The Genesis and Growth of Tumors

III. Effects of a High-Fat Diet*

Albert Tannenbaum, M.D.

(*From the Department of Cancer Research, Michael Reese Hospital, Chicago, Ill.*)

(Received for publication March 28, 1942)

Watson and Mellanby (10) have found that feeding mice a diet containing 12.5 to 25 per cent butter fat causes a definite increase in the incidence of skin tumors produced by tarring. The results of Baumann and his associates (1, 2, 5, 6) are in the same direction. In numerous experiments they have shown that skin tumors of the mouse, induced either by ultraviolet light or carcinogenic hydrocarbons, are formed in greater numbers and at an earlier time in mice receiving a high-fat diet than in control mice consuming the basal rations. In contrast to these results, the same investigators have found that the production of sarcomas by carcinogenic hydrocarbons is not significantly altered by a high-fat diet.

This communication is a report of the effects of dietary fat on both the genesis and growth of tumors. The tumors utilized were the spontaneous breast tumor, induced skin tumor, induced sarcoma, and primary lung tumor of the mouse. The investigations demonstrate that increasing the fat content of a basic ration exerts diverse effects on the formation of different types of tumors; these effects range from a striking augmentation of the formation of spontaneous breast tumors to a possible inhibition of the formation of sarcomas induced by a carcinogenic hydrocarbon. An attempt has also been made to clarify the mechanism by which fat affects the genesis of tumors.

METHODS

In all experiments pure strain mice were used, obtained from the Roscoe B. Jackson Memorial Laboratory or derived from their stock. They were divided into groups equivalent as to age, weight, and sex, usually 50 for the experimental group and 50 for the control group. Each animal was numbered and a separate record of its progress was kept. The animals were inspected for tumors biweekly, at which time they were weighed unless they bore skin carcinomas or subcutaneous tumors. Postmortem examination was performed when the tumors became large, at the death of the animal, or at the termination of the experiment. The lesions were recognized as tumors by their appearance and progressive growth; the type of tumor was established by gross examination and sectioning. Histological examinations were made of many tumors, selected at random, and of all those lesions about which doubt existed; the results of the histological studies indicated that the gross examinations were reliable. Percentages of tumor formation were computed on the basis of the number of animals alive at the time the first tumor appeared in either group of the experiment (effective total). The "tumor count" refers to the number of animals which developed tumors.

All animals were fed ad libitum and had free access to water. In each experiment the control group was fed a basic ration relatively low in fat, but adequate for growth, while the second group was fed the same basic ration modified by the substitution of fat.[1] Two basic rations were employed, modified in such a way that 3 experimental high-fat diets resulted. The diets were prepared by mixing the dry components with sufficient water to form an easily molded mash, which was cut into equal blocks, each containing a definite amount of the dry mixture. The actual average food consumption per animal was obtained each week by weighing back the food left in the cages. These values were not obtained in our earlier experiments.

Diet 1.—The control diet (1c) was a basic ration consisting of cracked spring wheat, 145; Purina dog chow meal, 40; skimmed milk powder, 15; and white milled flour, 25. The high-fat diet (1f) was prepared from the basic ration by substituting 25 parts of fat for 25 of wheat, and 5 parts of vitamin-free casein for 5 of flour. On Sunday an equivalent amount of Purina dog chow checkers was fed to both the control and high-fat groups. The approximate compositions of the diets were as follows:

	Control (1c), per cent	High-fat (1f), per cent
Protein	17	17
Fat	3	12
Carbohydrate	64	58
Ash	3	3

* This investigation was aided by a grant from the National Cancer Institute.

[1] Hydrogenated cottonseed oil (kremit), generously furnished by Armour and Company.

Downloaded from cancerres.aacrjournals.org on May 1, 2015. © 1942 American Association for Cancer Research.

Diet 2.—The control basic ration (2c) was the same as in diet 1. The high fat diet (2f) was made by substitution, in a manner similar to that used in preparing high-fat diet 1f, but differing in that 75 parts of fat replaced 50 of wheat. Otherwise, the method of preparation of the diets, daily feeding, and Sunday feeding were the same as with diet 1. The approximate compositions of the diets were as follows:

	Control (2c), per cent	High-fat (2f), per cent
Protein	17	15
Fat	3	28
Carbohydrate	64	46
Ash	3	3

Diet 3.—Experience and refinement of technic resulted in diet 3. The control diet (3c) consisted of 1.4 gm. Purina dog chow meal, 0.9 gm. skimmed milk powder, and 1.9 gm. cornstarch. This amount was fed daily to each animal. The high-fat diet (3f) was prepared by substituting an isocaloric amount (0.9 gm.) of hydrogenated cottonseed oil for the 1.9 gm. of starch. Thus equicaloric amounts of the 2 diets contained equal quantities of protein, vitamins, and minerals, and differed only in the fat and carbohydrate content. The approximate compositions of the diets in grams per mouse per day were as follows:

	Control (3c), gm.	High-fat (3f), gm.
Protein	0.62(15%)	0.62(19%)
Fat	0.08(2%)	0.98(31%)
Carbohydrate	2.92(70%)	1.22(38%)
Ash	0.16(4%)	0.16(5%)

It is to be noted that the fat content of the 3 high-fat diets was 12 to 31 per cent in comparison with a fat content of 2 to 3 per cent for the 2 control rations.

