Abstracts
Reports of Experimental Research

Carcinogenic Compounds


In view of reports that the potency of carcinogens may be altered by the agents in which they are carried, methyl salicylate and benzene were compared as solvents for methylcholanthrene.

Four groups of mice were painted twice weekly with methyl salicylate, benzene, methylcholanthrene in methyl salicylate, and methylcholanthrene in benzene respectively. Papillomas, epidermoid carcinomas, spindle cell sarcomas, and tumors composed of two types of neoplastic tissue appeared at the site of application of the carcinogen in both methyl salicylate and benzene. No tumors occurred in mice painted with either solvent alone. No difference was found in tumor incidence, type, and time of appearance in the mice painted with methylcholanthrene in methyl salicylate and methylcholanthrene in benzene.—Authors' summary.


Tests of the carcinogenic activity of 70 new compounds related to benzanthracene, dibenzanthracene, methylcholanthrene, and benzpyrene have given further evidence of a high degree of chemical specificity. Slight changes in structure are followed by major changes in activity. Several hydroxy derivatives of active compounds have shown little or no ability to induce tumors.

A new compound containing sulfur, 4,9-dimethyl-5,6-benzo thiophanthrene, has proved highly carcinogenic. Radioactive sulfur in this compound could serve as a tracer for studying the local metabolism of an active carcinogen at the site of tumor induction.—Authors' summary.


In several experiments involving 124 mice, epidermal hyperplasia, caused by repeated applications of methylcholanthrene, was examined at intervals from 11 to 64 days and regenerative hyperplasia, at the edges of excised areas of skin, was examined at several intervals between 10 and 19 days. Regional diversity in structure was localized, irregular, and seemingly haphazard in methylcholanthrene hyperplasia, whereas in regenerative hyperplasia it was correlated with distance from the excised area. In the methylcholanthrene hyperplasia focal variations were of greater amplitude, the basement membrane and granular layer were slightly more definite, acanthosis and hyperkeratosis were generally more marked, and the spinous cells were somewhat less eosinophilic. Intranuclear viscosity was decreased in both kinds of hyperplasia. This change was progressive to malignancy in the methylcholanthrene hyperplasia and only temporary in regenerative hyperplasia. In both there was demineralization, but this was more irregular in the methylcholanthrene hyperplasia.—Authors' abstract.


Bakelite disks were implanted into 13 rats. Of 9 surviving rats 20 months of age or over in this experiment, 4 developed tumors around the bakelite. In a similar series of 10 mice, 6 surviving at 18 months of age showed no tumors. These tumors were fibrosarcomas which were not transplantable. A very low hazard of bakelite carcinogenicity is suggested because of the prolonged exposure necessary for tumor production in rats and their absence in mice. A discussion of the low carcinogenicity of bakelite ingredients is included.—R. C. R.


Pellets of purified 20-methylcholanthrene were implanted in the cerebral meninges, the right cerebral hemisphere, and the cerebellum of 103 C3H mice of the male sex.

In all, 48 tumors were produced in this manner: 25 gliomas, 13 sarcomas, 7 mixed gliomas and sarcomas, and 3 unclassified. Among the gliomas were present examples of astrocytoma, glioblastoma multiforme, medulloblastoma, oligodendroglioma, and spongioblastoma polare. Within certain limits the site of pellet implantation was a determinant of the type of intracranial neoplasm which developed.

The rate of growth of the sarcomas was much greater than of the gliomas. The average time when the sarcomas appeared was 195 days as against 279 for the gliomas.

The method of subcutaneous transplantation was employed for the study of the growth behavior of these intracranial neoplasms. From 9 to 14 subtransplants were made of many of these tumors with results that indicated a much more rapid growth of the sarcomas than the gliomas. Frequently, unclassifiable primary gliomas developed characteristic structural patterns in the transplants which made identification possible. This method of study also permitted the separation of so-called “mixed” tumors into their component parts.—Authors' summary.

