The vascular reaction of the mouse to normal and neoplastic transplants and wounds. Glenn H. Algire, and Harold W. Chalkley. (National Cancer Institute, Bethesda 14, Md.)

Microscopic studies by in vivo methods were made of the vascular reaction of the mouse to wounds, and to implants of normal and neoplastic tissue. The wounds or implants were made in tissue included within a transparent chamber introduced into a dorsal skin flap in the mouse. Photographs and daily quantitative measurements were made of the vascular levels in the surrounding normal tissue and in the implant or wound site.

The initial stages were similar in all. There was an accumulation of leucocytes in the involved area, followed by capillary dilatation, and new capillary proliferation at about the fourth to sixth day. The vascular levels in aseptic wounds attained the level of the normal subcutaneous connective tissue that was used as a base line, then stabilized. Implants of adult liver and spleen attained a vascular level double that of the connective tissue, then subsided to the base line. Tumor implants rapidly attained a vascular level double that of the connective tissue, and maintained this level during the period of observation (15 to 25 days). Tumor vessels originated as capillaries and remained so. Capillaries in wounds and about implants of adult tissues differentiated into arterioles and venules. Evidence is presented that tumor tissue possesses the property of continuously eliciting new capillary endothelial growth from the host and thus establishing and maintaining a rich nutritive supply. It is suggested that this property, rather than some vague “autonomy” of the tumor cell is, from the standpoint of the host, an important expression of the neoplastic change.

Relation of genes to mammary tumor development in the mouse. W. E. Heston. (National Cancer Institute, Bethesda 14, Md.)

It is now accepted that genetic differences can vary the probabilities that a mouse will develop a mammary tumor. From recent work on gene chemistry it is reasonable to expect that these genetic differences can be manifested as enzymatic differences affecting specific metabolic reactions leading to the development of the tumor. Although the identification of the specific genes and of the specific reactions with which each is concerned are probably still far in the future, we have accumulated evidence that points to the general fields in which at least certain of these genetic differences are manifested.

There is evidence that genetic differences can result in variation in response of the mammary tissue to the hormonal and/or the milk agent stimulation. In this case the primary gene action may occur in the mammary tissue cell.

Experiments have shown that certain genetic differences are manifested as variation in the hormonal stimulation. Here one can hardly predict where the primary gene action occurs other than that it is probably within the endocrine system.

Experimental results have shown that certain genetic differences can affect variation in the propagation and transmission of the milk agent. Since the milk agent has been demonstrated in various organs and tissues there is no evidence that in this case the primary gene action is limited to any particular tissue. Such gene action not only may influence the development of the mammary tumor of the individual but by affecting variation in the transmission of the agent also may cause variation of tumor development in the daughters or foster-nursed females.

This demonstrated intimate interrelation between the chromosomal factors and the milk agent presents a concept in many respects not unlike the gene-cytoplasm relationship concept of normal differentiation involving the cytoplasmic determiners plasmagens and plastogenes.

Transplantation of spontaneous primary hepatomas in mice of strain C3H. Edward L. Burns, and John R. Schenken. (Department of Pathology and Bacteriology, Louisiana State University School of Medicine, New Orleans 13, La.)

Transplantations of spontaneous primary hepatomas arising in 3 C3H strain male mice were made into 28 young C3H mice as follows:

- Tumor tissue was transplanted subcutaneously into 11 mice, intraperitoneally into 4, and into the anterior chamber of the eye in 4; a saline emulsion of tumor tissue was injected into the anterior chamber of the eye in 5 mice; sterile filtrates of tumor tissue were given intradermally, subcutaneously, and intrahepatically to 1, 1, and 2 mice respectively.

The transplants grew in 1 of the 11 mice inoculated subcutaneously, and in 3 of the 4 animals inoculated intraperitoneally. No tumors grew in the animals of any other group. The transplanted tumors were found from 9.1 to 20.5 months after the transplants were made. They formed solid, rounded, lobulated masses measuring from...
1 to 2 cm. in diameter, and were either red or yellow in color. Microscopically they closely resembled the primary neoplasms.

THE INFLUENCE OF CALORIC RESTRICTION ON TUMOR FORMATION AND ON THE LEVEL OF BLOOD SUGAR IN MICE. H. P. RUSCH, V. R. POTTER, and R. O. JOHNSON. (McArthur Memorial Laboratory, Medical School, University of Wisconsin, Madison 6, Wis.)