RESULTS

Effects of a High-Fat Diet on the Formation of Spontaneous Breast Tumors

Experiment 1.—The control and experimental groups were each composed of 44 female dba mice, matched as to their birth dates, number of litters, and litter dates (12 in each group were virgin). At an average age of 38 weeks (range, 32 to 48 weeks) they were placed on their respective diets: diet 1c, control, and the corresponding high-fat diet (1f) described under "Methods." The experiment was continued until all the animals had died. There was no observable difference in the general health and appearance of the mice in the 2 groups, and the rate of nontumor deaths was approximately the same in both groups.

The results as shown in Table I and Fig. 1 A reveal that more tumors were formed in the high-fat group. Twenty-four tumors (55 per cent) arose in the F11 group receiving the high-fat diet in contrast to 14 tumors (32 per cent) in the F12 group fed the basic diet. The tumors in the high-fat group arose at a mean age of 70 ± 3.1 weeks in comparison with 72 ± 5.7 weeks for those of the control group.

Experiment 2.—Experiment 1 was repeated on 2 groups of 50 virgin dba mice. At an average age of 24 weeks (range, 18 to 32), they were placed on the control (1c) and high-fat (1f) diets. The experiment was terminated when the mice had attained an average age of 2 years, at which time only 3 of the control group (F22) and 2 of the high-fat group (F21) were alive and without tumors.

The results are shown in Table II, and the cumulative tumor counts are graphically represented in Fig. 1 B. Thirty-two spontaneous breast tumors (64 per cent) arose in the high-fat group in comparison with 16 tumors (32 per cent) in the control group. The tumors in the high-fat group appeared at a mean age of 62 ± 1.8 weeks, compared with 74 ± 3.1 for those of the control group. Thus, the high-fat diet caused the formation of twice as many tumors and a significant shortening of the mean age of appearance. As in experiment 1, there was no observable difference in the general health and appearance of the 2 groups, and the rates of nontumor deaths were approximately the same.

The definite increase in the incidence of spontaneous breast tumors brought about by a fat-enriched diet is significant, and this effect is the most striking result obtained in our studies with various types of tumors. Also, the tumors appeared at an earlier time. There are certain quantitative differences in the results of the 2 experiments. The control groups of both experiments had 32 per cent tumors while the high-fat groups of experiments 1 and 2 had 55 per cent and 64 per cent respectively. Furthermore, in experiment 1, the high-fat diet did not significantly decrease the mean age at which the tumors appeared, while in experiment 2 the mean age of appearance of the tumors was shortened by about 3 months. The mice of experiment 2 were approximately 14 weeks younger than those of experiment 1 at the beginning of these experiments and were, therefore, subjected to the dietary differences for a longer period. It is suggested that if mice be fed a high-fat diet throughout their early adult life a more decided augmentation and acceleration of tumor formation occurs. When the animals of experiments 1 and 2 were classified into smaller subgroups, according to the age at which the diets were instituted, it appeared that the augmentation of tumor formation through the high-fat diet was less pronounced in the older subgroups.

Downloaded from cancerres.aacrjournals.org on May 1, 2015. © 1942 American Association for Cancer Research.

TABLE I: THE EFFECTS OF A HIGH-FAT DIET ON THE FORMATION OF SPONTANEOUS BREAST TUMORS IN DBA MICE

Average * age, weeks	F12: control, diet 1c			F11: high-fat, diet 1f		
	Mean weight, gm.	Animals alive and tumor-free	Cumulative tumor count	Mean weight, gm.	Animals alive and tumor-free	Cumulative tumor count
38	29	44	0	28	44	0
46	30	43	1	31	39	3
54	31	40	3	33	36	5
62	31	34	6	34	32	7
70	31	28	8	34	26	9
78	28	24	10	33	19	14
86	28	13	11	32	5	22
94	28	9	11	..	0	24
102	—	2	13	..	..	..
110	..	0	14	..	..	..

* Average age of mice at beginning of experiment (May 17, 1938): 38 weeks.