Hormones


Pooled urines from 2 sets each of cancerous and noncancerous men and women were separated into three prin-
cllaphic phenolic fractions containing presumably estrone, estradiol, and estriol. Bioassay of each fraction was performed, and it was found that (a) the sum of the estrogenic activity of the three fractions was higher in the noncancerous women's urines than in urine from cancerous women; (b) this was reversed in the case of the men's urines because of the higher titer of the nonketonic fractions; (c) the "estriol" fraction of noncancerous women's urines had a higher titer than the same fraction from cancerous women's urines; (d) the "estradiol" fraction of cancerous men's urines had a higher titer than the corresponding fraction of noncancerous men's urines. A further separation of certain nonketonic fractions indicates that the difference in titers between cancerous and noncancerous men is real and due probably to the estrogens presumably segregated into these fractions. A useful fractionation of estriol particularly is indicated. The implications of these findings are discussed.-Authors' summary.


Subcutaneous injections of deoxycorticosterone acetate failed to accelerate the appearance of mammary carcinoma in strain C3H female mice and no mammary tumors appeared in the males of this same group. Desoxycorticosterone injection also failed to increase the incidence of pulmonary tumors in 20 weeks after a 1 mgm. test dose. No gross or microscopic abnormalities were noted in the adrenals, pituitary, thyroid gland, gonads, liver, or spleen. No subcutaneous sarcomas were observed at the site of injection. It was concluded that desoxycorticosterone is not carcinogenic to mice.-R. C. R.


Subcutaneously administered stilbestrol is more toxic to C3H mice than it is when given orally. Retardation in weight increase is directly proportional to the size of the dose and is more marked when stilbestrol is given subcutaneously than when taken orally. This is not due to decreased food consumption but to some toxic action of the compound. If stilbestrol is stopped, the weight increase returns to the near normal level.

The animals show loss of weight, atrophy of the viscera, especially the spleen, decreased spermatogenesis of the testes, scrotal herniation, and development of mammary carcinoma. Liver lesions were not observed. In animals killed within a few weeks after cessation of treatment, there was observed squamous metaplasia of the coagulating gland, fibromuscular hyperplasia of the seminal vesicles, and myxomatous degeneration of the ejaculatory ducts. Brown degeneration of the adrenals was noted.

Adenocarcinoma of the breast developed in 18 of 22 C3H mice in an average period of 24 to 27 weeks following administration of 4.27 to 14.25 mgm. of stilbestrol. No lymphatic tumors were seen in any of the experimental animals.-R. C. R.


Large quantities of stilbestrol transplanted subcutaneously as pellets caused marked lowering in the weight gain increment. This decrease was proportional to the concentration of the stilbestrol in the pellet. Twenty five per cent pellets produce a mortality of 10% in strains C and C3H mice. Fibromuscular hyperplasia of the seminal vesicles, degeneration of the seminiferous epithelium, and partial arrest of spermatogenesis were observed after the first month of exposure to 10% pellets. After 3 to 4 months of similar treatment lack of spermatogenesis was observed and diffuse hyperplasia of interstitial cells of the testes occurred. Eleven months after pellets of various concentrations had been implanted, 13 testicular tumors were found in a total of 52 mice. The incidence of the tumors was roughly in direct proportion to the concentration of the stilbestrol in the tablet.

The tumors were white and pale with a dark brown surrounding tissue. Histologically they showed solid sheets of large polygonal or slightly elongated cells supported by sparse stroma. Large varicosities of capsular blood vessels were observed. Metastasis occurred in the suprarenal region in 3 animals. Seven of the mice developed lymphoid tumors. The appearance of these tumors was probably accelerated by the procedure. Strain C mice are resistant to mammary carcinoma but if these mice were nursed by C3H females and then received stilbestrol pellets the incidence of a mammary cancer occurrence increased to 50%. Foster nursing had no effect on development of testicular tumors.-R. C. R.

GENETICS


The author summarized work done heretofore on the host-tumor relationship in several strains of inbred mice or hybrids closely related genetically to the test animals. In this group of studies mice of strains L, C57 black, Y, C, I, A, and D were used. Intracutaneous transplantations of sarcoma 37 were made using minced tissue technic. Transplanted tumors in strains Y and D quickly killed their hosts. Tumors in C57 black and L strains grew fast for an initial 12 to 41 days and then completely regressed in most animals. Tumors transplanted into strains C and I grew much slower but in strain C the tumor eventually killed the animal. It regressed in strain I after 12 to 13 days. Strain A mice were shown to be homozygous in relationship to one spontaneous mammary tumor but showed marked variability in their degree of natural resistance to sarcoma 37.

