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The Induction of Intestinal Neoplasms in Rats with the Glycoside Cycasin and its Aglycone*

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With 8 Figures in the Text

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An investigation was started at the National Institutes of Health in 1961 into the question whether the seed of *Cycas circinalis* L., indigenous to Guam, possessed a neurotoxin which might explain the high frequency of certain neurologic diseases on that island. Interest in this particular plant came about through personal observations by WHITING who had studied the use of the plant as a source of food by the inhabitants and her subsequent familiarity with the literature on its toxic properties. The reader is referred to her review on toxicity of cycads which covers the period up to 1963 (WHITING).

While searching for evidence of neurotoxic effects in rats fed dried and ground seed of *Cycas circinalis* from Guam, it was noted that such material possessed marked *hepatotoxic properties* and that the degree of liver injury paralleled its concentration in the diet. The nature of the acute and subacute alterations in the liver suggested, furthermore, the possibility that the toxin in the crude material might be *carcinogenic* as well. This was confirmed in preliminary experiments in rats permitted to live sufficiently long for neoplasms to develop. The results of these early studies showed that neoplasms occurred predominantly in liver and kidneys in the majority of the rats which had been fed the crude cycad seed material over long periods of time [LAQUEUR et al. (1)].

Further search into the chemistry of cycads revealed that glycosides had been isolated from various members of the family of "cycadaceae" which were azoxyglycosides differing only in the sugar component. In *cycasin*, the glycoside isolated from *Cycas circinalis* and *Cycas revoluta*, the sugar was glucose, its chemical formula being β-D-glucosyl-oxyazoxymethane [NISHIDA et al. (1), RIGGS].

Subsequent studies showed that both the acute and long-term effects of the crude material could be reproduced as readily with the crystalline cycasin, suggesting that the effects of the crude material were essentially due to its content of cycasin [LAQUEUR (2)].

Further experiments in rats with the unstable aglycone of cycasin, methylazoxymethanol (MAM), isolated from cycad seed showed that it produced liver tumors and hyperplastic lesions in renal tubules (MATSUMOTO and STRONG). Earlier studies revealed that the aglycone produced hepatotoxic effects even after intraperitoneal administration, a route which was found ineffective in the case of cycasin [NISHIDA et al. (2), KOBAYASHI and MATSUMOTO (2)].

* Dedicated to Professor Dr. Dr. h. c. CARL KRAUSPE on the occasion of his 70th birthday.

The aglycone acetate recently synthesized by MATSUMOTO et al. (2) is considerably more stable than the aglycone itself and is presently being tested for its carcinogenic activity in germfree rats using various routes of administration.

While the majority of toxic, biologic and carcinogenic effects of cycasin or the aglycone were similar to those described with dimethylnitrosamine (DMN) [MAGEE and BARNES (1, 2), MAGEE and SCHOENTAL (3)], there was one notable exception in that neoplasms of the intestines developed with cycad materials but not with DMN. It is the purpose of this report to summarize our observations on intestinal neoplasms in rats fed the crude cycad material or cycasin and in rats given intraperitoneal injections of the aglycone. The discussion concerns the possible significance of these observations in relation to cycasin metabolism and future studies.

Material and Methods

The rats used in the majority of experiments were of the Osborne-Mendel (OM) and Sprague-Dawley (SD) strains maintained at NIH and obtained at weanling age. They were fed the basal diet until 30 days old when they were started on the experimental diets. Two groups were started on the experiment at 54 and 90 days respectively, to examine the effect of onset and established sexual maturity on the development of tumors. The pertinent data covering age, dose levels and duration of exposure are given in the accompanying Table 1.

Cycad meal (the crude ground and dried seed of *Cycas circinalis*) was prepared at the Institute from fresh seeds shipped from Guam. The dried material contained 2.3 gm of cycasin per 100 gm and was fed to the rats at a concentration of 1.0, 1.5 and 2.5 percent respectively.

Cycasin, isolated in crystalline form by the Department of Biochemistry of Kagoshima University, Kagoshima, Japan, was mixed with the basal diet at concentrations of 20, 40, 60, 100 and 400 mg per 100 gm diet[1]. The rats chronically exposed to the carcinogen in the diet were kept in the Department of Nutrition at Michigan State University and were shipped after autopsy to our laboratory[2]. Because of the long exposure, the total amount of cycad meal or cycasin consumed by these animals was not recorded (groups I to VIII of Table 1).

The rats exposed for short periods (groups IX to XV) were housed at NIH. Food intake was measured daily and the total amount of cycasin consumed was available for each rat, 30 days old at the start of the experiment and for the rats fed for 2 days only (group XV). Attempts to measure the food intake in the rats started at 90 days were abandoned because of spillage of food by the majority. The rats were housed individually and had free access to tap water at all times.

