Acceleration of the Development of Leukemias and Mammary Carcinomas in Mice by 9,10-Dimethyl-1,2-Benzanthracene*

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During comparative investigations into the reaction of different inbred strains of mice to treatment with carcinogenic hydrocarbons, it appeared in some experiments that leukemias or tumor formations occurred in greater numbers and earlier in the treated animals of strains in which tumors or leukemia develop spontaneously than in untreated animals of similar strains. An acceleration of the kinds of tumors occurring in these strains was evidently involved.

An account will be given in the present paper of experiments with 9,10-dimethyl-1,2-benzanthracene administered to 2 strains of mice, a mammary carcinoma strain, dilute brown, and a leukemic strain, Aka.

Material and Technic

Mice of 2 strains were used. One of these was Little's dilute brown, Dlb, among the untreated animals of which mammary carcinoma develops spontaneously in about 50 per cent of the females over 9 months old and leukemia in about 2 per cent of both males and females over 8 months old. The other strain was Furth's Aka, in which from 50 to 70 per cent of the animals that survive to the age of 8 months die of leukemia, usually lymphogenous leukemia.

Four to 8 months old mice of these strains were treated with 9,10-dimethyl-1,2-benzanthracene (prepared by Professor Haakon Lund, Aarhus, Denmark), the administration being in some cases by subcutaneous injection of from 0.5 to 1 mgm. dissolved in sterile olive oil and in others by painting the skin of the back 2 or 3 times a week with 0.5 per cent solution in benzene.

The substance employed is fairly toxic and the resistance of animals of different strains varies. Eighteen out of 20 Dlb mice died within 2 months of the subcutaneous injection of 1 mgm. The same dose was tolerated better by strain Aka, of which 8 out of 20 died in the course of 3 months. Similarly, painting every other day with 0.5 per cent of the solution caused a great loss of test animals, especially among the Dlb mice, whereas painting every 3rd day was tolerated quite well.

Experiments

Altogether 44 dilute brown mice were given from 0.5 to 1 mgm. 9,10-dimethyl-1,2-benzanthracene by subcutaneous injection. Twenty-five of these animals died either from intercurrent diseases, pneumonia or enteritis, or from the toxic action of the injection. Before the surviving 19 animals were 8 months old, 4 cases of leukemia (2 ♀, 2 ♂), 1 case of lymphosarcoma (♀), 3 cases of mammary carcinoma, and 1 case of ovarian carcinoma (all ♀) developed. No case of tumorous development or leukemia was observed in the control animals, siblings to the test animals, before they were 8 months old. In addition to these tumors, which were of the same types as those seen spontaneously in this strain, spindle cell sarcomas developed in 7 cases at the site of the injection. Five of these were observed in animals in which no other tumor was seen to develop and 2 were found simultaneously with a lymphosarcoma and a mammary carcinoma, respectively. The results of the experiment appear in Tables I and II.

Painting 50 animals of the same strain 2 or 3 times a week with the same substance produced the following results (Tables I and III): Seventeen of the animals died from intercurrent diseases or from toxic effects. Among the 33 surviving animals (16 ♀ and 17 ♂), there were 6 cases of lymphogenous leukemia (4 ♂, 2 ♀), 1 case (♀), of myelogenous leukemia, and 7 cases of mammary carcinoma (all ♀). Three of these 7 had 2 mammary carcinomas. Painting produced tumors in 24 of these 33 animals, 23 carcinomas and 1 sarcoma of the skin. Of these, 2 cases of cancer of the skin occurred in animals with leukemia, 4 in animals with mammary carcinoma; and 17 carcinomas of the skin and 1 sarcoma of the skin were observed in animals in which neither leukemia nor mammary carcinoma developed. No case of simultaneous leukemia and mammary carcinoma was observed.

