Abstracts

Experimental Research, Animal Tumors


Since the benzpyrene content of tar, as determined spectroscopically, ran parallel with its carcinogenic activity, the authors regard the presence of other carcinogenic agents in adequate concentration as improbable.—W. H. W.


It was observed that 26 of 29 mice subjected to urethane anesthesia and roentgen-ray exposure of a skin fold showed multiple pulmonary tumors. By a series of experiments it was determined that the urethane was the responsible agent, and that the roentgen-ray exposure, the anesthesia, and possible impurities in the urethane could be ruled out as factors in the increased incidence of lung tumors. In this first report it appeared that some increase in numbers of tumors occurs even after a single treatment with urethane. Strain A mice were also subjected to 14 weekly intraperitoneal injections of urethane, and the incidence of lung tumors was increased. Urethane, therefore, can be considered a carcinogenic agent for the induction of pulmonary tumors in mice. Tumors were not observed elsewhere.

The authors also include descriptions and microphotographs of these tumors and associated pulmonary changes. Lesions preliminary to the development of neoplasia were not found.—T. B. D.


Twenty years ago Deelman found (a) that tumors in tarred mouse skin tended to arise at the site of a wound, and (b) that they arose at such sites earlier than elsewhere. Many later workers have carried out similar experiments, with varying results. The paper describes experiments upon Simpson mice in which pieces about 0.8 cm. in diameter were excised at the time (fifth month) when papillomas began to appear from skin to which either (1) 3,4-benzpyrene (0.3% in liquid paraffin) or (2) 5,10-trimethyl-1,2-benzanthracene (0.06% in acetone) had been applied. Deelman's statement (a) was confirmed in 22 out of 40 mice, and statement (b) was confirmed in 9 out of 11 mice in experiment 2.—E. L. K.


When albino rats were fed 0.06% of p-dimethylaminoazobenzene for 4 months in a synthetic diet containing 5% corn oil, the incidence of hepatic tumors at 6 months ranged from 53 to 64%. However, when the corn oil was replaced by hydrogenated coconut oil, the tumor incidence never exceeded 8% while in most groups it was zero. This effect of the hydrogenated coconut oil persisted when the rats received 25~m~g~m~g of pyridoxine and/or 40 mgm. of ethyl linolate daily.

By means of an analytical method adequate for the quantitative determination of 1~m~m~g~g of p-dimethylaminoazobenzene, it was demonstrated that the azo dye was very stable in the diets in vitro. Attempts to demonstrate differences in the stability of the dye in the digestive tract were unsuccessful. It therefore appeared that the differences in carcinogenicity observed in the two oils were due to changes within the animal itself.—Authors' abstract.


Benzpyrene sarcomas in the subcutaneous tissue of the rat contain more than 5 times as much nucleoprotein phosphorus as the normal mother tissue.

The livers of the tumor rats contained between 2 and 3 times as much as those of normal rats.—W. H. W.


The activity of normal adult rat liver, regenerating rat liver, fetal rat liver, and transplanted rat hepatoma 31 with respect to 12 enzyme systems was studied. Normal adult and regenerating livers were found to be very similar in their enzyme activities, as were fetal liver and hepatoma, but there were marked differences between the 2 groups. Arginase, catalase, xanthine dehydrogenase, the urea synthetic systems, and cystine, cytochrome, and d-amino acid oxidases were lower in fetal liver and in hepatoma than in adult liver. Acid phosphatase was slightly, and alkaline phosphatase markedly, higher in fetal liver and in hepatoma than in adult liver.

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liver. Ribonucleosyltransferase, thymonucleosyltransferase, and amylase were about the same in all 4 kinds of hepatic tissue.—H. Q. W.


