THE INFLUENCE OF DIET ON THE PRODUCTION OF TUMORS OF THE LIVER BY BUTTER YELLOW*

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The aim of these experiments has been to determine how diet affects the occurrence of tumors and of cirrhosis produced by *p*-dimethylaminoazobenzene or butter yellow, and to define the relation of tumor production to cirrhosis. The great variety of structural change associated with the administration of the carcinogenic agent has offered the opportunity to study the pathogenesis of tumors in their relation to injury, hyperplasia, and other changes in the parenchymatous elements and supporting framework of the liver.

The Japanese workers (Sasaki and Yoshida (1); Kinosita (2)) who first produced tumors of the liver by means of *o*-aminoazotoluene and dimethyl aminoazobenzene (butter yellow) fed rats a diet consisting of brown rice supplemented by a small quantity of carrot. Animals so treated suffer considerable injury, and in some experiments almost half of them have died within 1 month. Nevertheless, of rats fed by Sigiura and Rhoads (3) only 3 per cent died during the first 2 months. Of the animals that survived from 91 to 220 days, 89 per cent were said to have had liver cancer.

A variety of modifications of the rice diet have diminished the frequency with which tumors of the liver are produced by butter yellow. Wheat bread in place of rice had this result (Kinosita (4)). When rats were fed with polished rice, carrot, and butter yellow by Nakahara and his coworkers (5), many died early in the course of the experiment, and of those that survived, 50 to 100 per cent had tumors after 5 months. The addition of dried, powdered liver in the proportion of one part to 9 parts of polished rice inhibited the production of tumors, but protein from fish did not have this effect. These observers sought for some substance present in liver that might explain its inhibitory effect, but of the substances tested, nicotinic acid alone diminished somewhat the number of tumors.

Nakahara and his coworkers and Sigiura and Rhoads found that the addition of 15 per cent of yeast to the rice diet inhibited the production of tumors so that none appeared within a period of approximately 280 days after the beginning of butter yellow administration. The significance of this observation is doubtful because the addition of this quantity of yeast modifies considerably the protein as well as the vitamin content of the diet. Some inhibition of tumor development was found when 6 or 3 per cent of yeast was added to the diet and the same result was observed with 0.25 per cent of an ether extract of yeast.

Kensler and his associates (6) found 97 per cent of tumors after about 120 days in

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rats receiving butter yellow together with unpolished rice and carrot. This diet supplied each rat with 6 mg. riboflavin daily. When a supplement of 5 mg. riboflavin and 3 mg. nicotinic acid was added, the frequency of tumors was reduced to one-half, but with the addition of 200 mg. riboflavin and 2 gm. casein daily, tumors after 150 days were reduced to 3 per cent. Neither riboflavin nor casein given alone in the same quantities reduced significantly the incidence of tumors. The difficulty of interpreting these results will be evident when the relation of proteins to the production of tumors and of cirrhosis is considered.

Production of Tumors of the Liver by Butter Yellow in the Presence of Diets That Induce Cirrhosis

Butter yellow has been added to the different diets that have been used in the proportion of 0.06 per cent. Experiments of a number of observers indicate that the quantity of protein or of fat in the diet influences the occurrence of tumors produced by butter yellow or of cirrhosis in the presence or absence of the carcinogenic agent. In most of the experiments that have been described, the ingredients of the diet have been apportioned by their gross weight. A better though still inexact comparison is possible when an estimate of the relative caloric value of protein, fat, and carbohydrate is recorded. (See Tables I to IV.) It is noteworthy that animals may increase the quantity of any necessary constituent by consuming a larger total quantity of food.

The weight of animals serves as an index of their state of nutrition under the conditions of the experiments. Graphs showing body weight of animals have been prepared, and the results of these observations are recorded in Tables I to IV. Mortality of animals during the early months of butter yellow administration measures its toxicity as modified by diet.

In one group of experiments (Table IV) animals have been observed during a period of 1 year and at the end of this time the few survivors remaining have been killed. In most experiments animals have been killed after approximately 5 months. In some experiments animals have been killed at different intervals after the beginning of butter yellow feeding.

In order to correlate the present study with those that have preceded, it has been desirable to determine the fate of rats receiving butter yellow and fed on a diet of brown rice and carrots such as that used by Japanese workers and many others who have produced hepatic tumors by means of butter yellow. This diet, with or with no butter yellow, has failed to maintain body weight. When it has been given with butter yellow (see Table I, diet M) weight has diminished rapidly and death has occurred within 4 months in 7 of 20 animals (35 per cent). Nodular cirrhosis has been found and has usually been advanced in animals that have lived more than 4 months.

