

THE INFLUENCE OF DIET ON TRANSPLANTED AND SPONTANEOUS MOUSE TUMORS.*

BY PEYTON ROUS, M.D.

(From the Laboratories of The Rockefeller Institute for Medical Research.)

PLATE 21.

That cancer progresses relatively slowly in emaciated, old people has long been known; but the influence on the disease of general nutritive conditions as thus indicated has only lately attracted wide attention, following the observation that some strains of transplantable tumors grow badly, or not at all, in emaciated hosts. Moreschi¹ was the first to study the phenomenon systematically. He found that grafts of mouse sarcoma grew less frequently and more slowly in animals losing weight on a low diet. But, though he thus demonstrated that malnutrition of the host affects adversely bits of strange tissue as yet unvascularized and unattached, he did not take up the influence of the factor on large growths, on recurrences, and on the development of metastases, or, in other words, on neoplastic conditions such as require palliative treatment in human beings. Experiments in this direction which I began² shortly after Moreschi's paper was published demonstrated the fact that a tumor which does badly when transplanted to hosts previously underfed may be quite uninfluenced by dieting begun after the growth is vascularized and has started to develop. Nodules of the Flexner-Jobling rat carcinoma, a few millimeters in diameter, grew with equal rapidity in hosts emaciating on a restricted ration and in controls gaining weight on the same sort of food (text-figures 1 and 2). The Jensen rat sarcoma, on the contrary, even after it had reached a large size, was retarded in its development by under-

* Received for publication, August 1, 1914.

¹ Moreschi, C., *Ztschr. f. Immunitätsforsch., Orig.*, 1909, ii, 651.

² Rous, P., *Proc. Soc. Exper. Biol. and Med.*, 1910-11, viii, 128.

feeding the host. But the forces which determine the course of this tumor must be delicately balanced, for it often retrogresses without evident cause in whole series of healthy rats.

Not only have general nutritive conditions an influence on some transplanted tumors, but the character of the host's food may be important. Van Alstyne and Beebe³ have shown that tumor grafts

CONTROLS						FOOD LIMITED					
NO.	WEIGHT		TUMOR			NO.	WEIGHT		TUMOR		
	INITIAL	CHANGE	INITIAL	AFTER 1WK.	AFTER 2WKS.		INITIAL	CHANGE	INITIAL	AFTER 1WK.	AFTER 2WKS.
13	50	+10	.	•	•	1	60	0	•	•	•
14	50	+25	.	•	•	2	70	0	.	•	•
15	75	+25	•	•	•	3	75	+5	.	•	•
16	70	+15	.	•	•	4	65	0	•	•	•
17	75	+20	.	•	•	5	70	-5	.	•	•
18	90	+30	.	•	•	6	100	-20	.	•	•
19	80	+25	.	•	•	7	70	-15	.	•	•
20	50	+20	.	•	•	8	85	-15	.	•	•
21	75	+20	.	•	•	9	70	-5	.	•	•
22	65	+25	.	•	•	10	100	-10	.	•	•
23	75	+15	.	•	•	11	60	-10	.	•	D
24	90	+25	.	•	•	12	70	-10	.	•	D

TEXT-FIG. 1. The Flexner-Jobling adenocarcinoma, once it has begun to develop, grows with equal rapidity in rats gaining weight on a mixed diet and those underfed on the same food.

give rise relatively seldom to growths in animals fed for some time beforehand on a non-carbohydrate diet. Sweet, Corson-White, and Saxon⁴ kept mice on a modification of a food devised by Mendel and Osborne⁵ that prevents the growth of rats because of the lack of certain constituents; and they found that a mouse car-

³ Van Alstyne, E., and Beebe, S. P., *Jour. Med. Research*, 1913-14, xxix, 217.

⁴ Sweet, J. E., Corson-White, E. P., and Saxon, G. J., *Jour. Biol. Chem.*, 1913, xv, 181.

⁵ Osborne, T. B., Mendel, L. B., and Ferry, E. L., *Ztschr. f. physiol. Chem.*, 1912, lxxx, 307.

cinoma had poor success in such hosts. Unfortunately it is not certain whether the results of these investigations are to be attributed to a specific lack in the foods employed or to the circumstances that the diet of the specially fed hosts differed from that of the animal furnishing the tumor transplanted to them. That such a difference may adversely affect tumor grafts has repeatedly been shown⁶; and

CONTROLS						FOOD LIMITED						
NO.	WEIGHT		TUMOR			NO.	WEIGHT		TUMOR			
	INITIAL	CHANGE	INITIAL	AFTER 1 WEEK	AFTER 2 WEEKS		AFTER 4 WEEKS	INITIAL	CHANGE	INITIAL	AFTER 1 WEEK	AFTER 2 WEEKS
1	116	+30	•	•	•	1	89	-35	•	•	•	•
2	75	+45	•	•	•	2	98	-81	•	•	•	•
3	100	+32	•	•	•	3	105	-23	•	•	•	•
4	82	+25	•	•	•	4	132	-24	•	•	•	•
5	107	+91	•	•	•	5	155	-32	•	•	•	•
6	88	+36	•	•	•	6	102	-22	•	•	•	•
7	85	+22	•	•	•	7	95	-43	•	•	•	•
8	105	+13	•	•	•	8	88	-17	•	•	•	•
						9	86	-25	•	•	•	•

TEXT-FIG. 2. This records findings similar to those of text-figure 1. But the dieting was begun when the tumors were larger and was continued for a longer time. The underfed animals lost greatly in weight.

it was with tumor grafts that the investigators mentioned obtained their positive results. Van Alstyne and Beebe found a non-carbohydrate diet ineffective when it was begun on the day that the tumor was implanted. Sweet and his collaborators made experiments only with tumor grafts.