The activity of arginase, catalase, zanthine dehydrogenase, acetaldehyde dehydrogenase, and ribonucleosyltransferase was determined in a number of normal mouse tissues and mouse tumors. The normal tissues included liver, breast, lymph nodes, marrow, spleen, kidney, muscle, skin, lung, intestinal and gastric mucosa, thymus, and pancreas. The tumors included 4 strains of hepatoma, 2 spontaneous mammary lymphomas, and 4 strains of carcinoma and sarcoma. For each of the enzymes the range of activity of the different normal tissues was very wide, although it was somewhat less for thymonucleosyltransferase than for most of the other enzymes. Among the different tumors the range of activity of each enzyme was less than for the different normal tissues. The difference is probably due to the decrease in the specific functional activity which takes place in many tissues when they become neoplastic.—H. Q. W.


Previous work has shown that the liver catalase activity of mice, rats, and human subjects bearing various neoplasms is depressed. In the present paper the authors show that there is no depression in the catalase activity of the livers of pregnant mice and of mice bearing growing embryonic implants.—H. Q. W.


The ascorbic acid content of 22 tumors of rats and mice, and of comparable normal tissues was determined. It was found that the ascorbic acid concentration of the tumors ranged from 15 to 70 mgm. per 100 gm. of fresh tissue. The ascorbic acid content of the tumors was not related to that of the tissues of origin. No correlation between ascorbic acid concentration and rate of growth was evident. Neither age of host nor site of transplantation materially affected the ascorbic acid concentration in the tumor.—H. Q. W.


Observations were made postoperatively upon patients with gastrointestinal cancer and, as controls, upon patients with non-neoplastic disease of the gastrointestinal tract or with gynecologic disorders who had undergone intra-abdominal operations. It was found that cancer patients frequently developed a negative nitrogen balance, but so, too, did the control patients and to as great a degree. The serum proteins, however, fell to a lower level in the cancer patients, hence it seems possible that the protein stores may be less in patients with gastrointestinal cancer than in the control groups studied.—J. G. K.


The urinary excretion of creatine and creatinine was increased following the intravenous administration of glycine to normal subjects and to patients with benign gastrointestinal disorders. It failed to increase in 21 of 25 patients with gastrointestinal cancer and hepatic cirrhosis who had been given comparable amounts of glycine. It is suggested that this failure in the patients with gastrointestinal cancer is due to their coexisting hepatic insufficiency. The simultaneous ingestion of choline, as a source of free methyl groups, by patients with gastrointestinal cancer or hepatic cirrhosis, also failed to increase the urinary output of creatine and creatinine.—Authors' abstract.


A transplantable lymphatic leukemia that characteristiclily infiltrates the thymus extensively was inoculated into 2 groups of middle-aged rats. Normal rats of this age have atrophied thymus glands and are resistant to leukemia—only 46.9% of 32 inoculated animals developed the disease. The survival time in this group was 9.7 days. In rats adrenalecrotomized 15 days before inoculation the thymus is stimulated and susceptibility increased—90.3% of 31 rats developed leukemia. The average survival time of adrenalecrotomized animals following inoculation was 6.2 days.

In a second set of experiments adrenalectomy was shown to diminish the resistance induced in normally susceptible young rats by the injection of homologous defibrinated blood 2 weeks before inoculation with leukemic cells. With the blood injection alone, 33.9% of 59 inoculated rats developed leukemia. When rats were adrenalectomized before being injected with defibrinated blood, 76.8% of 43 inoculated animals developed leukemia. When they were adrenalectomized after the blood injection, 92.9% of 42 inoculated rats developed the disease. Control rats, and rats adrenalectomized but not treated otherwise, were 96.5 and 100% receptive respectively.—R. B.


The preventive action of synthetic progesterone against abdominal fibroids elicited by 24 estradiol in the guinea pig was obvious when only 13 to 24 mgm. of the 3-keto-steroid were absorbed daily from a subcutaneously implanted tablet.
The antifibromatogenic quantity of progesterone was less than the quantity of the fibromatogenic estrogen absorbed simultaneously.

There was still some preventive action with quantities of progesterone smaller than 15 pgm. daily (transitional zone).

