THE RESTORATION OF LOST ORGAN TISSUE*

The Rate and Degree of Restoration

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When the usual relations that exist between organ weight and body weight are altered by the removal of part of an organ, a complete or partial restoration occurs in certain organs but not in others. In mammals the removal of a limb, an eye, or part of the brain is followed by no restoration. When one Cowper's gland is removed the remaining gland grows no larger (1) and, as we shall show in this paper, the excision of one seminal vesicle, half of the prostate gland, or one uterine horn does not cause any very appreciable change in the part that remains. But when we remove one testicle we find there is a slight increase in the weight of the remaining organ, a greater increase is seen when half of the total suprarenal (2) or ovarian (3) or renal tissue (4) is removed, and when part of the liver (5) or lung (6) is excised there is a complete restoration of the lost tissue.

Compensatory hypertrophy is the term commonly used to cover all these instances of organ increase after loss of tissue but, even at the cost of breaking with usage it seems to us preferable to employ merely descriptive words and say that what happens in all of these organs is a restoration of lost tissue. That is all that our present knowledge warrants. "Hypertrophy," in the histological sense, is never all that occurs for there is always hyperplasia and in some cases there may be no hypertrophy. "Compensatory," since it implies a knowledge we do not possess, is a word that tends to still questioning as to the mechanism of organ restoration. That is unfortunate because with more knowledge might come the capacity to intervene in clinical situations in which the rate and degree of restoration of organ tissue lost through disease may be a matter of great moment.

In this paper we give data on the relation between the growth rate of intact organs and the growth rate of organs whose total mass had been halved by operative removal. We assume that the increase that occurs in the remaining organ when one of a pair is removed is due to growth. We

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do so because we know that the increase is not the result of an accumulation of water or of fat, and that on microscopic examination the enlarged organ shows an increase in the structure proper to the organ concerned. We can call this growth even while we recognize that it must be a special form of growth since, though all organs grow, only some are capable of this particular sort of growth, a growth that is occasioned by a reduction in total organ mass and that, as we shall show, takes place at rates very different from those observed during organ growth in general. The question we are concerned to answer is whether or not the factors that determine the general rate of growth of organs are operative also for this special sort of growth. We have shown (7) that there are certain organs, for instance, the kidney, whose general rate of growth is at all times the same relative to the growth of the body, so that no matter whether the rat is 30 or 200 days of age the ♂ kidney grows at 0.717 times and the ♀ kidney at 0.648 times the rate at which the body increases in weight. So also there is a constant relation maintained between the growth rate of the ♂ suprarenal gland and the body as a whole. But this is not true for the testicle, the ovary, or the ♀ suprarenal. During youth their growth is slow relatively to body growth but at about 70 days of age they begin to grow more rapidly than the body and then, rather suddenly, their growth slows and finally stops altogether. Now if the restoration of lost organ tissue is influenced by the factors that determine for each organ its characteristic mode of growth we shall find that the rate of restoration is accelerated during the periods when organ growth is rapid and that it is slowed when there is no longer any growth at all.

But before dealing with organs whose capacity to grow after reduction in organ mass is unquestioned we report observations on organs which manifest this capacity to a very slight degree, if at all.

Observations on the Prostate, Seminal Vesicle, and Uterus

The prostate gland in the rat can be divided at operation and about 50 per cent removed. The judgement as to what constitutes 50 per cent is fallible but presumably the error will be small if the number of trials is large. In rats whose age was about 235 days half of the prostate was excised, and a similar operation without removal of any part of the gland was carried through on rats of the same age. 10 days later it was found that we could select from the experimental and control rats a group of 22 rats with half a prostate gland, that had an average body weight of 335 gm., and another group of 22 rats with intact prostates whose average body weight was also 335 gm. In this control group the average prostate weight was 311 mg. while in the experimental group the remaining half of the

prostate weighed 178 mg. If no growth of the remaining half had occurred the weight should have been half of 311 or 155.5 mg. The actual weight is 178 mg. which is 57 per cent of the control instead of 50 per cent. This might be taken as indicating growth of the remaining half of the prostate but it is not a convincing result. The probable error of the controls was ± 4.4 mg. and of the experimental ± 5.5 mg. giving a critical ratio of 3.2 which is just statistically significant. But in view of the fact that this 7 per cent increase in weight might have been due in part to scar tissue we do not think a decision is possible on the basis of these observations. We can however conclude that if growth occurs at all the degree of restoration must be small.