When adequate vitamins (supplied by Vegex[1] and Oleum percomorphum[2]) have been added to the rice-carrot diet (see Table I, diet N) no tumors have

[1] Vegex is prepared from yeast (Vegex, Incorporated) and contains the B group of vitamins.

[2] Oleum percomorphum (Mead Johnson and Co.) has been used to provide vitamins A and D.

TABLE I

Showing the Occurrence of Tumors and Other Lesions in Rats That Received Butter Yellow with Diets M, N, O, and P, and Were Examined after 4 to 5 Months

Diets	M	N	O	P
Contents of diets:				
Rice, *gm.*	100	100	75	90
Corn meal, *gm.*			25	
Olive oil, *cc.*	2	2	2	2
Crisco, *gm.*				10
Mineral salts, *gm.*		2.9		
Carrot	1 gm. daily		1 gm. daily	1 gm. daily
Vegex, *gm.*		6.0		
Oleum percomorphum, *gm.*		0.18		
Per cent caloric value in diet of:				
Protein, *per cent*	8.7	10.4	9	7
Carbohydrate, *per cent*	82.2	79.5	82	66.9
Fat, *per cent*	9.1	10.1	9	26.1
No. of rats	20	10	10	10
Change in body weight	Decreased rapidly	Decreased	Decreased	Decreased rapidly
No. of rats surviving after 4 mos.	13	10	8	5
Lesions in rats surviving after 4 mos.:				
Nodular cirrhosis	13	1	8	5
Cystic ducts	12		6	3
Cholangiofibrosis	10		5	4
Hepatomas	7(1)		5	4(1)
Cyst-adenomas			(1)	1
Cholangiomas	2(1)			
Total No. of rats with tumors	9	0	5	5

Figures in parentheses represent tumors each of which occurred in an animal that died with another more advanced neoplasm. One animal on diet M died after 116 days, and another on diet P after 111 days with trabecular hepatomas. These tumors are not included in the table.

been found in animals examined after 4 months, and macroscopically recognizable cirrhosis has been found in only one animal.

One-fourth of the rice in the rice-carrot diet has been replaced by corn meal (see Table I, diet O) because Maynard, Fronda, and Chen (7) have obtained evidence which suggests that corn meal supplies some beneficial substance

deficient in rice. No diminution of the severity of cirrhosis or of the frequency of hepatomas has been evident.

The addition of one part of fat (Crisco) to 9 parts of rice (diet P) has not significantly changed the severity of cirrhosis or the frequency of tumors. It is noteworthy that the addition of fat to the diet by weight decreases the per cent caloric value of the protein in it.

When crude linoleic acid was substituted by György and his coworkers (8) for lard in an otherwise adequate diet, animals lost weight and died with progressive anemia. The toxicity of linoleic acid was diminished rather than increased when butter yellow (0.06 per cent) was added to the diet. These observers noted that butter yellow in the presence of oxygen (air) was decolorized by linoleic acid and less effectively by aracidonic or by oleic acid. They found that rice added to these mixtures prevented decolorization of butter yellow, and suggested that the rice contained an anti-oxidant that protected butter yellow in the presence of unsaturated fatty acids but failed to protect it in the presence of saturated fatty acids such as those in Crisco or butter. They stated that these observations did not exhaust all possibilities concerning the influence of rice upon the production of butter yellow tumors. György and his associates did not show that unsaturated fats were more favorable than saturated fats to the production of tumors.

In order to obtain some insight into the significance of rice in the production of tumors and of cirrhosis, this substance has been substituted for a part of the sugar (Table II, diet H) in a diet (diet C) in which protein is in large part supplied by casein, and tumor production by butter yellow in the presence of the two diets has been compared. In two other diets (diets I and II) casein has been slightly reduced and rice has been increased. Though the caloric values of protein in the diets containing rice are greater than that in the rice-free diet, the frequency of tumors after 4 or 5 months has been much greater with the diets containing rice. No tumors have appeared in 10 animals examined after 5 months of feeding with diet C containing butter yellow, but with the addition of rice replacing sugar and thus increasing the protein level of the diet, approximately half of the animals have had hepatic tumors of which 2 in 14 have been accompanied by metastases. With the rice-containing diets there has been more cirrhosis than with the rice-free diet, but grossly recognizable nodular cirrhosis such as occurs in animals fed on rice (Table I, diet M) has been found only when rice has formed 62 per cent of the weight of the diet (diet II).

