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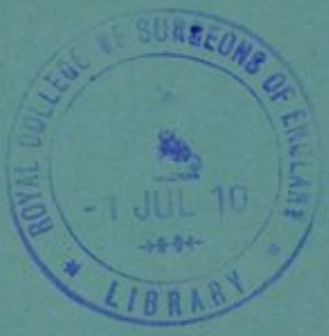

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On the Relative Sizes of the Organs of Rats and Mice bearing Malignant New Growths.

By Dr. F. MEDIGRECEANU (Bucharest).

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(From the Laboratory of the Imperial Cancer Research Fund.)

The object of the present investigation has been to determine the effects of the growth of tumours on the weight of the principal organs of the body. The fundamental conception on which the work is based is that the weights of the different organs of normal animals bear a relatively constant ratio to the total weight of the body.

Such investigations are capable of throwing light on many debatable points of cancer metabolism, and give important indications of promising directions for future more detailed work. The previous investigations of workers in the Imperial Cancer Research Fund (Cramer, Haaland, Murray), and recently by Moreschi, in Ehrlich's Institute, have dealt with this subject from the standpoint of the ratio of tumour-weight to total body-weight and the influence of the former on the latter and on the normal growth of the body. In the present investigation a closer analysis of the factors is attempted, in reasonable expectation that under the influence of the physical and chemical changes taking place in the bodies of animals bearing tumours, definite aberrations from the normal relations may be produced. From a consideration of these aberrations it may be possible to infer the nature of these changes.

Method.

The following precautions have been taken to avoid the sources of error which would impair the comparability of the numerical data. Normal and tumour-bearing animals (tumour-animals) were chosen which were free from obvious illness, looked healthy and strong even when bearing large tumours. They were killed by fracture-dislocation of the cervical vertebræ. Estimations were made on 300 animals. With few exceptions the mice were taken three at a time, the rats singly. In all cases the comparisons are made with total body-weight *less the contents of the alimentary canal.*

The abdominal organs were removed in the order—spleen, alimentary canal, kidneys, liver. The thorax was then opened, blood-clots removed, and lungs and heart excised. The heart was separated from the lungs and the

blood-clots removed from its cavities. The unopened alimentary canal was first weighed, then split open throughout its length and washed with 0·75-per-cent. salt solution till the wash-water remained clear. It was then dried rapidly between filter-paper. All the organs were weighed in closed weighing bottles, after which the moisture was driven off in a drying oven kept at 103° to 105° C. for 40 to 50 hours, and the weight of the dry substance determined. The tumour weights include the fluid and necrotic parts as well as the growing parenchyma. Hence, in comparison with the results obtained from normal animals, especial weight must be laid on the *ratios* of the weights of organs to *body-weights minus tumour*.

Normal Ratios.

A large number of normal mice belonging to different age-periods were examined. The variations due to age are most marked when the animals pass from a milk (sucking) to a vegetarian (adult) diet. The alimentary canal is relatively twice as heavy in animals a few days after the establishment of vegetarian diet as at nine days (milk diet). During the remainder of life the ratio remains fairly constant with a slight diminution in old age. Nearly identical variations are presented by the liver. Heart and lungs are, on the contrary, relatively larger in sucking mice. The kidney shows only small variations, whether we compare animals of different ages or individuals of the same age. The spleen varies enormously, but is relatively smaller in sucking and young animals than in adults. It follows that comparisons are only allowable between animals of the same age. Equally extended observations have not been considered necessary in the case of rats, and in these the control observations have been restricted to normal animals of the same weight as the tumour-animals. Considerations which will be fully dealt with in a later paper led me to undertake experiments in which rats were fed with a uniform diet (150 c.c. milk, 350 grammes rice or oatmeal, and 60 grammes bread) for several weeks or months. The weight-ratios of some organs were found to be modified by this diet, *e.g.*, those of the alimentary canal, heart, and kidneys were relatively smaller, that of the lungs larger, and that of liver unaltered. A number of tumour-rats were fed on the same diet, and the control estimations are taken from normal rats correspondingly fed. In the same way the tumour-rats fed on the ordinary laboratory diet are compared with similarly fed normals.