The appearance of neoplasms can be delayed and the incidence of tumors reduced when experimental animals are given a diet restricted in calories. Although the mechanism of tumor inhibition caused by decreased caloric intake is unknown, there is some indication that neoplastic cells fail to proliferate until the nutritive energy rises above a critical level. To test this theory, the level of blood sugar was determined in mice receiving either high or low calorie diets of various compositions, and the results were compared with the incidence of tumor formation in the various groups. The mice were given a single subcutaneous injection of 200 mgm. of 3,4-benzpyrene dissolved in corn oil. The groups on the restricted calories received a calculated 5.5 calories per mouse per day, and the other groups an average of 9 calories per mouse per day. Tumors were observed from 2 to 3 weeks earlier in the mice on the high caloric diets, and the tumor incidence in these groups at 4 months was 85 per cent as compared to 40 per cent for the mice restricted in calories. With the exception of 1 group the mice on high caloric diets had higher levels of blood sugar (125 to 150 mgm. per cent) than those on the restricted diets (90 to 100 mgm. per cent). One group receiving a high caloric intake, though carbohydrate was largely replaced by increased amounts of casein and fat, showed the same rate of tumor formation as the other groups on the same caloric intake, but at a level of blood sugar that was only slightly higher than was observed in the mice on restricted calories.

CASTRATION EFFECTS IN RELATION TO THE INHERITED HORMONAL INFLUENCE IN MICE. FERN W. SMITH, and JOHN J. BITTNER. (Department of Physiology, Division of Cancer Biology, University of Minnesota Medical School, Minneapolis 14, Minn.)

Female mice of the high cancerous A and C3H stocks and 2 groups of their reciprocal hybrids, 1 with and 1 without the active milk agent, were castrated at time of weaning and observed for evidence of hormonal stimulation. At 7 months normal A strain virgins have as high an occurrence of estrous cycles as do normal C3H virgins. Among castrates of the same age there is a complete lack of estrus in A strain mice in contrast to the high value, comparable to the normal, observed among the C3H and hybrid mice. As Woolley, Fekete, and Little noticed in their C3H and dba stocks, the C3H and, in addition, the hybrid castrates showed gross and microscopic hyperplasia of the adrenal cortex. Uterine and mammary gland development with tumors followed in the C3H animals and the hybrids with the milk agent. Those hybrids lacking the milk agent, in spite of adrenal changes, showed no precancerous mammary lesions or tumors. Animals of the A strain failed to show the indication of hormonal stimulation mentioned above.

The lack of the inherited hormonal factor is partially responsible for the low tumor incidence in normal virgins of the A stock. Virgin C3H mice possessing this factor have a much higher incidence. Since the adrenal changes appeared only in those animals with the inherited hormonal influence, it seems probable that the changes among the castrate animals of those strains and their reciprocal hybrids may be dependent upon this character. The presence of the milk agent, however, is essential for tumor development among the hybrids. The A strain castrates, lacking the inherited hormonal influence, may show modified mammary and adrenal growth but no other evidence of hormonal stimulation.

GENETIC FACTORS IN THE ETIOLOGY OF MAMMARY CANCER IN MICE. JOHN J. BITTNER. (Department of Physiology, Division of Cancer Biology, University of Minnesota Medical School, Minneapolis 14, Minn.)

Observations on reciprocal hybrids between the high cancer A and the low cancer B (C57 black) stocks demonstrated that the mice of both sexes of the former strain transmitted the inherited susceptibility for spontaneous mammary cancer. For the expression of the susceptibility, both the milk agent and hormonal stimulation of breeding were necessary.

When breeding females of the high cancer A and C3H stocks and their reciprocal hybrids were studied, the incidence observed in hybrids of the F1 and F2 generations was comparable to that of the parental stocks. These data suggested that either the genes producing the inherited susceptibility in the two high cancer stocks were the same or, if different genes were involved, any combination of dominant genes would produce susceptibility in the F2 hybrids. Whereas the virgin females of the A stock have a low incidence, virgin females of the C3H stock and the reciprocal hybrids between the A and C3H stocks frequently develop mammary cancer. Thus the mice of the C3H stock transmit, in addition to the genes producing the inherited susceptibility for mammary cancer, genes that determine whether or not virgin females will give rise to this type of cancer. This character, now being called the inherited hormonal influence, is another inherited condition to be considered in the etiology of mammary cancer, at least in virgin animals.

ANTIGENIC CHARACTER OF THE CANCER MILK AGENT IN MICE. ROBERT G. GREEN, MARYE M. MOOSEY, and JOHN J. BITTNER. (Department of Bacteriology and Immunology and the Department of Physiology, Division of Cancer Biology, University of Minnesota Medical School, Minneapolis 14, Minn.)