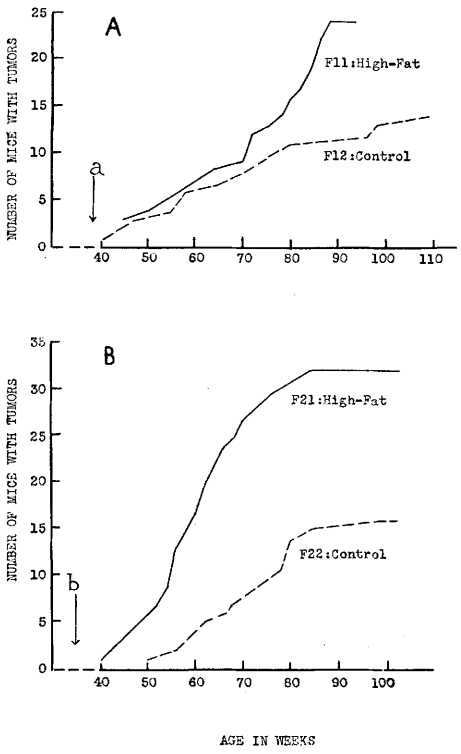

Fig. 1.—Effects of a high-fat diet on the formation of spontaneous breast tumors in dba female mice. Curve of cumulative number of tumors. (a) Diets instituted at 38 weeks. (b) Diets instituted at 24 weeks.

EFFECTS OF A HIGH-FAT DIET ON THE FORMATION OF INDUCED EPITHELIAL TUMORS

These experiments were performed with 3 different strains of mice. The skin tumors were induced by a 0.3 per cent benzene solution of 3,4-benzpyrene. Twice weekly, in general, one drop of the solution, containing about 0.05 mgm. of the carcinogen, was applied to the interscapular region by means of a dropping pipette. Tumors were recorded as papillomas or carcinomas, but since most of the papillomas eventually became carcinomas, and the exact time of conversion was not always recognizable, the tumor counts include both types.

Experiment 3.—Two groups, each containing 45 JAX Swiss females, were placed on their respective control and high-fat diet 2 when they were about 10 weeks of age. They received 32 applications of the benzpyrene solution during the following 20 weeks. The average daily food consumption for the high-fat group (K1) was 3.0 gm. per mouse compared with 3.3 gm. for the control animals (K2). The experiment was continued for 42 weeks following the initial application of the carcinogen.

TABLE II: THE EFFECTS OF A HIGH-FAT DIET ON THE FORMATION OF SPONTANEOUS BREAST TUMORS IN DBA VIRGIN MICE

Average * age, weeks	F22: control, diet 1c			F21: high-fat, diet 1f		
	Mean weight, gm.	Animals alive and tumor-free	Cumulative tumor count	Mean weight, gm.	Animals alive and tumor-free	Cumulative tumor count
24	27	50	0	26	50	0
32	30	50	0	31	50	0
40	31	50	0	34	49	1
48	33	50	0	36	44	5
56	34	47	2	38	36	13
64	33	38	5	37	25	20
72	32	26	7	33	15	28
80	31	14	14	34	8	30
88	28	8	15	—	4	32
96	—	5	15	—	3	32
102	—	3	16	—	2	32

* Average age of mice at beginning of experiment (June 30, 1938): 24 weeks.

The results are shown in Table III. Twenty-eight skin tumors (67 per cent) were formed in the high-fat group and 22 tumors (51 per cent) in the control group. The mean time of appearance of the tumors in the high-fat group was 23 ± 1.3 weeks, compared with 24 ± 1.7 for those of the control group.

Experiment 4.—Two groups of 50 C57 black male mice, all born within a span of 3 weeks, were transferred to their respective control and high-fat diet 3 when they were 10 weeks of age. At 16 weeks of age they received the first of 26 semiweekly applications of the benzpyrene solution. The animals of the control group (S0) consumed an average of 3.5 gm. per day in comparison with 3.0 gm. per day for the high-fat group (S1). It is to be noted that these amounts of food contained approximately the same quantities of essential dietary components (protein, vitamins, and minerals) and were approximately isocaloric.

Downloaded from cancerres.aacrjournals.org on May 1, 2015. © 1942 American Association for Cancer Research.

The results are given in Table IV and the tumor counts are graphically presented in Fig. 2 A. In the high-fat group (S1), 17 mice (35 per cent) developed tumors compared with 13 (27 per cent) in the corresponding control group (So). The mean time of appearance of the tumors in the high-fat group was 31 ± 2.8 weeks, compared with 34 ± 3.0 in the control group. Toward the end of the experiment skin ulcerations occurred in approximately equal numbers in both groups.

Experiment 5.—Two groups of 50 mice each were made up of dba male mice born within a span of 6 weeks. At 10 weeks of age the groups were placed on their respective control and high-fat diet 3. Four weeks later the first of 19 semiweekly applications of the benzpyrene solution was begun. The average

TABLE III: THE EFFECTS OF A HIGH-FAT DIET ON THE FORMATION OF INDUCED SKIN TUMORS IN MALE SWISS MICE

Weeks after first application *	K2: control, diet 2c			K1: high-fat, diet 2f		
	Mean weight, gm.	Animals alive and tumor-free	Cumulative tumor count	Mean weight, gm.	Animals alive and tumor-free	Cumulative tumor count
1	21	45	0	20	45	0
11	25	43	0	26	40	2
15	27	37	3	28	36	6
19	29	32	7	30	34	7
23	31	30	8	32	25	15
27	33	21	17	35	16	23
31	33	19	19	35	14	25
35	32	19	19	38	11	27
39	34	16	21	38	10	28
42	35	15	22	39	9	28

* Thirty-two applications of benzpyrene solution beginning March 10, 1939.

daily food intake per mouse was 4.0 gm. for the control group and 3.1 for the high-fat group. Again, as in the previous experiment, the animals were fed ad libitum; yet the 2 groups consumed isocaloric amounts of food containing approximately equal quantities of essential dietary components.