Methylazoxymethanol, the aglycone prepared from cycasin by Dr. MATSUMOTO, was injected at 3 dose levels intraperitoneally into 6 female Fischer rats averaging 210 gm in body weight (Table 2). The tissues obtained at autopsy were forwarded for pathologic studies to our laboratory.

At autopsy, the tissues were fixed in buffered (pH 7.0) 10 per cent formalin. Selected areas were prepared for histologic examination by routine dehydration and paraffin-embedding procedures. Special staining techniques included WILDER'S reticulum stain, the periodic acid leukofuchsin reaction with diastase controls for glycogen and mucins supplemented by the mucicarmine stain, the Weigert-van Gieson and the ferrocyanide reaction of Perls (methods outlined by LILLIE).

Results

The results of the various experiments with crude cycad meal and cycasin are summarized in Table 1 with respect to the occurrence of intestinal tumors. These *neoplasms* ranked in relative frequency next to tumors of the liver and kidneys

[1] Cycasin used in this study was obtained through the courtesy of Drs. KURLAND and WHITING of NINDB, NIH.

[2] Dr. OLAF MICKELSEN, Department of Nutrition, Michigan State University, generously provided the rats after long-term exposure to cycad meal and cycasin, and Dr. HIROMU MATSUMOTO the rats injected intraperitoneally with the aglycone for inclusion in this study.

[LAQUEUR (2)]. Since neoplasia was not observed at any site in rats exposed o the carcinogen for less than six months, the number of rats alive six months after the first contact with the agent are listed in column VII. Differences in number of rats between columns VI and VII are due to several factors such as intercurrent incidental diseases, toxicity of the compound (see group XIII in which only 9 out of 45 rats survived longer than six months), and early sacrifice of two groups of rats to determine acute changes in the liver at certain dose levels (groups XI, XII and XIII). Column VIII gives the number of rats which had neoplasms in either liver, kidneys or intestines. The difference between columns VII and VIII indicates, therefore, the number of rats, six months or older, without neoplasm.

Both Sprague-Dawley and Osborne-Mendel rats developed sufficient numbers of intestinal tumors to exclude strain differences at least for these two strains. Careful macroscopic and microscopic examinations of 110 control rats of equal or older age in both strains failed to reveal a single neoplasm of the small or large

Table 1

Summary of pertinent information on various experimental groups treated with cycad materials

Groups	I	II	III	IV	V	VI	VII	VIII	IX	X		
	Strain*	Sex	Age at start in days	Compound fed	Duration of feeding	Initial nos. of rats	Rats surviving 6 months	Rats with neoplasms at any site	Rats with intestinal tumors	Classification of intestinal tumors		
										Adenoma	Carcinoma	Total
					Chronic exposure							
I	S.D.	♀	30	1% c.m.**	6—9 mos.	20	20	18	1	0	1	1
II	S.D.	♀	30	1.5% c.m.	6—9 mos.	20	20	20	2	1	2	3
III	S.D.	♀	30	200ppm***	6—9 mos.	20	20	16	4	4	1	5
IV	S.D.	♀	30	400 ppm	6—9 mos.	20	14	14	3	3	1	4
Total						80	74	68	10	8	5	13
V	S.D.	♂	30	1% c.m.	6—9 mos.	20	18	12	3	2	1	3
VI	S.D.	♂	30	1.5% c.m.	6—9 mos.	20	18	18	7	9	3	12
VII	S.D.	♂	30	200 ppm	6—9 mos.	20	19	12	9	6	6	12
VIII	S.D.	♂	30	400 ppm	6—9 mos.	20	15	13	8	10	3	13
Total						80	70	55	27	27	13	40
					Short exposure							
IX	O.M.	♂	30	2.5% c.m.	13 days	20	17	16	5	4	1	5
X	O.M.	♂	90	2.5% c.m.	21 days	25	23	19	7	5	3	8
XI	O.M.	♂	30	400 ppm	13 days	30	14	12	0	0	0	0
XII	O.M.	♂	30	600 ppm	13 days	40	16	16	2	1	2	3
XIII	O.M.	♂	30	1000 ppm	13 days	45	9	9	3	2	3	5
XIV	O.M.	♂	90	1000 ppm	21 days	25	23	20	9	7	5	12
XV	S.D.	♂	54	4000 ppm	2 days	12	12	7	3	2	2	4
Total						197	114	99	29	21	16	37

* S.D. = Sprague-Dawley; O.M. = Osborne-Mendel.

** c.m. = cycad meal, lot 3662, containing 2.3% cycasin.

*** ppm = cycasin, parts per million.

intestine. A benign gastric polyp arising from the prepyloric region in an Osborne-Mendel male rat, 423 days old at death, was the only neoplastic lesion of the entire digestive tract among the controls.