In the next experiment one seminal vesicle was excised and the weight of the remaining organ was compared with the weight of both seminal vesicles in control rats whose vesicles had been exposed but not removed. The age

TABLE I

Time after operation when killed	Body weight when killed	Number of rats in each group	Seminal vesicle		Remaining seminal vesicle as per cent of both control organs
			Experimental remaining organ	Control both organs	
days	*gm.*		*mg.*	*mg.*	*per cent*
5	241	38	108	190	57
10	251	42	107	210	51
20	260	32	109	206	53

at operation was 110 days. Observations were made at 5, 10, and 20 days after operation, and experimental and control animals were selected that had the same average body weight. The results are given in Table I.

Here again the result is uncertain. The only statistically significant increase is at 5 days after operation and again we do not regard the result as decisive and conclude only that very little if any restoration has occurred.

In the last experiment one uterine horn was removed from 37 rats that were 90 days old. 20 days later the remaining uterine horn was found to weigh 148 mg. In 37 control rats of the same average body weight 20 days after operation both horns weighed 310 mg. In this case, therefore, there was no evidence of any restitution.

Observations on the Kidney, Ovary, Testis, and Suprarenal Gland

The paired organs of the body in which we know that restitution occurs are the kidneys, the suprarenal cortex, and the ovaries. The hitherto published evidence with respect to the testis is insufficient. These organs are

well suited for our purpose because they include those whose rate of growth relatively to that of the body is constant (the kidney and ♂ suprarenal) and those whose rate of growth varies widely at different periods of the growth cycle (the ♀ suprarenal, the ovary, and the testis). So in rats of both sexes one kidney, one suprarenal gland, and one gonad were excised. This operation was performed on rats of 30, 70, 110, and 220 days of age. The

TABLE II *a*

Females

Age at operation	Time after operation when killed	Body weight when killed	Number of rats in each group	Ovaries		Suprarenals		Kidneys		Remaining organ as per cent of both control organs		
				Experimental remaining organ	Control both organs	Experimental remaining organ	Control both organs	Experimental remaining organ	Control both organs	Ovaries	Suprarenals	Kidneys
days	*days*	*gm.*		*mg.*	*mg.*	*mg.*	*mg.*	*mg.*	*mg.*	*per cent*	*per cent*	*per cent*
30	2	52	35	12.0	21.6	8.0	14.2	314	500	56	56	63
"	5	59	64	13.7	23.3	10.0	16.7	387	574	59	60	67
"	10	70	37	15.6	26.3	11.6	18.9	447	633	59	61	71
"	20	95	37	20.7	33.6	15.1	25.1	596	805	62	60	74
"	40	130	26	49.2	68.8	26.3	36.8	732	955	72	72	77
70	2	138	37	41.1	72.8	26.6	43.2	645	1052	56	62	61
"	5	136	40	46.0	77.4	27.5	43.7	661	1002	59	63	64
"	10	140	54	47.9	76.6	27.5	43.5	700	1005	63	63	70
"	20	151	33	57.8	85.8	30.8	48.3	764	1094	67	64	70
"	40	166	31	64.5	86.3	33.2	45.1	806	1104	75	74	73
110	5	167	78	50.5	89.4	31.8	51.6	720	1117	57	62	65
"	10	173	51	53.5	89.1	32.5	51.1	764	1144	60	64	67
"	20	175	47	58.0	87.6	32.2	48.9	800	1168	66	66	69
"	40	182	34	62.5	92.9	33.3	48.3	828	1184	67	69	70
220	5	198	36	46.9	82.3	28.1	46.0	774	1206	57	61	64
"	10	203	21	52.2	78.5	30.3	49.8	834	1304	67	61	64
"	20	204	33	57.9	85.3	30.0	49.5	841	1280	68	61	66
"	40	201	40	60.3	84.0	32.0	45.6	900	1298	72	70	69