The results are shown in Table V and Fig. 2 B. Thirty-nine skin tumors (78 per cent) were formed in the high-fat group, in comparison with 34 tumors (68 per cent) in the control group. The mean time of appearance of these tumors was 27 ± 2.2 and 31 ± 1.8 weeks respectively.

It should be noted from the tables and figures that in the stage of each experiment when only a few tumors had formed (21 to 24 weeks) the percentage difference in the incidence of tumors in the 2 groups was relatively large. However, by the time the experiments were terminated (42 to 56 weeks) larger numbers of tumors had formed in both groups, resulting

TABLE IV: THE EFFECTS OF A HIGH-FAT DIET ON THE FORMATION OF INDUCED SKIN TUMORS IN MALE C57 BLACK MICE

Weeks after first application *	So: control, diet 3c			S1: high-fat, diet 3f		
	Mean weight, gm.	Animals alive and tumor-free	Cumulative tumor count	Mean weight, gm.	Animals alive and tumor-free	Cumulative tumor count
†	24	49	0	24	50	0
0	28	49	0	28	50	0
13	34	49	0	36	50	0
17	35	47	2	38	45	4
21	38	46	2	40	43	5
25	39	43	4	41	40	6
29	38	42	4	42	38	7
33	40	39	6	44	36	9
37	40	35	6	44	31	11
41	39	26	10	42	24	14
45	38	21	11	40	21	15
49	—	19	13	—	15	17

* Twenty-six semiweekly applications of benzpyrene solution beginning Aug. 2, 1940.

† Diets started on June 24, 1940, 6 weeks before first application of carcinogen.

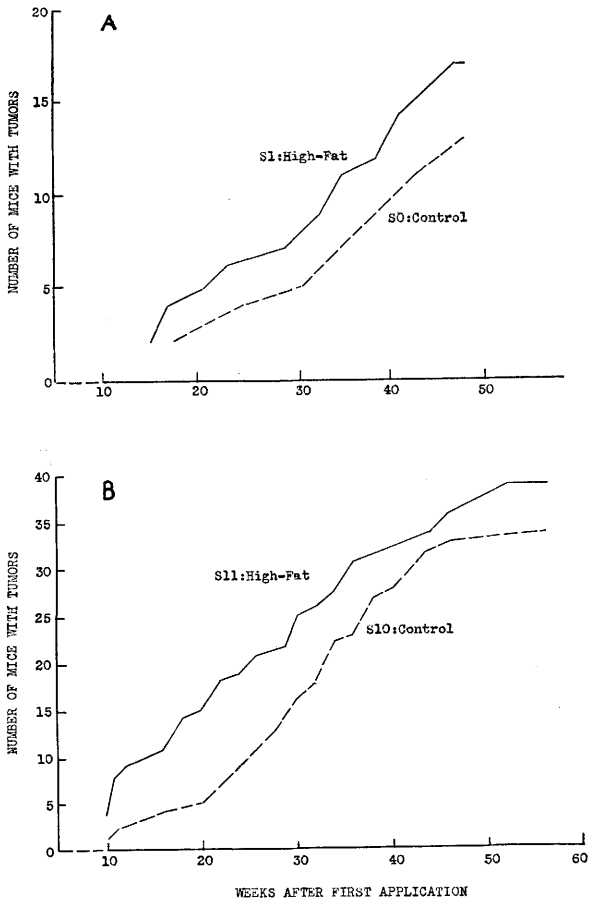

FIG. 2.—Effects of a high-fat diet on the formation of induced epithelial tumors. Curve of cumulative number of tumors.

Downloaded from cancerres.aacrjournals.org on May 1, 2015. © 1942 American Association for Cancer Research.

in smaller relative differences in the incidence of tumors. These facts in no way alter the interpretation of the results, but do indicate that the magnitude of the effect appears to be greater in the early stages of the experiments.

In 2 experiments on JAX ABC mice comparable results were obtained when the fat content of the basic ration was increased by the addition of 10 per cent wheat germ oil, instead of hydrogenated cottonseed oil.

Thus, all 5 experiments with induced skin tumors show the same results: A high-fat diet produced a definite increase in the incidence of skin tumors and shortened the mean time of appearance of these tumors. Although the differences in any one experiment are not of significant magnitude statistically, the results are remarkably consistent and are in qualitative agreement with those obtained by other workers (2, 5, 6, 10).

