Abstracts
Experimental Research, Animal Tumors


Through an error 5 rats were given a much larger amount of methylcholanthrene than was intended—1 cc. of a 1.25% solution in beef fat intraperitoneally, thrice in a period of 12 days. The only one to survive died 3½ months later with peritoneal sarcomatosis. No metastases were found.—W. H. W.


Numerous experiments have proved the carcinogenicity of the benzyrene contained in tobacco tar. As a prophylactic measure, therefore, the smoking habit must be vigorously fought.

Experiment provides an answer to the question why all smokers do not develop cancer; there is required in addition a predisposed soil. Fortunately this is not present in everyone, just as it is not present in every animal of an experiment, but it can result from many influences, and if the necessary conditions are fulfilled a smoker must inevitably die of cancer.—W. H. W.


Three cases are reported of pituitary adenoma in white rats in which carcinogenic substances had been implanted in the brain. These adenomas of the anterior lobe were combined, in one rat, with gliomas of the brain, and in a second rat, with tumor of the pars nervosa and of the pars tuberalis.—S. A. G.


A short discussion of the various theories regarding the causes of bronchogenic carcinoma is given. In addition the more recent experimental attempts to produce lung tumors are briefly reviewed. A description is given of the method employed in this experiment carried out upon rats. It consists in forming a bronchial fistula by a two stage operation for exteriorization of the lung. The fistula is then treated with 3,4-benzpyrene in olive oil 2 to 3 times a week.

A type of epithelium similar to transitional epithelium was produced a week after treatment was begun. In 2 to 3 weeks an early squamous epithelium appeared. By the end of 6 weeks metaplasia of the bronchial epithelium to a well differentiated stratified squamous type had occurred. Many animals succumbed to infection, and in many, an infection in the bronchus destroyed the epithelium.—Authors' abstract.


Experiments on spontaneous and transplanted tumors in animals suggest that castration will not influence favorably the course of mammary carcinoma in man. Indeed, it may even benefit the cancer by upsetting the hormonal balance.

The results of experiment accord with the clinical observation that most malignant tumors in women arise during or shortly after the menopause, and the change in hormonal relationships at that time may be regarded not only as a predisposing, but as an exciting cause.—W. H. W.


Experiments were undertaken to note the effect of androgens on the apparent relationship existing between brown degeneration of the adrenals and mammary carcinoma in the Paris mouse. The adrenal degeneration occurred frequently in this high tumor strain but was also produced by estrinization. Mammary tumors also were produced after estrogens. In testosteroneized female mice of the RIII strain the incidence of mammary carcinoma was reduced from 52.2% to 19.4%. In the same series brown degeneration of the adrenals was reduced from 80.9% in the controls to 56.5% in tumor-free treated mice. In testosteroneized mice exhibiting tumors brown degeneration of the adrenals was not diminished (85.7%). The diminution of a stimulating factor in the mammary gland, and an inhibiting factor in the adrenal gland appears to represent more than a casual relationship, established perhaps, by the effects of testosterone. The lowering of tumor frequency may presumably be due to reduction of the growth activity of the mammary gland epithelium, when associated in testosteroneized mice with adrenal changes.—Author's abstract.


Abdominal fibroids produced in the female guinea pig in the course of 80 days by subcutaneously implanted pellets of α-estradiol ceased growing after a tablet of

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synthetic progesterone was subsequently implanted and allowed to act simultaneously with the estrogen for 34 to 52 days.

Besides this prevention of tumorous growth there was, in the progesterone period, also a considerable regression of existing fibroids. This is inferred from the fact that the fibrous tumorous effect in animals that were exposed for 80 days to the action of estradiol alone, and subsequently for 34 to 52 days to the action of both estradiol and progesterone, was only about 58% of that found in animals sacrificed after having been exposed during 80 days to the action of estradiol alone.

Regression, i.e., the difference in the average fibromatogenic effect between the estradiol group and the groups treated subsequently with progesterone, was statistically as significant as was prevention.