Without exception, all intestinal *neoplasms* occurred *distal to the ileocecal valve*; the great majority were in the proximal one-half of the colon. A few were noted in the cecum and an occasional one as low as the recto-sigmoid. All tumors included in the table were seen grossly and were microscopically confirmed, permitting a benign or malignant classification. In several instances, multiple tumors were found, the largest number of separate tumors being four. Sections of the intestinal wall between multiple tumors were examined to exclude the possibility of one being metastatic to the other.

Table 2. *Effect of methylazoxymethanol injected intraperitoneally in female Fischer rats**

Single dose	No. of injections	Total dose	Duration of observation	Intestinal tumors			
				Duodenum		Colon	
mg		mg	days	Adenoma	Carcinoma	Adenoma	Carcinoma
2	10	20	237				
4	4	16	244				1
4	7	28	238		1		
4	9	36	238		1	2	1
4	12	48	238		1		
6	2	12	237				

* Compiled from data of MATSUMOTO.

Further examination of Table 1 indicates that male Sprague-Dawley rats had a considerably higher incidence of intestinal tumors than did the females of the same strain and on identical regimens. The incidence of intestinal tumors relative to the total number of rats with tumors is 49.1 per cent for the males and 14.7 per cent for females. Expressing the incidence of intestinal neoplasms relative to the initial total number or to the total number surviving six months lowered the percentage values but did not abolish the sex differences in frequency of tumor development. The total number of intestinal tumors among the male rats with intestinal tumors (40 tumors in 27 rats), however, differed only slightly from the corresponding number in females (13 tumors in 10 rats).

Comparison between male rats fed diets containing 400 ppm of cycasin for 13 days and those fed the same concentration for 6—9 months (groups VIII and XI) suggested that the duration of exposure positively influenced tumor development in the intestinal tract. Furthermore, the latent period in rats exposed for a few days was longer than in rats exposed for 6—9 months. The shortest induction periods were 188 days for the chronically exposed rats and 250 days for the briefly exposed rats. Taking the groups of rats on short and long-term exposure as wholes, the time required for intestinal tumors to develop averaged 294 days (188—343) for the chronically exposed rats and 370 days (250—479) for the short exposure group of rats.

Table 3 shows the calculated cycasin intake in groups of rats in which food consumption was measured, the number of rats with intestinal tumors and the respective total number of tumors for each group. Although increasing the cycasin

Table 3. *Mean cycasin intake of male Osborne-Mendel rats with neoplastic disease*

Constants	Cycasin intake in mg for 13 days in 30 day old male Osborne-Mendel rats			
	2.5% cycad meal*	cycasin, 400 ppm	cycasin, 600 ppm	cycasin, 1000 ppm
Mean	59.56	63.10	81.70	98.50
Number of observations	16	12	16	8
St. Deviation	6.21	7.80	12.12	13.15
St. Error	1.55	2.25	3.03	4.65
Number of rats with intestinal tumors	5	0	2	3
Total number of intestinal tumors	5	0	3	5

* Lot of cycad meal, No. 3662, containing 2.3% cycasin. Calculated from measured food intake over 13 day period.

concentration resulted in slightly greater tumor production, attention should be called to the first two columns of this Table in which no statistical difference between the means of cycasin intakes could be demonstrated ($P = .2$); yet a striking difference in tumor formation was found in favor of cycad meal. Dissimilarities in effects between cycad meal and cycasin were observed previously in

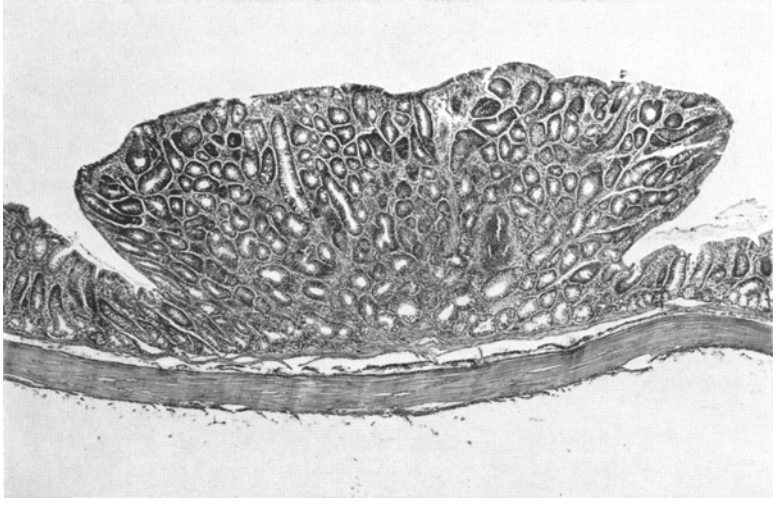

Fig. 1. Sessile adenoma of colon in male O.M. rat fed crude cycad meal for 253 days. Age at death, 283 days. This rat had also a carcinoma of cecum, a hepatoma with pulmonary metastases and bilateral kidney tumors (see also Fig. 4). H.E. × 30

studies concerned with early metabolic changes in the liver, and it was pointed out that cycad meal may contain substances other than cycasin which may variously affect certain parameters of cycad toxicity (Williams and Laqueur).