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Twenty mice of leukemic strain Aka were given subcutaneous injections of 1 mgm. 9,10-dimethyl-1,2-benzanthracene. A part of this series of experiments has been published previously (6). Eight of these animals died from intercurrent diseases or from intoxication. Among the 12 survivors leukemic changes developed in 9, and these animals died at ages varying from 15 to 21 weeks. An ovarian carcinoma was found in 1 animal. Five developed spindle cell sarcomas and 2 developed carcinoma of the skin at the site of the injection. Two of the sarcomas were found in animals without leukemia, 2 in animals with leukemia, and 1 in a mouse with ovarian carcinoma. One of the 2 carcinomas appeared in an animal with reticular cell hyperplasia in the lymphnodes. The results are summarized in Tables I and IV.

TABLE I: RESULTS OF TREATING MICE WITH 9,10-DIMETHYL-1,2-BENZANTHRACENE

	9,10-Dimethyl-1,2-benzanthracene	No. of animals treated	No. of animals surviving	No. developing leukemia or lymphosarcoma before 8 months	No. developing mammary carcinoma before 9 months	No. developing malignant tumors at site of injection
Strain Aka	1 mgm. injected subcutaneously	20	12	9	0	7
	0.5% solution in benzene applied cutaneously	14	11	10	0	7
	Total	34	23	19	0	14
	Untreated controls	40	40	0	0	..
Strain Dlb	0.5-1 mgm. injected subcutaneously	44	19	5	3	7
	0.5% solution in benzene cutaneously 2-3 times a week	50	33	7	7 *	24
	Total	94	52	12	10	31
	Untreated controls	40	36	0	2	..

* Three of these mice had multiple mammary carcinomas.

TABLE II: RESULTS OF TREATING DILUTE BROWN MICE WITH 0.5 MGM. 9,10-DIMETHYL-1,2-BENZANTHRACENE INJECTED SUBCUTANEOUSLY

Mouse no.	Age at death, in weeks	Changes at site of injection	Other findings
188 ♀	21	Lymphosarcoma 15x15x5 mm. large	All lymphnodes large, 3-5 mm. Spleen large, 29x9x8 mm., variegated, dark red. Liver, kidneys, thymus not enlarged. Lymphosarcomatosis in lymphnodes and spleen, with hemorrhages. Leukemic infiltration in liver.
190 ♀	15	None	Mammary carcinoma near left foreleg, 12x12 mm. A 3x3 mm. node in left lung. Many small abscesses in the kidneys.
390 ♀	29	Fusocellular sarcoma 26x20x4 mm	Typical mammary adenocarcinoma 15x10x10 mm. in perineum.
393 ♀	18	None	Stem-cell leukemia. Most lymphnodes 8-10 mm. in size. Mesenteric lymphnode 25 mm. Spleen and liver enlarged. Thymus normal. Blood: 69,000 leucocytes/c.mm. with 91.5% stem-cells/c.mm. myeloblasts.
411 ♀	36	None	Mammary adenocarcinoma, 19x17x10 mm., in left axilla.
412 ♀	24	None	Leukemia. Many lymphnodes 10 mm. Mesenteric lymphnode 19 mm. Spleen large, thymus 10x9 mm. Liver and kidneys moderately enlarged. Blood: 181,500 leucocytes/c.mm. with 97.5% stem-cells, mostly myeloblasts.
418 ♀	22	None	Leukemia. Many lymphnodes 9-15 mm. Mesenteric lymphnode 19 mm. Thymus 10x6 mm. Spleen large, reddish blue. Liver and kidneys not enlarged. Blood leukemic.
424 ♀	26	Fibrosarcoma 17x17x12 mm	Mesenteric lymphnode 10x3 mm., blood-red. Right ovary 9 mm., whitish-yellow, dark red in parts. Uterus distended, filled with blood. Ovarian tumor resembling granulosa cell type. Hyperplasia of lymphnodes.

The following results were obtained by painting the skin of the back of 14 Aka mice 3 times a week with a 0.5 per cent solution of 9,10-dimethyl-1,2-benzanthracene: Three died from intercurrent diseases; 10 of the 11 survivors died within 20 weeks with more or less pronounced leukemic or lymphosarcomatous changes,

and 5 died with carcinoma at the site of injection. The results appear in Tables I and V.