On the contrary, quantities of pregnanediolone or of allo-pregnanedione equal to antifibromatogenic quantities of synthetic progesterone, or quantities several times greater than the latter, were unable to prevent abdominal fibroids elicited by estradiol.

Since pregnanediolone so far is not known to be progestational, our findings suggest that antifibromatogenic activity is concomitant to a certain extent with the progestational one.

This suggestion was corroborated by experiments with the nonprogestational Δ16-dehydroprogesterone, which revealed no antifibromatogenic activity even when quantities were absorbed that were 6 times greater than the antifibromatogenic threshold of progesterone.

When quantities were absorbed that were 10 to 30 times greater than the antifibromatogenic threshold of progesterone, the three nonprogestational steroids revealed some antifibromatogenic action comparable with that observed in the transitional zone with progesterone. This suggests that the three steroids might show progestational activity also if proper quantities were used.—Authors' summary.


The fibromatogenic action of subcutaneously implanted tablets of the 17-caprylic ester and of the dipropionic ester of α-estradiol was prevented with quantities of progesterone not far from, or identical with, those that are necessary to antagonize the fibromatogenic action of free α-estradiol (antifibromatogenic threshold).

Our results suggest that the antagonistic action of this steroid against estradiol is effected not by interfering in the inactivation of estrogens in the liver but by rendering the reacting tissue unable to respond to the action of estrogens.—Authors' summary.


Experiments on two strains not hitherto used have confirmed the influence of the milk factor upon the incidence of mammary cancer. Foster nursing of high-cancer strain RIII females by females of 'S' low-cancer strain reduced the incidence of mammary cancer in RIII females from 83 per cent at an average age of 8.5 months to 6.6 per cent at an average age of 9.3 months. Foster nursing of low-cancer strain 'S' females by females of RIII strain increased the incidence of mammary cancer in 'S' strain of mice from less than 1 per cent at an average age of 19 months to 29.6 per cent at an average age of 15.2 months.”—E. L. K.


To determine the characteristics of the inherited susceptibility to spontaneous mammary cancer in mice, reciprocal matings were made between mice of the cancerous A and low cancerous C57 black (B) strains to produce mice of the F1, F2, and F3 hybrid generations. The mice of the first generation either were nursed by their mothers or were fostered by females of the reciprocal stock to give 4 groups. The mice of each group were continued through the F3 generation. Four groups of hybrids of the backcross generations to the low cancerous stock were also observed and were derived by mating the reciprocal F1 and F2 females to males of the B stock. All females were used as breeders to insure an adequate estrogenic stimulation of the mammary glands.

In this study the mice of the A stock were assumed to be homozygous for the inherited susceptibility for mammary cancer and the mice of the B strain were considered to be nonsusceptible.

No significant difference in the incidence of cancer was observed in the reciprocal hybrids that received the active mammary tumor milk agent, indicating that there was no intrauterine influence. Likewise, the females of the F1 generations had approximately the same incidence as did the females of the cancerous A stock. The data obtained in the other hybrid generations either were in accord with the hypothesis that the inherited susceptibility was a single dominant, or more tumors were observed than would be expected according to this theory. In some generations the progeny of cancerous females had a higher incidence than did the progeny of noncancerous mothers.

Few spontaneous mammary tumors resulted in mice that were nursed by or descended from mothers nursed by females of the low cancerous strain.

The determination of the make-up of the inherited susceptibility was made more difficult in the hybrids because: (a) The incidence was influenced by the age at which the mothers developed spontaneous tumors. (b) The incidence was influenced by the litter in which the mice were born.

A considerable number of the mice of the nonsusceptible (low cancerous) strain developed mammary cancer after receiving the active milk agent. These observations indicate that some nonsusceptible mice may develop mammary cancer because of the inciting influence of the milk agent and the estrogenic stimulation. Thus all mammary tumors in mice do not result from the same causes.

Because there was no method of differentiating between mice that were somatically cancerous and those genetically cancerous, it was impossible to determine the number of factors transmitted, but it is probable that multiple factors were involved in the inherited susceptibility for spontaneous mammary cancer in mice.—Author's abstract.
Karinomstudien IV. Weitere Beiträge zur Frage der Unempfänglichkeit der Milz für Karzinom.