Grossly the tumors, whether benign or malignant, were either broadly sessile or pedunculated with wide or narrow stalks, or infiltrating as in the case of several carcinomas (Figs. 1—3). Bleeding from the rectum was seen in only a few rats in which large polypoid carcinomas had ulcerated. Variable degrees of intestinal dilatation accompanied by hypertrophy of the muscular coat proximal to the new growth was apparently the result of partial obstruction. Intussusception of the

proximal bowel wall was a frequent finding, localizing the site of intraluminal tumors. In most respects, then, the tumors resembled those seen in human material except for the predominant localization in the upper half of the colon.

Microscopically, both benign and malignant neoplasms were generally associated with abundant production of mucus and present in all but 3 rats with carcinomas

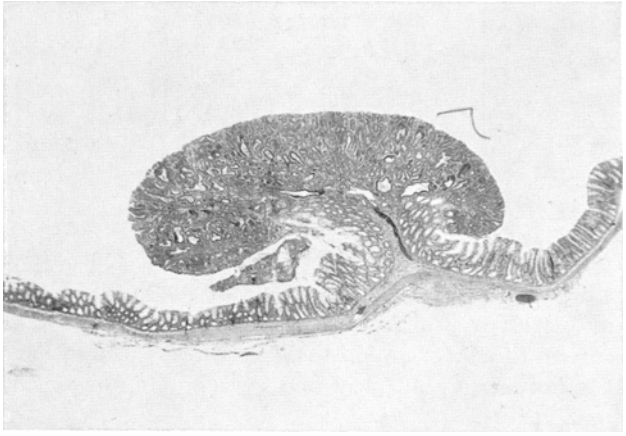

Fig. 2. Adenomatous polyp of colon in male O.M. rat fed crude cycad meal for 21 days. Age at death, 346 days. This rat had a separate adenomatous polyp of colon and bilateral kidney tumors. H.E. × 15

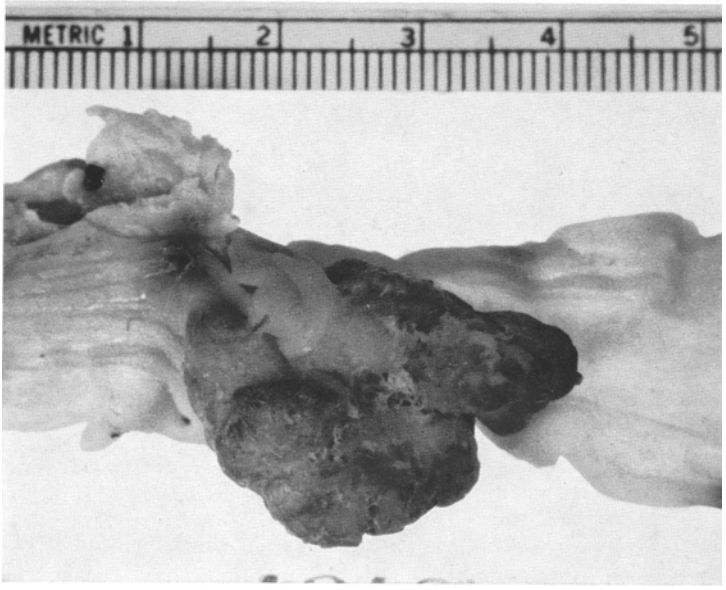

Fig. 3. Polypoid carcinoma of colon in male O.M. rat fed cycasin for 13 days during which it consumed 73 mg of the glycoside. Killed 455 days later. This rat had also a hepatoma and bilateral kidney tumors. H.E. × 2

(Fig. 4). *Metastatic spread* had occurred in 4 rats with colonic carcinomas, and mucin production by tumor cells was a prominent feature in all, individual tumor cells resembling "signet ring" cells. Special stains such as mucicarmine or the periodic acid Schiff reaction preceded by diastase demonstrated the mucinous character of the intracellular material. For the differential diagnosis between