⁶ Haaland, M., *Berl. klin. Wchnschr.*, 1907, xlv, 713. Stahr, H., *Centralbl. f. allg. Path. u. path. Anat.*, 1909, xx, 628.

Altogether the work mentioned shows that the development of tumor grafts can in many cases be prevented or retarded by underfeeding the host or by putting it on a special diet. By the first method certain transplantable tumors can be checked or retarded in their course even after they have reached a large size. The method is ineffectual with established growths of one kind at least, the Flexner-Jobling rat carcinoma, despite the fact that grafts of this tumor, as yet unvascularized, are easily influenced. Whether recurrences and metastases of such a growth will behave like the parent tumor, or, like new made grafts, prove sensitive to influences exerted through the diet is not yet known; nor has the influence of special diets on large tumors been adequately looked into. Apart from certain suggestive clinical instances nothing is known as to the influence on spontaneous growths of alterations in the food of the host. The present study is concerned with some of these points.























































THE INFLUENCE ON TRANSPLANTED TUMORS.

Several mouse tumors and the Flexner-Jobling adenocarcinoma of the rat were used. The mice which served as hosts were not merely underfed so that they lost weight but were given as their sole diet Sweet's modification of Mendel's food.⁷ It was thought that in this way more outspoken results might be obtained. Rats, as in previous experiments with the Flexner-Jobling growth, were underfed on a standard bread compounded of oatmeal, corn-meal, rye flour, milk, and sugar with a measured quantity of fresh milk to moisten it. Experiments later to be described show that Sweet's food has no special influence on this tumor.

In the attempt to learn whether the development of metastases can be influenced by diet, experiments were carried out with two metastasizing mouse carcinomata, kindly furnished by Dr. Tyzzer and by Dr. Bashford, respectively. One was a growth of the Japanese waltzing mouse, the other strain 63 from the laboratories of the Imperial Cancer Research Fund. But as both these tumors, even after they had reached a considerable size, were markedly checked in their growth by underfeeding the host on Sweet's

⁷ A food composed of starch, lard, lactose, agar, a salt mixture, and gluten obtained by washing wheat flour.

food (text-figure 3), it seemed useless to observe the effect of the treatment on secondaries, since the number of these secondaries is of course directly dependent on the activity of the primary neoplasm. The Flexner-Jobling tumor could not be utilized because it had ceased to metastasize with sufficient regularity. A strain of mouse carcinoma (native strain No. 33) which never gives secondaries, was tested and found to be markedly held back by the dieting.

CONTROLS						FOOD LIMITED					
NO.	WEIGHT		TUMOR			NO.	WEIGHT		TUMOR		
	INITIAL	CHANGE	INITIAL	AFTER 10 DAYS	AFTER 20 DAYS		INITIAL	CHANGE	INITIAL	AFTER 10 DAYS	AFTER 20 DAYS
1	9	+4				1	9	-2			
2	9	+2				2	10	0			
3	9	+2.5				3	9	-2			
4	9	+4				4	9	-2			
5	9	+2.5				5	9	-2.5			
6	11	0				6	9	-2			
7	9	3.5				7	9	-2			
8	9	1				8	9	-2			
						9	9	-2.5			
						10	10	-2.6			

TEXT-FIG. 3. A transplantable adenocarcinoma of the Japanese waltzing mouse was markedly retarded in its growth by underfeeding the host on Sweet's food. The diet was begun after the tumors had reached a considerable size. The controls were full fed on a mixed ration.

The effect of underfeeding upon recurrences was studied with the Flexner-Jobling adenocarcinoma. Just as three years previously, this growth was uninfluenced by changes in the nutritive condition of the host instituted after it had reached considerable size (text-figures 4, 5, and 6). Rats about three fourths grown with subcutaneous tumors resulting from inoculation of the same material were paired against one another according to body-weight and size of the tumors, and one of each pair was underfed so that it grad-

CONTROLS							FOOD LIMITED								
NO.	WEIGHT			TUMOR				NO.	WEIGHT			TUMOR			
	INITIAL	CHANGE AT OPERATION	FINAL CHANGE	INITIAL	AFTER 7 DAYS	AFTER 14 DAYS	AFTER OPERATION REAPPEARANCE GRAFT		INITIAL	CHANGE AT OPERATION	FINAL CHANGE	INITIAL	AFTER 7 DAYS	AFTER 14 DAYS	AFTER OPERATION REAPPEARANCE GRAFT
1	85	+45	+57					1	80	-13	-18				
2	85	+25	+28					2	80	-2	0.0				
3	44	+18	+28					3	85	-10	-12				
4	67	+10	+23					4	88	-13	-18				
5	82	+18	+33					5	73	-3	-9				
6	82	+13	+22												

TEXT-FIG. 4.

