Abstracts

Reports of Research


A solution of carcinogen (e.g., methylcholanthrene, 3,4-benzpyrene, 1,2,5,6-dibenzanthracene) in acetone is added drop by drop to distilled water, and the mixture is then dialyzed in a cellophane bag against distilled water for 2 or 3 hours to free it from acetone. Stable colloidal solutions of “more than 1% concentration” can be prepared.—E. L. K.


9,10-Dimethyl-1,2-benzanthracene is highly carcinogenic for the rabbit’s skin, producing multiple, progressively growing warts after 5 weeks’ application, and malignant tumors after about 16 weeks’ application. By comparison solutions of “more than 1% concentration” can be prepared.—E. L. K.


A suspension in olive oil of 2-acetylaminofluorene was given by stomach tube thrice weekly to 17 CBA mice, of which 12 lived for more than 1 month. The highest total dosage was 1 gm. in 65 weeks. Of 6 mice (1 male, 5 females) treated for more than 1 year, 4 females and the male developed primary neoplasms of the bladder. Other tumors were a fibromyoma, and a sarcoma, of the uterus; and hepatomas (in 3 males and 2 females) coexistent in 3 cases with vesical neoplasms. There were no mammary tumors. Spontaneous tumors of the liver and the uterus, but not of the bladder, may occur in this strain. The bladder tumors were (1) in the male, generalized benign transitional cell papillomatosis practically filling the vesical cavity; (2) similar to (1), with apparent downgrowth; (3) papilloma with malignant subepithelial downgrowth; (4) transitional cell carcinoma penetrating through muscularis to serosa; (5) “massive infiltrating carcinoma completely breaching the muscular wall.” Thus only (1) was considered to show no malignant portions. No metastases were found. Ten photomicrographs are included.—E. L. K.


A fuller report than appeared in Schweiz. med. Wochenschr., 72:1070. 1942; abstr. in Cancer Research, 4:654. 1944. Of 12 rabbits living more than 3 years after implantation of chromium, arsenic, or cobalt into the femur, 8 developed cancer at the site of the depot or in the lungs.—M. H. P.


Abderhalden’s protective enzymes from the urine of patients with carcinoma were separated into a protein and a low molecular weight fraction by treatment in a circulating dialyzer by Manegold’s method (Kolloid-Ztschr., 56:7. 1931), preferably at pH 5.5 to 6, for 2 to 3 days. After neutralization neither the dialyzate nor the material remaining within the dialyzing apparatus showed enzymic activity, but when the 2 substances were mixed, activity was evident. The inner liquid was thermolabile, the outer, stable to heating at 100°C for 30 minutes. The authors postulated that the separation was into coenzyme and apoenzyme. Since, with many such pairs of enzymes, the action specificity is determined by the coenzyme, and the substrate specificity, by the apoenzyme, an attempt was made to see whether this was the case with regard to the protective enzymes. Investigations in which coenzyme and apoenzyme were interchanged, however, had only slight success, since the specificity became lost as the protective enzyme solution was concentrated. The concentrated enzyme solution cleaved all carcinoma substrates nonspecifically. Strong cleavage was obtained by addition of 1:20,000 to 1:100,000 trypsin (itself inactive) to apparently inactive defense proteinas.—M. H. P.


Waldschmidt-Leitz and his associates have proposed the
use of the test for $d$-peptidases as a diagnostic method in cancer. The present authors oppose this. Of 14 sera from patients without carcinoma, 2 attacked $d$-alanlyglycyglycine, whereas of 16 sera from patients with carcinoma, 5 hydrolyzed this tripeptide. The peptidase activity was measured with the aid of the Willstätter titration. If the colorimetric Zimmermann method, employing o-phthalaldehyde, was used as recommended by Waldschmidt-Leitz, the number of positive reactions increased to 11 in the carcinoma sera group and to 6 in the control group. The Zimmermann reagent is considered unsuitable for quantitative following of the cleavage of polypeptides.—K. G. S.

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**Uber die Spaltung der $d$-Peptide durch Krebssera.**


d-Leucylglycine was hydrolyzed 10% by serum from a patient with keloid, not at all by serum from normal or cancerous persons, nor by serum from normal or benzpyrene-treated rats. Ultraviolet and roentgen irradiation gave no consistent results with regard to the appearance of ability to cleave $d$-peptides. The cleavage was studied by the alcohol titration method of Waldschmidt-Leitz ([Angew. Chem., 55:324. 1938].—M. H. P.