TABLE V: THE EFFECTS OF A HIGH-FAT DIET ON THE FORMATION OF INDUCED SKIN TUMORS IN MALE DBA MICE

Weeks after first application*	S10: control, diet 3c			S11: high-fat, diet 3f		
	Mean weight, gm.	Animals alive and tumor-free	Cumulative tumor count	Mean weight, gm.	Animals alive and tumor-free	Cumulative tumor count
†	23	50	0	23	50	0
0	26	50	0	25	50	0
8	29	50	0	29	50	0
16	32	46	4	31	38	11
24	30	40	9	31	30	19
32	32	31	18	34	23	26
40	31	20	28	32	18	31
48	—	8	33	33	11	36
56	—	3	34	—	7	39

* Nineteen semiweekly applications of benzpyrene solution beginning Sept. 7, 1940.

† Diets started Aug. 10, 1940, 4 weeks before first application of carcinogen.

EFFECTS OF A HIGH-FAT DIET ON THE FORMATION AND GROWTH OF INDUCED SARCOMAS

Experiment 6.—Two groups, each of 40 JAX Swiss female mice 10 weeks of age, were given a single subcutaneous injection of 0.15 mgm. of 3,4-benzpyrene in 0.2 cc. of lard in the interscapular area. At that time they were placed on their respective control and high-fat diet 2. The control group (L30) consumed a daily average of 3.0 gm. per mouse compared with 3.4 gm. for the high-fat group (L1).

Fewer tumors were formed in the high-fat group. The results are given in Table VI and Fig. 3 B. Twelve sarcomas (30 per cent) arose in the high-fat group in comparison with 19 sarcomas (49 per cent) in the control group. The mean time of appearance of the tumors was 25 ± 2.7 and 25 ± 1.4 weeks respectively.

The rate of growth of the tumors in the 2 groups did not differ. The 13 tumors measured in the normal group (L30) had a mean growth index[2] of 13 ± 1.1

TABLE VI: THE EFFECTS OF A HIGH-FAT DIET ON THE FORMATION OF INDUCED SARCOMAS IN FEMALE SWISS MICE

Weeks after injection*	L30: control, diet 2c			L1: high-fat, diet 2f		
	Mean weight, gm.	Animals alive and tumor-free	Cumulative tumor count	Mean weight, gm.	Animals alive and tumor-free	Cumulative tumor count
0	19	40	0	19	40	0
8	24	40	0	26	40	0
16	28	37	1	32	38	2
24	30	27	11	36	32	7
32	31	18	18	40	27	9
40	31	17	19	42	21	12
48	34	15	19	43	18	12
52	34	15	19	42	16	12

* Single injection of 3,4-benzpyrene on May 22, 1939.

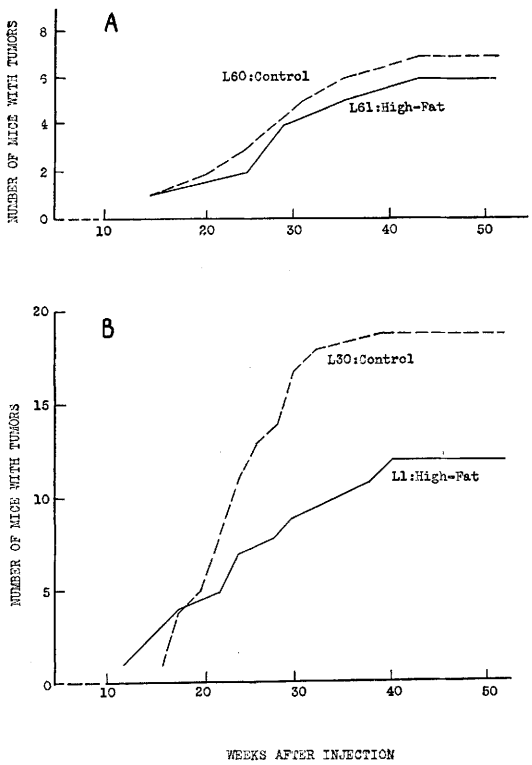

FIG. 3.—Effects of a high-fat diet on the formation of induced sarcomas. Curve of cumulative number of tumors.

[2] Growth index $= \frac{\text{Change in size of tumor}}{\text{Interval in days}} \times 10$

Size of tumor = Length plus breadth in millimeters as measured by calipers; estimated error less than 10 per cent.

Downloaded from cancerres.aacrjournals.org on May 1, 2015. © 1942 American Association for Cancer Research.

compared with 13 ± 2.3 for the 9 tumors measured in the high-fat group (L1).

Experiment 7.—At 9 weeks of age 40 JAX ABC mice were placed in the control group (L60) and 37 mice in the high-fat group (L61). A single subcutaneous injection of 0.1 mgm. of 3,4-benzpyrene in 0.2 cc. of lard was given in the interscapular region. Diets 2c and 2f were again utilized. The daily average food consumption per mouse was 3.6 and 3.3 gm. for the control and high-fat groups respectively.