Hybrid mice produced by mating strains I and Y showed 100% susceptibility of the F1 and Y backcross generations and 50% susceptibility of the I backcross generation. This suggests that progressive tumor growth in these mice is controlled by a single dominant factor. If susceptibility is inherited as a single dominant factor as suggested above, then mating two resistant strains should give a high percentage of resistance in the hybrids.
This did no occur when strains L and I were mated. The F1 hybrids were 87% susceptible, F2 were 60% susceptible, and about 80% and 30% susceptibility of L and I backcross respectively occurred.

The conclusion is that the natural resistance of parent strains gives no indication of degree of natural resistance of their hybrids and that one series of hybrids is not sufficient for formulation of any general conclusions regarding inheritance of natural resistance.—R. C. R.


A 25% incidence of tumors occurs in fostered C3H mice which remain with their maternal parent only 17 hours after birth. This suggested to the author the possibility that some of the same strain mice may develop tumors when taken from the parent at birth. Young C3H mice obtained by operative removal from the parental uterus were fostered with C57 black females. None of these animals developed mammary cancer. Only 3 of a group of 15 young C3H mice taken directly from the parent at birth and fostered on C57 black females developed mammary cancer.

In a second series, young C3H mice were foster nursed by C57 black mice for 7 to 14 days and then were nursed on C3H black females for 3 days. Tumors of the breast developed in 100% of the group suckling the C3H mothers at 7 days and in 84% of those suckled by C3H females when 14 days old. This suggests an increased resistance to the milk factor as the animals grow older.—R. C. R.


A review of the literature on this phase of the work conclusively shows that mammary cancer in mice is controlled by the presence of an extrachromosomal influence transmitted in milk, and an inherited susceptibility of the mice to the action of the milk influence. The purpose of this paper is to report observations on the incidence of mammary carcinoma in animals carried beyond the first hybrid generation in an attempt to establish the role of the paternal parent in later generations of mice.

C3H strain females were mated with I strain males. Females from this mating were backcrossed with I strain males. This was repeated with females of the first I backcross generation to give the second backcross generation. Similar backcross breedings were done with Y strain mice using C3H strain females to produce the F1 generation of this series. The F1 hybrids of C3H females and I males were more susceptible to tumor development than the F1 hybrids of the C3H×Y mating. As progressively more backcrosses were done, the Y backcross group became more and more tumor resistant. F2 hybrids from strain C3H crossed with strain I showed a higher cancer susceptibility than the F2 generation of C3H×C57 Black mice.

These relations tend to show that genetic factors are of considerable importance because they determine the susceptibility of the mouse to the nongenetic influences present in milk of the mother. The incidence of tumors in these various groups elucidates the importance of chromosomal factors derived from the paternal parent in mammary carcinoma incidence in mice.—R. C. R.


Two highly inbred strains of mice, Ak and Fc, which differ rather widely (approximately 70 to 2%) in the incidence of spontaneous leukemia (lymphoid and myeloid) have been used to study the inheritance of susceptibility to this disease. The data, covering the parental, reciprocal F1, F2, F3, and various backcross generations, include records on 4,787 mice. The data indicate that susceptibility to spontaneous leukemia is inherited, probably on a multiple-factor basis, and that it is influenced by undetermined environmental factors. The common logarithm of the percent leukemia in a population is a simple function of the percentage of heredity from the high leukemia stock. No consistent evidence was obtained to demonstrate that either maternal influence or sex linkage were involved in susceptibility. There is some evidence that the female mouse is more susceptible to leukemia than is the male. Susceptibility to mononuclear leukemia is also inherited, probably as a multiple-factor dominant character, but with an extremely low degree of penetrance (2.7% in the Ak stock). The type of leukemia as well as the degree of susceptibility is subjected to the laws of heredity.—Authors' abstract.


In an effort to open up new leads and to further the study of a maternal influence affecting the incidence of mammary gland tumors in mice, an investigation of the blood was started. This is a report of work with the whole blood. Inbred JAX C3H mice which have had their tumor incidence lowered by foster nursing on inbred JAX C57 black mice were injected when 1 to 3 months of age with 0.5 cc. of whole blood secured from normal inbred high tumor JAX C3H male and female mice 2 to 4 months of age. Significant differences now appear between the injected mice and their litter-mate controls. The mice of both groups are well beyond the average tumor age for breeding females of the untreated and un-fostered JAX C3H strain.—Authors' abstract.