In rabbits unsuccessfully inoculated with the Brown-Pearce carcinoma the spleen was enlarged, though not so much as in those successfully inoculated. Histologically, however, there was no difference.

A future article will show that rabbits that resist grafts of this tumor produce a specific antibody against it, the presence of which can be demonstrated by complement-fixation.

While rabbits were less receptive to the tumor than pigmented ones, but their susceptibility could be considerably increased by splenectomy. Metastasis was more common than in the pigmented, and the daughter tumors were larger, especially in the kidney, and more malignant.

Two examples of metastases in the spleen are described which, unlike those in other organs, showed no tendency to infiltrate. There was a pronounced atrophy of the lymphoid-macrophage system in these spleens.—W.H. W.


It was found that complement-fixing antibodies against the Brown-Pearce tumor were present in the blood serum but not in the aqueous humor of the eye in rabbits bearing this tumor or immune to it. Absence of antibodies is suggested as the reason for the successful growth of the Brown-Pearce tumor in the anterior chamber of the eye when it will not grow in the usual sites of transplantation. After puncture of the anterior chamber complement-fixing bodies were present possibly because of an alteration in permeability of the capillaries of the eye.—C. J. L.


Earlier histological and growth studies on the transplantable mouse tumor 15091a had suggested that regression followed the acquisition by the host of a resistance against the implanted tumor. In the present experiments no acquisition complement-fixing antibodies against the tumor antigen could be demonstrated in sera of mice in which the tumor had regressed or had failed to grow after 2 or 3 implantations.

Injection of an aqueous extract of tumor 15091a into rabbits produced antibodies that reacted not only with the homologous antigen, but also with heterologous antigens from 5 spontaneous mammary carcinomas and 2 methylcholanthrene-induced sarcomas, irrespective of the strain of mice in which they arose. The reaction was weaker with 1 spontaneous carcinoma and 2 other induced sarcomas. No reaction was obtained with 2 spontaneous mammary carcinomas. The antiserum did not react with the majority of antigens prepared from normal mouse liver, kidney, brain, or mouse sera. These results are interpreted as indicating a similarity in antigenic composition between transplantable tumor 15091a and spontaneous and induced malignant tumors, but a difference between tumor 15091a and normal mouse tissue. The specifically reacting portion of the 15091a antigen was soluble in ether and alcohol.—J.L.M.


Pieces from the deep surface of 15 epitheliums induced in the skin of C57 mice by 3,4-benzpyrene in 280 days were covered with sulphapyridine and implanted subcutem in 18 three months old mice of the same strain. Thirteen grafts from 10 mice were successful, and several of these had been carried on to the third, fourth, or fifth passage at the time of writing. "Histologically they are all malignant—squamous carcinomata. There are two main types, a highly anaplastic growth which progresses to central necrosis, and a keratinising growth in which the centre becomes horny. These types may co-exist, but one or the other is generally predominant." The characters of the primary and grafted tumors are shown well in 6 microphotographs. A similar experiment with an inbred strain of albino mice gave no successful grafts.—E. L. K.


Chromophobe adenoma-like lesions of the hypophysis were found in 92 of 362 albino rats of the Yale strain. The frequency increased with advancing age, reaching 60% in male rats and 30% in female rats 600 and more days old. The lesions varied in size from microscopic nodules to masses weighing as much as 367 mgm. and were usually composed of cells with vacuolated chromophobic cytoplasm and oval nuclei containing coarse granules of chromatin.

Homologous intraocular transplants of adenoma-like tissue from two spontaneous lesions in male rats were carried into second and third serial intraocular generations. Transplants grew in 21 of 42 male recipients, but in none of 4 female recipients. Growth of transplants was extremely slow, and was often preceded by a latent period of several months. The growth rate was not accelerated in subsequent transfers, and the morphology did not change. Transplants grew as well in young as in old rats, and their fate was not influenced by the strain of the recipient. The presence of spontaneous adenoma-like lesions in the pituitaries of the hosts did not affect the behavior of transplants.