The therapeutic action of progesterone on existing fibroids elicited by estradiol was revealed to be much more considerable when the frequency of animals with large abdominal fibroids and especially the frequency of large fibroids per animal was compared in the different groups.

The decrease in frequency of large abdominal fibroids per animal amounted to 81% in 5 to 7½ weeks under the influence of progesterone.—Authors' summary.


The microscopic structure of uterine and other abdominal fibroids induced in the guinea pig by the continuous action of a-estradiol, and subsequently subjected to the simultaneous action of progesterone, was compared with that of similar fibroids that underwent regression after withdrawal of the estrogen.

The structure of tumors that were still present 34 to 53 days after the beginning of progesterone treatment was similar to that of tumors that shrank after withdrawal of the estrogen. In both cases the most conspicuous findings were the disappearance of the spindle-shaped cells (fibroblasts) from the periphery of the tumor, and the transformation of the tumor into a uniform mass of more or less hyalinized collagenous tissue with small scattered nuclei.

The statement that the influence of progesterone uterine or other abdominal fibroids undergoes structural changes characteristic of regression and similar to those taking place after the withdrawal of estrogen, fully corroborates the conclusion drawn in the previous paper, that fibroids induced by estrogens in the course of several months begin to regress when progesterone is added subsequently and allowed to act simultaneously with the estrogenic hormone.—Authors' summary.


It is demonstrated that high reproducibility of results is obtained in experiments on the induction of tumors with ultraviolet radiation if experimental conditions are properly controlled and the results are given suitable statistical treatment. The accuracy to be expected in comparing experimental groups is discussed. New information on the dose-response curve and the effect of animal age on tumor development is also considered.—K. R. P.


The author discusses the problem of establishing an index of tumor growth that can be used in comparative studies. From the fundamental equation for exponential growth, equations are derived for the determination of such an index.—K. R. P.


In describing his investigations on the influence of carcinogenic hydrocarbons upon the metabolism of various tissues the author says that benzpyrene exerted no effect on that of renal cortex and testis from the rat.—W. H. W.


Tumor tissue (sarcoma), though it is not generally classed as a glycogen-metabolizing tissue, displayed a high phosphorylase activity. The phosphorolytic breakdown of glycogen by this tissue is, however, very slow as compared with that of other tissues. This apparent discrepancy is due to the low phosphoglucomutase activity of tissue sugar. (The source of the sarcoma is not stated.)—E. L. K.


The activities of d-amino acid oxidase, uricase, and choline oxidase, in livers of rats bearing transplanted hepatoma 31 and Walker carcinosarcoma 256, and in the nuclei isolated from the liver cells, were determined. Hepatoma 31 caused depletion of the apoenzyme of d-amino acid oxidase more than its coenzyme in the livers of rats bearing this tumor. The activities of uricase and of choline oxidase were also decreased in the livers of rats bearing transplants of hepatoma 31. The concentrations of d-amino acid oxidase, uricase, and choline oxidase were low in the nuclei isolated from the liver cells of rats bearing transplants of hepatoma 31. Walker carcinosarcoma 256 did not cause appreciable decrease of d-amino acid oxidase, uricase, or choline oxidase, in the livers of rats bearing this tumor. Choline oxidase could not be detected in the isolated liver cell nuclei of rats bearing transplants of hepatoma 31 or Walker carcinosarcoma 256, nor could it be detected in the nuclei isolated from cells of normal rat liver.—Author's abstract.


The activities of d-amino acid oxidase, uricase, and choline oxidase were determined in two tumors, hepatoma 31 and Walker carcinosarcoma 256, and the results were...
compared with determinations on the same enzymes in normal rat liver. Nuclei isolated from hepatoma 31 also were studied. The amount of the apoenzyme of d-aminooxidase was low in both tumors and in nuclei isolated from hepatoma 31. Addition of the coenzyme of d-aminooxidase to whole tissue of hepatoma 31 raised the activity of d-aminooxidase from about 3% of the activity in normal rat liver to approximately 12%. Experiments with nuclei isolated from hepatoma 31 and from normal rat liver cells gave parallel results. However, addition of the coenzyme to whole tissue of the Walker carcinosarcoma 256 did not increase the activity of d-aminooxidase in this tissue, which remained almost zero. Both hepatoma 31 and nuclei isolated from it contained very little uricase, and uricase could not be detected at all in the Walker carcinosarcoma 256. However, normal rat liver and nuclei isolated from it are fairly rich in uricase.

