Abstracts

Reports of Research


The author has developed a process for obtaining 3,4-benzpyrene which "seems sufficiently promising for application of the method on a large scale as a practical means for supplying this important hydrocarbon." A crude distillate of tar (200 to 240° C./0.1 mm. Hg.) is extracted with concentrated sulfuric acid and the extract diluted with water and extracted with benzene; the benzene extract is washed and dried, adsorbed on and eluted from alumina, and the eluate is dried and recrystallized. Ten grams of tar distillate gave 75 mgm. of almost pure benzpyrene. A quantitative test on a tar distillate to which was added pure benzpyrene gave almost 100% recovery—I. H.


It has previously been shown that fat from the same species of animal when used as a solvent for benzpyrene inhibits carcinogenesis; this effect can, however, be reproduced by phosphatides (lecithin, cephalin) from other species. It has now been found that cholesterol strongly enhances carcinogenic activity. Hydrogenated fats and cod liver oil (rich in polyethenoid fatty acids) were not anti-carcinogenic.

"The rate of elimination of benzpyrene from mice was measured by its chromatographic separation and fluorimetric estimation. By comparison with pure tricaprylin, elimination was significantly accelerated by the presence of dissolved cholesterol and delayed by the phosphatides. The high tumour incidence with the former, and the low incidence with the latter are opposed to the view that slow elimination favours carcinogenesis. It is presumed that this effect is primarily connected with the rate of oxidative metabolism of the carcinogen, which is depressed by phosphatides, probably through their antioxidant properties, and accelerated by cod liver oil and cholesterol in varying degrees. Up to a certain limit, the rapid metabolism of the hydrocarbon favours carcinogenesis, while depression of carcinogen metabolism is anticarcinogenic. This would accord with the hypothesis that the hydrocarbon is not itself the true carcinogen, but that the active formation of an oxidized metabolite determines the activity. In this case the metabolite of the hydrocarbon must be considered as the true carcinogen." [The complete data are not included in the summary from which this abstract was made.]—I. H.


No spontaneous tumor or leukemia has been observed during the last 4 years in the strain of Wistar rats used; mammary cancer could be produced in them by implanting stilbestrol pellets under the skin. 2-Acetylaminofluorene (4 mgm. daily) was given in the food to 104 rats, 93 of which developed malignant tumors; of these 34 hepatomas and 3 mammary cancers occurred in uncastrated males, and 11 hepatomas and 23 mammary cancers occurred in uncastrated females. Nearly all the animals showed cystic cholangiomas, which were not regarded as malignant. Only 1 out of 11 spayed rats developed mammary cancer. 2-Acetylaminofluorene has no estrogenic activity. "An unusual type of tumour which was observed in 16 instances is a carcinoma arising from the ductus acusticus externus. It originates in the sebaceous glands of the duct, or starts as malignant papilloma from the squamous epithelium." These tumors occurred in both sexes with about the same frequency. Five adenocarcinomas of the gut occurred. The hepatomas frequently formed metastases in the lung, as did the carcinomas of the ductus acusticus in 3 cases. Three liver tumors and 3 breast cancers were transplanted. One spayed rat developed leukemia; subcutaneous injection of the blood in 3 young rats produced rapidly growing tumors and later, a leukemic blood picture. Intravenous injection of such blood or of tumor cells produced leukemia and local tumors.

Most of the tumors mentioned above appeared between the 180th and 280th day. Five male rats were painted with 2-aminofluorene in acetone; after 280 days all the animals showed malignant hepatoma, and 1 of them had also a carcinoma of the ductus acusticus. There was no alteration in the painted skin.—E. L. K.


A glioma is reported in 1 of 12 rats that were fed from the age of 2 months, for a 24 week period, on a diet containing 0.5 gm. of 2-acetylaminofluorene per kgm. of food. The animal died 2 weeks after incoordination of movement and a slight paresis were first observed. Post-mortem examination revealed asymmetry of the cerebral hemispheres, with the left enlarged frontally. Sections showed an infiltrating neoplastic growth extending throughout the olfactory bulbs, the white matter of the frontal and temporal lobes, and the anterior and main part of the lateral ventricle. It also invaded the lepto-
meninges. The tumor was diagnosed histologically as a glioma of the type "glioblastoma isomorphe" of Rio-Hortega.—R. J. L.