RADIATION


Nucleic acid adsorption bands fall at 2600 A. It is at this wave length that mutations in unprotected cells are observed. Nucleic acid is most condensed in the chromosomes and it varies during the different stages of mitosis. It was thought by the authors that some idea about the effect of ultraviolet radiation on living cells could be obtained by irradiating sodium thymonucleate in vitro.
Changes in the structural viscosity and streaming birefringence were determined in specimens which were irradiated. Irradiation was done by use of three special low pressure mercury-vapor lamps placed symmetrically around the thymonucleate solutions. The solution for test was placed in a fused quartz tube and a control was irradiated in a soft glass tube which absorbed all radiation below 3,300 A. Observations were made on the solutions between 4 and 120 hours of irradiation.

The structural viscosity and streaming birefringence decreased progressively with the progression of the irradiation. This was interpreted as being due to depolymerization of the asymmetrical molecules of the thymonucleate solution into smaller, less asymmetrical molecules. The energy to which the nucleate was exposed was estimated to be \(5.3 \times 10^{-17}\) quanta. It was considered possible that the energy of the radiation could be transferred easily to the bonds which hold the macromolecule of nucleic acid together. This could break the bond and thus cause the molecular change noted in this experiment. This breakdown of the nucleic acid macromolecule may be responsible for changes in chromosomes which result in mutations.—R. C. R.

**Biochemistry and Nutrition—Chemotherapy**


Liver tissue and tumors arising directly from liver tissue are suitable for respiratory studies because of the large number of active enzymes in the cells. The alterations of these enzymes can be readily followed when the liver cells become malignant. The enzymes amylase, catalase, and xanthine dehydrogenase were selected for this study. The xanthine dehydrogenase of hepatic tumor was found to be half as active as normal rat liver but its activity in normal liver and liver from tumor-bearing animals was the same. Xanthine dehydrogenase in fetal rabbit livers was extremely low. Catalase activity in hepatic tumor tissue was found to be extremely low in comparison to the normal. The effect of transplanted hepatic tumor and of Jensen sarcoma similarly reduced the liver catalase activity. No difference was found in amylase activity between the normal and tumor-bearing livers. Enzymes of rapidly regenerating liver tissue were found to be about as active as in normal liver. The contrast between the enzyme activity of rapidly regenerating liver and malignant liver tissue was sharp and very definite.—R. C. R.


Pantothenic acid is necessary for growth in young animals and for life in both young and adult animals. The deficiency produces thinning of the hair about the nose, over the scalpula, flanks, and lower abdomen, scaling in the same regions, a feeling of slight thickening of skin about the nose, and occasional crusting about the nose. Apathy, squatting and dragging the hind quarters, and awkward gait are also manifestations of the disease.

Morphologically, the adrenals and osseous systems showed no changes similar to those observed in rats on similar deficiency. The heart and liver showed sudanophilic material on occasional slides. A few renal sections showed enough sudanophilic material to be characteristic of fatty degeneration. The process in the skin appears to be a hyperkeratotic, atrophic, and desquamative dermatitis. The nervous system showed myelin degeneration in sciatic nerves and the spinal cord.

The inability of the animals to survive complete pantothenic acid avitaminosis indicates that this disease is a biochemical one showing morphological evidence in only a few tissues.—R. C. R.


Tumor growth in mice as measured by calipers was compared in animals receiving a normal diet and those having pantothenic acid deficiency. Rate of tumor growth in control animals was much more rapid than in the mice on pantothenic acid deficiency. One hundred gamma doses of calcium pantothenate caused marked stimulation of tumor growth which approximated that of the control animals. Tumor growth rate in deficient animals became less as the deficiency became more severe. Dietary inadequacy except for pantothenic acid does not appear to be significant in this experiment. Pantothenic acid deficiency is too severe on the host to be considered as a practical adjunct to tumor therapy.—R. C. R.