**Metabolic Studies in Patients with Cancer of the Gastro-Intestinal Tract. XX. Lipotropic Properties of Protein.**


Previous studies have shown that patients with gastrointestinal cancer suffer from hepatic dysfunction. This study was undertaken to see if the return toward normal hepatic function induced by the feeding of high protein diets was associated with the restoration of a normal chemical composition of the liver. Seven patients with gastrointestinal cancer were given 2.5 gm. of complete protein per kgm. per day for from 10 to 21 days. At laparotomy, the concentrations of fat in their livers were all within normal limits. Nine patients with gastrointestinal cancer who received 75 gm. of amino acids during the 10 hours before operation were found at laparotomy to have liver fat concentrations as abnormally high as those of fasted patients.—M. B.

**A Possible Relationship in Animals between Tumor Susceptibility and Stability of Tissue Proteins.**


Beginning with the 19th or 20th day after implantation of the Jensen sarcoma, when a pause in the rate of tumor growth generally occurred, the muscle protein of the sarcomatous rats was split more readily by cathepsin from the tumors, or by extracts of the livers of sarcomatous rats, than was the muscle protein of healthy controls. The muscle proteins of 9 rats with extraordinary resistance to Jensen sarcoma (each rat having resisted 4 successive transplantations) were hydrolyzed much less readily than those of susceptible animals. On the fourth day after transplantation, the skin proteins of some rats showed greater proteolysis by liver cathepsin than did the skin proteins of healthy animals; subsequently the cleavage of skin proteins of the sarcomatous animals showed an inhibition, rather than an augmentation. A similar inhibition was noted in the skin proteolysis in rats inoculated with Krichevsk-Sinelnikov sarcoma. In some cases of rapid growth of Jensen sarcoma, there was a pronounced increase of skin proteolysis on the 14th day; in cases of very slow tumor growth, an increase in protein breakdown did not occur even 3 months after transplantation.

The cleavage of proteins of whole blood, serum, and plasma by liver enzymes was much lower in cancer-bearing animals and human beings than in healthy controls. Ultraviolet irradiation increased skin proteolysis in healthy and tumor-bearing rats, and in 3 of 5 tumor-resistant rats. When 40 rats were inoculated with Jensen sarcoma, then freed surgically from the developed tumors, and reinoculated 6 to 8 days later with the same type of neoplasm, 14 rats proved resistant to the second implantation, and 9 of these 14 also resisted effects by ultraviolet irradiation upon skin proteolysis. Subcutaneous injection of 3 mgm. of methylcholanthrene in petrolatum considerably decreased skin proteolysis in 10 of 16 rats; benzpyrene, a less active carcinogen, was also less active in inhibiting skin proteolysis, and dibenzanthracene, weakest carcinogen of the 3, did not affect skin proteinolysis in doses of 6 mgm.—M. H. P.

**Thymonucleic Acid in Tumors.**


The evidence is reviewed that shows that thymonucleic acid plays an important role in normal cells and that some tumors have a disturbed balance of nucleic acids. Thymonucleic acid is combined with protein to form the nucleoprotein of chromatin. It plays an important part in the transmission of hereditary characteristics by the genes, in mitosis, in nucleic acid synthesis and balance, and in the protein synthesis of the cell.

Observations on tumors, by the use of macrochemical methods of analysis of thymonucleic acid or visual inspection of Feulgen stained material, are contradictory and inconclusive. Photometric histochemical observations by means of the Feulgen reaction have shown that some epidermoid carcinomas of mice and human beings, and leukemic blood cells of patients contain increased amounts of thymonucleic acid.

Cytochemical studies indicate that the cytoplasm of malignant cells contains increased amounts of ribonucleic acids and suggest that the heterochromatic region of the chromatin plays a specific role in carcinogenesis. The observations in tumors of stickiness, non-disjunction, displacement, and clumping of chromosomes, of polyplod...
cells with increased number and volume of chromosomes, of more frequent mitoses, of enlarged nucleoli, and of multinucleate and giant cells are cytologic evidence of abnormalities of nucleic acids in neoplastic cells.

Extracts of cells containing nucleic acids and their breakdown products have a growth-promoting effect on other cells. That thymonucleic acid may induce a specific, predictable change transmissible to subsequent generations of cells has been shown in work with pneumococci. The Shope papilloma virus and the mammary tumour-inducing milk factor of mice contain nucleic acids.

Thymonucleic acid is located in the regions of the chromosome that are most susceptible to mutation. Similar wave lengths of ultraviolet light produce a breaking down of the polymerized sodium thymonucleate, mutations in chromosomes, and carcinoma of the skin. Somatic mutations leading to neoplasia might be produced by alterations in the complex macromolecule of thymonucleic acid. An initial slight modification in the thymonucleoprotein could, during a variable latent period, lead to a progressive and ultimately irreversible imbalance of nucleic acids. Such a theory of an intracellular cause of neoplasia will be established or disproved by subsequent investigation.—Author's abstract.