first age is well before puberty, the second at the beginning of the most rapid growth of the gonads and ♀ suprarenal, 110 days is the time at which the animals are first adult and at 220 days the growth of the ovary and testicle and ♀ suprarenal has practically stopped. Right and left organs were taken from alternate animals and the effect of asymmetry was thus cancelled so that on the average 50 per cent of the total organ tissue was removed. In an equal number of control rats the same operation was

carried through but no organs were removed. This was done on the same day as the operations on the experimental groups so that seasonal variation might be excluded as a factor. In the groups in which the organs were removed at 30 and at 70 days of age the rate of restoration was measured 2, 5, 10, 20, and 40 days after the operation, and in the 110 and 220 day old groups at 5, 10, 20, and 40 days.

TABLE II*b*

Males

Age at operation	Time after operation when killed	Body weight when killed	Number of rats in each group	Testes		Suprarenals		Kidneys		Remaining organ as per cent of both control organs		
				Experimental remaining organ	Control both organs	Experimental remaining organ	Control both organs	Experimental remaining organ	Control both organs	Testes	Suprarenals	Kidneys
days	*days*	*gm.*		*mg.*	*mg.*	*mg.*	*mg.*	*mg.*	*mg.*	*per cent*	*per cent*	*per cent*
30	2	49	38	204	357	8.1	13.6	316	498	57	60	64
"	5	59	72	245	383	9.9	15.8	392	555	64	63	71
"	10	80	56	384	576	11.8	18.9	507	690	67	62	74
"	20	111	66	697	1102	13.4	20.3	691	896	63	66	77
"	40	165	68	1109	1800	16.4	24.7	932	1174	62	66	79
70	2	160	27	1079	2024	17.0	27.2	803	1253	53	63	64
"	5	168	67	1162	2200	16.7	25.8	798	1208	53	65	66
"	10	173	66	1208	2270	17.6	26.7	844	1235	53	66	68
"	20	191	34	1202	2179	18.0	27.2	936	1303	55	66	72
"	40	205	31	1288	2393	16.0	24.2	911	1344	54	66	68
110	5	217	39	1125	2227	17.8	28.9	830	1411	50	62	59
"	10	219	25	1195	2205	19.0	28.9	946	1430	54	66	66
"	20	235	66	1295	2279	18.8	25.9	1018	1522	57	73	67
"	40	257	35	1295	2360	18.5	26.2	1099	1586	55	71	69
220	5	292	61	1362	2592	20.6	34.2	1132	1766	53	60	64
"	10	304	24	1379	2552	22.9	35.9	1179	1816	54	64	65
"	20	304	39	1456	2668	23.1	35.7	1204	1776	55	65	68
"	40	302	48	1445	2558	22.5	34.1	1251	1836	57	66	68

Since 50 per cent of each organ had been excised, if the weight of the remaining organ at any time after the operation was found to be 50 per cent of the weight of both control organs we judged there had been no restitution, if it weighed 100 per cent of the weight of the controls restoration was complete, while any intermediate value between 50 and 100 per cent indicated the degree of approach towards complete restoration. These comparisons were made on the basis of the average organ weights of groups of control

and experimental rats, each containing an equal number of animals, the number varying from 21 to 72. In order to avoid the error inherent in any device for the correction of differences in body weight, each experimental and corresponding control group was brought to an identity of average body weight by rejecting the heaviest individuals from the heavier group and the lightest from the lighter until there was no longer any difference. The body weights given in Table II thus refer to both the experimental and control groups. The organ weights are given in absolute terms except in the last three columns where the weight of the single organs of the experimental animals is expressed as a percentage of the weight of both organs of the controls.