No case of spontaneous leukemia was observed in the 40 untreated control animals up to the age of 8 months during the period of the experiment.

Whereas no case of leukemia and only 2 cases of mammary carcinoma occurred during the experimental period of 9 months among 36 untreated control animals of Dlb strain, 12 cases of leukemia or lymphosarcoma and 10 of mammary carcinoma, 3 of which

TABLE III: RESULTS OF PAINTING DILUTE BROWN MICE WITH 0.5 PER CENT SOLUTION OF 9,10-DIMETHYL-1,2-BENZANTHRACENE IN BENZENE 2 OR 3 TIMES A WEEK

Mouse no.	Age at death, in weeks	Changes at site of injection	Other findings
216 ♀	31	Papillomas	2 mammary carcinomas in left axilla and left inguinal region, 15x12x10 mm. and 10x10x5 mm. Adenocarcinomas with metaplasia to squamous cell epithelium.
229 ♀	23	Papillomas	Lymphogenous leukemia. Lymphnodes 5-9 mm. Spleen large, 20x7 mm. Liver, kidneys, and thymus not enlarged. Leukemic infiltration in all organs.
256 ♀	22	Epilation	Lymphogenous leukemia. Lymphnodes 10 mm. Spleen 25x9 mm. Liver moderately enlarged. Thymus normal. Blood: 13,600 leucocytes with 92% large, atypical lymphocytes. Typical lymphogenous leukemia.
257 ♀	31	Papilloma; carcinoma	Mammary adenocarcinoma, 10x10x10 mm., on right side of neck.
261 ♂	21	Papilloma	Lymphogenous leukemia. All lymphnodes enlarged 2-5 mm. Spleen 20x5 mm. Liver enlarged. Thymus normal. Blood: 9,300 leucocytes, 87% atypical lymphocytes. Lymphatic leukemic changes in spleen and lymphnodes.
262 ♀	29	Papilloma	Mammary adenocarcinoma, 25x20x25 mm., in right side. In left axilla a subcutaneous squamous cell carcinoma, 5x5 mm.
263 ♀	32	Squamous cell carcinoma	Mammary adenocarcinoma, 10x10x10 mm., in left side.
267 ♀	24	Papilloma	Mammary adenocarcinoma, 30x25x15 mm., in left inguinal region.
268 ♀	29	Squamous cell carcinoma	Mammary adenocarcinoma, 15x15x10 mm., in left axilla.
270 ♀	22	Epilation	Myelogenous leukemia. Many lymphnodes 6-10 mm. Spleen 22x6 mm. Mesenteric lymphnode 22 mm. Liver and kidneys slightly enlarged. Thymus moderately enlarged. Blood: 71,900 leucocytes, 90% myeloblasts, 4-5% myelocytes. Leukemic infiltration in all organs.
272 ♀	25	Carcinoma and leukemic infiltrations	Lymphogenous leukemia (stem-cell ?). Many lymphnodes 6-7 mm. Mesenteric lymphnode 12 mm. Spleen 22x10 mm. Liver and kidneys slightly enlarged. Thymus normal. Blood: 41,000 leucocytes, 95.5% "blasts" (lymphogenous ?). Leukemic infiltrates in liver and lymphnodes. Severe lymphosarcoma-like infiltration subcutaneously at the site of painting.
277 ♀	34	Squamous cell carcinoma	2 mammary adenocarcinomas, 15x15x10 and 10x10x15 mm., in left side and right inguinal region. Adenocarcinomas with patches of metaplasia to squamous cell epithelium.
308 ♂	34	Squamous cell carcinoma	Lymphogenous leukemia. Many lymphnodes 5 mm. Mesenteric lymphnode 25 mm. Spleen 20x10 mm. Liver greatly enlarged. Kidneys moderately enlarged. Thymus normal. Great leukemic infiltrations in liver, kidneys, spleen, and lymphnodes. Large lymphosarcomatous infiltrations in stroma of skin carcinoma and subcutaneous tissue.
310 ♂	38	Squamous cell carcinoma	Leukemia. Lymphnodes not enlarged. Spleen 30x10 mm. Liver enlarged. Severe leukemic changes in spleen and liver with fairly large (myelogenous ?) cells. Hemorrhages in the spleen.