Choline oxidase could not be detected in transplants of hepatoma 31, in nuclei isolated from this tumor, or in Walker carcinosarcoma 256. This enzyme is present in normal rat liver tissue but absent from normal rat liver cell nuclei.—Author's abstract.


Methods are described by which the yield and purity of the hemorrhage-producing bacterial filtrate have been improved. A simple synthetic medium containing only 3 inorganic salts and glucose was found to support the growth of Serratia marcescens (Bacillus prodigiosus) and to be especially valuable in that it facilitated purification of the active agent by not containing the numerous complex contaminants ordinarily introduced by the usual nutrient broth. Concentration of the desired fraction from large volumes of bacterial filtrate is reported to be most easily achieved by chloroform precipitation. Repeated precipitation with ethyl alcohol followed by dialysis gave highly potent preparations.

The active fractions were rich in polysaccharides, and the best preparations were negative for protein. Results of microanalysis are given. The material is stable, its potency remaining intact in aqueous solution or in the dry state unchanged over long periods of time. Between pH 1 and 10, none of the active agent dialyzed through cellophane; none was destroyed except in solutions of greater acidity.

The most active preparation obtained had a potency of 130,000 m.t.u. (mouse tumor units) per cc. This is in contrast with a potency of 100 units per cc. for a commercial preparation of Coley's mixed toxins. The minimum hemorrhage-producing dose contained 0.1 μgm. of total solids.

The lethal dose of the various concentrates ranged from 100 to 1,000 times the minimum hemorrhage-producing dose.—K. R. P.


This report describes the experimental development of methods for more accurate bioassay of the bacterial hemorrhage-producing factor. It was found, as expected, that the use of greater numbers of mice improved the consistency and reliability of the data. More accurate determination of the presence or absence of hemorrhage by internal examination of the tumors also contributed to the value of the assay. Testing the sterility of the tumor brei ruled out the occasional variation arising from bacterial contamination. As a further aid to consistency, unusually resistant or sensitive batches of tumors were detected by controlling each bioassay with a standard preparation of previously determined potency.—K. R. P.


The active concentrate obtained from Serratia marcescens culture filtrate was purified by tryptic digestion and found to retain its activity. Elementary analysis of a number of preparations following trypsin treatment gave the following average values (%): carbon, 47.5; hydrogen, 7.1; nitrogen, 2.2; phosphorus, 1.1; "acetyl," 2.2; ash, 3.5. Methoxyl was not found. A single determination for sulfur showed less than 0.2%. Nitrogen and "acetyl" were found in quantities about half those obtained prior to digestion with trypsin.

Optimal hydrolysis of the active material yielded aldohexose, hexosamine, methylpentose, and the components of a phospholipid. Approximately two-thirds of the material consisted of sugar residues of which the greater part was aldohexose. The phospholipid was apparently in a firmly bound complex. Neither polypeptide nor protein could be demonstrated.

A number of experiments on the chemical behavior of the trypsin-digested material are reported, and the results are correlated with potency changes arising from the manipulations.

The activity of aqueous solutions was not destroyed at 37°C. From 60°C to 100°C, the potency was lost at rates that increased with the temperature. Hydrolytic changes resulting from acid and alkali treatments at various temperatures were studied, and decreases in potency were detected by bioassay.—K. R. P.