The results given in Table II show that in these organs the rate and degree of restoration is not at all influenced by the factors that determine their rate of natural growth. Thus during the time when the growth of the gonads and ♀ suprarenal is suddenly accelerated there is no greater or more rapid restoration than when the same measurements are made at a time when their growth has stopped. Indeed in the case of the testes the greatest degree of restoration occurs before puberty, *i.e.* during a period when organ growth is slow. The question we raised is thus answered quite decisively in the negative.

If the question is put as to whether the age of the animal has any effect it is only in the case of the kidney that we observe a gradual decrease in the degree of restoration as age advances. In the age period covered in these experiments this effect is only slight, but we can confirm and extend the observation already recorded (8) that in very young rats unilateral nephrectomy is followed by a considerably greater enlargement of the remaining kidney than occurs in the youngest of our present groups, for when we removed one kidney from 17 newborn rats we found 40 days later that the single kidney weighed 86 per cent of the weight of both kidneys of litter mate controls of equal body weight.

From all the observations made at different ages we can derive a general growth curve for each of these organs. This is possible because as far as the rate of restoration is concerned there is no significant difference between the age groups, so that we can combine all observations made at 5, 10, 20, and 40 days. In the case of the kidney sex makes no difference for we find that the curves for all age groups in ♂ and ♀ rats are almost exactly superimposable. These combined curves are given in Fig. 1.

The differences between the curves for these four organs with respect to the rate of restoration seem to us, for the present at least, to be much less important than their similarities. The principal difference is that while

the kidney, the ♂ suprarenal, and the testicle seem to have approached their maximum degree of restoration in 40 days, the curves for the ♀ suprarenal and ovary are still rising on the 40th day after operation. But when measurements are made 80 and 120 days after operation there is no significant increase in the weight of the remaining organ, so in all cases the curves

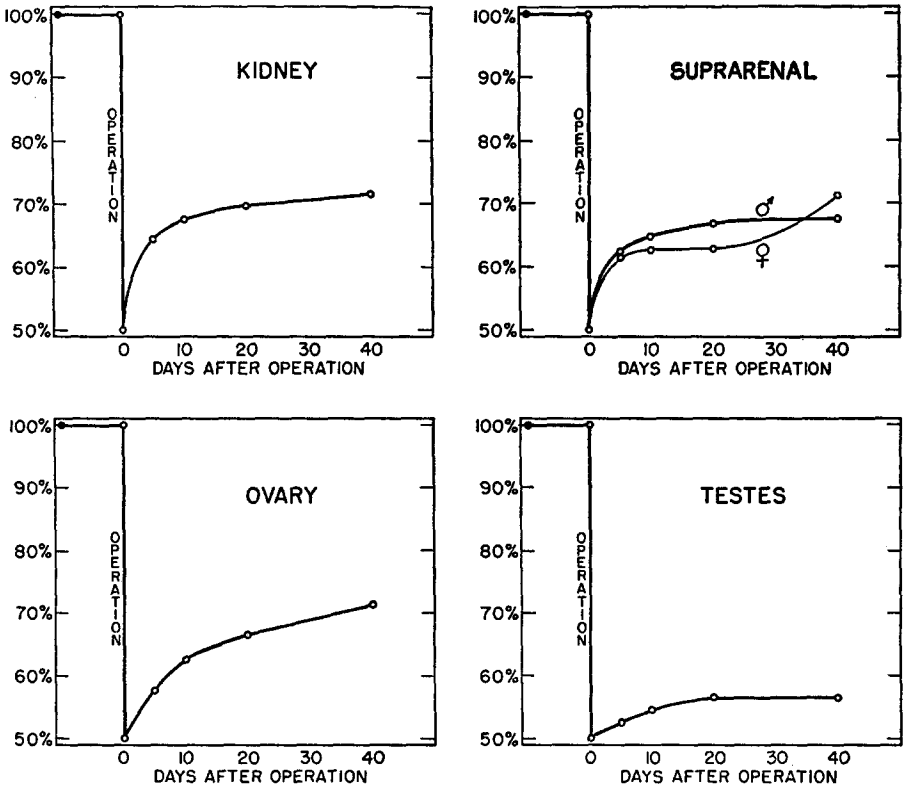

FIG. 1. Restoration as per cent of total organ weight.