A continuation of an earlier investigation (ibid., 25:90. 1944; abstract in Cancer Research, 8:56. 1945) upon the simultaneous administration by mouth of 2-acetylamino-fluorene and allyl-thiourea, in which benign and malignant tumors of the thyroid were produced. The administration of 2-acetylamino-fluorene followed by allyl-thiourea produced multiple adenomas of the thyroid, but no malignant tumors, while allyl-thiourea alone produced single adenomas only.—E.L.K.


Prolonged continuous thyroid hyperplasia produced by the goitrogenic agent in Brassica seeds leads to the formation of thyroid adenomas.—E.L.K.


Studies were made of the effects of yeast and thymus nucleates on the decolorization rate of methylene blue in tissue extracts. The effects of the added nucleates varied with the conditions of the experiments when normal liver extracts were employed. At low dye concentrations both types of nucleate depressed the rate of decolorization, while at relatively high dye concentrations an acceleration of decolorization resulted; at intermediate concentrations of dye yeast nucleate accelerated, whereas thymus nucleate depressed the decolorization rate. When extracts of hepatoma were studied, however, an accelerating effect of both types of nucleate depressed the rate of decolorization, although found to be dependent upon dye concentration, appeared to be augmented by the addition of nucleates. Coenzyme I was found to be responsible in a considerable measure for the decolorization of methylene blue, but it was found that this factor was active only in the presence of the bicarbonate ion. The implications of the various findings were discussed.—R.A.H.


Rapidly proliferating tissue (embryonic and neoplastic) contains more water than adult and normal tissue; ions that favor hydration of proteins also accelerate glycolytic activity of normal tissues and tumors (inhibiting ions have the opposite effect), and finally, increased glycolytic activity is closely connected with rapid proliferation. In regard to this self-contained scheme the author states: "In all probability, the increase in tissue water is due in great part to a rise in water content of the cellular constituents, and this rise is likely to be associated with an increased hydration of cell proteins. The most important kinds of proteins, in this connection, appear to be those which constitute the protein components of enzymes, and, in particular, of such enzymes as are involved to a varying extent in the breakdown of carbohydrates.

"These considerations suggest, therefore, that the intensity of carbohydrate breakdown in a growing tissue, and consequently the rate of cell proliferation, depends largely on the degree of hydration of corresponding enzyme proteins, so that, within limits, an increase in hydration stimulates and a decrease inhibits that enzymatic activity. The suggestion attempts to elucidate the biological significance of the increased water content of rapidly growing tissues by relating it, through the concept of protein hydration, to the metabolic process which serves as the source of energy for cell proliferation. ..."—I. H.


Rat sarcoma 39, Bagg mouse carcinoma 755, and the RC mouse carcinoma of Taylor were grown successfully in fertile incubated hen's eggs. The mortality of the eggs was very high, 73% by the 17th day of incubation, making this method a poor one for the routine growth of tumor tissue. The yolk from eggs bearing the rat sarcoma 39 did not produce sarcomas when injected into susceptible rats; save in one instance in which the centrifuged sediment of such yolk was effective. Injection of such yolk did not confer immunity on young rats. Yolk from eggs bearing either of the two mouse mammary carcinomas frequently reproduced the tumor when injected into susceptible mice. It was equally effective in male and female mice. Repeated attempts to filter the tumor agent through Berkefeld N or V candles were unsuccessful. Freezing and thawing of yolk, or lyophilization destroyed tumor-producing activity, as did heating at 48 to 50 °C. for 30 minutes. If yolk from tumor-bearing eggs was diluted 1:1 with saline and centrifuged at low speed (2,600 r. p. m.) for 5 minutes, tumor activity could be demonstrated almost universally in the fatty cream found above the centrifuged yolk and in the bloody sediment at the bottom, but not in the watery yolk between. The tumor-producing layers contained cells easily demonstrable under the microscope. Tumor-producing activity was not closely correlated with red blood cell content nor could it be released by hemolysis from sediments containing red cells. Most of the tumor-producing activity could be removed by simple filtration through filter paper. Tumor-producing activity of the fatty layer was destroyed by extraction with ether. In the authors' opinion, the tumor-producing capacity of egg yolk from yolk sacs in which mammalian tumors have

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been grown is due to the presence in it of viable tumor cells. No convincing evidence of the presence of a virus or filterable agent has been encountered in their experiments.—Authors' summary.