Growth curves of C3H mice on an artificial diet deficient in pantothenic acid showed loss of weight. Supplementing the diet with thiamin, pyridoxine, riboflavin, nicotinic acid, and choline increased the growth slightly. With the addition of pantothenic acid the growth curve increased very rapidly. A daily supply of 20 to 30 gamma of the vitamin is adequate for the mouse. Rapid recovery occurs upon adding pantothenic acid supplements. Paralysis of the hind legs, loss of hair, thickening of the skin, and myelin degeneration in the spinal cord are manifestations of deficiency. Death occurred in deficient rats in from 8 to 10 weeks.—R. C. R.


Three groups of mice of subline 212 were used in this experiment. The first group was maintained on Purina dog chow. The second group was fed a synthetic high cystine diet; and the third group was fed a low cystine diet. All mice on alternate days were painted with a 0.2% solution of methylcholanthrene in ethyl ether. Controls ingesting high and low cystine diets were painted with ethyl ether for a period of 100 days.
A high incidence of leukemia occurred in the first group. No aortic sclerosis was observed. The second group showed a 92.3% incidence of leukemia with 26.6% having aortic sclerosis. Mice fed a low cystine diet developed leukemia in only 17.1% of the cases and 94.2% of them showed sclerosis of the aorta.

The latent period for leukemia in the third group was prolonged. The shorter life span of animals fed low cystine diets may account for the low incidence of leukemia in this group. The arteriosclerosis can be accounted for as a toxic action of methylcholanthrene in the absence of cystine as a detoxifying agent.—R. C. R.

### Clinical and Pathological Reports

#### Gastrointestinal Tract


This paper is a statistical analysis of 416 cases which came to necropsy between January, 1910 and July, 1937. The most important early symptom was a change in bowel habit. Seventy-six% of lesions within 10 cm. of the anal ring were not diagnosed by the referring physician. In 172 patients subjected to operation, the two main causes of death were peritonitis (46.7%) and pneumonia (17.4%).—G. De B.


Two hundred and sixty-four patients with proved gastric cancer were admitted to the New York Hospital from September, 1932, to 1940. Of these, 88(33.3%) were found to be inoperable clinically, and 91 (34.5%) were inoperable by exploratory laparotomy. In 21 cases a palliative gastroenterostomy was done; in 7 cases miscellaneous other procedures were carried out; and in 16 cases a palliative gastric resection was done. Only 41(15.5%) of the entire 264 cases were considered curable by surgical methods. The combined operative mortality for palliative resections was 10.5%. There was a 5-year survival in 44.4% of the operable cases.

The author emphasizes the importance of careful physical examination and evaluation of early symptoms of gastric carcinoma. A discussion of the merits and pitfalls of roentgen examination, gastric analysis, gastroscopy, and stool analysis was presented.

The inoperability of gastric carcinoma is primarily due to a late diagnosis and errors in interpretation and execution of diagnostic procedures.—R. C. R.


The development of pancreatico-duodenectomy is briefly traced from the original animal experiments of Coffey in 1909 to Whipple's latest modification of his multiple stage operation in humans. Six types of operations are illustrated. A case report is presented in which a one-stage resection of the duodenum and head of the pancreas was performed for an adenoma of the ampulla of Vater. The patient succumbed to uremia on the 5th day.—A. M.


This is the case report of a patient who was first seen and successfully treated for typical pernicious anemia with combined system disease and who returned 5 years later in relapse. X-ray and gastroscopic studies showed a polyloid gastric carcinoma. Gastric resection was performed. The high incidence of adenomatous polyps and carcinoma in pernicious anemia is discussed and the necessity for repeated x-ray and gastroscopic studies in these patients is stressed.—A. M.


A 50-year-old male had had a gastric resection for a “borderline” polyp, responsible for symptoms of 5 years’ duration. Thirteen years after this operation he had a second palliative resection for a carcinoma of the stomach with metastases to regional nodes.—A. M.


A case of scirrhous carcinoma of the stomach with multiple peritoneal implants which succumbed to acute intestinal obstruction. Biopsy of characteristic implants at two operations showed only “chronic inflammation.”—A. M.


This paper is essentially a plea for earlier diagnosis in cases of gastrointestinal malignancy. A survey of metropolitan New Haven revealed that only 2% of patients...