DISCUSSION

The use of 9,10-dimethyl-1,2-benzanthracene in painting the skin of the back and for subcutaneous injection produced local tumors at the site of treatment in 22 out of 52 Dlb and 19 out of 23 Aka mice, both inbred strains. It also caused the accelerated appearance of the tumorous diseases characteristic of these strains.

were multiple cancers, appeared among 52 animals treated. The relatively slight tendency of this strain towards the development of leukemia was thus accelerated to a pronounced degree by the treatment, the number of cases being very greatly increased, from about 2 per cent in the untreated animals to about 23 per cent. The disease developed far earlier in the lifetime of the animals than is usual, for the leukemic

animals died at ages of from 4 to 7 months, whereas spontaneous leukemia does not develop in animals of this strain until they are over the age of 8 months.

It was also possible to accelerate the development of mammary carcinoma in this strain. Its incidence does not seem to have been increased, but the tumors developed far earlier in the animals treated than in those not treated. Mammary carcinoma developed earlier than is usual in this strain in 10 out of 26 females, most had any sign of leukemia. The animals died when they were from 4 to 7 months old, whereas spontaneous leukemia does not usually develop until after the age of 9 or 10 months. The number of cases of disease also seemed to be increased to about 82 per cent, although the figures are too small for a definite conclusion to be drawn.

Of particular interest is the fact that pronounced lymphosarcomatous infiltration was observed in the

TABLE IV: RESULTS OF TREATING AKA MICE WITH 1 MGM. 9,10-DIMETHYL-1,2-BENZANTHRACENE INJECTED SUBCUTANEOUSLY

Mouse no.	Age at death, in weeks	Changes at site of injection	Other findings
2444 ♂	20	Epilation	Lymphosarcoma, 10x10 mm. in left inguinal region. Lymphnodes 5 mm. Mesenteric lymphnode 20 mm. A lymphosarcoma 30x10 mm. around right kidney. Thymus slightly enlarged. Blood: 32,100, leucocytes 96% atypical lymphocytes. Lymphogenous leukemic infiltration in liver, bone marrow, and lymphnodes.
2447 ♀	21	Reticulo-sarcoma 15x15 mm	Spleen and lymphnodes moderately enlarged. Reticulo-sarcomatosis in spleen, liver, lymphnodes. Blood normal.
2450 ♀	29	Polymorphocellular sarcoma 38x22x20 mm.	Solid carcinoma of right ovary, 10x10x10 mm., granulosa cell type. No sign of leukemia. Liver and marrow normal.
2451 ♀		Epilation. Ulceration	Lymphogenous leukemia. Lymphnodes 6-10 mm. 15x10 mm. lymphosarcoma at upper pole of right kidney. Liver, spleen, thymus only slightly enlarged. Blood: lymphogenous leukemia. Lymphogenous leukemic infiltration in lymphnodes. Liver normal.
2453 ♀	19	Epilation	Lymphosarcoma of the axilla, 10x5x3 mm. Organs otherwise normal. Blood normal.
2454 ♀	20	Squamous cell carcinoma with ulceration.	Reticular cell hyperplasia in spleen and lymphnodes. Blood: anemia, 9,600 leucocytes, 96% lymphocytes.
2456 ♂	20	Fusocellular sarcoma	Atypical lymphogenous leukemia. Lymphnodes 5 mm. Spleen 20x6 mm. Thymus slightly enlarged. Pronounced leukemic changes in liver. Blood: 46,800 leucocytes, 90% atypical lymphocytes.
2458 ♀	18	Lymphosarcoma 15x7 mm	Many lymphnodes, lumbar and inguinal, enlarged, 5 mm. Lymphosarcomatosis with extensive invasive growth into the surrounding tissues. Blood normal. A squamous cell carcinoma 18x18x14 mm. in perineum.
2460 ♂	15	Fusocellular sarcoma 5x3x2 mm	Lymphosarcoma. Lumbar lymphnodes 5 mm. Thymus slightly enlarged. Lymphosarcoma with invasion into diaphragm.
2463 ♀	19	None	Leukemic lymphosarcomatosis. Lymphnodes in neck 15x10x10 mm. Other peripheral lymphnodes 4 mm. Mesenteric lymphnode 20x7 mm. Lumbar lymphnode 13x5 mm. Thymus 10x10 mm. Blood: 45,500 leucocytes, 85% atypical lymphocytes. Bone marrow: lymphogenous leukemic. Lymphnodes: lymphosarcoma with extensive invasion of the musculature.