The experiment indicates that rice contains some product that increases the production of tumors even in the absence of significant cirrhosis. Of 8 tumors that have appeared in animals fed on diets containing rice and casein (diets H and I) 6 have occurred in the absence of cirrhosis recognizable by gross examination.

A diet containing casein was prepared by Miller and his associates (9) with

the purpose of imitating the low protein content of the diet of rice and carrots widely employed by those who have produced hepatic tumors with butter yel-

TABLE II

Showing the Occurrence of Tumors and Other Lesions in Rats That Received Butter Yellow with Diets C, H, and I, and Were Examined after 4 to 5 Months

Diets	C	H	I	II
Contents of diets:				
Casein, *gm*	14.7	14.7	10.7	6.7
Sugar, *gm*	54			
Rice, *gm*		54	58	62
Crisco, *gm*	21.8	21.8	21.8	21.8
Olive oil, *cc*	2	2	2	2
Mineral salts, *gm*	3.6	3.6	3.6	3.8
Vegex, *gm*	3.7	3.7	3.7	3.7
Oleum percomorphum, *gm*	0.22	0.22	0.22	0.22
Per cent caloric value in diet of:				
Protein, *per cent*	12.9	17.3	14.2	11.1
Carbohydrate, *per cent*	43.8	35	37.8	40.6
Fat, *per cent*	43.3	47.7	48	48.3
No. of rats	10	10	10	
Change in body weight	Maintained	Increased	Increased	Increased
No. of rats surviving after 4 mos.	10	9	10	8
Lesions in rats surviving after 4 mos.:				
Nodular cirrhosis	0	0	0	3
Cystic ducts	2	1	5	8
Cholangiofibrosis	4	4	3	7
Hepatomas	0	3	2(1)	4(1)
Hepatomas with metastases			1	
Cholangiomas			2(1)	1(1)
Cholangioma with metastasis				1
Total No. of rats with tumors	0	3	5	6

Figures in parentheses represent tumors occurring in an animal that died with another more advanced tumor.

low, but vitamins adequate for growth, not present in the rice-carrot diet, were added. Their diet consisted of crude casein, cerulose, salts, cotton seed oil (5 per cent), cod liver oil (2 per cent), and rice bran concentrate (Vitab, of National Oil Products Co.) containing thiamin, riboflavin, pyridoxine, pantothenic acid,

and nicotinic acid. On this diet, with casein constituting from 9 to 12 by weight, the incidence of tumors produced by butter yellow was said to have been from 90 to 100 per cent after 4 months, and the liver was severely cirrhotic. Butter yellow in combination with the diet at this protein level was profoundly toxic, and mortality was from 30 to 50 per cent within 4 months. When the proportion of casein was increased to 18 or 40 per cent, the development of tumors was retarded, but even with a diet containing 40 per cent of protein, though no tumors were found after 4 months, 5 of 7 animals had tumors after 6 months. Protein of egg white or of liver retarded the development of tumors in smaller quantities (12 to 13 per cent of diet).

Rats to which Edwards and White (10) gave butter yellow together with a diet consisting of casein (technical casein of Lister Bros., New York) 6 per cent, sucrose 15 per cent, starch 50 per cent, and lard 25 per cent, supplemented by salts, yeast, and cod liver oil, acquired hepatic tumors with advanced cirrhosis.

When in my experiments a similar diet (diet G_1) containing 9 per cent of casein by weight, that is 8.6 per cent of total calories, has been given with butter yellow, all of 10 animals have died within 3 months. When the diet (diet G_3) has contained 12 per cent of casein (Table III) 5 of 10 animals have died within 4 months. Animals that have lived approximately 3 months have had nodular cirrhosis and 2 that have survived 150 days have acquired far advanced nodular cirrhosis and small hepatomas. This diet is evidently too toxic to be favorable for the purposes of the experiments, but within the period of survival has produced cirrhosis and tumors more rapidly than any other that has been used.

Observations of Blumberg and McCollom (11), of György and Goldblatt (12), and of Webster (13) indicate that cirrhosis may be produced by modifications of diet alone, and appears in rats fed diets with low protein and high fat content. György and Goldblatt found cirrhosis after 100 to 150 days in rats fed on a diet containing 8 per cent of casein and 40 per cent of fat (chiefly lard) or 10 per cent of casein and 22 per cent of fat (chiefly Crisco).