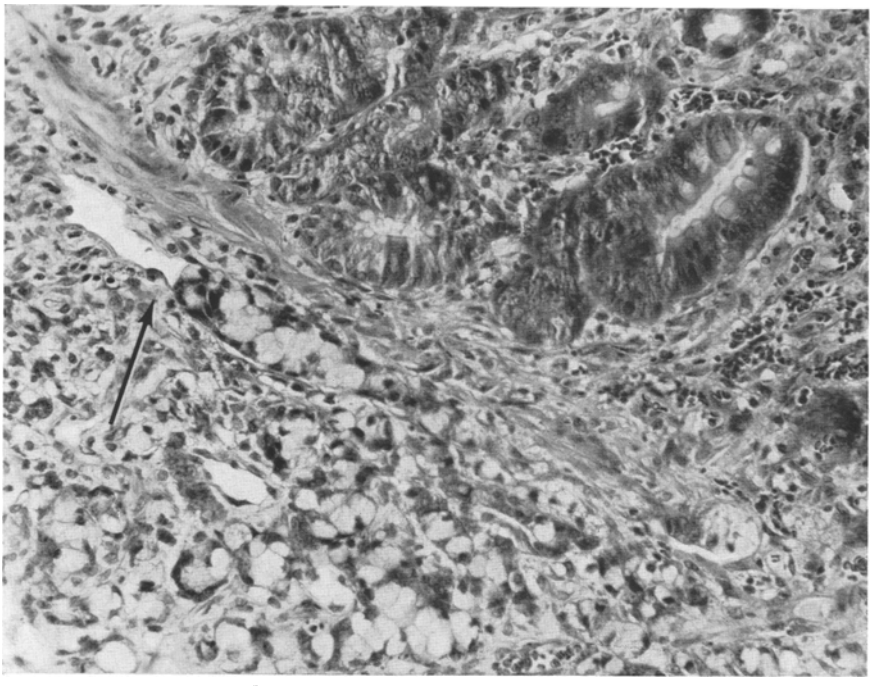

Fig. 4. Same animal as in Fig. 1. Mucinous adenocarcinoma invading submucosa and a lymphatic space at arrow. H.E. × 200

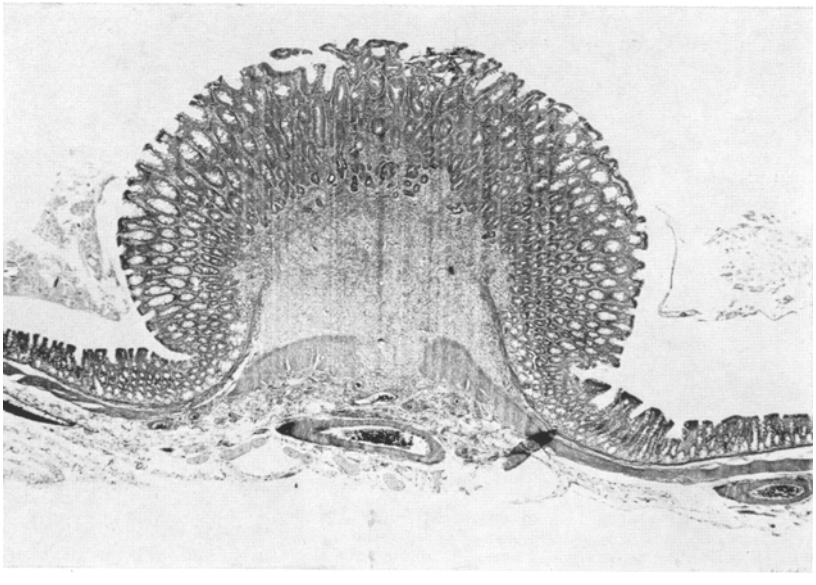

Fig. 5. Nodule in colon, 4.5 cm from cecum, in female S.D. rat fed cycasin for 9 months. Age at death, 339 days. No other neoplasms. Tumor cells fill the submucosa and have destroyed in part the muscularis mucosae with extension into lamina propria. There is also separation of the muscular coat by tumor cells along blood vessels. H.E. × 25

polypoid carcinoma and adenomatous polyp, reliance was placed on the invasive character of the former, in addition to changes in the glandular pattern and in