It is concluded that chromophobe adenoma-like lesions of the rat hypophysis are essentially neoplastic in character.—Authors' abstract.


Evidence is presented supporting the view that the tumor arose originally from relatively undifferentiated
cells of the outer adrenal cortex. Detailed pathologic and cytopathologic descriptions of material prepared with many staining technics are given, and numerous microphotographs are included. During transplantation the following changes developed: (1) rapid increase in growth rate, (2) more intense eosinophilic staining of cell cytoplasm, (3) prevalence of smaller cells with filamentous mitochondria in later generations, whereas large cells with spherical mitochondria were characteristic of the first two generations, and (4) disappearance of cells with lipid droplets in later generations. The transplanted tumors grew more rapidly in male animals, although the original tumor occurred in a female. No gross or histologic changes could be found in other organs of the host animals, except a focal edema that was noted in the deeper layers of the endometrial stroma of the uterus.—T. B. D.


A bilateral foam cell carcinoma of the adrenal cortex was found in a rabbit that 6 months previously had received an intravenous injection of the dye T-1824. The testes were completely atrophic.—Authors' abstract.


A continuation of the author's work on lymph nodes in mice in various conditions namely, (a) x-radiation, (b) treatment with Na 1,2,5,6-dibenzanthracene-9,10-endo αβ succinate, (c) development of sarcomas induced by this compound or by methylcholanthrene, (d) grafting of sarcoma induced by methylcholanthrene, or of S 37, sub cutem or (e) intraperitoneally, and (f) injection of Na taurocholate sub cutem. Lymph nodes from such mice have now been examined after staining by the Unna-Pappenheim method, a normal node being stained of the endometrial stroma of the uterus.—T. B. D.

The diminution of size of the nodes and spleen not irradiated is an early and constant feature of the changes observed and is coincident with the diminution of lymphocytes. No evidence was found of the development of plasma cells from lymphocytes. Proliferation of reticulum seems to start at the periphery and spread inwards to the medulla, and the plasma cells appear to develop in these areas. The appearances suggest that the plasma cells may be derived from the reticulum cells. The possible relationships between plasma cells and sarcoma cells are discussed. The paper is illustrated by 13 microphotographs.—E. L. K.


The author draws attention to the frequently noted observation that in cases of leukemia, Hodgkin's disease, and lymphosarcoma irradiation of lymph nodes in one area may be followed by a reduction in size of the spleen or nodes in nonirradiated areas. The object of the experiment reported was to determine whether or not this is the result of some substance transmitted by way of the blood stream.

Human marrow from which most of the non-nucleated erythrocytes had been removed was suspended in a cerebrospinal fluid-like medium and 2 samples irradiated with 400 r at 200 kV. The suspensions were then centrifuged, and 4 combinations were prepared as follows: irradiated cells (1) in an irradiated medium, and (2) in a nonirradiated medium; nonirradiated cells (3) in an irradiated medium, and (4) in a nonirradiated medium. After a period of incubation cell counts were made.

The results showed no effect attributable to the presence of any substance in the medium from irradiated cells, and the only evidence of growth arrest was seen where the cells themselves had been irradiated.

The diminution of size of the nodes and spleen not irradiated is explained by the circulation of irradiated cells, and the author suggests that general body irradiation should be the method of choice in the treatment of these diseases.—J. F.


The author presents an historical review of the development of artificial radioactivity and stresses its importance in biological and medical research and suggests the possibility of its future use in therapy. Radio-sulfur has been used as a tracer-substance in synthetic vitamin B. Radio-iron has been used in the study of absorption and utilization of iron in normal and anemic dogs. The use of radio-phosphorus in the treatment of leukemia is explained on the basis of the high uptake of phosphorus to form the nucleoprotein of the leukemic cells. Radio-iodine is shown to be of use in studying iodine metabolism and reference is made to its possible value in the treatment of hyperthyroidism. In carcinoma of the thyroid
it seems to be of no value since the cancer cells do not take up iodine as do the normal cells of the thyroid gland. Numerous radioactive elements are discussed and their usefulness explained. The elements rendered radioactive by the cyclotron have relatively short periods of radioactivity and so will do relatively little harm in the body and their presence and concentration can always be determined by the use of the Geiger counter and by photography.

