serum of these mice. The esterase activity in the high mammary cancer strain diminished on foster nursing by the low mammary cancer strain mothers, while the esterase activity in the low mammary cancer strain increased on foster nursing by high mammary cancer strain mothers. These results were statistically significant.

No significant change was observed in the liver esterase on foster nursing.

A probable interpretation of these findings in relation to spontaneous mammary cancer in mice is discussed.—Authors' summary.


Three patients who had undergone total gastrectomy for carcinoma of the stomach exhibited a conspicuous steatorrhea, and one of them showed conspicuous creatase for carcinoma of the stomach exhibited a conspicuous steatorrhea, and one of them showed conspicuous creatase activity.

Anemia of normocytic, normochromic type were noted in these 3 patients. The anemias apparently were not related to deficiency of dietary protein, intrinsic or extrinsic factors, or to the presence of infection. They may have been associated with a disturbance in alimentary digestion and in one case with bone marrow dysfunction.—W. A. B.


Chemical determinations of the liver were made on 13 patients who had various diseases of the stomach and were subjected to operation. There were 8 cases of carcinoma, and 1 case each of polyp, gastric ulcer, duodenal ulcer, gastritis, and Boeck's sarcoid. Biopsy of the liver was done immediately upon opening the peritoneal cavity and again just before closure. During the course of subtotal gastrectomy there was an average increase of 1% hepatic water, a shift of fluids between intracellular and extracellular positions, an average loss of 45% of the hepatic glycogen, an average increase of 1.97 g/m2 % of total lipids, and a fluctuation in the content of hepatic protein with an increase in hepatic albumin and a decrease in hepatic globulin.—W. A. B.


Allino mice were placed in a motor-driven rotating cage and subjected to certain periods of forced exercise preceding and following inoculation with a transplantable fibrosarcoma. The rate of growth of the tumors was then compared to a control series in mice receiving the same daily caloric equivalent of food but not subjected to forced exercise. The exercised mice gained less weight and the rate of tumor growth was also less than that observed in the control series.—Authors' abstract.


Studies were undertaken on 822 control mice, 1,799 estrogen-treated mice, 378 estrogen-androgen-treated mice, and 65 androgen-treated mice from 7 inbred strains. Humoral treatment was begun when the animals were 22 to 141 days old and continued for either 10 weeks to 3 months or until death. All hormones were injected subcutaneously in oily solutions or implanted subcutaneously as pellets. Nine estrogenic chemicals at one or several dosage levels were used.

Malignant lymphomas occurred in 1.34% of the control mice, 11.9% of the estrogen-treated, 2.34% of the estrogen-androgen-treated, and in 1.54% of the androgen-treated mice. The incidence was approximately 1% among the estrogen-treated mice of 3 strains (C3H, CBA, and PMO), 5% in the JK and C121, and 2% in the C57 and A. The incidence of spontaneous lymphomas was not paralleled by the incidence of such tumors among the treated mice. The treatment of mice with large doses of estrogen for periods of 10 weeks to 2 months was followed by an incidence of lymphomas as high as, or higher than, that occurring after continuous treatment. Small doses of hormone were associated with a low incidence of lymphomas. Female mice treated with estrogens tended to have a higher incidence of tumors than males. The simultaneous administration of androgen tended to prevent the high incidence of lymphomas. The different estrogenic chemicals, when given in physiologically comparable amounts, were approximately equally effective.

The tendency for estrogens to be more effective in increasing the incidence of lymphoid tumors among some strains of mice than among others could not be associated with any concomitant peculiarities of these strains in their response to estrogen, such as the tendency to acquire mammary, hypophyseal, or testicular tumors or the responsiveness of the skeletal tissues.—Authors' abstract.


For thorough cleaning of glassware used in vivo methylcholanthrene carcinogenesis experiments, detergents such as soap or trisodium phosphate are considered inade-
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quate, while dichromate-sulfuric acid cleaning solution is objectionable because of adsorption of chromium salts on the glass. The best results are obtained with hot 80% sulfuric acid plus a small amount of nitric acid. Tests show that 1 mgm. lots of crystalline methylcholanthrene alone or with serum added are charred within a few minutes at room temperature by this solution. With gentle warming the charred material is cleared and put into solution.

The glassware cleaning apparatus is described in detail.— R. B.


The photomicrographic apparatus is constructed in such a manner that all manipulations can be carried out while the image is under observation. Since the microscope is inverted and enclosed in an air bath, photographs can be taken of living cultures in their normal position in Carrel flasks or hollow ground slides. The whole apparatus is mounted on a concrete base which in turn is insulated from the floor by Vibracork. Details of the construction of the apparatus and photographs illustrating it are given in the paper.—R. B.