Analysis of the occurrence of spontaneous tumors in the first 10 brother-by-sister generations of two lines of rats showed one to be long-lived with a relatively high incidence of tumors and the other relatively short-lived with few spontaneous neoplasms. The first 10 brother-by-sister generations of Copenhagen line 2331 had an average life span of 19.6 ± 0.13 months, and 450 neoplasms were observed in 20% of the rats that survived for at least 1 year. Of these growths, 80% involved the thymus gland. Rats of the first 10 brother-by-sister generations of the Fischer line 344 survived an average of 12.8 ± 0.11 months, and only 42, or 1.7%, of those rats that survived for 8 months developed tumors, of which 20 were mesenteric lymph node sarcomas, and none involved the thymus gland.

The 11th to 20th brother-by-sister generations of these lines, which were the contemporaries of the reciprocal F1 and backcrossed hybrids, showed the same respective predominance of tumors of the thymus gland and mesenteric lymph nodes, but showed for each a significant reduction in the average life span. These Copenhagen line 2331 rats lived an average of 16.2 ± 0.16 months, and the Fischer line 344 rats an average of 10.4 ± 0.09 months.

Reciprocal F1 hybrids between these two inbred lines had a longer average life span than their contemporaneous relatives of either parent line. Progeny of Fischer line 344 males and Copenhagen line 2331 females lived an average of 17.7 ± 0.43 months, and the reciprocal hybrids 20.9 ± 0.35 months. No thymic neoplasms were observed in the F1 hybrids, and the incidence of mesenteric lymph node sarcomas was lower than that observed for Fischer line 344 rats. The percentage of tumors involving miscellaneous organs and tissues was greater than that observed for the low tumor parent line. There was no evidence of the maternal transmission of either susceptibility or resistance to the common laboratory diseases.

Progeny of the F1 hybrids backcrossed to the long-lived higher tumor line lived longer and had a significantly higher tumor incidence than the progeny of these hybrids that were backcrossed to the low tumor short-lived line. Mesenteric lymph node sarcomas were observed in all groups of backcrossed hybrids in a proportion not significantly different from that observed in the Fischer line 344 parent line. Thymic neoplasms were observed in 3 of the 4 categories of backcrossed hybrids but in a significantly lower percentage of rats than was observed for the Copenhagen line 2331 or thymus tumor susceptible parent line.

Spontaneous neoplasms involving miscellaneous organs and tissues occurred in both parent lines and in all the hybrid groups. Longevity and hybrid vigor seemed to be potent influences in the incidence of these neoplasms.—Authors' abstract.


Ultimobranchial tissue occurs as cysts in the thyroids of young sheep. The stratified squamous epithelium lining these cysts may develop in two directions. In active thyroids the undifferentiated clear cells of the basal layer may transform into typical thyroid-like tissue. On the other hand, in hyperplastic and atrophic thyroids the more dense suprabasal cells of the cyst epithelium transform into aberrant thyroid tissue, which in some cases forms conspicuous adenoma-like masses.—R. B.


The histological characteristics of 2 tumors of the small intestine, one occurring in a mouse and the other in a rat, are given. Both tumors contained numerous Paneth cells, and the staining reactions of these elements were studied and compared with those of normal Paneth cells. Ten tumors of the small intestine were found recorded in the files of the National Cancer Institute, and Paneth cells were noted in 7.—R. A. H.