CONTROLS							FOOD LIMITED								
NO.	WEIGHT			TUMOR				NO.	WEIGHT			TUMOR			
	INITIAL	CHANGE AT OPERATION	FINAL CHANGE	INITIAL	AFTER 7 DAYS	AFTER 14 DAYS	AFTER OPERATION REAPPEARANCE GRAFT		INITIAL	CHANGE AT OPERATION	FINAL CHANGE	INITIAL	AFTER 7 DAYS	AFTER 14 DAYS	AFTER OPERATION REAPPEARANCE GRAFT
1	112	+53	+38					1	82	+5	-4				
2	125	+15	+18					2	110	-13	-18				
3	75	+21	+27					3	115	-38	-38				
4	120	+27	+34					4	102	-22	-18				
5	82	+38	+44												
6	80	+24	+31												
7	118	+22	+45												

TEXT-FIG. 5.

CONTROLS							FOOD LIMITED															
NO.	WEIGHT			TUMOR				GRAFTS	NO.	WEIGHT			TUMOR									
	INITIAL	CHANGE AT OPERATION	FINAL CHANGE	INITIAL	AFTER 7 DAYS	AFTER 14 DAYS	AFTER 21 DAYS			INITIAL	CHANGE AT OPERATION	FINAL CHANGE	INITIAL	AFTER 7 DAYS	AFTER 14 DAYS	AFTER 21 DAYS	GRAFTS					
1	74	+28	+41					•	•	•	•	•	•	•	•	•						
2	101	+32	+44					•	•	•	•	•	•	•	•	•						
3	75	+32	+40					•	•	•	•	•	•	•	•	•						
4	100	+48	+77					•	•	•	•	•	•	•	•	•						
									1	88	-32	-24					•	•	•	•	•	•
									2	152	-24	-47					•	•	•	•	•	•
									3	108	-30	-43					•	•	•	•	•	•

TEXT-FIG. 6.

TEXT-FIGS. 4, 5, AND 6. These give the results of three experiments with the Flexner-Jobling adenocarcinoma, designed to test the effect of underfeeding on recurrences and operative disseminations (grafts) of this growth. Half of the animals were underfed on a mixed diet, half full fed; and after several weeks all were operated upon. The tumor was removed save for a small fragment, and two auto-implantations were made in the subcutaneous tissue.

In one series of underfed animals (text-figure 4) the recurrences and grafts grew less well than in the controls; in a second series (text-figure 5) no notable differences were observed; while in the third growth was far better in the underfed animals.

usually lost in weight. The controls were full fed on the same diet and grew rapidly. After several weeks of dieting, when the experimental animals had become thin, all were operated upon by a uniform procedure. The tumor was removed save for a fragment about one and one half millimeters in diameter, which was left with its vascular connections intact; and two autotransplantations were made of small bits to the subcutaneous tissue of the flanks. The feeding was not changed. The results varied strikingly from experiment to experiment. In one series of thin animals the development of recurrences and grafts was much delayed, in another it occurred with the same rapidity as in the controls, and in a third it was much more rapid (text-figures 4, 5, and 6).

Evidently in these experiments with the Flexner-Jobling tumor factors sufficient to cause a complete reversal in the findings were uncontrolled. Without doubt one such factor is the resistance elicited in the host by the implanted alien tissue. This resistance

has been often studied. That it may lead to the retrogression of transplanted tumors, even when large, or prevent recurrences of them is well known. Through the instability that it introduces it may have been responsible for the sensitiveness to alterations in the host's diet shown by the transplanted mouse tumors used in the present work. Against spontaneous tumors such a resistance has not been demonstrated despite repeated attempts. So the findings with transplantable tumors can hardly be taken as a basis for generalizations regarding the effect of diet on spontaneous growths.

THE INFLUENCE ON SPONTANEOUS TUMORS.

Some hundred and fifty spontaneous mouse tumors were obtained for the work. All had arisen as lumps in the mammary glands of old females, and all except three were carcinomata, these three being examples of carcinoma sarcomatodes. The histology of the growths was varied.