Chemical Treatment of Tumors. VIII. Ultra centrifugal and Electrophoretic Analysis of the Hemorrhage-Producing Fraction from Serratia marcescens (Bacillus prodigiosus) Culture Filtrate. KAHLER, H., SHEAR, M. J., and HARTWELL, J. L. [National
Three preparations of the polysaccharide fraction from culture filtrates were analyzed. The sedimentation constant of the major component at pH 7.4 was different for each preparation. For one fraction at pH 4.1 (0.35), the diffusion constant was 0.89 x 10^-7 cm^2/sec, and the sedimentation constant at 20°C was 70.5 x 10^-12 cm/g units. These two values gave a molecular weight of about eight million under these conditions. The particle shape was markedly nonsymmetrical. About 90% of each preparation was found by electrophoresis and sedimentation to be made up of a single component, and the hemorrhage-producing activity resided for the most part in this material. — K. R. P.


Alloxan, the ureide of mesoxalic acid, when injected intravenously, produced specific necrosis of islet cells in the pancreas and epithelium of the convoluted tubules of the kidneys in rabbits. These observations are in confirmation of the work of Dunn, Sheehan, and McLetchie.

In dogs, intravenous injection of alloxan also injured specifically the islet cells and convoluted tubules of the kidney. The islet cells in these animals, however, did not exhibit the extensive coagulation necrosis observed in the kidney was manifested physiologically by diabetes mellitus and uremia. Following injection there was a brief period of hyperglycemia and then a brief period of hypoglycemia; at the end of 48 hours hyperglycemia again was present and persisted for varying intervals.

The islet cells appeared more sensitive to the effects of alloxan in that some animals exhibited hyperglycemia and relatively transient or no uremia.

In dogs, 200 to 500 mgm. of alloxan per kilo was fatal in from 1 hour to 6 days, the animal having died with definitely elevated blood glucose and blood N.P.N. After total doses of 100 to 150 mgm. per kilo the animals sometimes survived with transitory diabetes and with or without transitory impaired renal function. In one dog a sustained diabetes mellitus (over 28 days) without elevated blood N.P.N. was observed.

Four human patients with carcinomatosis, one presenting an insulin-producing islet cell carcinoma of the pancreas, received intravenous injections of alloxan. Transitory beneficial effects were observed in the patient with insulin-producing islet cell carcinoma, following injection of 600 mgm. to 1 gm. per kilo, in that attacks of hyperinsulinism were abolished for 10 to 20 days following each series of injections, whereas before the injections he had 2 to 5 severe attacks a day. In the other 3 patients also, comparably larger doses of alloxan were given than in the dogs and rabbits, with effects on the blood and sugar in only one instance. Hence it appears that the human subject is much more resistant to the action of alloxan than the dog or rabbit. — Authors' summary.


Whole plasma from rats with inoculated leukemia characterized by extensive liver involvement and hemorrhagic tendency shows little difference in prothrombin time from normal rat plasma. A pronounced deviation is evident when the leukemic plasma is diluted 1:1 and 1:2 with saline and compared with normal plasma similarly diluted. The results indicate that a plasma prothrombin deficiency exists in the type of transmissible rat leukemia studied. The present observations are in accord with those of Kark and Lozner, who found that dilution of human plasma may bring out evidences of prothrombin deficiency not demonstrable on undiluted plasma. — Author's abstract.


Evidence of the presence of tumor antibodies in fowl sarcomas is adduced from experiments with the author's sarcoma strain, which is believed to have originated in tissue cultures exposed to the action of dibenzanthracene, and the specificity of which (as compared with other fowl sarcomas) is stated to have been demonstrated by experiment.

The site of antibody formation against the tumor agent is considered, with reference to two types of tumor showing local immunity reactions. These are (1) a hard tumor showing overgrowth of fibrous tissue following tumor-cell destruction; (2) a tumor with liquefied center, forming a cyst lined by myxomatous tissue, where the liquefaction is regarded as an exaggeration of the mucinous degeneration of the stroma usually in myxosarcomas, and which is represented as an attempt at combating tumor growth.

The significance of these two types of slow-growing tumor is discussed. — A. H.