In Table VII and Fig. 3 A the results of this experiment are given. Six sarcomas (16 per cent) were formed in the high-fat group, 7 (18 per cent) in the control group. The mean time of appearance of these tumors was 29 ± 3.9 and 28 ± 3.5 weeks respectively.

TABLE VII: THE EFFECTS OF A HIGH-FAT DIET ON THE FORMATION OF INDUCED SARCOMAS IN FEMALE ABC MICE

	L60: control, diet 2c			L61: high-fat, diet 2f		
Weeks after injection*	Mean weight, gm.	Animals alive and tumor-free	Cumulative tumor count	Mean weight, gm.	Animals alive and tumor-free	Cumulative tumor count
0	18	40	0	18	37	0
7	25	40	0	27	37	0
15	32	39	1	34	36	1
23	35	38	2	41	35	1
31	38	33	5	44	31	4
39	39	31	6	45	30	5
47	40	30	7	44	29	6
51	40	29	7	42	25	6

* Single injection of 3,4-benzpyrene on May 27, 1939.

As in the previous experiment, growth rates of tumors were studied. No appreciable difference was found between the mean growth indices of the tumors in the control and high-fat groups: 14 ± 1.3 (6 tumors) and 13 ± 2.7 (4 tumors) respectively.

Thus, a high-fat diet definitely does not increase the formation of induced sarcomas; under selected conditions of carcinogenesis it may even inhibit their formation. The results of these 2 experiments with induced sarcomas are in decided contrast to those obtained with spontaneous breast tumors (considerable increase) and induced epithelial tumors (moderate increase).

EFFECTS OF A HIGH-FAT DIET ON THE FORMATION OF PRIMARY LUNG TUMORS

Three of the experiments reported (experiments 3, 6, and 7) were performed on strains of mice that normally develop primary lung tumors. At the termination of these investigations it seemed expedient to utilize the postmortem examination records to study the effects of the high-fat diet on the formation of primary lung tumors. Primary epithelial lung tumors were found in relatively equal numbers in the control and high-fat groups. However, one must consider that these results were observed in animals which were not much over one year of age, well before the maximum number of lung tumors is expected. The tumors in both groups were, on the average, from 1 to 3 mm. in diameter. Table VIII shows the results of this study. It is evident that a high-fat diet has no significant effect upon the genesis of primary lung tumors. Watson and Mellanby (10) reported that there was a slight increase in the number of lung tumors in their high-fat groups. However, it is difficult to compare our finding with theirs since they considered only lung tumors in animals with tumors of the skin while we considered only those of animals free from other tumors. They stated that the lung tumors in their animals were both metastatic tumors and primary lung tumors, and it is probable that the metastatic tumors were more numerous in the high-fat animals since their skin tumors were formed earlier.

DISCUSSION

The most striking result of these investigations is the diversity of effects produced by a high-fat diet: The incidence of spontaneous breast carcinoma in the mouse was significantly increased; the formation of induced skin tumors was also increased, but probably to a lesser extent; the primary lung tumor incidence was unaffected; and the formation of induced sarcomas was unaffected or actually inhibited. Furthermore, whenever an increase in the incidence of tumors occurred, there was also a shortening of the mean time of appearance. The results, summarized in Table VIII, are the outcome of investigations in which: (a) at least 2 experiments were performed with each type of tumor; (b) various strains of mice were used; (c) adequate numbers of animals were employed; (d) the experiments were continued for a sufficiently long period; (e) the general health of both the control and experimental groups was good; and (f) the number of nontumor deaths was not unusual and was of the same order in both groups.

Some investigators have reported that fat-enriched diets produced a decided greasiness of the skin in their animals. We have noted only the slightest oiliness of the skin in animals on the diets containing 31 per cent fat, and none in the animals on the diet containing 12 per cent fat. The animals on the high-fat diets were heavier, in general, and had a greater proportion of fat, as well as more, in the fat depots (subcutaneous, genital, perirenal, mesenteric, etc.).

The assumption is made that in a qualitative sense the diverse effects of a fat-enriched diet observed in

Downloaded from cancerres.aacrjournals.org on May 1, 2015. © 1942 American Association for Cancer Research.

these experiments are essentially real, and dependent on the type of tumor. There is no reason to believe that fat must act in only one way. It seems to us that the effects reported in this communication may be the resultant of two properties of fat: (a) "solvent action" on the carcinogen; and (b) "cocarcinogenic action" on the developing tumor cell. Under certain conditions solvent action may concentrate the carcinogen in a particular area, while under other conditions it may remove the carcinogen, as from a site of injection. Cocarcinogenic action may be considered to be a