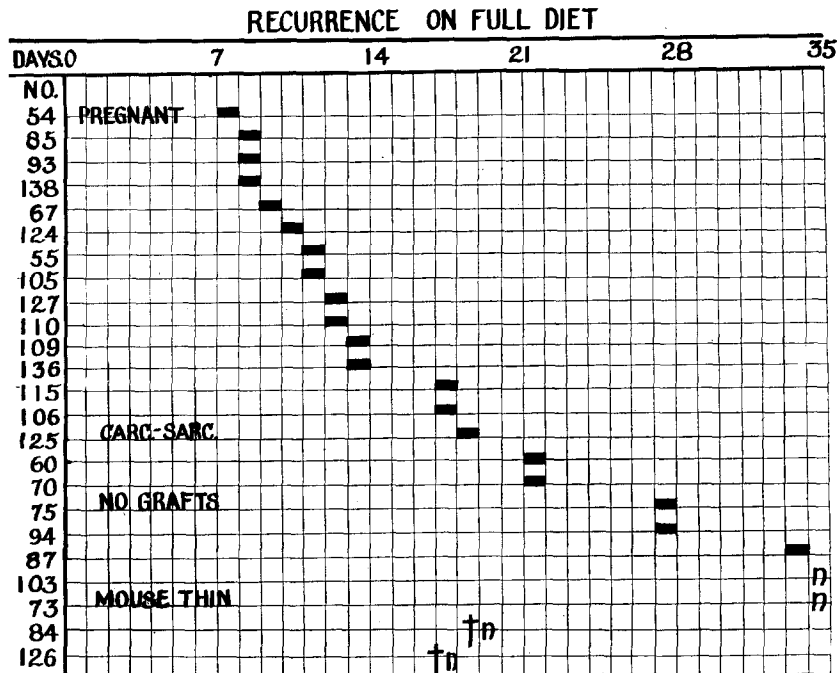
The tumor mice were divided into three groups of the same general character. One group which served as control was full fed on ordinary diet (bread and milk, grain); a second was underfed on Sweet's modification of Mendel's food for some days prior to operation and thereafter throughout the term of observation; and the third was given ordinary diet before operation, and an abundance of Sweet's food afterwards. Each animal had a jar to itself, provided with a water bottle. As in the experiments with the Flexner-Jobling carcinoma the tumors were removed save for a fragment about one and one half millimeters in diameter which was left with its vascular connections intact; and two autotransplantations of similar bits were made into the subcutaneous tissue of the animals' flanks. These latter bits may be taken to represent in some sort disseminations at the time of operation. The wounds were closed with very fine silk and usually healed by first intention. When there were multiple tumors, as frequently happened, all save one were taken out *in toto*, and a fragment of this one was left and implantations made as usual. The mice were kept for thirty-five days after operation and weighed and examined frequently. Haaland⁸ has found

⁸ Haaland, M., *Fourth Scientific Report of the Imperial Cancer Research Fund*, 1911, 1.

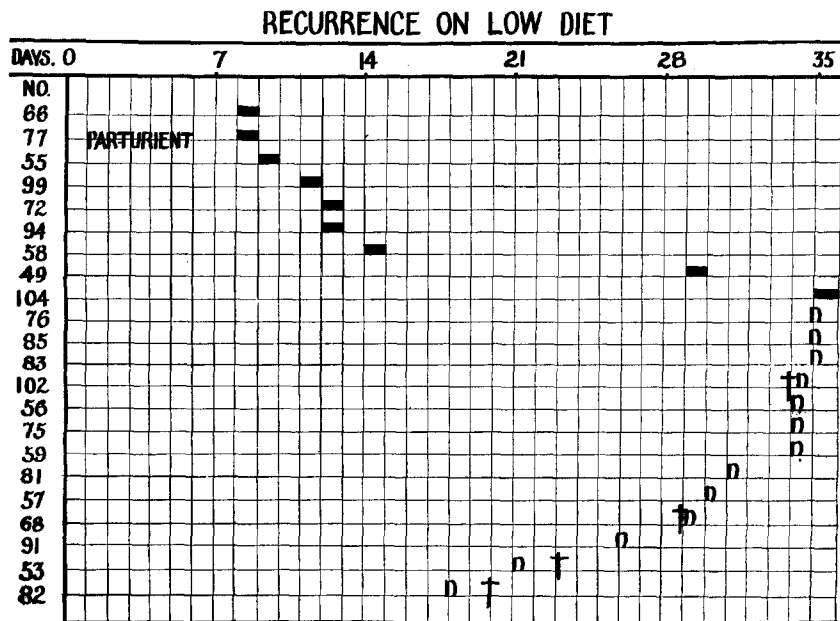
that grafts of spontaneous mouse tumor implanted in the animal furnishing the growth usually began to develop within thirty-five days. Text-figure 9 confirms his findings.

Many complications and deaths occurred among the operated mice, diminishing the number that could be used for a comparison. Some of the animals had very large tumors and were already emaciated. These were ruled out. In the charts are figured the results in mice surviving two weeks or longer without wound infection, or severe illness, or gaping of the wound that would affect the recurrence. As was to have been expected, much the largest proportion of deaths from intercurrent causes was in the underfed mice. Constant vigilance was needed to ensure that the food they received was sufficient to support life, and yet so little that they lost in weight. Minor ills such as otitis, scabby skin, and conjunctivitis were about equally frequent in the three series. Recurrences and growth of the grafts were first recorded as such when growing nodules larger than the original tumor fragments had made their appearance. The recurrences usually developed from the tumor bit left in the wound; but often, especially in the control group, they were multiple, or diffuse in the scar. Owing to the way in which the operation was carried out tumor cells must have been scattered throughout the wound in practically every case.