of the animals dying from their carcinomas at the age of 7 or 8 months, whereas spontaneous mammary cancer rarely develops before the age of 9 months. Acceleration of the development of tumors was also evident when 3 of the 10 animals died with double mammary carcinoma which, although occurring spontaneously, is far more rare. When mice of strain Aka, in which spontaneous leukemia develops in from 50 to 70 per cent of all animals, were treated with 9,10-dimethyl-1,2-benzanthracene, accelerated development of leukemic conditions occurred in 19 out of 23 animals at a time when none of the 40 control animals subcutaneous tissue at the site of painting in the cases of 5 of 11 mice of this strain that had been painted with a solution of carcinogenic hydrocarbons; and this applies both to animals in which papillomas had developed and to those in which the painting had produced carcinoma. No other sign of hyperplasia or malignant growth in the lymphatic system was found in 3 of these 5 animals, whereas general leukemic changes as well as skin infiltration was found in 2 cases.

This fact seems to indicate that in strain Aka the cells of the lymphatic system have a particular ten-

dency to react to carcinogenic influence by developing manifest malignant tumors, and that this inherited tendency applies to the whole of the lymphatic system. The development of the tumor began in these 5 cases at the sites of the painting, which were selected purely fortuitously. The same conditions are observed in strain Dlb, in which 2 of the 7 animals developed leukemia after they had been painted (Table III).

Kreyberg (10) and Cramer (4) painted mice of a high mammary carcinoma strain with tar, but observed no acceleration of the development of cancer. Nor did Bonzer and Connal (2) find any variation in the incidence of mammary carcinoma in animals painted with tar. Dobrovolskaïa-Zadvadskaïa and Adamova (5) treated mice of a strain bearing 50 per cent mammary carcinoma with dibenzanthracene or radon, but did not observe any increase in the number of mammary cancers. On the other hand, Maisin and Coolen (13) reported that they had obtained an increase in the number of mammary cancers