TABLE VIII: THE DIVERSE EFFECTS OF A HIGH-FAT DIET ON THE FORMATION OF DIFFERENT TYPES OF TUMORS

Type of tumor	Group, experiment number	Number of mice (effective total)	Tumors, per cent	Mean time of appearance, weeks
Spontaneous breast carcinoma	F12: control	44	32	72 ± 5.7 *
	F11: high-fat	44	55	70 ± 3.1
	F22: control	50	32	74 ± 3.1
	F21: high-fat	50	64	62 ± 1.8
Induced skin tumors	K2: control	43	51	24 ± 1.7 †
	K1: high-fat	42	67	23 ± 1.3
	S0: control	49	27	34 ± 3.0
	S1: high-fat	50	35	31 ± 2.8
	S10: control	50	68	31 ± 1.8
	S11: high-fat	50	78	27 ± 2.2
Induced sarcomas	L30: control	39	49	25 ± 1.4 †
	L1: high-fat	40	30	25 ± 2.7
	L60: control	40	18	28 ± 3.5
	L61: high-fat	37	16	29 ± 3.9
Primary lung tumors	K2: control	15	52	52 ‡
	K1: high-fat	9	44	
	L30: control	15	27	62
	L1: high-fat	16	25	
	L60: control	29	34	60
	L61: high-fat	25	36	

* Mean age of mice.
† Mean time after first application of carcinogen.
‡ Mean age of mice at time of examination.

metabolic stimulation of carcinogenesis. In the light of this hypothesis the effect of a high-fat diet on the genesis of the tumors studied will be discussed.

Spontaneous breast tumors.—It is possible that a high-fat diet increases the formation of spontaneous breast tumors principally through the action of larger quantities of estrogenic hormone held in solution in the larger amounts of adipose tissue surrounding the breasts of mice on a fat-enriched diet. For this type of tumor the solvent action and cocarcinogentic action may act together to produce the augmentation observed.

Induced skin tumors.—According to Beck and Peacock (3) chemical carcinogens disappear from the surface of mouse skin within a few days. Using similar methods we have found that the carcinogen tends to disappear somewhat more rapidly from the surface of the skin of mice that are on a high-fat diet. This suggests that the carcinogen may be carried into the skin more rapidly in such mice. There is at least one fact, however, that argues against solvent action as the cause of the observed augmentation of tumor formation: Experiments in which fat-enriched diets were fed during various phases of the tumor process (6, 8) suggest that fat feeding in the period *following* the application of the carcinogen is more effective in increasing the formation of tumors. This fact, however, is compatible with the view that the increased tumor incidence is due to cocarcinogenic action.

Induced sarcomas.—Baumann, Jacobi, and Rusch (2) carried out experiments with large dosages of carcinogen (0.5 to 1.25 mgm.), obtaining high percentages of tumors in both the control and high-fat groups. There was no significant difference in tumor formation. On the other hand, our experiments were carried out with 0.1 and 0.15 mgm. of 3,4-benzpyrene and resulted in what may be an inhibition of tumor formation. It is possible that this lack of agreement may be due to different dosages [3] of carcinogen.

It is generally believed that the injected carcinogen gradually disappears from the animal's body. It is probably removed from the injected solvent by a partition between the solvent and the subcutaneous tissue (fat) of the animal. Through increased solvent action a given amount of carcinogen, dissolved in a medium such as lard, would probably be removed at a faster rate if injected into subcutaneous tissue containing large amounts of fat (high-fat group) than if injected into subcutaneous tissue of normal animals (control group). Under these conditions a comparatively smaller "effective dose" (in contrast to the amount injected) would remain at the injection site in the high-fat animals, resulting in fewer tumors. This view is given credence since: (a) in our high-fat animals the lard cysts disappeared more rapidly, suggesting that there may also be a more rapid removal of the carcinogen from the injection site; and (b) Peacock and Beck (7) have shown that groups of mice in

[3] It is now generally believed that a dose of carcinogen large enough to produce tumors in practically 100 per cent of the animals employed may mask or override the effect of an experimental procedure. A smaller dose might permit the effect to be disclosed. The effectiveness of a given quantity of carcinogen is dependent on many factors. In referring to a dose as "high" we imply that in a particular experimental procedure this dose produced tumors in practically all the animals; a "low" dose, on the other hand, is one that produces only a small percentage of tumors even when the experiment is permitted to continue throughout the life span of the animals.

Downloaded from cancerres.aacrjournals.org on May 1, 2015. © 1942 American Association for Cancer Research.

which the carcinogen was retained at the site of injection for a shorter time developed fewer tumors.

The difference between the removal rates of carcinogen in the control and the high-fat group may result, depending on the original dose of carcinogen, in diverse effects. It is probable that the rate of removal of carcinogen from an injection site is proportional to the original dose of carcinogen. Bryan and Shimkin (4) have shown that if the percentage of tumors induced by a given dose of carcinogen is plotted against the logarithm of the dose, an ∫-shaped curve is obtained. Consequently, it may be expected that proportionate decreases (due to a high-fat diet) in the effective dosage of carcinogen would result in a lesser effect on tumor incidence when the injected dose is either high or low (at the extremities of the ∫-curve) than when the carcinogen is injected in intermediate amounts (middle of the ∫-curve). This hypothesis would explain the negative results of Baumann, Jacobi, and Rusch (2), in which high dosages were used, the negative results of our own experiment 7, in which a low dosage was used, and the decrease in tumor incidence observed in our experiment 6, in which an intermediate dosage was employed.