A comparison of text-figures 7 and 9 with text-figures 8 and 10 shows that in the mice losing weight, as a result of underfeeding with Sweet's modification of Mendel's food, recurrences and the growth of tumor grafts were delayed in most cases and prevented in many throughout the term of observation. In 83 per cent. of the twenty-four mice on ordinary diet a recurrence was noted, and in only 41 per cent. of the twenty-two underfed mice. The effect on growth of the grafts was somewhat less marked. They grew in 68 per cent. of the controls and 41 per cent. of the underfed animals, appearing on the average fifteen days after operation in the former and twenty-five days after it in the latter. In the controls the new tumors enlarged much more rapidly, and coalescing recurrences throughout the healed wound were relatively frequent. A few of the tumors in the underfed animals,—and these the most malignant histologically,—were little if at all affected by the dieting,

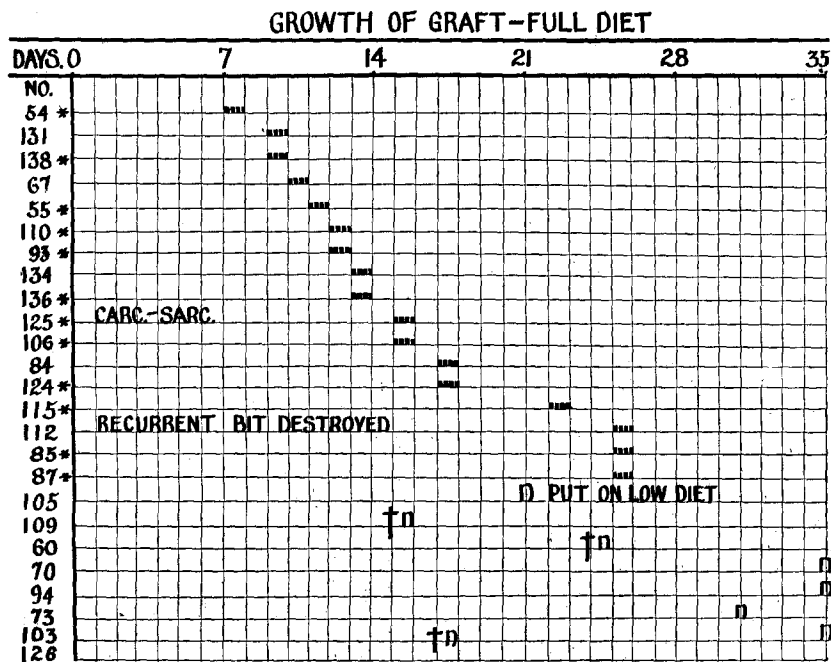


TEXT-FIG. 7.

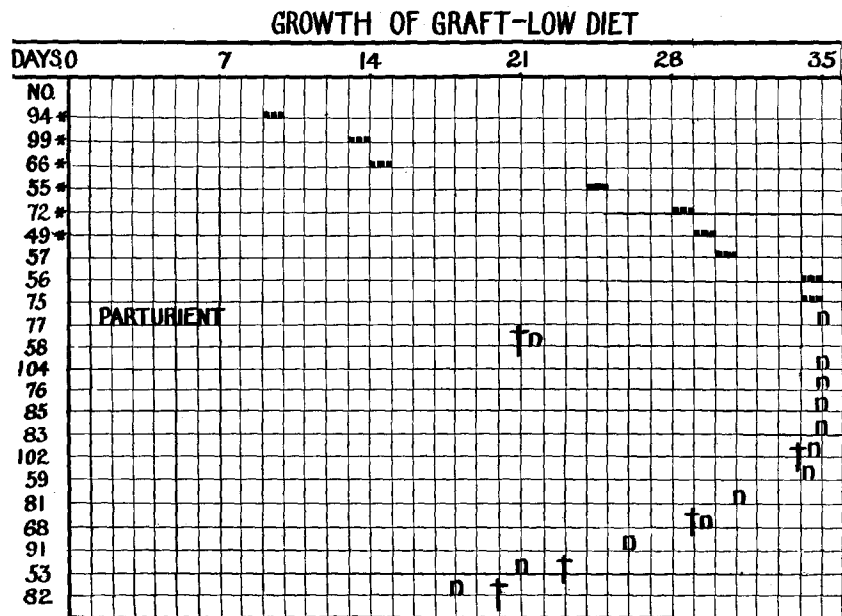


TEXT-FIG. 8.

TEXT-FIGS. 7 AND 8. These give the time of appearance of recurrences of the spontaneous tumors of a series of mice fed abundantly on a mixed diet, and of another series underfed before and after operation on Sweet's food. In the first column are the numbers designating the mice. The distance of the black dashes from the ordinate indicates how soon after operation the recurrences appeared. N = no recurrence.



TEXT-FIG. 9.



TEXT-FIG. 10.