The amount of agent extracted from Rous No. 1 sarcomas was inversely proportional to the duration of growth in the host. Tumors less than 40 days old all contained some agent, while after 40 days all tumors proved to have non-filterable. The appearance of the tumor bore no relation to the amount of agent obtained in extracts. It is pointed out that experiments designed to test for the existence of such agents are more likely to succeed if very
young grafts are used for extraction, since the increase in tumor material obtained with older grafts may not compensate for the reduction in the amount of agent that may result. It also follows that a slowly-growing tumor, though bearing a filterable agent, will be non-filterable for the greater part of its life in any host.—A. H.


The serum of fowls tested 1 to 2 years after recovery from Rous No. 1 tumors possessed a high content of neutralizing antibodies to the Rous agent. The demonstration of active antibody in such fowls is regarded, by analogy with other virus diseases, as proof of the presence of tumor virus, although tumors are not produced.—A. H.


Various carcinogenic hydrocarbons, in common with a number of sex hormones, elicit a characteristic abnormality in the mitosis of rabbit fibroblasts in vitro; some of the chromosomes are excluded from the equatorial plate and take no further part in cell division. The course of mitosis is not disturbed, however, and the division rate is not materially reduced.

This irregularity, which the author regards as the most significant primary disturbance in neoplasia, he refers to the action of some substance related to the steroids.—W. H. W.


A method is described for ascertaining nucleocytoplasmic ratios without resort to tedious drawing and size measurement technics. It has as its basis the probability that the ratio between the sums of large numbers of hits and misses of random points upon nuclei and cytoplasms will correspond to the ratio between the sizes of these cell components. The procedure is not limited to this problem alone but can be used to ascertain the proportions of the fractions of total volume occupied by any morphologic constituent of the tissue or organ studied. Tests of the method that show its degree of accuracy when applied to the analysis of fixed and stained preparations are presented. —K. R. P.


Tumors developed in approximately 80% of the NH mice that had received a single subcutaneous injection at 60 days of age of 1 mgm. of methylcholanthrene dissolved in 0.1 cc. of sesame oil. In the 694 tumor-bearing animals presented here the order of frequency of tumor types was: fibrosarcoma, epidermoid carcinoma, mammary carcinoma, and bronchiogenic carcinoma. The epidermoid growths were all squamous cell carcinomas. These were present in 34.7% of the tumor-bearing animals and tended to occur earlier than the other types. In the animals that showed only skin tumors the average latent period was 115 days, and 84.7% of the neoplasms were evident upon gross examination made prior to 150 days after injection with carcinogen. For the total group of fibrosarcomas (animals without skin or mammary tumors) the average latent period was 180 days, and 50.5% of the tumors appeared within 150 days. The frequency of epidermoid carcinomas was greater in the NH0 mice than has been reported for other strains of mice and for other rodents treated in a similar manner with methylcholanthrene.—Authors' summary.


A genetic analysis of cells from spontaneous and induced neoplasms was made by studying their transplantation pattern in inbred and hybrids of known genetic composition. This was compared with the behavior of grafts of normal spleen. Tumors induced in the Ak or RF strains were found to grow well in hybrids of these stocks. They may grow in both inbred lines or only in the line of origin. Tumors induced in the hybrids grew in hybrids and in both, or one, or neither of the parental lines. Tumors arising spontaneously in these lines were transplantable to the F₁ hybrids and to the line of origin, but not to the unrelated line. The spontaneous tumors arising in hybrids that were studied grew in hybrids and grew well in one of the parental lines, but not at all in the other line, or grew poorly in both. Spontaneous and induced leukemias arising in the Ak stock grew well in the line of origin and fairly well in the unrelated C3H inbred stock. Leukemias arising in the F₁ hybrids between the Ak and C3H stocks grew in F₁ hybrids and in both parental lines. The same relationship exists between Ak and C3H mice with regard to transplantability of neoplasms other than leukemia.

The conclusion is reached that the transplantation pattern of leukemias and tumors arising in inbred and hybrids may differ from that of normal splenic tissue, which uniformly follows a single scheme. Induced leukemias and tumors may differ greatly among themselves, but there is a transplantation pattern characteristic of each neoplasm, which is retained through numerous passages. These observations suggest that the immediate change that makes some cells cancerous may be a somatic mutation.—Authors' abstract.