Ratios in Tumour-animals.

Alimentary Canal.—The general impression of all the estimations has been that, under the experimental conditions thus far investigated, the relative

weight of the alimentary canal to "body-weight less tumour" falls within or near the normal ratio. It is remarkable that in most cases (*cf.* the figures for mouse tumours, Table I, and for rat tumours, Table II), the relative weight of the alimentary canal diminishes with the size of the tumour, whether the latter is carcinoma or sarcoma, growing rapidly or slowly. Only in 8 to 10 out of 200 cases, and then especially in animals with small tumours, did the weight ratio of the alimentary canal reach the highest physiological value. A hypertrophy of this organ-system could not be demonstrated during the several stages of growth studied for the tumours examined.

Liver.—The liver, on the contrary, appears hypertrophied in all cases when the ratio to "body-weight less tumour" is taken. This holds for spontaneous as well as transplanted tumours. A direct parallel subsists, up to a certain

Table I.

No.	Age.	Ratio: tumour-weight to body-weight.	Digestive tract.	Liver.	Heart.	Kidneys.	Lungs.	Spleen.
			Normal Mice.—Ratio of Organ-weight to Body-weight.					
12	51 days	—	1 : 20·8	1 : 13·8	1 : 148·4	1 : 60·9	1 : 119·3	1 : 81·4
21	3 mos.	—	1 : 20·4	1 : 12·7	1 : 157·8	1 : 57·9	1 : 120	1 : 54·4
18	5 „	—	1 : 23·3	1 : 14·4	1 : 168	1 : 53·9	1 : 121·5	1 : 73·3
24	Old	—	1 : 22·7	1 : 13·7	1 : 159·1	1 : 53·9	1 : 113	1 : 80·7
			Pregnant Mice.—Ratio of Organ-weight to Body-weight less Fœtus.					
4	—	—	1 : 24·5	1 : 10·5	1 : 160·6	1 : 60·4	1 : 123·1	1 : 111·1
			Mice with transplanted Tumours.—Ratio of Organ-weight to Body-weight less Tumour.					
			A. Rapidly-growing Strains.—"63," "J," "B," "199."					
33	3–4 mos.	1 : 2·3	1 : 22·1	1 : 9·9	1 : 116·1	1 : 55·7	1 : 96·7	1 : 43·6
43	3–4 „	1 : 3·3	1 : 21·2	1 : 11·0	1 : 138·1	1 : 56·5	1 : 101·8	1 : 62·4
			B. Intermediate Strains.—"50," "39," "100," "92."					
10	3–5 „	1 : 2	1 : 21·7	1 : 10·1	1 : 118·7	1 : 53·3	1 : 83·4	1 : 53·3
27	3–5 „	1 : 3·6	1 : 19·8	1 : 10·1	1 : 125·7	1 : 52·8	1 : 110·3	1 : 48·9
			C. Slowly-growing Strains.—"62," "T," "93," "173."					
9	3½–6 „	1 : 1·7	1 : 20·0	1 : 9·2	1 : 128·8	1 : 54·1	1 : 119·5	1 : 50·3
27	3½–6 „	1 : 4·0	1 : 18·3	1 : 10·9	1 : 123·3	1 : 53·0	1 : 108·1	1 : 35·5
			Mice with Spontaneous Carcinomata.					
1	Old	1 : 1·4	1 : 25·6	1 : 8·9	1 : 114·5	1 : 53·8	Metastases	1 : 56·3
1	„	1 : 3·5	1 : 25·1	1 : 7·3	1 : 128·1	1 : 61	„	1 : 40·2
1	„	1 : 3·6	1 : 23·2	1 : 9·9	1 : 101·4	1 : 56	„	1 : 54·7
1	„	1 : 3·6	1 : 23·5	1 : 10·6	—	1 : 55	„	1 : 44·1

Table II.