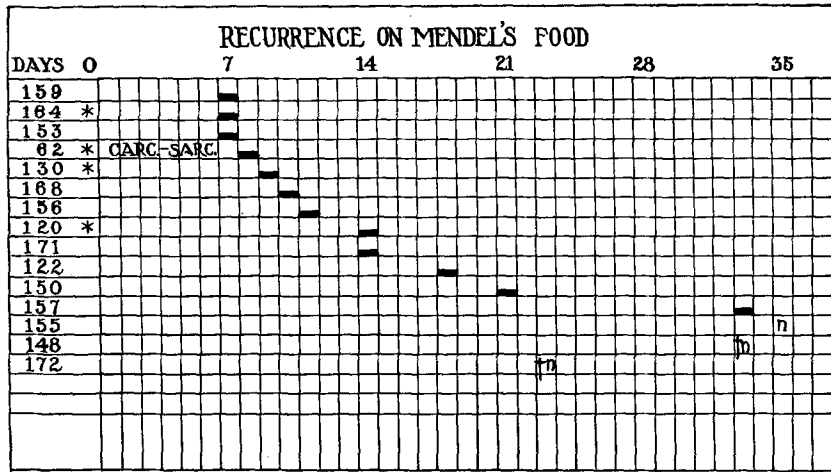
TEXT-FIGS. 9 AND 10. The time of appearance of growing grafts in the mice of text-figures 7 and 8. A star after the number of a mouse indicates that in this animal there was a recurrence as well.

as far as could be observed. Recurrences of these growths took place and grafts of them enlarged with practically the same rapidity as in the most malignant instances among the controls.

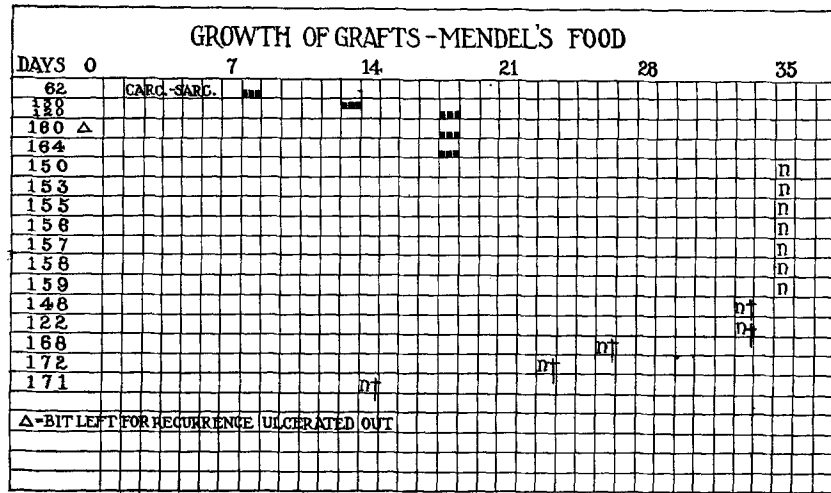
The treatment that secured these results in the dieted mice was drastic. By the time of operation the animals had lost, on the average, 12 per cent. of their weight and at the end of the thirty-five days 24 per cent. But as most were fat when obtained, the actual emaciation was less than is suggested by the figures. Toward the end of the fourth week the mice showed almost regularly an aversion for the special food, and it became necessary to supplement this with a little bread and milk if they were to remain alive.

The results were not permanent in that cures were effected. Some of the mice which showed no sign of tumor during the period of underfeeding were put on ordinary diet at its completion, and practically without exception they developed recurrences or growing grafts, or both, soon after regaining their weight. Some of the control animals in which the tumor had reappeared were transferred to the underfed group, and when they had begun to lose weight were operated upon a second time according to the usual procedure. Occasionally the results were striking. A carcinoma solidum which recurred on the control diet eight days after operation failed to reappear in the thirty-six days in which the host was underfed following a second operation, only to recur again, and within four days, when the control diet was resumed. In this animal the grafts did not grow.

It has been of special interest to determine whether results similar to those in the underfed group could be obtained in mice kept in nitrogenous equilibrium on the special diet. But in the work to this end an unexpected obstacle was met with. Rats stay in good health and retain their weight for long periods when fed on Mendel and Osborne's food; but on Sweet's modification of this as prepared in our laboratory mice were found to do badly. For example, nine healthy, adult mice weighing an average of twenty grams lost an average of 4.4 grams during three weeks in which they were given the food in abundance. Young animals fare even worse. Some old females maintain equilibrium for ten days or two weeks, but the majority begin to lose weight within a few days and by the



TEXT-FIG. 11.



TEXT-FIG. 12.

TEXT-FIGS. 11 AND 12. The time of appearance of recurrences and grafts, respectively, of the spontaneous tumors of mice fed abundantly on Sweet's food from the time of operation. In text-figure 11 a star after the number of a mouse indicates that the grafts also grew.

end of the fourth week are thin, cold, and weak, refuse the food and soon die unless supplied with another ration. All of the mice with spontaneous tumors, full fed on Sweet's food after operation, emaciated rapidly toward the end of the period of observation, their average loss of weight after thirty-five days being 30 per cent. or slightly more than that of mice underfed on the same diet.

Although the end results as regards loss of weight were nearly the same in the mice underfed and the mice full fed on Sweet's food, there were essential differences in the conditions imposed on the two groups of animals. The group which received an insufficient ration of the diet for some days prior to operation was losing weight when it was performed, whereas the mice of the other group were operated upon when still well nourished on an ordinary diet, and, being given thereafter an abundance of the special food, they lost little weight for some days. The effect of these differences is plainly to be seen in text-figures 11 and 12 which have to do with the results in the animals of the latter group. Recurrences in them (text-figure 11) took place as frequently and as soon as in the control animals (text-figure 7). Growth of the grafts (text-figure 12) on the other hand was delayed as greatly as in the underfed mice (text-figure 10).





