The production, physical and biological effects of the neutron ray is also briefly described.—J. F.


The possible influence of irradiation-killed tumor cells on other living tumor cells was studied on mouse sarcoma 37 in young Dilute Brown male mice. With the technic used this tumor produces 100% takes. Previous work has shown that it can be completely inactivated by 5,000 r doses of 200 kv. roentgen rays delivered *in vitro*, and by the same dose applied tangentially to well established tumors *in vivo*. In the present work 3 types of experiments were done. (1) Tumor pulp killed by irradiation *in vitro* was mixed in various proportions with viable tumor pulp, and the mixtures inoculated into mice. (2) Well established small tumors were enveloped in subcutaneously inoculated irradiation-killed pulp. (3) Viable tumor pulp was inoculated in the center of large tumors that had been killed by irradiation *in vitro*. In all cases, the viable cells grew as though no dead cells were present in the immediate neighborhood. The author concludes that, for this tumor, irradiation-killed cells or their decomposition products exert no inhibitory influence on the growth of potentially viable tumor cells.—H. Q. W.


One hundred and thirty-two chemicals, largely organic compounds, were injected repeatedly into mice of several different strains bearing spontaneous or transplanted tumors. No effective therapy was discovered.—R. B.


Cultures of *Paramecium multimicronucleatum* were exposed continuously to methylcholanthrene (1γ per ml.) for over 4 years. After the 35th culture transfer the carcinogen-exposed paramecia survived longer when placed under partial starvation than did control organisms. After the 50th transfer population levels in the experimental cultures were higher than in the controls. After more than 4 years (140th transfer) the population levels were still higher, but the individual animals were about one-half the size of the control organisms.

Phenanthrene (1γ per ml.) destroyed paramecia after 10 culture transfers.

Paramecium cultures exposed continuously to eosin (10 mgm. per ml.) were first stimulated, then depressed, and finally destroyed after 3 years. The same type of result was obtained with crystal violet (0.4γ per ml.) over a shorter period (35 days).

Cultures of flat worms (*Stenostoma tenuicaudatum*) exposed to phenanthrene or radium irradiation survived for a while but eventually died. Methylcholanthrene produced a temporary increase in the population of worm cultures. The worms were still alive and vigorous after 2 years.—R. B.


*Escherichia coli* and *Eberthella typhosa* were killed within a few days or weeks by continuous exposure to high temperature (45 or 47° C.) but survived discontinuous exposure (alternate days) apparently indefinitely. During this treatment their heat tolerance was gradually increased.

One series of *Eberthella typhosa* cultures exposed discontinuously to high temperature gave rise to an altered form of organism which grew very rapidly under anaerobic conditions but poorly or not at all under aerobic conditions. It was not agglutinated by *E. typhosa* antiserum, and was non-motile. Smears showed a mixture of gram-positive and gram-negative forms.—R. B.


The author believes that our present information regarding the blood-vascular system is inadequate and suggests that more detailed study of it might furnish an explanation of the so-called paradoxes of the spread of metastases and abscesses.

Injection of the dorsal vein of the penis in monkeys, which drains directly into the prostatic plexus of veins, shows, on compression of the inferior vena cava, a direct connection with the vertebral system of veins. This suggests that such a route may be the one by which carcinoma of the prostate spreads to the vertebrae and thence via the inferior vena cava to the general circulation.—J. F.


A brief review of the most important historical developments in the production of tumors by extrinsic and intrinsic chemical agents, with a presentation of the more recent contributions to the subject.—F. E. S.
Experimental Research, Animal Tumors

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