The diets which, with the addition of butter yellow, have produced well characterized nodular cirrhosis have been low in protein content, but in most instances low in fat content as well. The diet of Edwards and White contained 25 per cent of fat, but that of Miller only 7 per cent. Butter yellow with a diet similar to that of Miller and containing 12 per cent of casein and 7 per cent of fat (diet G_3, Table III) with rice bran extract (Vitab) produced advanced nodular cirrhosis after from 3 to 5 months. Nevertheless, another diet (diet C, Table II) containing approximately 14.7 per cent of casein and 23.8 per cent of fat, with vitamins in the form of Vegex and Oleum percomorphum, produced only insignificant cirrhosis after 4 to 5 momths.

A diet (diet M, Table I) consisting of rice and a little carrot with enough oil to

TABLE III

Showing the Occurrence of Tumors and Other Lesions in Rats That Received Butter Yellow with Diets G_1 and G_2 and Were Examined after 4 to 5 Months

Diets	G_1	G_2
Contents of diet:		
Casein, *gm*	9	12
Cerulose, *gm*	80	77
Cotton seed oil, *gm*	5	5
Cod liver oil, *gm*	2	2
Mineral salts, *gm*	4	4
Vitab	4 drops daily	4 drops daily
Per cent caloric value in diet of:		
Protein, *per cent*	8.6	11.5
Carbohydrate, *per cent*	76.4	73.5
Fat, *per cent*	15	15
No. of rats	10	10
Change in body weight	Decreased rapidly	Decreased
Average duration of life, *days*	42.3	126.3
No. of rats surviving after 4 mos.	0*	5†
Lesions in rats surviving after 4 mos.:		
Nodular cirrhosis		5
Cystic ducts		5
Chalangiofibrosis		3
Hepatomas		4
Hepatomas with metastases		1
Cholangiomas		(1)
Total No. of rats with tumors		5

Figures in parentheses represent tumors occurring in an animal that died with another more advanced tumor.

* Cholangiofibrosis recognized microscopically was found in one animal that died after 31 days and in another after 71 days.

† In one animal that died after a period on butter yellow and diet less than 4 months (116 days) there were multiple trabecular hepatomas and cystic ducts.

dissolve the butter yellow given with it has produced advanced nodular cirrhosis within 4 or 5 months. The caloric value of the protein it contains is approximately 8.7 per cent, of fat, 9.1 per cent, and of carbohydrate, 82.2 per cent. It is evident that cirrhosis of the liver is produced by butter yellow in the absence of a high level of fat in the diet.

Production of Tumors of the Liver by Butter Yellow in the Presence of Diets That Inhibit Cirrhosis

Replacement of carrot in the rice-carrot diet by an adequate supply of vitamins provided by Vegex extracted from yeast and by Oleum percomorphum has prevented the appearance of tumors within 4 or 5 months following administration of butter yellow, and has almost completely inhibited the production of nodular cirrhosis (Table I, diet N). In the experiments recorded in Table IV in which rats received abundant protein (diets C, E, and B) and adequate vitamins, it has been possible to observe the production of hepatic tumors by butter yellow in the presence of scant or no cirrhosis. These experiments are further concerned with the relation of carbohydrate and fat to the establishment of conditions favorable to the appearance of tumors.

Diets consisting of casein and sugar together with adequate vitamins have been unfavorable to the maintenance of adult rats. On a diet (Table IV, diet A) containing 13 per cent of its caloric value in casein and 88 per cent in sugar, body weight has not been maintained, and death has occurred within 4 months in 4 of 18 animals. On a similar diet (diet B) containing more casein (41 per cent of its caloric value) and less sugar (59 per cent), weight has been somewhat better maintained, but the average duration of life has been the same. On these two diets tumors have developed slowly. Their frequency has been small and not evidently greater with one diet than with the other.

On diets containing fat, even though carbohydrate has been lacking (diets B and E) rats receiving butter yellow have maintained or increased their body weight during 8 or 10 months, and the incidence of tumors has been high, reaching with diet B 100 per cent in animals that have died after 4 months.

The diets used in this experiment represent a wide range of protein levels, namely, 41 per cent in diet E, 13 per cent in diets C and B, and only 7 per cent in diet F. Yet tumors have been about equally frequent, and malignant tumors with metastases have been present without conspicuous difference (3 to 5) in all of these groups. It is noteworthy that cirrhosis which is far advanced in animals fed on a rice diet has been inconspicuous in animals of this experiment. With protein levels from 13 to 41 per cent there has been no macroscopically recognizable cirrhosis, the lesion, not infrequently absent, being incipient, that is, with new formation of cellular tissue, but no collagenous fibers or early cirrhosis with scant formation of collagenous fibers. When the protein level is at approximately 7 per cent, cirrhosis has been incipient or early, but in two instances the lesion could be designated as beginning nodular cirrhosis because inconspicuous irregularity of the surface was recognizable by gross examination.