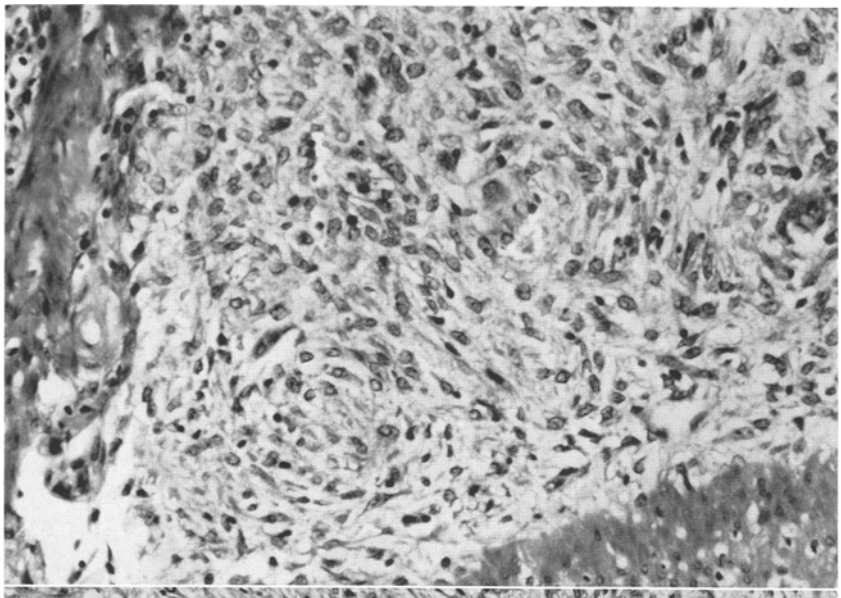

Fig. 6

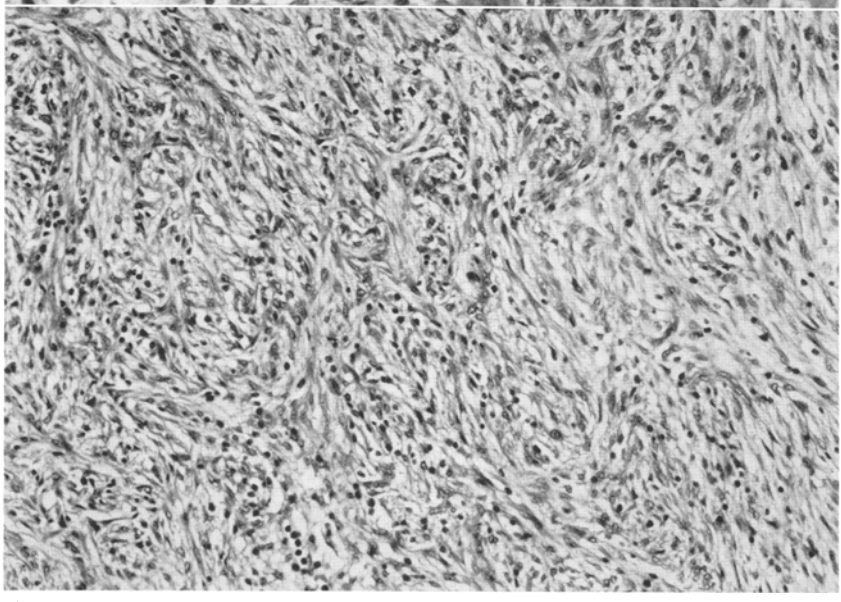

Fig. 7

Fig. 6. Cellular details of nodule shown in Fig. 5. Left margin of picture shows muscularis mucosae, the bottom, parts of the inner muscularis. Note whorls and suggestion of palisading to the right of center. H.E. × 260

Fig. 7. General pattern of tumor cells in large polypoid tumor of colon, 8 cm from cecum in female S.D. rat fed cycasin for 9 months. Age at death, 340 days. This rat had also a well differentiated hepatoma and a unilateral kidney tumor. Ulceration at the tip of the polyp following intussusception explains the permeation of the tumor by inflammatory cells (dark stained nuclei). H.E. × 160

the cytology of the epithelial cells which in themselves were regarded as insufficient evidence of malignancy. In comparing the benign adenomatous polyps with the polypoid carcinomas, particularly when they occurred in the same animal, no convincing evidence was found that the carcinomas arose in previously

benign polyps. Osseous metaplasia was noted in the stroma of four mucinous carcinomas and in one adenomatous polyp.

In addition to the neoplastic epithelial lesions involving the large intestine, 6 rats had submucosal nodules or polypoid masses covered largely by colonic mucosa with normal or slightly atypical glands (Fig. 5). These lesions were not included in Table 1. In the two larger polyps, granulation tissue formed the superficial layer with loss of glandular structures at these sites. The underlying submucosa and the tunica propria were infiltrated by masses of fairly uniform, spindle cells with vesicular nuclei containing a small compact nucleolus. These

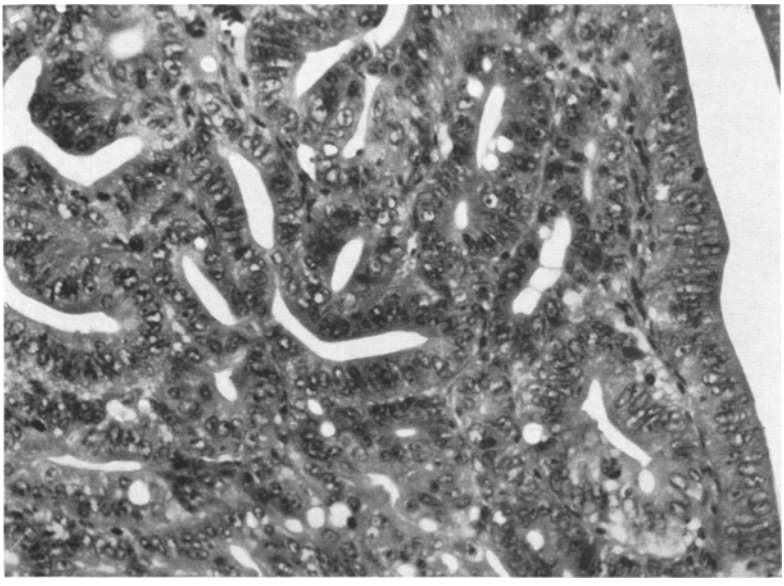

Fig. 8. Adenocarcinoma of duodenum with few mucus producing cells among neoplastic epithelial cells in female Fischer rat after 12 indraperitoneal injections of 4 mg of the aglycone of cycasin. Rilled 238 daps after first iujection. H.E. × 260