A photometric histochemical technic was employed, in which the amount of thymonucleic acid was determined by the absorption of complementary monochromatic light by sections of tissue stained by the Feulgen reaction. Comparative measurements were made on the adjacent normal epidermis, hyperplastic epidermis, and epidermoid carcinomas of 11 specimens removed from patients.

The mean amounts of thymonucleic acid per unit volume of tissue were larger in carcinomas than in normal epidermis and were least in hyperplastic epidermis in which there is relatively less nuclear material. Compared with normal and hyperplastic epithelium, the nuclei of some carcinomas showed statistically significant increases in amount of thymonucleic acid per cell; in no instance was the amount significantly decreased. Such variations in the mean amount of thymonucleic acid in the cells of epidermoid carcinomas support the hypothesis that in some types of neoplasia there is a disturbance of the nucleic acids—Authors' abstract.


Respiratory studies of a variety of healthy tissues of Helianthus annuus, of bacteria-containing tumor tissues, bacteria-free secondary tumors, graft tumors, and tissue cultures of the same plant, and of genetically tumefacient tissue cultures and graft-induced tumors on Nicotiana have led to the conclusion that these various pathological states do not result in any apparent significant qualitative change in the respiratory picture, but do result in a considerable lowering of the respiratory level. If this lowering is real and not merely an artefact due to the greater amount of nonliving tissue present in pathological growths, it may be considered similar in kind to long recognized characteristics of animal neoplasia.—Author's abstract.


When rats were inoculated with Jensen sarcoma in the second and third weeks of pregnancy, a strong inhibition of the growth rate of the tumor was observed. On the other hand, mating of sarcoma-bearing rats had no effect on the development of the tumor.

By the injection of 50 to 200 I.U. of Prolan (prepared from pregnancy urine) an inhibition or regression of the tumor was produced in 5 of 9 males and in 7 of 14 females; spontaneous regression occurred in only 17 of 150 rats. Treatment with Preloban from pituitary glands had no comparable effect. The authors suspect that the activity of the Prolan preparations is due to an as yet unidentified component of the pregnancy urine.

The presence of sarcomas of medium size (8 to 15 gm.) led to an average blood cell sedimentation value of approximately 6 mm. in 1 hour; rats bearing large Jensen sarcomas had sedimentation values of about 17 mm. in 1 hour.

The intramuscular injection of lanthanum nitrate or sodium tungstate increased the sedimentation rate but did not cause a diminution in the size of the tumor, although under other experimental conditions a diminution in tumor size has occurred with the former compound. Effects of the various preparations on the pyruvic acid level of the blood are tabulated.—K.G.S.


A review.—M. H. P.


Two groups of mice belonging to the cc strain, from 1 to 13 months of age, were autopsied at monthly intervals. The groups consisted of (a) 20 intact virgin females, and (b) 34 gonadectomized females. Ovariectomy was performed when the mice were 1 to 3 days of age. Adrenal cortical carcinomas were found only in the ovarietomized mice. These occurred in 100% of the 21 females 6 to 12 months of age inclusive, and in none of the 20 intact mice. Progressive changes in the adrenal cortex preceding the appearance of the carcinomas are described.—Authors' abstract.

Two groups of mice belonging to the ce strain, from 1 to 13 months of age, were autopsied at monthly intervals. The two groups consisted of (a) 26 intact virgin females, and (b) 34 gonadectomized females. Ovariectomy was performed when the mice were 1 to 3 days old. Growth and development of accessory sex organs occurred after the appearance of adrenal cortical tumors in the ovariectomized females. Effects attributable to estrogenic and androgenic hormones were recorded.—Authors' abstract.


Observations have been made on 33 intact and 39 castrated strain ce male mice. Data were obtained at monthly intervals on animals ranging in age from 1 to 13 months. Adrenal cortical carcinomas were observed in 15 of 19 castrated mice killed at 7 to 12 months of age inclusive. In 4 cases the tumors were bilateral so that the 15 mice carried 19 tumors. No such carcinomas were found in 15 intact strain ce male mice killed during the same age period. The adrenal tumors were preceded by certain definite changes in the cortex, which involved pronounced focal increase in subcapsular cells and later, localized cell hypertrophy. The condition of the accessory sex organs in the castrated mice indicated that they were being subjected to: (a) an estrogenic type of influence in some individuals, and (b) an androgenic type of influence in other individuals. There was some evidence that the difference between individuals was in some cases due only to a variation in proportion of estrogens and androgens, both possibly being present at the same time.—Authors' abstract.