Embryonic cells of the chick were grown in culture media containing the following fluorescent chemicals: chlorophyll, dibenzanthracene, and methylcholanthrene, each in a concentration of 1 to 50,000; and neutral red and eosin, each in a concentration of 1 to 100,000. The cells divided and grew normally in the dark. But when exposed to a bright light the dividing cells became abnormal, while resting cells remained undamaged and were able to resume normal mitotic activity if returned to the dark. The injury to the dividing cells consisted in a shortening of the spindle and an agglutination of the chromosomes on the equatorial plate. In addition mitochondria and other granules moved into the space previously occupied by the spindle; and on the surface of the cell many blebs appeared. Eosin and neutral red acted on the cells more rapidly than did chlorophyll or the carcinogens.—R. B.


The literature is reviewed regarding the mode of action of colchicine, and the chemotherapeutic results obtained from its use in the treatment of cancer in experimental animals and in man. In extremely low concentration this drug acts as a mitotic poison inhibiting the formation of the spindle; in somewhat greater concentration it may also cause a distortion of the chromosomes. When tumor-bearing animals are injected with the highest tolerated
doses of colchicine, hemorrhage and necrosis similar to those seen following the injection of certain bacterial filtrates are noted within the tumors. Some very striking results have been reported from the use of colchicine in the treatment of malignant growths in experimental animals; in some instances complete regression of the lesions resulted. In general, large doses were employed, much larger than required for mitotic poisoning and in the range causing capillary damage. Tumors that responded to colchicine therapy were of types that are also radiosensitive, and, by means of x-ray and colchicine combined, therapeutic results superior to those obtained by either method alone have been obtained. The results of therapy in a limited number of human cases have not been as successful as might have been hoped for on the basis of animal experimentation. Sixty references.—R. A. H.


The custom of using only 10 to 25 animals in testing chemicals for therapeutic effects on cancer is criticized. While positive results with small numbers are significant, negative results may not be. Thus, on the basis of probability statistics it is shown that tests done with groups of 10 animals might fail to detect the therapeutic effects of chemicals having a true effectiveness of less than 25%. Similarly, tests done with groups of 28 animals might fail to detect as therapeutic, chemicals with less than 10% true effectiveness.—R. B.


Experimental (foreign body), subcortical, space-occupying lesions in dogs produced high voltage, slow (delta) waves in the electroencephalogram, changes that resembled the electroencephalographic alterations seen in some cases of intracerebral space-occupying lesions in man. Normal rapid activity disappeared, and flattening of waves occurred with subdural and extradural space-occupying lesions. The amount of abnormality can be varied by minor shifts in electrode placement in cases of focal damage to the brain.—M. E. H.


This is a short review of the literature on lymphocytes and cancer, in which it is pointed out that cancer tissue and sites of action of carcinogenic stimuli frequently contain increased numbers of lymphocytes, while conditions (e.g., inanition, radiation) that reduce the growth and incidence of tumors also reduce the number of circulating lymphocytes.—R. B.


A statement of a theory relating viruses and pathogenic plant mitochondria (plastids) to hypothetical cancer-inducing mitochondria.—R. B.


A brief biographical sketch, with portrait photograph and a list of publications from 1902 to 1945.—M. H. P.

Clinical and Pathological Reports

**Clinical investigations are sometimes included under Reports of Research**

**Therapy—General**


Since 1931, metallotherapy has been employed in the treatment of all cancer patients in the clinic of Professor J. Maisin and found (data published elsewhere) to be effective alone and as an adjuvant to other forms of therapy. Observations on 20 patients maintained on a low calcium diet showed that when barium saccharate was given orally (10 drops of 1:10,000 dilution every other day) the urinary excretion of calcium was increased. Therefore, cancer patients being treated with barium saccharate are now given supplementary calcium to compensate for this calcium loss.—G. H. H.

**Etiology**


This is an interpretation of data quoted from the literature in support of the author's thesis that ischemia is an important intrinsic cause of cancer.—E. E. S.

**Radiation**


Scattered radiation measured near the surface of the skin was found to be 18 times greater with 35 mm. photofluorographic technic than with 14 by 17 inch film technic. The person examined was the chief source of scatter. Sufficient radiation to exceed safety limits (.01 r daily) can be received, if the operator is careless. Behind lead screens the margin of safety is not exceeded. An extension cone to the x-ray tube reduces stray radiation.—R. E. S.


The types of irradiation injury encountered after ex-
**Reports of Research**


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