TABLE V: RESULTS OF PAINTING AKA MICE WITH 0.5 PER CENT SOLUTION OF 9,10-DIMETHYL-1,2-BENZANTHRACENE 3 TIMES A WEEK

Mouse no.	Age at death, in weeks	Changes at site of injection	Other findings
5031 ♀	15	Papilloma	Lymphosarcoma in the underlying subcutaneous tissue.
5032 ♀	17	Squamous cell carcinoma	Leukemic lymphosarcomatosis. All lymphnodes 3-5 mm. Widespread infiltration along the spine. Liver: lymphogenous leukemia. Lymphosarcomatous changes in lymphnodes, in infiltrations around the spine, and in the skin under painting-tumor. Blood leukemic.
5033 ♂	19	Epilation	Thymus is enlarged 7x9 mm., otherwise normal conditions. Nonleukemic hyperplasia of thymus. Blood normal.
5035 ♀	17	Squamous cell carcinoma	Killed because of paralysis of hind legs. Thymus very large, 20x15 mm. Thymus: leukemic changes with invasion of heart. Spine: severe lymphatic infiltrations epidurally and in musculature. Marrow: lymphogenous leukemia. Blood normal. Spleen and liver normal.
5036 ♀	17	Squamous cell carcinoma	Myelogenous leukemia. Peripheral lymphnodes 4-5 mm. large. The spleen somewhat enlarged. Blood: leucocytes not increased, 12.5% myeloblasts, 2.5% myelocytes. Spleen and lymphnodes consist almost entirely of myeloid tissue with large myelocytes and myeloblasts. Invasive growth around lymphnodes.
5038 ♀	18	Papillomas	Leukemic lymphosarcomatosis. A 15x10x10 mm. large lymphosarcoma in the submaxillary region. All peripheral glands 8-15 mm. Liver and spleen enlarged, thymus slightly enlarged. Blood: 170,000 leucocytes, 97% atypical lymphocytes and lymphoblasts. Liver, kidneys, pronounced lymphogenous leukemic infiltrations. All lymphnodes: lymphosarcomatous infiltration with ingrowth into the surroundings.
5039 ♀	15	Papillomas; incipient carcinoma. Lymphosarcomatosis.	Lymphosarcomatosis. Killed because of paralysis of hind legs. All lymphnodes are enlarged. Fairly extensive infiltrations in the musculature along the spine. Leukemic changes in the lymphnodes. Enormous lymphosarcomatous infiltration in and around the spine.
5040 ♀	20	Squamous cell carcinoma. Lymphosarcomatous infiltration in skin.	Subleukemic lymphosarcomatosis. Most lymphnodes enlarged, 5 mm. Mesenteric lymphnode 20x10 mm. Blood: 17,800 leucocytes, 87.5% atypical lymphocytes. Lymphosarcoma in skin under painting-tumor. Lymphnodes: lymphogenous leukemic.
5042 ♀	13	Papillomas	Severe lymphosarcomatous infiltration in subcutaneous tissue and musculature under the papillomas. Organs normal.
5043 ♀	18	Papillomas	Massive lymphocytic infiltration in subcutaneous tissue. No signs of leukemia in organs.

No antagonism was observed between the occurrence of the painting tumor and the development of mammary carcinoma or leukemia. The action of carcinogenic substances or tar on mice of inbred strains has been investigated repeatedly, but it was only recently that attention was directed to the fact that, in addition to the production of tumors at the site of painting, acceleration of the tumors characteristic of the strain can be attained.

by painting with methylcholanthrene or benzpyrene. Pronounced acceleration of the development of mammary carcinoma has been obtained in a number of experiments with estrogenic substances, by Lacassagne (11) and others. That a similar acceleration can also be obtained by painting with carcinogenic hydrocarbons appears from the experiments reported in this paper and, more particularly, from the results of another experiment in which painting with methylcholanthrene was employed (7).

The accelerated occurrence and increased incidence of leukemia or lymphosarcoma after carcinogenic action have been observed

repeatedly in strains with low and with high incidence of spontaneous leukemia.

Lacassagne (11) and Perry and Ginzton (18) found that treatment with estrogenic substances increased the incidence of leukemia or lymphosarcoma in the strains they used. Krebs, Rask-Nielsen, and Wagner (9) found 19 cases of leukemia among about 5,000 animals of a non-inbred stock treated with x-rays, whereas they found only 3 cases among 10,500 untreated animals. Furth and Furth (8) irradiated mice of an inbred strain and found that the incidence of leukemia increased seven or eightfold in 775 test animals, as compared with 1,290 control animals. Finally, convincing experiments have been published in which treatment with carcinogenic hydrocarbons has caused considerable acceleration of the cases of leukemia in the strain concerned.

Morton and Mider (15, 16) investigated dilute brown, Dba, mice of a strain in which from 80 per cent to 90 per cent of the breeding females developed mammary carcinoma at a mean age of 10.6 months. It is stated that lymphoblastoma occurs commonly in both sexes between 650 and 800 days. After painting with methylcholanthrene, 0.5 per cent solution in benzene, once a week at various sites, thus avoiding local tumors, leukemia appeared in 48 out of 60 animals at a far younger age, all the animals dying within 226 days. The earliest case was observed on the 69th day after a total of 10 paintings.