Immunological studies of the cancer milk agent in mice are being made by the utilization of high-speed centrif-
tigates of cancer tissue suspensions as the infective agent. The centrifugates, collected between 15,000 and 95,000 gravity, were previously demonstrated to contain the milk agent. Such centrifugates have been injected into rabbits to produce antiserum. Rabbits were given 5 injections of centrifugate at 5 day intervals, each dose representing 4 gm. of spontaneous mouse tumor suspended in 3.5 cc. of saline solution. The rabbits were bled for the production of antiserum 9 and 10 days after the last injection.

A group of 30 mice was injected with a centrifugate equivalent of 0.25 gm. of tumor tissue suspended in 0.5 cc. of rabbit immune serum, the mixture being allowed to stand at room temperature 2 hours before injection. The antiserum was a pooled mixture of the sera of 3 cc. of normal rabbit serum, 5 have developed mammary cancer. Thirty mice were injected with a similar amount of a centrifugate equivalent of 0.25 gm. of tumor tissue suspended in 0.5 cc. of rabbit immune serum, the mixture being allowed to stand at room temperature 2 hours before injection. The antiserum was a pooled mixture of the sera of 3 rabbits immunized as described above. At 8½ months, 2 of the 30 mice have developed tumors. Of 30 mice injected with similar amounts of centrifugate suspended in 0.5 cc. of normal rabbit serum, 5 have developed mammary cancer at 6½ months.

These results, although reported after a relatively short time, would seem to indicate that the milk agent stimulates antibody production and therefore is antigenic. This character, combined with previously demonstrated characteristics of the milk agent, those of ultramicroscopic size and reproduction in association with living cells, would seem to identify the milk agent of mouse carcinoma as a filterable virus.

NET RESISTANCE AGAINST TUMOR GROWTH: COMBINED EFFECT OF ESTROGENS, MILK FACTOR, AND GENETIC FACTOR. WILLIAM T. SALTER and L. MURIEL SCHLEGEL. (Department of Pharmacology, Yale University, New Haven, Conn.)

When the growth of implanted sarcoma 180 was studied in pedigreed mice, resistance was most frequent under the following circumstances: (a) The host animal normally showed a low incidence of spontaneous tumors; (b) the source of the implanted tumor was a low tumor strain; and (c) preliminary "immunity" was produced by inoculation (in the tail) of tumor raised in a low tumor strain. The incidence of takes was highest when these features were reversed. Intermediate combinations gave intermediate results. The studies emphasize the complex nature of susceptibility toward tumor growth. They indicate a partial analysis of such resistance. They suggest that, quite independently of the origin of neoplasms (carcinogenesis), somatic factors may be varied so as to retard neoplastic growth.

RELATIVE THIAMINE DEFICIENCY IN CANCEROUS INDIVIDUALS. RIGBY C. ROSKELLEY, L. MURIEL SCHLEGEL, and WILLIAM T. SALTER. (Department of Pharmacology, Yale University, New Haven, Conn.)

There is a high incidence of thiamine deficiency in cancer patients encountered in a general hospital. This incidence is considerably greater than in patients suffering from other diseases. When the thiamine tolerance of cancer patients is tested, they show a diminished ability to store free thiamine. If a large dose of thiamine is administered the peak of urinary excretion is frequently reached at the third hour. Thereafter, thiamine excretion falls in approximately logarithmic fashion. By appropriate calculations an index of the free thiamine store can be established for comparative purposes. Part of the effect is attributable to the incidence of cancer in the higher age brackets. Even so, there remains evidence of a relative thiamine deficiency in certain cancer patients who have previously been flooded with thiamine.

ATTEMPTS TO PRODUCE CANCER IN RHESUS MONKEYS WITH CARCINOGENIC HYDROCARBONS AND ESTROGENS. CARROLL A. PFEIFFER, and EDGAR ALLEN.* (Department of Anatomy, Yale University, New Haven, Conn.)

The treatment of monkeys (Macacus rhesus) used in cancer experiments from 1936 to the present is summarized below.

### Table: Treatment of Monkeys

<table>
<thead>
<tr>
<th>No. of monkeys</th>
<th>Chemicals</th>
<th>Period of treatment years</th>
<th>Dosage Weekly, mgm.</th>
<th>Total, mgm.</th>
<th>Injections in oil ***</th>
<th>Painted in benzene ***</th>
<th>Pellets</th>
</tr>
</thead>
<tbody>
<tr>
<td>17</td>
<td>MC</td>
<td>½-8</td>
<td>2-4</td>
<td>26-1500</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>10</td>
<td>BP</td>
<td>½-8</td>
<td>2-4</td>
<td>28-690</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>6</td>
<td>DBA</td>
<td>½-8</td>
<td>2-4</td>
<td>18-450</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>E</td>
<td>variable</td>
<td>0.0085-591</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
</tbody>
</table>

* Many animals received a combination of chemicals. Monkeys treated less than ½ year are not included.
** MC = methylcholanthrene, BP = benzpyrene, DBA = dibenzanthracene, and E = estrogens.
*** Control animals were treated with benzene and sesame oil for 1 to 2 years.