There is a simple explanation for these facts. Under ordinary conditions (text-figures 7 and 9) the appearance of a recurrence precedes by a considerable period the development of grafts,—as would naturally follow from the circumstance that the bit left for a recurrence possesses a vascularization and other connection with the tissues, whereas the grafts must acquire this, a proceeding which takes some days. During these days the mice fed on Sweet's food had begun to lose weight, and the grafts on starting to grow had the factor of general malnutrition against them. The bits left for recurrences, on the other hand, were able to begin growing almost at once, at a time when the dieting had just been started, and the animals were still well nourished.

All in all the findings show that it is possible in many cases to hinder the development of bits of spontaneous mouse tumor disseminated at operation, by feeding the animal after operation on a special diet that entails a gradual loss of weight. In order to delay

the development of recurrences from tumor bits left *in situ* a more drastic treatment is required, namely, dieting that entails loss of weight previous to the operation.

THE NATURE OF THE INFLUENCE.

In what way are these results brought about? Has Sweet's modification of Mendel's food an influence to check the growth of tumors other than that exerted through the loss of weight that it entails? There is some reason to doubt this. Several experiments made with rats carrying the Flexner-Jobling tumor show that this growth is as unaffected by a diet of Sweet's food as by underfeeding on a mixed diet (text-figure 13). But to settle the point definitely

LOW DIET					SPECIAL DIET				
NO.	WEIGHT		INITIAL	AFTER 3WKS	NO.	WEIGHT		INITIAL	AFTER 3WKS
	INITIAL	CHANGE				INITIAL	CHANGE		
1	95	-23			1	65	0		
2	66	-18			2	72	-10		
3	87	-15			3	82	-1		
4	70	-16			4	77	-12		
5	47	-7			5	42	-5		

TEXT-FIG. 13. This shows that a diet of Sweet's food had no more effect upon the development of the Flexner-Jobling tumor than had underfeeding on a mixed diet.

tumors more sensitive to alterations in the general nutrition must be used.

The effects of the dieting can scarcely be to stimulate immunity processes in the host. For, as has been pointed out, the tumor cells are merely held in check, remaining alive and capable of rapid growth when the host is returned to ordinary food and regains its weight. In many instances, doubtless, the cells suffer directly from the general starvation of the body. There is reason to suppose, though, that most of the effect on them is indirect, through a limitation in the host's ability to form a connective tissue scaffolding and vascularization for their support. Whether the absence of this "stroma

reaction" is the essential factor in resistance to tumors, as assumed by Russell,⁹ need not be here discussed. It is sufficient to know that all tumors and grafts of tumors, except those developing wholly by the invasion and replacement of normal structures, need in the course of their growth a stroma furnished by the host. In mice losing weight the proliferative activity of the host's tissues,—on which the elaboration of a stroma must ultimately depend,—is much decreased. This is shown, first by the extreme slowness with which wounds heal in these animals, and second by the delayed organization about inert, foreign bodies. I have found that clean, well apposed wounds frequently stay unhealed for a week or ten days. The encapsulation of agar-agar injected beneath the skin is also very slow.

Experiment 1.—Sixteen rats about three fourths grown were paired against one another according to weight, and half were full fed, half underfed on the same diet of mixed food. When the underfed group had begun to lose weight all were injected subcutaneously in each flank with 0.08 c.c. of 1.5 per cent. agar in Ringer's solution. The agar was cooled in the syringe, and forced through a small needle, whereby it was broken into many small fragments. It was kept from extending back along the injection track by pressure with a rubber-covered clamp. Thus each rat received in its subcutaneous tissue two discs or buttons of fragmented agar. Seven days after the injection the animals were killed and sections made through the center of each agar disc.

The reaction to agar has been often studied and need not be described further than to say that, following endothelial migration, strands of connective tissue extend among the bits of jelly which are at length wholly encapsulated and, little by little, penetrated and absorbed. These processes were found to be far advanced in the control animals of the present experiment, at a time when in the dieted ones a capsule about the agar was almost lacking and organization was just beginning (plate 21, figures 1 and 2). The experiment has been several times repeated, using both rats and mice, with the same results.

If the loss of weight caused by underfeeding retards the growth of tumors, how does it happen that tumors progress so rapidly in emaciating human beings? Probably in some instances because in

⁹ Russell, B. R. G., *Third Scientific Report of the Imperial Cancer Research Fund*, 1908, 341.

man, as in mice, certain tumors are able, *ab initio*, to obtain their food with ease in a starving body. It seems likely that certain other tumors during their development gain in the ability to obtain food through the survival and proliferation of the cells most suited to cope with the increasingly difficult conditions.¹⁰ According to this idea a tumor made up at first of a mixture of cells sensitive and insensitive to alterations in the general nutrition would, as the host emaciated, come to consist of elements little affected by the circumstance. Some experiments were performed to test the hypothesis. Transplanted tumors which had grown for some weeks in full fed hosts and hosts underfed to the point of emaciation were transferred to underfed individuals. According to the premises, the tumors from the underfed hosts should have given the better results. But no differences were noted.