Brues and Marble (3) attained very similar results by painting with tar Bagg albino mice, in 2 per cent of which leukemia occurs spontaneously. Various kinds of tar were tested and it appeared that the occurrence of the cases of leukemia was proportional to the carcinogenic properties of the tar employed, as expressed by the number of papillomas appearing at the site of painting and by the time that lapsed before these papillomas appeared. Lymphogenous leukemia was obtained in 20 out of 40 mice painted with the most active carcinogenic tar. It is worthy of note that mice of another strain, Little's C57 black, reacted to the same treatment with the development of papillomas only, leukemia developing in no instance.

The appearance of leukemic diseases and of mammary carcinoma in animals of inbred strains can thus be accelerated when the animals are submitted to carcinogenic influences. Treatment with x-rays, estrogenic substances, or carcinogenic hydrocarbons has brought about an accelerated development of leukemia, and an accelerated development of mammary carcinoma has been observed after treatment with estrogenic substances and carcinogenic hydrocarbons. As has been mentioned, however, acceleration is not always observed when animals of tumor-bearing strains are treated with carcinogenic substances; and we still do not know what factors actually determine such acceleration.

Dosage undoubtedly plays a part in carcinogenic influence. An experiment with Aka mice, in which the animals were painted with a 0.5 per cent solution of 9,10-dimethyl-1,2-benzanthracene in benzene only twice a week and with a smaller quantity of the solution, was carried out simultaneously with that mentioned above. Under these conditions only 2 cases of accelerated leukemia were found in 38 mice, against 10 cases in 11 mice in the experiment previously mentioned.

In the experiments that have been published up to the present, reports have been given of the acceleration of tumors or leukemia that occur spontaneously in the strains concerned, while animals of tumor-free strains have not reacted in a similar manner according to the reports of Brues and Marble (3) and Lacassagne (12).

It is certainly not yet clear how the acceleration observed is to be interpreted. Recent research with mice of inbred strains has clearly shown that intrinsic inherited factors cooperate with extrinsic non-inherited factors when spontaneous tumors and leukemia are developed. It is obviously simple to regard the acceleration demonstrated in the experiment reported above as the consequence of an artificial increase of the extrinsic factors which, in conjunction with the genetic tendency of the animals to have tumors, results in earlier and more frequent manifestation of tumors. The fact that tumor-free strains react differently from tumor strains may indicate that even excessive exogenous influences cannot force the production of a tumor in an organism without a suitable genetic foundation.

Numerous experiments have shown that various exogenous influences, each in itself carcinogenic, can "potentiate" each other's influence by simultaneous action. For example, this has been shown to occur in the cases of dibenzanthracene and estrone, by Perry and Ginzton (18); irradiation with x-rays and carcinogenic hydrocarbons, by Mayneord and Parsons (14); and irradiation with x-rays and benzpyrene, by Mottram (17). It is not yet clear whether such features are analogous with the "potentiation" seen in the simultaneous action of tumor-producing virus and other carcinogenic influence, as in the experiments of Rous and Kidd (19, 20), with tar and Shope fibroma virus. Finally, how the cooperation between the genetic tendency to tumors and exogenous carcinogenic influence, observed in the experiments reported here, is to be related to the above-mentioned "potentiating" influence of two different exogenous influences cannot be decided at present.

Summary and Conclusions

1. Reports are given of the results of experiments with 9,10-dimethyl-1,2-benzanthracene administered to 2 inbred strains of mice, a strain with high incidence of mammary carcinoma and low incidence of leukemia, Dlb, and a strain with high incidence of leukemia, Aka.

2. Pronounced acceleration of the tumors characteristic for the strains, evident in increased incidence and especially in distinctly earlier appearance of the particular tumor, has been produced in these strains of mice by both subcutaneous injection of, and painting with 9,10-dimethyl-1,2-benzanthracene.

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