cells frequently were arranged in aggregates forming small whorls or in bundles where the plane of sectioning paralleled the long axis of the cells (Figs. 6—7). Groups of tumor cells were often bordered by vascular channels in which collagen fibers were demonstrable with the van Gieson stain while collagen was not found in relation to individual tumor cells. WILDER'S reticulum stain showed delicate fibers between tumor cells in some areas but not uniformly throughout the lesion. Mitotic figures were readily found, but varied in number from area to area and nodule to nodule; none appeared abnormal.

Although definite classification of these tumors is difficult, several types of neoplasms could be excluded with some degree of certainty. The localization of small lesions in the submucosa, the distribution of the reticulum fibers in such nodules and the absence of stainable intracellular mucin seemed to exclude an epithelial origin. Lack of stainable collagen made a fibromatous nature of the lesion unlikely, and the regularity and uniformity of the cells as well as the absence of abnormal forms of cell division were against a collagen-poor fibrosarcoma. A possible origin from muscle could be ruled out from the localization of the tumors and the preservation of the inner and outer coats of the muscularis. The possibility that such lesions may have a histogenic background in mesenchymal components of MEISSNER'S plexus is entertained.

The observations on rats injected intraperitoneally with the aglycone are incomplete but important enough to be summarized briefly. Among the 6 rats listed in Table 2, 4 had tumors of the intestinal tract with the duodenum being the primary site of mucinous adenocarcinomas in 3 (Fig. 8). The 2 rats without intestinal tumors had neoplasms in other sites such as liver and kidneys. Although the details of the mechanisms in inducing duodenal neoplasms after intraperitoneal injection of the aglycone are presently not clear, the possibility that the aglycone or its metabolite is excreted through the bile appears intriguing, particularly since two of the carcinomas occurred in the midportion of the duodenum while sparing stomach, pyloric area and the first part of the duodenum.

Discussion

In our original report on the carcinogenic properties of cycad meal, the occasional development of colonic neoplasms was mentioned although a causal relationship between the carcinomas and the consumption of the cycad meal appeared uncertain. The experiments summarized in this report established beyond reasonable doubt that the crude cycad material, the crystalline glycoside, cycasin, extracted from the crude material, as well as the aglycone of cycasin were carcinogenic for the intestinal mucosa of the rat. A study of Table 1 indicates, however, that considerable variations existed in the relative incidence of intestinal neoplasms between different experimental groups. Increasing the concentration of cycad material did not uniformly or strikingly raise the incidence of intestinal neoplasms, although duration of treatment and, possibly, age at first exposure seemed to favor the development of such neoplasms. Thus, carcinomas of the colon were found independent of the total dose above 45 mg given either as cycasin or cycasin-containing crude material.

The unpredictability of intestinal neoplasms led to the more general question, why rats which had neoplastic growth at other sites failed to develop intestinal tumors, and why certain rats had no malignant disease at all, although the total amount of cycasin ingested was well within the tumor inducing range. There was the additional observation that those tumors which did develop occurred predominantly in the proximal half of the colon, suggesting that a local situation might prevail in this segment of the intestinal tract which was absent from or less influential in the other segments.

Considerations of this nature led us to explore the possibility that the chemical structure of the carcinogen might be important in this respect. Information was already available that the glycoside when injected intraperitoneally was inert and nearly all could be recovered in the urine but that the aglycone when injected similarly was highly effective (KOBAYASHI and MATSUMOTO). These two observations suggested that an enzymatic cleavage of the whole glycoside occurred which changed the inert glycoside into a highly active substance. The respective enzyme, a β-glucosidase [KOBAYASHI (1)], could be of mucosal or bacterial origin, depending upon whether the first breakdown of cycasin occurred in the structures of the wall or in the lumen of the alimentary tract. To test these possibilities the whole glycoside (2000 ppm) was incorporated into the diet and fed to germfree rats for 20 days. During this period, the rats consumed, on the average, 650 mg of cycasin without showing the slightest effect of cycasin toxicity as measured by body