SUMMARY.

Previous work has shown that the growth of grafts of transplantable tumors can be in many cases prevented or retarded by underfeeding the new host or by putting it on a special diet. The effect of such treatment on large tumors has been little studied; and the effect on metastases and recurrences has not been studied at all. Apart from certain clinical observations nothing is known as to the influence on spontaneous tumors of alterations in the diet.

Experiments with transplanted rat and mouse tumors along the lines thus suggested show that large growths of certain strains are checked in their development by underfeeding the host upon a special diet (Sweet's modification of one of Mendel and Osborne's foods) or in some cases by simple underfeeding. Two metastasizing mouse tumors are instances in point. They stopped growing or grew very slowly in hosts underfed on the special diet. The Flexner-Jobling rat carcinoma, on the other hand, was unaffected by the most rigorous underfeeding on a mixed diet when this was begun after the tumor had been growing for a short period. Experiments

¹⁰ Loeb has shown that tumors in mice treated with colloidal copper undergo regressive changes at first, but that a strain of cells unaffected by the drug may survive, from which the tumor eventually proliferates (Loeb, L., personal communication).

to test the influence of underfeeding upon recurrences of this tumor gave results that varied from series to series of animals. The findings strongly indicate that generalizations from work with transplanted tumors as regards the effects of diet on spontaneous growths are unwarranted.

By underfeeding on Sweet's food mice with spontaneous tumors, beginning some days prior to operation, it has proved possible in most cases to delay for a relatively long period the development of recurrences and the growth of tumor bits (grafts) disseminated at the time of surgical interference. The treatment entailed great loss of weight. Tumor mice kept on ordinary diet previous to operation, but put thereafter on an abundant ration of Sweet's food, developed recurrences as early as the tumor mice on ordinary diet; whereas the growth of auto-implants was, relatively speaking, much delayed. These results seem attributable rather to a gradual malnutrition induced by the special food than to the circumstance that it lacked a growth principle. In none of the dieted mice was a definite cure obtained. Ordinarily a recurrence appeared and the grafts began to grow soon after the host, again on ordinary food, had regained weight.

A few spontaneous tumors seem absolutely unaffected by the most rigorous dieting.

Wounds heal with marked slowness in animals that have become thin as a result of dieting, and an inert foreign body (agar-agar) injected subcutaneously is very slowly encapsulated and organized. In these facts may be found a suggestion as to the method whereby dieting delays tumor growth. For it may well be that, with a lessened proliferative activity of the host tissue, the elaboration of a vascularizing and supporting stroma such as most tumors depend upon for their growth, at least indirectly, is much delayed.

The rapid growth of tumors in emaciating individuals is not incompatible with the present findings. Such growth may be consequent upon a selection in the host of those cells most fit to cope with the increasingly difficult nutritive conditions. But experiments designed to demonstrate this have been unsuccessful.

It is conceivable that recurrences of certain human tumors and



FIG. 1.

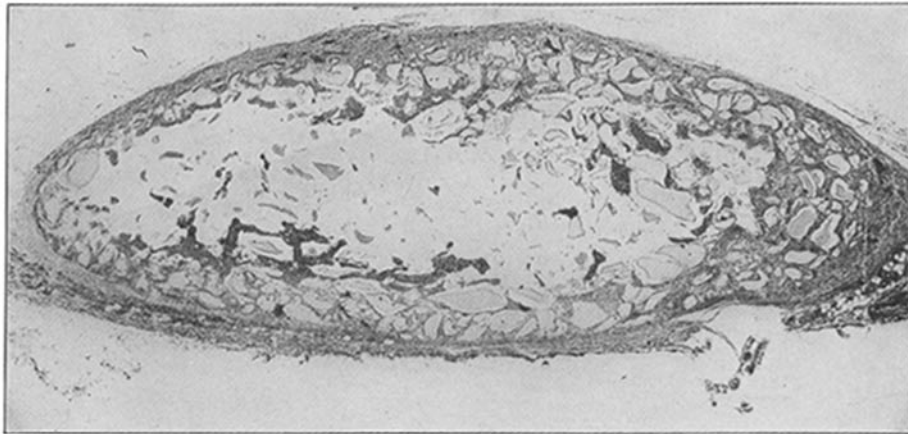


FIG. 2.

(Rous: Influence of Diet on Tumors.)

the development of metastases may be delayed or prevented for a period by methods somewhat similar to those employed against spontaneous mouse tumors in the present investigation. But generally speaking only the more malignant human tumors would require such palliative measures, and these are precisely the ones that would prove,—if experience with mice is an index,—least amenable to alterations in the nutrition of the host.

It is a pleasure to acknowledge the help of Dr. Linda Lange in this work.

EXPLANATION OF PLATE 21.

FIG. 1. Cross-section through an agar mass removed seven days after its injection into the subcutaneous tissue of a young rat which was losing weight as the result of underfeeding on a mixed diet. The encapsulation and organization are slight as compared with them in figure 2.

FIG. 2. Cross-section of an agar mass from a full fed control rat. Methylene blue and eosin.