The author points out that even the discovery of a direct external causative agent of cancer would not do away with the need to explain individual susceptibility. He quotes from Waaler's statistical survey of the familial incidence of cancer, concluding that different types and sites of tumor growth behave in a different manner genetically. Studies of identical twins show that there is a definite
hereditary localization factor for certain types of tumors. Reference is made to investigations with inbred mouse strains showing that undoubtedly different genetic behavior in susceptibility to tumors of a particular type exists. Most workers agree that there is an inheritable specificity for tumor type and tumor site. However the factor of heredity is not the sole cause of cancer growth, and other influences play a role. Other aspects of cancer research mentioned briefly are the role of a virus, carcinogenic substances, and the influence of the endocrine glands. Recognition of the effects of heredity in the causation of cancer may lead to the development of some means of prophylaxis.—E. E. S.


Abstracts of general discussions.—A. Cnl.

Clinical and Pathological Reports

HEREDITY


In a family of 7 children 6 were found to have polyposis. In 2, malignant change developed in the polyps. The father of the children died of carcinoma of the rectum at the age of 48, and the paternal grandfather succumbed to “cholera morbus.” The author recommends early and radical operation as the treatment of choice.—G. H. H.

THERAPY—GENERAL


The author emphasizes the danger in relying on morphine for relief of severe pain associated with carcinoma of the mammary gland since many patients may survive for a long period. The pain is often due to invasion of the brachial plexus. The procedure of choice was found to be intraspinal division of dorsal roots. Other procedures are discussed, and objections to their use are offered. An illustrative case is presented.—E. E. S.

RADIATION—DIAGNOSIS AND THERAPY


The first reported case of sarcoma of the neck following roentgen therapy of Graves’ disease is described. Degenerative radiation changes (pigmentation and telangiectasis) in the skin of the neck occurred 2 years after the treatment. Eighteen years later a fibrosarcoma developed at the site of these skin changes. Five months after excision of the tumor a recurrence was noted. A radical neck dissection resulted in freedom from recurrence for a period of 23 months.—S. A. G.


Seventy-five patients with proved cancer of the breast received intensive preoperative roentgen therapy. Pathologic studies after subsequent mastectomy revealed no evidence of the primary tumor in 13% of the cases. The fact that 63% of the axillary nodes were found to be involved indicates that no cancerocidal action of the radiation occurred in these deposits. In view of these findings the author believes that radical mastectomy should be recommended as the treatment of choice in operable cancer of the breast without the delay and questionable benefit of preoperative roentgen therapy.—S. A. G.


Treatment by radiation can be effected by radium, radium emanation, and low, high, and super voltage roentgen rays. The selection of the method to be used depends on the convenience of application and upon the depth and size of the tumor. Irradiation causes degeneration of tumor cells and premature aging, i.e., fibrosis, of the tumor bed. There is no evidence that tumor growth is stimulated by such treatment. Tumors originating from the white blood cells, blood forming organs, gonads, and tissues of embryonic type are the most sensitive. Tumors arising from nerve tissue, bone, or muscle are characteristically resistant. A few general observations concerning technic are made. The author believes preoperative irradiation has some beneficial effect. Postoperative irradiation should be attempted only when it is known that the tumor is of a high grade of malignancy or when surgical removal is incomplete. The majority of patients referred for radiation therapy are incurable. Treatment in these cases is purely palliative and systemic reactions should be avoided. The hazards of treatment are injury to normal tissues and systemic reactions such as roentgen sickness and injury to blood-forming organs, but the latter is regarded as of minor importance. Any source of infection should be removed before treatment is undertaken.—E. E. S.


The author reviews 20 cases in which cancer of the cervix or corpus uteri followed irradiation therapy and concludes that the previous irradiation of the benign condition was probably not the cause of the malignant change.—A. K.


The various types of radiation cancer, both human and experimental, have certain fundamental features in common. The exact amount or dose of radiation necessary for the production of radiation cancer is not known, nor is it...
Experimental Research, Animal Tumors

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