* Deceased.

Almost all organs and tissues that frequently become cancerous in the human subject were treated, including the abdominal and pelvic viscera. The mammary received the longest treatment, although multiple sites were used in all animals. Carcinogens were also injected intravenously and administered orally. Methylcholanthrene and dibenzanthracene caused more pronounced local reactions than benzpyrene. Following injections in oil these consisted of firm non-inflammatory fibrotic masses, areas of granulation tissue, and encapsulated cysts of the injected material. Following painting they consisted of hyperkeratinization...
with loss of hair, cystic hair follicles, cystic sebaceous
glands, and papillomatous masses or wart-like excrescences.
Pellets became encapsulated in dense fibrous connective
tissue surrounded by numerous round cells and phagocytes.
This reaction sometimes progressed until distinct, firm,
noninflammatory, fibrotic masses were produced. The
lesions just described might persist, regress, or become
infected and ulcerate. Metaplasia of the mammary ducts
and of the epithelium of the cervical glands occurred.
Malignant tumors were not found.

HORMONAL FACTORS IN THE GROWTH OF
TRANSPLANTED TESTICULAR TUMORS IN
MICE. W. U. GARDNER. (Department of Anatomy,
Yale University, New Haven 11, Conn.)

Testicular interstitial cell tumors occur in estrogen-
treated mice of some strains (observations reported pre-
viously by several investigators). In our laboratory these
tumors have grown, subsequent to transplantation, only
in estrogen-treated mice. Two different testicular tumors
were transplanted for 4 and 9 generations. One arose in a
hybrid mouse (A × C3H) and one in an A strain mouse.
Both primary neoplasms metastasized to lumbar or
perirenal nodes, and histologically resembled tumors pre-
viously described.

The tumors were grafted into genetically related or
unrelated mice of inbred strains, or into hybrid groups.
Stilbestrol, in either oily solution (0.25 mgm. weekly)
or compressed pellets (4 to 8 mgm., 1 part stilbestrol and
3 parts cholestrol) was the estrogen used.

(A) The tumors grew (1) only in genetically related
mice and (2) only in such mice given estrogens.

(B) The transplants in untreated, genetically related
mice regressed; they were not detected or found only
when sought under ultraviolet light (bright orange
fluorescence).

(C) The tumors (2) were capable of growth up to 7 months subsequent to trans-
plantation if estrogen treatment was inaugurated. Hist-
ologically the tumors contained predomina-
ently macrophages and few or no recognizable tumor cells.

(D) When growth had started during a period of estro-
gen treatment the tumors persisted or continued to grow
subsequent to cessation of treatment.

(E) The tumors persisted subsequent to hypophyse-
tomy although the hosts lost weight.

(F) The transplants in different animals grew at variable
rates, and contained various amounts of myelopoietic and
hematopoietic cells.

SPONTANEOUS INTERSTITIAL CELL TUMORS OF
THE TESTIS IN DOGS. CHARLES W. HOOKER,
CARROLL A. PFEIFFER, and JOSEPH DeVITA.
(Department of Anatomy, Yale University, New
Haven 11, Conn.)

An attempt has been made to compare spontaneous
tumors of the interstitial cells of the testes of dogs with
those of the same cells in estrogen-treated mice of the
A strain. To this end the testes of 38 old dogs of several
breds have been studied microscopically. Seven inter-
stitial cell tumors were found. As in the estrinized mice,
the tumor masses were well circumscribed and contained
many engorged vascular spaces. The tumor cells were
like "second generation" tumor cells of the mice, except
in one tumor that was composed of cells resembling those
of the "second" and "third generations." Small nodules of
interstitial cells like the earliest tumors of the mice
were present in 6 testes. The intertubular tissue exhibited
no remarkable feature in 9 testes. In 14 testes and in the
nontumorous portion of the 13 testes with small or large
tumors the intertubular tissue was like that described many
years ago by Goodpasture and Smith. The Leydig cells
were hypertrophied, highly vacuolated, and contained large
cytoplasmic granules. Many were in various stages of dis-
integration. Among the Leydig cells were many cells con-
taining a yellow pigment. These are structural features
regularly present in the testes of A strain mice in the early
months of treatment with estrogen. Apparently, therefore,
the spontaneous tumors of the dogs resemble those arising
in estrogen-treated A strain mice with respect to structure
and to developmental stages.