Diets A and D, which contain almost no fat and fail to maintain weight and life in the presence of butter yellow on the one hand, and diets C, F, E, and B, which on the other hand have high fat content, and during a period of months maintain body weight, give opportunity to compare production of tumors in

animals on unfavorable and on favorable diets. This comparison is possible only when the duration of administration of butter yellow is taken into consid-

TABLE IV

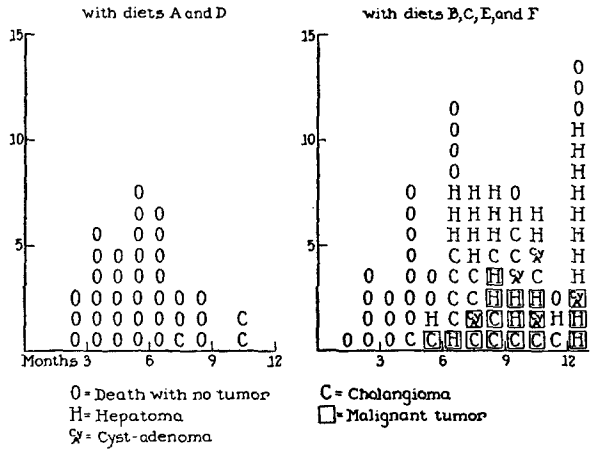
Showing the Occurrence of Tumors and Other Lesions in Rats That Received Butter Yellow with Diets A, B, C, D, E, or F, and Were Examined at Death or after 12 Months

Diets	A	D	F	C	E	B
Content of diet:						
Casein, *gm*	11.3	37.7	7.4	14.7	55.1	21.1
Sugar, *gm*	83	56.5	61.4	54.0		
Crisco, *gm*			23.8	23.8	36.5	68.2
Mineral salts, *gm*	2.7	2.7	3.6	3.6	4.0	5.1
Vegex, *gm*	2.8	2.8	3.7	3.7	4.1	5.3
Oleum percomorphum, *gm*	0.17	0.17	0.22	.22	0.25	0.32
Per cent of caloric value in diet of:						
Protein, *per cent*	13	41	7	13	41	13
Carbohydrate, *per cent*	87	59	49.5	43.5		
Fat, *per cent*			43.5	43.5	59	87
No. of rats	18	19	20	20	20	20
Change in body weight	De-creased	Main-tained	Main-tained	Main-tained	In-creased	In-creased
Average duration of life, *days*	167.2	166.3	220+	230.3+	240.9+	290.7+
No. of rats surviving after 4 mos.	14	17	18	16	17	17
Lesions in surviving rats:						
Nodular cirrhosis	0	0	2	0	0	0
Cystic ducts	0	1	12	7	11	12
Cholangiofibrosis	4	5	8	3	6	0
Hepatomas			3(5)	2(3)	7(2)	11(1)
Hepatomas with metastases			1	1	3	3
Cyst-adenomas			(1)	1(1)	(2)	1(5)
Cyst-adenomas with metastases			1		1	1
Cholangiomas	1	2	6(3)	3	2(1)	1
Cholangiomas with metastases			1	4	1	
Total No. rats with tumors	1	2	12	11	14	17

Figures in parentheses represent tumors occurring in an animal that died with another more advanced neoplasm.

eration, because animals on unfavorable diets die sooner and have less opportunity to develop tumors. Text-fig. 1 shows the frequency of tumors in the two groups of animals. No animals have died with tumors before the end of 4 months. Of 15 animals on diets almost devoid of fats, that have lived 5 or 6

months, none have acquired tumors; whereas on favorable diets that have contained fat, 16 animals have lived the same length of time, and 10 have acquired tumors. Of 6 animals of the first group that have lived 7 and 8 months, one has acquired a tumor, but of 16 animals of the second group that lived during the same period, all have had tumors. Tumors with metastases have been found only in animals on fat-containing diets that have maintained body weight, but this relation is not significant because the number of tumors in animals on unfavorable diets has been very small, and the duration of life shorter.



TEXT-FIG. 1. Tumors found at intervals of months during the administration of butter yellow given with (1) inadequate diets (diets A and D) that contained little fat or (2) diets (diets B, C, E, and F) that contained fat and maintained body weight (see Table IV).