Gonadectomy was performed at 2 days of age on 70 females and 61 males of the extreme dilution ce strain of mice. Adrenal cortical carcinomas arose in many of them. The total percentage of adrenal tumors was 91.90 in the females, and in 45.94% of the males. Only animals more than 3 months old are included in these figures. A histological study with photomicrographs is presented.—Authors' abstract.


Of the virus disseminated into the host's tissues from a developing Rous sarcoma, only about 20 minimal infective doses was found in the richest tissue—the spleen. It is suggested that the whole of this can be referred to the amount contained in the blood and phagocytic cells present in the tissues.—A. H.


Addition of the antibiotic substance notatin, 0.2 mgm., together with 2 mgm. of glucose, to 0.5 ml. of a suspension of the Rous agent, equivalent to 1,000 minimum infective doses, resulted in almost complete loss of viral activity in 1½ hours. Notatin without glucose caused merely a slight reduction in the activity of similar suspensions, and glucose alone was without effect. In relation to the known susceptibility of the Rous virus to oxidizing agents, it is pointed out that notatin exerts its antibiotic activity by means of hydrogen peroxide, produced in the oxidation of glucose to gluconic acid.

In contrast with such activity against the Rous agent in vitro, no effects upon the virus were observed in vivo, when notatin was administered either to fowls bearing the Rous sarcoma or to normal fowls ½ hours prior to the inoculation of active filtrate.—A. H.


An emulsion of this tumor in saline, when injected into the thigh muscles of a mouse, produces a large tumor in 7 days, but if the emulsion is made in 2% histone (from calf thymus, carcinoma 2146, or mouse liver) or protamine (from herring sperm) in saline, the rate of growth is slowed to one-half or less, but the inhibition is transient. Proteins from human plasma, and egg albumin have no such effect.—E. L. K.


The proliferation of Saccharomyces cerevisiae in Williams' medium was promoted by saline extracts of mouse embryo, of adult mouse brain, heart, spleen, liver, kidney, and testis, of mouse adenocarcinoma 15091a and dbr, and of 7-day chick embryos. On an equal weight basis, brain, liver, and embryo were most potent as sources of proliferation-promoting substances, and chick embryo was more potent than adult or embryo mouse tissues. Ultraviolet absorption spectra of 4 of the extracts are

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The nature of the active substances is unknown.—M. H. P.


A number of mouse and rat tumors including a bronchogenic carcinoma, sarcoma 180, an ovarian embryoma, an experimentally induced hepatoma, 2 mammary carcinomas, and sarcoma 39 were successfully transplanted to certain sites in alien species. The heterotransplantable tumors, in contrast to a group not transferable in this manner, possessed the ability to invade and metastasize in the parent strain and to survive and grow in unrelated strains. On this basis it was concluded: first, that in mice, as well as in man and in the rabbit, invasion marks the attainment of autonomy; and second, that from the viewpoint of autonomy true homologous transfer and heterologous transfer possess the same significance.—Authors’ summary.


Sarcomatous transformation of the stroma is a common occurrence during the transplantation of mammary carcinomas of high cancer strain mice. The histological evidence of sarcomatous change was confirmed by study of the growth characteristics of tumors in vitro before and after they had undergone transformation. In tissue cultures mammary carcinomas exhibited the typical epithelial growth pattern; with few cells of the monocyte-macrophage type; and by their inhibiting fibroblastic growth. Of the factors responsible for the frequency of sarcomatous change in the high mammary cancer strains, special significance is attributed to: (a) the considerable stimulation of fibroblastic growth by the carcinoma cells; and (b) stromal cells surviving transplantation because the cells of the graft are homozygous with those of the new host.—Authors’ summary.

Clinical and Pathological Reports

Clinical investigations are sometimes included under Reports of Research

TRAUMA


The author analyzes 13 cases of cancer of the penis, seen at the Barnard Free Skin and Cancer Hospital, in every one of which a history of a single trauma to the penis was present and the growth followed all the postulates laid down by Segond as necessary to establish the causal relationship between trauma and the later development of cancer.—J. L. M.


Two cases of generalized metastasis first brought to attention by trauma were carefully studied. In one case the primary tumor was in the lung, in the second, in the stomach. Metastasis developed at the site of the trauma, and apparently all the requirements for indicating a relationship between trauma and tumor were established. However careful study of other metastatic areas showed the same appearance without injury. Deliberate trauma to other areas failed to produce metastasis. It was concluded that there was probably no scientific proof of a causal relationship and that the unknown laws of metastasis influence the localization of secondary deposits.—R. E. S.

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