THE DEPENDENCE OF TUMOR FORMATION ON
THE DEGREE OF CALORIC RESTRICTION.
ALBERT TANNENBAUM. (Department of Cancer
Research, Michael Reese Hospital, Chicago 16, Ill.)

In previous publications it has been reported that
caloric restriction results in an inhibition of tumor forma-
tion in the mouse. This effect has been demonstrated
for spontaneous mammary and lung tumors, for induced
sarcomas and epitheliomas, and for leukemias. In general,
the caloric intake of restricted animals was approximately
60 per cent or less of the ad libitum intake. In the present
experiments, which were performed with spontaneous
mammary and induced skin tumors, the caloric intakes
were graded. The diets for the various groups differed only
in their carbohydrate content, and ranged in caloric value
from approximately 60 per cent to 90 per cent of the
ad libitum diet. The results of the experiments indicate
that any degree of caloric restriction may exert some in-
hibitory effect on the formation of the two types of tumors
studied. The inhibitory effect does not appear to be
directly proportional to the degree of caloric restriction,
tending rather to show upper and lower limits.

THE DEPENDENCE OF TUMOR FORMATION ON
THE COMPOSITION OF THE CALORIE-RE-
STRICTED DIET AS WELL AS ON THE DEGREE
OF RESTRICTION. ALBERT TANNENBAUM.
(Department of Cancer Research, Michael Reese Hos-
pital, Chicago 16, Ill.)

The inhibitory effect of caloric restriction on the for-
mation of tumors in mice is dependent on the actual degree
of this restriction. The present experiments, which em-
ployed the spontaneous mammary and the induced skin
tumor, were performed to confirm this finding and also
to ascertain the significance of the composition of the diet
at any particular level of caloric restriction. Three types
of restricted diets were utilized: (a) diets in which the
caloric restriction was achieved by limiting the carbohy-
drate component only; (b) diets in which caloric restriction was achieved by limiting the amount of the control high in fat content. Furthermore, it is demonstrated that the augmenting effect of a high fat diet on the formation of tumors occurs at all levels of caloric restriction studied. This augmenting effect is mediated through some specific action of the ingested fat.

PHOSPHOLIPIDS IN HUMAN NEOPLASMS. KEN. NETH W. BUCHWALD, and LEONA HUDSON. (State Institute for the Study of Malignant Diseases, Buffalo 3, N. Y.)

The phospholipids of tumor cells and nuclei were isolated from autopsy specimens. The nuclei were first separated from the tumor cells by the procedure of Stoneburg. The phospholipids in the nuclei and whole tumor tissue were isolated according to Brodie's procedure. In the phospholipid fraction the phosphorus was determined by the method of Kuttner and Lichtenstein, and the choline according to Haven's modification of Beattie's procedure.

To date 8 neoplastic growths have been examined. The phospholipids varied over a wide range. Whole tissue gave a maximum of 7.59, minimum 1.06, and mean 3.46 gm. per 100 gm. dry tissue. Nuclei gave a maximum of 9.70, minimum 2.88, and mean 6.47 gm. per 100 gm. dry nuclei. In all specimens the phospholipid in the nuclei was higher than in the whole tissue. The analysis for choline in whole tissue gave a maximum of 0.56, minimum 0.20, and mean 0.37 gm. per 100 gm. dry tissue and in nuclei a maximum of 1.33, minimum 0.27, and mean 0.80 gm. per 100 gm. dry nuclei. The higher choline content of phospholipids in the nucleus indicates a larger proportion of lecithin in the nucleus than in the whole cell. The molar ratios of choline to phosphorus indicate that the cephalin content varies more than the lecithin and sphingomyelin. This ratio was higher in the nuclei than in the whole cell. Although the molar ratios varied for each tissue analyzed they were of the same magnitude in both nuclei and whole cells of the same specimen. The data thus far collected is evident that variations in the phospholipid content of human neoplasms is produced by changes in the cephalin fraction rather than in the lecithin or sphingomyelin.

THE PHOTOMETRIC STUDY OF NUCLEIC ACIDS IN HUMAN TUMORS. ROBERT E. STOWELL. (Department of Pathology, Washington University School of Medicine, St. Louis 10, Mo., and the Barnard Free Skin and Cancer Hospital, St. Louis 3, Mo.)

The nucleoproteins and their constituent nucleic acids have important vital functions in normal cells. There is increasing evidence that the nucleic acids of the nucleus and cytoplasm are altered in some malignant cells.