Butter yellow has produced few tumors in rats fed on diets almost wholly lacking in fat, but with diets rich in fat, tumors have been frequent and their number has increased with the fat content of the diet.

The Relation of Cirrhosis to the Production of Tumors of the Liver

Nodular cirrhosis produced in rats by butter yellow given in association with rice and carrot or with other appropriate diet, is characterized by hyperplastic nodules of parenchyma surrounded by dense fibrous tissue, and resembles closely Laennec's cirrhosis. The recognition of macroscopically evident nodular cirrhosis is an index of the progress of this disease, but absence of gross changes in the liver does not exclude the presence of microscopically demonstrable cirrhosis. The latter for convenience may be designated incipient cirrhosis, when formation of collagenous fibrils has not yet begun, and early cirrhosis when, though the lesion is not evident on gross examination, some formation of collagenous fibrous tissue is found on microscopic examination.

Two lesions produced by butter yellow may be designated cystic ducts, and cholangiofibrosis. One is characterized by cystic dilatation of newly formed bile ducts, and the other by dilatation of similar ducts with acute inflammation and new formation of fibrous tissue about them. It will be shown in an accompanying paper (14) that both of these lesions undergo changes that transform them into neoplasms.

In the experiments recorded in Table IV, rats to which butter yellow has been administered have been maintained on selected diets until death, or up to 12 months. The relation of tumor production, cystic ducts, and cholangiofibrosis to cirrhosis has been as follows:—

	No. of animals	No. of animals with tumors of liver	Per cent with tumors	Per cent with cystic ducts	Per cent with cholangio-fibrosis
With no cirrhosis	37	6	16%	19%	0
With incipient cirrhosis	55	31	56%	34.5%	29%
With early cirrhosis	24	21	87.5%	62.5%	33%
With nodular cirrhosis	2	2	(2)	(2)	(2)

This tabulation shows that a large part of the tumors have occurred in livers with only trivial cirrhosis, and in six instances in its absence, but their frequency has increased with advancing cirrhosis. Cystic ducts and cholangiofibrosis are not apparently caused by cirrhosis, for they occur in the presence of incipient cirrhosis.

In the experiments recorded in Tables I, II, and III, animals have been examined from 4 to 5 months after the beginning of the administration of butter yellow. They give opportunity to compare the rapidity with which tumors appear on the one hand in animals fed with diets (diets M, O, and P of Table I, and diet G_3 of Table III) that produce nodular cirrhosis within this time, and on the other hand in animals fed with diets (diet N of Table I, and diets C, H, and I of Table II) that produce no macroscopically recognizable cirrhosis. In this group of experiments, the relation of tumors, cystic ducts, and cholangiofibrosis to cirrhosis has been as follows:—

	No. of animals	No. of animals with tumors of liver	Per cent with tumors	Per cent with cystic ducts	Per cent with cholangio-fibrosis
With no cirrhosis	16	2	12.5%	12.5%	12.5%
With incipient cirrhosis	14	4	29%	29%	21%
With early cirrhosis	8	3	37.5%	50%	37.5%
With nodular cirrhosis	31	22	71%	68%	77%

The per cent figures in the foregoing tabulations are in some instances based upon a small number of animals, and have little value. They indicate conveniently the number of animals with tumors, cystic ducts, or cholangiofibrosis, and in animals that have died within 12 months, on the one hand, and in those examined after 4 to 5 months, on the other, they show the same relation to cirrhosis. In the latter group two tumors have been found in animals with no cirrhosis, but the incidence of tumors has increased with the severity of cirrhosis, and more than two-thirds of the animals with nodular cirrhosis have had tumors. The same statements can be made concerning cystic ducts and cholangiofibrosis, which will be shown to be precursors of neoplasms.

CONCLUSIONS

The presence of fat in the diet accelerates the production of hepatic tumors by *p*-dimethylaminoazobenzene (butter yellow), and when its quantity is very small, few are produced.

Butter yellow with diets consisting in large part of rice, or with other diets with low protein content, causes nodular cirrhosis, but, rice substituted for sugar in a diet containing protein, fat, and butter yellow with adequate vitamins accelerates the production of tumors though the added rice is insufficient to induce nodular cirrhosis. Rice favors the production of hepatic tumors by agencies that are not yet explained.

Butter yellow produces hepatic tumors in the absence of cirrhosis, but with diets that produce cirrhosis, the frequency of tumors and of their precursors, cystic ducts and cholangiofibrosis, increases with the severity of cirrhosis.

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