weight gain, food intake and microscopic examination of the tissues [LAQUEUR (2)]. No tumors have been found among the germfree rats up to one year after first exposure to large amounts of cycasin. Subsequent experiments in which urine and feces were collected during the time that germfree rats were fed cycasin, showed that the glycoside was recovered nearly quantitatively from urine and feces which indicated that cycasin had been absorbed by the intestinal mucosa without having been cleaved and excreted as such. In contrast, only from 15 to 35 per cent of the ingested cycasin could be recovered from conventional rats given the identical cycasin concentration, the remainder apparently having been metabolized (SPATZ et al.). These findings indicated that the first cleavage of cycasin into its aglycone occurred within the intestinal tract and that, at least the greater part, if not all of the β-glucosidase, was of bacterial origin. It also became apparent from the difference in recovery rates among conventional rats that the ability to cleave cycasin varied considerably from rat to rat, perhaps depending on the type of bacterial flora and its ability to provide the necessary enzyme. Therefore, if it could be shown that the bacterial flora and its ability to provide the specific enzyme varied not only between rats but also between intestinal segments, a partial explanation for the complete absence of neoplasia in some rats, for the variability of cycasin metabolism as observed by its excretion pattern, and for the localization of intestinal tumors to the colon could be entertained. Such studies are now in progress. The recently observed tumors in the duodenum after repeated intraperitoneal injection of the aglycone are of particular interest and seem to support the notion that tumors can develop at various sites along the intestinal tract as long as the carcinogen is available in the form of the highly reactive aglycone. In view of these recent findings, an exploration of a possible local effect of the aglycone on the epithelial cells of the intestinal tract is highly desirable. A partial answer may come from experiments under way in which the synthetic aglycone acetate was given to germfree rats by various routes.

Although cycasin and particularly its aglycone have several biologic effects in common with DMN, the development of intestinal neoplasms has only been reported after a single intravenous injection of a different nitrosocompound methylnitrosourea, at levels of 70 to 100 mg/kg body weight [DRUCKREY et al. (1)]. The same compound given orally in drinking water did not produce tumors of the intestines but only of the forestomach [DRUCKREY et al. (2)].

That very short exposures of rats to large amounts of cycasin can also be followed by neoplastic disease in the large intestine is apparent from group XV of Table 1. The three rats with colonic neoplasms had consumed an average of 57 mg of cycasin during the 48 hours of exposure, and the latent period was from 370 to 384 days. Previous observations with certain nitrosamine compounds [SCHOENTAL, DRUCKREY et al. (1)] indicated that neoplastic disease developed after single exposures, and our experiments with cycasin point in the same direction.

Recent studies by KOBAYASHI and MATSUMOTO (2) and in our laboratory (SPATZ et al.) indicate that the unmetabolized cycasin is excreted rapidly in urine and feces so that it is no longer demonstrable in the excreta 48 hours after discontinuation of feeding. If a local effect on the colonic mucosa by the cleaved glycoside is assumed to be instrumental in localizing the tumors to this site, the period of time during which carcinogenesis is initiated, appears, indeed, to be very short.

Summary

Experiments are described dealing with the carcinogenic effects of (1) the crude cycad seed material, (2) the glycoside, cycasin, a β-D-glucosyloxyazoxymethane, isolated from the crude material, and (3) the first metabolic breakdown product of cycasin, the aglycone of cycasin or methylazoxymethanol, on the intestinal tract of rats. While the crude material and cycasin produced tumors exclusively located in the large intestine, the aglycone when injected intraperitoneally, resulted in neoplasms of the small intestine as well. Supportive experiments in germfree animals are cited which indicate that cycasin *per se*, whether present in the intestinal tract or absorbed and excreted, is innocuous. Apparently, the glycoside is converted in conventional rats into the highly toxic aglycone through a β-glucosidase of bacterial origin. Hence, it would seem likely that the carcinogenicity of the crude cycad material and of cycasin depends on a bacterial flora capable of providing the enzyme necessary for the liberation of the aglycone.

Experimentelle Krebserzeugung im Darmkanal von Ratten mit dem Glykosid Cycasin und seinem Aglykon

Zusammenfassung

Während Cycasin sowie seine Muttersubstanz, das Endosperm der *Cycas circinalis*, ausnahmslos Tumoren im Dickdarm hervorriefen, gelang es mit dem Aglykon nach intraperitonealer Injektion auch Tumoren im Duodenum zu erzeugen. In keimfreien Tieren ist das Cycasin auch in sehr großen Dosen wirkungslos, wird aber von der Darmwand absorbiert und von den Tieren zum größeren Teil ausgeschieden. Dem keimfreien Tier fehlt die Glucosidase, die normalerweise das Cycasin in sein sehr toxisches Aglykon und Zucker spaltet. Die Möglichkeit besteht deshalb, daß eine erfolgreiche Krebserzeugung mit Cycasin an eine Darmflora gebunden ist, die das notwendige Enzym für die Spaltung liefern kann.

Literature

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