The relative amounts of nucleic acids of the ribose and deoxyribose type have been determined in a series of human tissues, and the measurements on various normal and neoplastic tissues have been compared. The histochemical measurements were made with a special photometric instrument consisting of a light source, light filters, microscope, photocell, and amplification and recording apparatus. The thymonucleic acid was measured by determining the absorption of monochromatic light in tissues stained by the Feulgen reaction. Ribonucleic acid was estimated by photometrically determining the decrease in staining of cells after treatment with the enzyme ribonuclease, which splits ribonucleic acids. The results are related to the amounts per unit volume of tissue and per cell. As compared with the corresponding normal tissues, it is evident that variations in the phospholipid content of normal and neoplastic tissues have been compared. The histochemical measurements were made with a special photometric instrument consisting of a light source, light filters, microscope, photocell, and amplification and recording apparatus. The thymonucleic acid was measured by determining the absorption of monochromatic light in tissues stained by the Feulgen reaction. Ribonucleic acid was estimated by photometrically determining the decrease in staining of cells after treatment with the enzyme ribonuclease, which splits ribonucleic acids. The results are related to the amounts per unit volume of tissue and per cell. As compared with the corresponding normal tissues, statistically significant increases in the amounts of thy- monucleic acid per unit volume of tissue were found in an adenocarcinoma of the rectum, a primary carcinoma of the liver, an epidermoid carcinoma of the epiglottis, and a leiomyosarcoma. The amounts of the thymonucleic acid per cell were significantly increased in the primary carcinoma of the liver and adenocarcinoma of the bronchus. An adenocarcinoma of the prostate and a leiomyosarcoma contained increased amounts of ribonucleic acid per unit volume of tissue and per cell. The measurements are being continued.

THE CATHEPTIC ACTIVITY OF NORMAL AND NEOPLASTIC MOUSE TISSUES. MARY E. MAVER, and THELM A DUNN. (National Cancer Institute, Bethesda 14, Md.)

The cathetic activities of several spontaneous and induced mouse neoplasms were compared, and the effects of these neoplasms upon the cathetic activities of the liver, spleen, and lungs of the tumor-bearing mice were studied. The activities were determined by the quantity of tyrosine liberated in 10 minutes by the proteolytic action of an extract of the tissues on a solution of hemoglobin at pH 3.5. The activities of extracts of spontaneous mammary carcinomas of the A and C3H strains and the first transplants of these tumors were greater than the activities of tumors that have been transplanted over a period of years—such as the Crocker sarcoma 180, sarcoma 37, and the Taylor mammary carcinoma. The spontaneous tumors also showed more cathetic activity than the transplants of induced tumors, including the hepatomas induced by injecting 2-amino-5-azotoluene or carbon tetrachloride, and the intestinal adenocarcinoma induced by giving methylcholanthrene in the drinking water.

The livers and spleens of mice bearing some of the neoplasms were augmented in size and had increased proteolytic activity. These changes were not always directly related to the size of the tumors, since some smaller spontaneous neoplasms caused more change than many of the larger transplanted tumors. An attempt has been made to correlate these changes in cathetic activity in the liver and spleen with the degree of extramedullary hematopoiesis and the number of lymphocytes present in these tissues.
since lymphoid tissue, as represented by the spleen and thymus, showed the greatest normal catheptic activity. The transplants of spontaneous and induced leukemia, which kill rapidly by the infiltration of leukemic cells, also produced the most rapid increase of catheptic activity in the organs of mice with these leukoses.

**EFFECT OF NUCLEATES ON DEHYDROGENASES IN LIVER AND HEPATOMA. JESSE P. GREENSTEIN, and HAROLD W. CHALKLEY. (National Cancer Institute, Bethesda 14, Md.)**

Tissue extracts possess the capacity of decolorizing methylene blue under anaerobic conditions. The addition of xanthine to such extracts results in an increase in the decolorization rate when the relative proportion of dye to substrate is high (measure of xanthine dehydrogenase activity). When the relative proportion of dye to substrate is very low, the addition of the latter results in the decolorization rate when the relative proportion of xanthine to such extracts results in an increase in the decolorization rate when the relative proportion of dye to substrate is high (measure of xanthine dehydrogenase activity). This holds true for the addition of sodium desoxyribosenucleate to extracts containing high concentrations of dye results in retardation of decolorization of uniform extent whether xanthine is present or not; therefore under these conditions the xanthine dehydrogenase activity is relatively little affected. On the other hand, in the presence of very low concentrations of the dye, the presence of the nucleate results in an acceleration of decolorization when xanthine is added, yielding not only a positive dehydrogenase activity but in greater magnitude than in the presence of high concentrations of dye. This effect is less definite in hepatoma extracts than in extracts of liver.