Primary lung tumors.—The incidence of this type of tumor is unaffected by a high-fat diet. This may be due to the fact that fat is not deposited in the lung; thus, neither the solvent action nor the cocarcinogenic action of fat would be expected to exert any effect on the formation of primary lung tumors.

Growth of tumors formed in animals on a high-fat diet.—Baumann, Jacobi, and Rusch (2) found that the growth rate of tumors of the ear in mice, induced by ultraviolet light, appears to be unaffected by a high-fat diet. In our experiments with induced sarcomas there was no significant difference in the mean growth rate of tumors developing in animals of the control and fat-enriched groups. These results are not unexpected since it is probable that only dietary changes which drastically affect the health and weight of a tumor-bearing animal will significantly alter the growth rate of its tumor.

Significance.—The same factors which lead to an increased incidence of cancer in mice on a high-fat diet may be responsible for the increased incidence of cancer observed in overweight human subjects (9). It should also be pointed out that these investigations indicate the danger of generalizing from the results of an experimental procedure on only one type of tumor.

SUMMARY

1. By utilizing the spontaneous breast carcinoma, induced skin tumor, induced sarcoma, and primary lung tumor of the mouse, the effects of a high-fat diet on the genesis of tumors were studied.

2. The most striking result of these investigations is the diversity of effects produced by a high-fat diet: (a) The incidence of the spontaneous breast carcinoma was significantly increased. (b) The incidence of the induced skin tumor was increased. (c) The incidence of the primary lung tumor was unaffected. (d) The incidence of the induced sarcoma was unaffected or actually inhibited.

3. A high-fat diet not only produced a definite increase in the incidence of spontaneous breast and induced skin tumors, but also shortened the mean time of appearance of these tumors.

4. The mean growth rate of sarcomas arising in the high-fat group was not significantly different from that of sarcomas arising in the control group.

5. A twofold action of a high-fat diet (solvent action and cocarcinogenic action) is postulated to explain the diverse effects on tumor formation.

REFERENCES

1. Baumann, C. A., and Rusch, H. P. Effect of Diet on Tumors Induced by Ultraviolet Light. Am. J. Cancer, **35**:213-221. 1939.
2. Baumann, C. A., Jacobi, H. P., and Rusch, H. P. The Effect of Diet on Experimental Tumor Production. Am. J. Hyg., Sect. A, **30**:1-6. 1939.
3. Beck, S., and Peacock, P. R. The Latent Carcinogenic Action of 3:4 Benzpyrene; Results of Intermittent Applications to the Skin of Mice. Brit. J. Exper. Path., **21**:227-230. 1940.
4. Bryan, W. R., and Shimkin, M. B. Quantitative Analysis of Dose-Response Data Obtained with Carcinogenic Hydrocarbons. J. Nat. Cancer Inst., **1**:807-833. 1941.
5. Jacobi, H. P., and Baumann, C. A. The Effect of Fat on Tumor Formation. Am. J. Cancer, **39**:338-342. 1940.
6. Lavik, P. S., and Baumann, C. A. Dietary Fat and Tumor Formation. Cancer Research, **1**:181-187. 1941.
7. Peacock, P. R., and Beck, S. Rate of Absorption of Carcinogens and Local Tissue Reaction as Factors Influencing Carcinogenesis. Brit. J. Exper. Path., **19**: 315-319. 1938.
8. Tannenbaum, A. Unpublished data.
9. Tannenbaum, A. Relationship of Body Weight to Cancer Incidence. Arch. Path., **30**:509-517. 1940.
10. Watson, A. F., and Mellanby, E. Tar Cancer in Mice. II: The Condition of the Skin When Modified by External Treatment or Diet, as a Factor in Influencing the Cancerous Reaction. Brit. J. Exper. Path., **11**:311-322. 1930.

Downloaded from cancerres.aacrjournals.org on May 1, 2015. © 1942 American Association for Cancer Research.

AACR American Association for Cancer Research

Cancer Research

The Journal of Cancer Research (1916–1930) | The American Journal of Cancer (1931–1940)

The Genesis and Growth of Tumors. III. Effects of a High-Fat Diet

Albert Tannenbaum

Cancer Res 1942;2:468-475.

Updated version	Access the most recent version of this article at: http://cancerres.aacrjournals.org/content/2/7/468.citation

E-mail alerts	Sign up to receive free email-alerts related to this article or journal.
Reprints and Subscriptions	To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.
Permissions	To request permission to re-use all or part of this article, contact the AACR Publications Department at permissions@aacr.org.

Downloaded from cancerres.aacrjournals.org on May 1, 2015. © 1942 American Association for Cancer Research.