The equipment is designed for taking motion pictures simultaneously of fibroblast cultures exposed to methylcholanthrene and of control cultures.

Many interesting special features are incorporated into the apparatus to make it as convenient and automatic as possible.—R. B.


Fibroblasts from a 100 day old C3H male mouse were cultured for 291 days on a medium consisting of chicken plasma, horse serum, chick embryo extract, and saline. Experimental cultures were then exposed to 1 γ of 20-methylcholanthrene per cc. of the fluid phase of the medium for periods ranging from 6 to 406 days, after which the carcinogen was omitted from the medium and the cultures observed for an additional 257 to 536 days.

The growth of carcinogen-treated fibroblasts, as determined from measurements of diameters of cultures, was retarded beginning at 6 to 19 days. Morphologic changes were apparent after the cultures had been exposed for 40 days to the carcinogen. These changes consisted of a shortening of cell processes followed later by the development of lateral irregularities on the blunted processes. These irregularities were suggestive of amoeboid rippling or frothing. With continued exposure to the carcinogen the cells developed numerous short lateral strands or ribbons of cells, and finally massive sheets of cells. The cytoplasm of cells treated by the carcinogen for long periods became very granular.

These morphologic changes occurred gradually and became more pronounced as the length of the period of exposure to the carcinogen increased. Growth rate also was progressively retarded. After 406 days in the methylcholanthrene-containing medium, cultures grew very slowly and would probably have died with additional exposure to the carcinogen. After removal from the carcinogen the cultures grew somewhat faster, but still at a reduced rate compared with the controls. This apparently permanent reduction in growth rate was proportional to the length of time during which the cultures had previously been exposed to the carcinogen. Observations extending for more than 1 year following removal of the carcinogen from the culture medium showed that the morphologic changes also persisted unchanged.

About 21 months after the original explantation, the control cultures began to display alterations of the same type as described above for the carcinogen-treated cultures. These changes in the controls occurred 2 to 8 months later than they did in the experimental cultures and were much less extensive on the whole. They could have occurred spontaneously, but the author inclines to interpret them as resulting from unavoidable trace contamination of the control cultures with methylcholanthrene.

The paper contains a detailed description of the tissue culture technic followed in these experiments.—R. B.


Cultures of C3H mouse fibroblasts exposed to methylcholanthrene as described in the preceding abstract were inoculated, usually intramuscularly, into young C3H mice. Control cultures were similarly inoculated. Sarcomas developed from all strains of fibroblasts, both carcinogen-treated and controls, after latent periods of 9 to 14 days or longer. These sarcomas have been carried on by subinoculation into C3H mice for 14 tumor generations. Metastases occurred in 6 out of 77 mice inoculated with 2 of the carcinogen-treated fibroblast strains. The remaining 3 carcinogen-treated strains and the control cultures did not produce metastases.

The experimental fibroblast strains tested for malignancy had been exposed to methylcholanthrene in culture for periods ranging from 6 to 406 days and then cultured for varying periods in the absence of the carcinogen. Seventy-six per cent of the inoculations of cultures treated with the carcinogen for 6 days produced tumors. Longer periods of exposure produced increasingly severe morphologic alterations in the cultures and a decrease in the percentage of tumors in inoculated mice. Cultures exposed to the carcinogen for 32, 111, 184, and 406 days produced tumors in 20%, 46%, 7.6%, and 7.6% of the inoculated mice respectively.

The percentage of inoculations giving rise to tumors was small (7.6%) for one control fibroblast strain displaying very slight morphologic alteration, but high (86%) for the other control strain which displayed more definite alterations.—R. B.


Autopsies were performed on a total of 838 C3H mice.
carrying inoculations or subinoculations of (a) C3H fibroblast cultures exposed to 20-methylcholanthrene, and (b) untreated control cultures. Tumors were found in 578 mice. Histological studies on 285 of these tumors showed that they were sarcomas made up usually of large spindle cells. The tumors invaded a large variety of organs and tissues. In 5 cases there were definite metastases to the lungs and in 1 case lungs and mediastinum were involved probably by metastases, but possibly by direct extension from a heavily invaded peritoneum.