**SUNLIGHT AS A CAUSAL FACTOR IN CANCER OF THE SKIN. HAROLD F. BLUM.* (Naval Medical Research Institute, Bethesda 14, Md.)**

Recent epidemiological studies by Dorn indicate a definite north-south distribution of cutaneous cancer incidence in the United States, the numbers being greater in the south. The incidence of internal cancer does not follow this distribution. These data have been compared with the distribution of annual insolation over the same latitude range by (A) total sunlight, (B) those ultraviolet wave lengths that induce tumors in mice and rats.

(A) varies so little with latitude that it cannot be considered as a cause of cutaneous cancer. (B) varies somewhat less with latitude than does cutaneous cancer incidence.

If (B) is assumed to be the causal factor in human cutaneous cancer, the difference in variation with latitude may be accounted for on the basis of seasonal changes in (B), if certain experimental findings are taken into account. Experiments on mice show that below a certain intensity the carcinogenic effectiveness of (B) falls off sharply, and that development of tumors is greatly dependent upon interval between exposures to (B) rest periods permitting some recovery. During the winter months the carcinogenic action of sunlight should be greatly reduced because of the low intensity of (B), and hence the winter season constitutes a period of rest from exposure that increases in length with latitude. The hypothesis that sunlight or, more correctly, a portion of sunlight (B), is the major causal factor in human cutaneous cancer is supported by its geographical distribution as well as by much other converging evidence both clinical and experimental.
The microscopic control confers the advantages of unprecedented reliability and conservatism. The unsuspected outgrowths that commonly extend out from the main cancer mass and constitute a not uncommon cause of failure by surgical or radiation procedures are systematically followed out and eradicated by the chemosurgical technic. Many cancers that are inoperable because of extent or difficult position, and cancers resistant to x-ray or radium therapy, are still amenable to chemosurgery.

The method is limited to tumors that are accessible because the procedure is carried out in stages. Special training and specially equipped clinics are desirable.

SPONTANEOUS AND INDUCED GASTRIC CARCINOMA IN MICE. LEONELL C. STRONG. (Department of Anatomy, Yale University, New Haven 11, Conn.)

Four types of malignant gastric tumors have appeared in mice of the NHO descent following the subcutaneous injection of 1 mgm. of methylcholanthrene dissolved in 0.1 cc. of sesame oil at 60 days of age. These are (a) squamous carcinoma of the forestomach; (b) adenocarcinoma derived from the gastric mucosa; (c) adenocanthoma; and (d) leiomyosarcoma. These tumors appeared only in hybrid mice selected genetically toward the suppression of the usually occurring local tumors such as fibrosarcoma and epidermoid carcinoma. Two selected sublines of the NHO have so far been continued for several generations; one is characterized by a very high incidence of gastric carcinoma following the subcutaneous injection of the methylcholanthrene. Mice of the other selected subline give rise to adenocanthoma following the same technic.

At 6 month intervals mice have been weaned from the first in the subline and kept under normal laboratory conditions. The incidence of spontaneous gastric carcinoma is increasing rapidly in the successive groups. At the present time an incidence between 95 and 100 per cent of spontaneous gastric carcinomas at 240 days of life is being obtained. The mice derived from methylcholanthrene-injected parents transmit the condition through at least 3 (untreated) generations. Linkage evidence available indicates that the susceptibility to induced gastric carcinoma in the parents is hereditarily determined.

PRELIMINARY STUDIES ON THE AUTONOMY OF THE ROUS SARCOMA AS MEASURED BY GROWTH OF THE TUMOR IN THE ANTERIOR CHAMBER OF GUINEA PIG EYES. E. W. SHRIGLEY. (Yale University School of Medicine, New Haven 11, Connecticut)

The Rous sarcoma grows in the anterior chamber of guinea pig eyes, as is shown by the fact that small grafts placed in this environment become vascularized, increase in size, and show mitotic figures. Unlike mammalian cancer in the anterior chamber, however, this vascularization takes place early, within 3 or 4 days, and maximum growth is reached in 2 or 3 weeks, after which regression occurs. No tumor has been observed to reach such a size as to fill the chamber completely. Moreover, serial transfer in the eyes of guinea pigs has proved unsuccessful beyond 2 passages. Evidence that the tumor cells survive in the eye is based not only on the observations mentioned above, but also on the fact that chicks develop sarcomas when inoculated with tumor that has been in the guinea pig eye for 10 or 12 days. The virus is likewise known to be present in these transplants, since birds inoculated with tumor tissue from the eye show hemorrhagic, nonneoplastic lesions in the liver and other organs that are characteristic of the Rous virus infection in individuals of low resistance.