No.	Age.	Ratio: tumour-weight to body-weight.	Digestive tract.	Liver.	Heart.	Kidneys.	Lungs.	Spleen.
Normal Rats.—Ratio of Organ-weight to Body-weight less Tumour.								
A. Usual Diet.								
5	2–4 mos.	—	1 : 19·7	1 : 19·9	1 : 180	1 : 94·6	1 : 140·3	1 : 132·4
B. Special Diet.								
9	2–4 „	—	1 : 30·3	1 : 19·9	1 : 205·9	1 : 122·7	1 : 102	1 : 114·7
1—2 Days after Litter.								
2	4½ „	—	1 : 29·8	1 : 16·6	1 : 211·8	1 : 109·4	1 : 114·4	1 : 148·7
Negative Rat (20 days after the Tumour had disappeared).								
1	4 „	—	1 : 29·3	1 : 15·6	1 : 198·8	1 : 103·7	1 : 74·8	1 : 145
Rats with Transplanted Tumours.								
Sarcoma.								
A. Usual Diet.								
2	3½-5 „	1 : 1·6	1 : 24·7	1 : 11	1 : 134·8	1 : 62·4	1 : 116·3	1 : 54·4
6	3–4½ „	1 : 3·6	1 : 24·2	1 : 13·2	1 : 158·6	1 : 67·2	1 : 110·6	1 : 115·1
B. Special Diet.								
7	3–5 „	1 : 2	1 : 28·9	1 : 12·1	1 : 138	1 : 61·1	1 : 99·4	1 : 101·4
Carcinoma.								
Usual Diet.								
3	4–4½ „	1 : 8·2	1 : 24·8	1 : 14·0	1 : 200·2	1 : 93·0	1 : 95·8	1 : 67·6

point, between the growth of the tumour and the weight of the liver, whether comparison is made between different tumours of the same strain, tumours of different strains, or spontaneous tumours. In a single case, and under exceptional circumstances, an aberrant result was obtained. A mouse with a tumour five months old, of strain "37," weighed 19·5 grammes, while its tumour weighed 22·5 grammes. The liver was of normal weight; it is not possible to exclude the possibility that a stage of hypertrophy had been passed through. Since this case stands alone, undue weight cannot be laid upon it.

The ratio of liver to "body-weight plus tumour" corresponds in the majority of cases with the normal values. Frequently, however, one finds, on the one hand, as *e.g.* with the rat-tumours (and also Tumour "39"), that the liver is too large in proportion to "body-weight plus tumour"; on the

other hand, especially when the tumours are very large, the ratio of liver to "body-weight plus tumour" is smaller than the normal value. The weight of the tumour usually includes an indeterminate quantity of dead material (necrosis and fluid), as already pointed out, so that more accurate comparisons are made with "body-weight less tumour," and on this basis the liver is always enlarged.

The constancy of this result makes a more detailed discussion desirable. It is necessary to be sure that the disturbance of the normal ratio is not only apparent and due neither to mere loss of weight in the other organs, nor to the liver reaching a weight equivalent to what it would have attained in the same animal during the natural augmentation of the body-weight. The first of these two possibilities is easily excluded. The liver is heavier than normal, even if the estimated loss in weight be added to the body-weight. One example may suffice. The quota contributed by the tumour to the total weight (body plus tumour) was calculated in a rat with transplanted sarcoma from daily weighings of the animal, and weekly estimations of the growth of the tumour. It was found that the maximum body-weight was 132 grammes 12 days before the animal was killed. The liver weighed 10·5 grammes at death. The ratio 10·5 : 132 : : 1 : 12·5 is higher than the normal 1 : 19·9. The tumour in this case weighed 55·7 grammes, and if we assume that this were merely a part of a normal animal, the total (rat plus tumour) reaches 180 grammes. The contents of the alimentary canal weighed 12·6, which, deducted from the gross weight, 180 grammes, gives 167·4 grammes, and thus the liver ratio 1 : 15·9 is higher than normal. Loss of body-weight does not introduce a disturbing factor in the majority of the cases examined, since most animals presented the same weight as at the time of inoculation. In some cases the body-weight had increased, and only in a few cases had it diminished. The differences in liver-ratio are, however, considerable, so that the second possibility can also be excluded. A rat was examined 20 days after complete disappearance of a transplanted sarcoma which had reached a size of 10 to 12 grammes. The liver was found to be enlarged still (*vide* Table II). This case should be compared with the results obtained in pregnant mice in which a hypertrophy of the liver was also noted (*vide* Table I); apparently this hypertrophy disappears in a short time after the birth of the young. There are, however, other differences between the livers of normal and tumour animals, such as the increased percentage of water in the latter (as high as 4 to 5 per cent. more than in normals), which indicate qualitative differences as well.