The various fibroblast strains produced sarcomas with different characteristics as follows: Control cultures and cultures exposed to the carcinogen for 6 or 32 days produced tumors with quite uniform cell pattern and limited capacity of invasion. There were no metastases and no appreciable numbers of giant cells or abnormal mitoses. Cultures exposed 111 days to the carcinogen gave rise to tumors with increased variability of cell pattern, and some giant cells, and abnormal mitoses. These tumors were more invasive and produced metastases in 5 cases. Finally, the tumors arising from cultures exposed 184 and 406 days to the carcinogen displayed great variability of cell pattern, numerous giant cells, and abnormal mitoses. The tumors were invasive but metastasized in only 1 case.—R. B.


The delayed lethal dose of x-rays for rat sarcoma cells cultivated in vitro is 2,000 r. This is less than half the equivalent dose for chicken normal fibroblasts, of which the proliferative capacity is irreversibly checked only after irradiation with 5,000 r.—Authors’ summary.


The minimum dose of x-rays that causes appreciable inhibition of growth rate in an irradiated sarcoma cell culture is 500 r. The corresponding dose for normal chicken fibroblasts is 2,500 r.—Authors’ summary.


In the course of determining the value of radioactive phosphorus as a therapeutic agent in leukemia, several chemical forms of the substance have been used. Small amounts of radioactive magnesium ammonium phosphate, phosphoric acid, or disodium phosphate may be used practically interchangeably so far as therapeutic effect and rate of excretion are concerned. In the preparation of radioactive phosphorus for therapeutic administration to human patients, phosphoric acid or magnesium ammonium phosphate are more readily prepared than dibasic sodium phosphate.—Authors’ abstract.


The author has had “many failures and a few striking results” and records in detail the successful treatment of a case of very extensive recurrence after excision of both breasts for carcinoma.—E. L. K.


Adult mammals show a natural resistance to alien transplants, whether the graft consists of normal or tumor tissues. Tissue culture methods were used to study the nature of the humoral factors or “cytoxins” responsible for this resistance. The technic consisted in injecting King A rats with tumor BA1 from mice of the Bagg albino strain, and then testing the effect of serum from the rats on cultures of mouse and other cells. The results showed that the serum so derived was toxic to all mouse cells, tumor or normal, regardless of the strain from which the cells were taken (Andervont, Bagg albino, or C57 black). However, the serum was not toxic to rat sarcoma, heart, or spleen, cultured in the same roller tubes as the mouse tissues for direct comparison. Thus the inoculation of mouse sarcoma cells into rats produced not an anti-tumor serum, but rather a general “anti-mouse” serum, the reaction being presumably of an antigen antibody nature.—J. B. B.


Tumors grew in 18% of surviving chick embryos, but further passage into mice was successful only so far as the second generation. The original paper should be consulted for a detailed description of the histological features of this tumor.—J. H.


These experiments were devised to test the validity of the hypothesis that genetic constitution is an important factor in the incidence of primary intracranial neoplasms induced with pure methylcholanthrene implanted intracerebrally. Of 6 strains of mice tested, namely, C3H, ABC albino, Bagg albino, C57 black, A albino, and dba, the first 4 strains yielded an incidence of 50% or better in primary intracranial neoplasms, whereas the last 2 strains were poor with respect to carcinogen-induced brain tumors. Only 4 of 22 A albino mice and 2 of 19 dba mice developed intracranial neoplasms. The incidence of brain tumors induced with methylcholanthrene is in no way related to the propensities that the different mouse strains show in regard to the development of spontaneous mammary tumors. Both the C3H and dba strains, for example, have a high incidence of spontaneous tumors of this variety, whereas the C57 black strain yields extremely few such tumors. Of 29 inbred dba mice (from brother-to-sister matings) only 1 developed an intracranial tumor following the intracerebral implantation of methylcholanthrene. Hybrids obtained by crossing pen-bred C3H and pen-bred dba mice yielded an intracranial tumor incidence.
The technique of radiation therapy is discussed at some length with particular stress on the use of adequate dosage. Reconstructive surgery may be necessary after treatment of large lesions. The end results were satisfactory in all but 12 of 146 patients treated by the authors.—C. E. D.


In the 2 cases reported an unusual type of tumor of the spinal cord was found. Both are particularly interesting since the symptoms had suggested a serious organic disease in a region remote from the central nervous system. In the first case the lesion was operable, and the patient received definite benefit from the removal of the tumor and postoperative roentgen therapy. In the second case the tumor was advanced and biopsy only could be performed. The outlook for return of function in this patient was poor.—J. L. M.


The authors report a case of chronic cystic arachnoiditis in which symptoms and findings closely simulated those of acoustic neurinoma. A second case is reported in which...
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