As soon as the Rous sarcoma becomes visible in the chick it will grow when transplanted into guinea pig eyes. On the other hand, virus-infected chicken tissue showing no macroscopic growth has not as yet, following residence in the guinea pig eye, produced tumors in chicks. Whether sarcomas that have persisted in birds for long periods of time are still transplantable to guinea pigs is yet to be determined.

Two other virus-induced chicken tumors have been grown in the anterior chamber of guinea pig eyes. Breast muscle of normal 2 day old chicks gives no evidence of growth in this environment.

SENSITIZATION AS THE FIRST PHASE IN SKIN CARCINOGENESIS. TRAUMA AND CANCER. W. CRAMER, AND W. L. SIMPSON. (Barnard Free Skin and Cancer Hospital, St. Louis 3, Missouri)

Repeated application over a long period of a chemical carcinogen dissolved in lanolin to the skin of mice fails to produce any of the chemical, histological, and cytological changes that follow a single application of the carcinogen dissolved in benzene. But while the skin does not show any demonstrable change from the normal it has undergone a lasting biological alteration in so far as it has been sensitized to the action of the carcinogen in benzene. This sensitization is, however, not specific for one particular carcinogen. The application of a single nonspecific trauma such as a burn to a "sensitized" skin induces cancer. (a) Sensitization is the first phase in the reaction of the skin to contact with a chemical carcinogen, inducing an increased susceptibility of the treated skin to the development of cancer. (b) Susceptibility can be acquired, and is not necessarily a fixed genetic factor. (c) The two main factors concerned in carcinogenesis, carcinogenic stimulus and susceptibility, may be linked together more closely than hitherto supposed as manifestations of the same agent. (d) The carcinogenic potentiality of a single nonspecific trauma has been established on an experimental basis.

FURTHER STUDIES ON THE RELATION BETWEEN RADIATION EFFECTS, CELL VIABILITY, AND INDUCED RESISTANCE TO MALIGNANT GROWTH. III. INDUCED RESISTANCE IN RATS OF AN INBRED STRAIN (HOMOZYGIOUS) TO A LYMPHOSARCOMA THAT ORIGINATED IN THE SAME STRAIN. ANNA GOLDFEDER.
In previous studies with mouse sarcoma 180 it was found possible to induce resistance in hybrid mice by implants attenuated by specific doses of x-radiation. This paper is concerned with the question whether or not the phenomenon can be applied to tumors of known genetic origin, grown in an inbred strain of animals. Accordingly, an inbred strain of animals and a tumor that originated in it were used in the present experiment. These were obtained from Dr. Halsey J. Bagg, and had the following characteristics: The rats, having been bred by continuous brother and sister mating for more than 15 years, were considered to be homozygous. The tumor, a reticulum cell type lymphosarcoma, originated in this strain of rats and had reached the 75th transplant generation at the start of this experiment. The tumor takes were 100 per cent in young rats, and spontaneous regression very rarely occurred.

Male rats 5 to 6 weeks old were used, with the same technical procedure as in the previous experiments.

Results: The threshold dose for implants of this rat lymphosarcoma lies between 2,200 and 2,500 r in air. Implants irradiated within these dosages either failed to grow or the tumors produced by them regressed after having reached a certain size. In both cases the rats became resistant to subsequent viable tumor implants.

Seven months have elapsed since the first set of rats was rendered "immune" to the tumor. Tests made recently revealed their persistent resistance to further viable implants.

Thus it is shown that the possibility exists of inducing resistance in an inbred strain of rats to a lymphosarcoma that originated in the same strain.

THE APPEARANCE OF HEPATOMAS FOLLOWING THE INGESTION OF 1,2-BENZANTHRACENE.

FLORENCE R. WHITE, and ALLEN B. ESCHENBRENNER. (National Cancer Institute, Bethesda 14, Md.)

1,2-Benzanthracene is frequently classed as a noncarcinogen, or at most as a compound possessing very weak carcinogenic activity. The literature describes the administration of this hydrocarbon to mice, rats, and rabbits by painting on the skin and by intravenous, subcutaneous, and intraperitoneal injections. Not every mode of administration was used on each species of animals. The only neoplasm reported was one epithelioma following the painting of 30 mice.

The purpose of this communication is to report the occurrence of hepatomas in 2 among 6 rats fed a relatively normal diet to which 0.06 per cent 1,2-benzanthracene had been added. The livers of both showed multiple tumors associated with cirrhosis and resembled those observed after feeding p-dimethylaminoazobenzene under similar circumstances.
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