More detailed investigations are being made to determine when the hypertrophy of the liver commences. So far the results have been

inconstant. Distinct hypertrophy was found, *e.g.* in one case with a tumour one-seventh of the body-weight, but the ratio fell within the normal in other cases for tumours of the same size.

Heart.—The heart is enlarged both in transplanted and in spontaneous tumours. In general the enlargement is proportional to the weight of the tumour (*cf.* Tumours "63," "50," rat-sarcoma, Table II). Exceptions are not infrequent. Rapidly growing tumours, *e.g.* "J," do not give so marked hypertrophy as those which grow more slowly with a richly developed blood-supply, *e.g.* "Tumours "50" and "39." The mechanical factors are in all probability mainly responsible. The pregnant normal animals examined did not present a corresponding enlargement of the heart.

Kidney.—The kidneys of tumour mice (and pregnant mice) showed only minor variations such as are met with in normal animals. The transplanted rat sarcoma, on the contrary, induced constantly an increase in the size of these organs. The enlargement could be recognised with the naked eye in animals with large tumours, and the weights were found to be double the normal expectation in many cases. This enlargement was directly proportional to the size of the tumours, as in the case of the liver and heart. The sarcomata of the Mouse "92," "37 sarcoma," "100 sarcoma," did not produce this change. Therefore it is not characteristic of the sarcomata.

Microscopical examination of the enlarged kidneys showed hyperæmia, with here and there hæmorrhages and degenerated cells. Mitoses seemed to be more frequent in the tubular epithelium than in normal kidneys.

Lung.—The results are inconstant. In one and the same strain normal and enlarged lungs are found and constant alterations are not produced.

Spleen.—As in normal animals, the spleen is subject to enormous individual variations in tumour-animals. Although exceptionally large spleens were found in many cases (*e.g.* Tumours "173," "B"), it is impossible to refer the hypertrophy to the presence of the tumours.

In conclusion, we desire to express our indebtedness to the Executive Committee and Director of the Imperial Cancer Research Fund for the facilities afforded for this investigation. It is a pleasure to acknowledge the assistance and interest of Dr. Bashford and his Assistants, Drs. Murray, Haaland, and Russell, and of Dr. Cramer.

Summary.

Weighing experiments on 200 rats and mice bearing tumours (13 transplantable and four spontaneous mouse tumours, 2 transplantable rat tumours) have shown:—

(1) No increase in weight of the alimentary canal as compared with normal ratios.

(2) Hypertrophy of the liver in all cases. Up to a certain point the hypertrophy is proportional to the weight of the tumour.

(3) Hypertrophy of the heart in most cases. This also is in general proportion to the size of the tumour.

(4) Kidneys of normal weight except in the case of a transplantable rat sarcoma in which hypertrophy is produced.

(5) Varying ratios for the lungs.

The most important result of the investigation has been the discovery of an enlargement of the liver, in animals bearing carcinomata and sarcomata, whether transplanted or naturally arising. The nature and causation of this hypertrophy is being further investigated. It would be natural to seek an explanation in an increased assimilation of food through the alimentary canal. The results show an absence of a corresponding hypertrophy of the digestive tract for tumour animals. Histological studies have not, so far, indicated any clear anatomical changes. In a future paper the hypertrophy of the liver will be considered from the standpoint of the intake and elaboration of food material from the intestinal canal, and of the excretory functions of the liver. The possibility will be considered of the circulation of abnormal products given off by the tumour, and the possibility that the liver may elaborate abnormal products to meet the special needs of the tumour.

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