must flatten out about the 40th day. Now all that is known favors the view that the increase in the ovary, testicle, and suprarenal is determined by pituitary hormones, while there is no reason at all to suppose that the enlargement of the kidney is so determined. Therefore it would seem that in this case entirely different mechanisms have produced very similar results. In each organ the rate of growth is at first very rapid. The observations made at 2 days after operation in some of the groups indicate that the maximum rate is attained at the very beginning so that there is no indication of the sigmoid form so characteristic of ordinary growth. There-

after there is a steadily decreasing rate until at about 20 days after operation the curves begin to flatten and at 40 days tend to become asymptotic to the abscissa. In biological terms such a result might be produced by a growth stimulus maximal at the start but becoming progressively weaker until it finally disappeared altogether.

As to the mechanism of restoration it is in the ovary that we have the clearest evidence. Arai (9) found that the remaining ovary increased in weight after unilateral ovariectomy because it had double the number of ripened follicles. Follicular ripening is induced by an anterior pituitary hormone. When one ovary is removed the other receives all of this hormone and so developes twice as many follicles. But we find that when one uterine horn is excised there is no increase in the weight of the remaining cornua. And Hertz and Meyer (10) observed that when testosterone propionate is administered a single uterine horn grows no larger than when both are present. Dr. C. F. Fluhmann had reached the same conclusion as a result of unpublished experiments. Now the size of the uterus is determined by a hormone made in the ovary and Dr. Fluhmann suggests that it is produced in such excess that the absence of half the uterine tissue may lead to no significant difference in the quantity obtained by the remaining half, its size being determined by the hormone concentration in the blood, a concentration that remains at about the same level whether one or two uterine horns are present. An extension of this hypothesis may be used to explain our results with the uterus, prostate, seminal vesicle, suprarenal cortex,[1] and testis. Of these organs only those have the capacity for restoration that are controlled by anterior pituitary hormones (suprarenal cortex and testis) while those that depend on estrogens and androgens from the gonads (uterus, prostate, and seminal vesicle) remain unchanged when their total mass is reduced.

Why does the restoration of the kidney, the suprarenal, and the ovary stop when only about 70 per cent of the original weight has been replaced? Why does the increase in testis weight stop at 56 per cent? In the ovary it stops because at that weight the usual number of follicles are again ripening and we may suppose that at the weight reached by the suprarenal and the testis there is again a restoration of the essential function of the organ. In the case of the kidney the failure to attain 100 per cent of the original weight is certainly not due to any structural limitation to further enlargement because, if the amount of protein eaten by the rat is increased, the

[1] MacKay and MacKay (2) found that after unilateral suprarenalectomy the increase in weight of the remaining suprarenal was due wholly to an increase in the mass of the cortical tissue.

single kidney can become larger than the original two kidneys. So it does not seem that this increase to only 70 per cent of the original amount should be regarded as a biological failure. It seems a more fruitful hypothesis to consider that a 70 per cent renal restoration is sufficient and to suppose that what we are observing is an equilibrium that was lost when half the kidney tissue was removed but one that in the end is wholly restored.

CONCLUSIONS

1. When half of the total kidney, suprarenal, ovarian, or testicular mass is removed the rate of growth of the remaining half is independent of the rate of growth of the organ at the time of removal.

2. The removal of half of the prostate, or seminal vesicular tissue, or of one uterine horn is not followed by any appreciable growth of the part that remains.

3. The rate of restoration of renal, ovarian, testicular, and suprarenal tissue after removal of half of these organs is at first very rapid, but quickly decelerates and at about 40 days after the removal there is a complete cessation of growth.

4. In none of these organs is all the lost tissue restored. In the testicle the 50 per cent left increases to 56 per cent and in the kidney, suprarenal, and ovary to 70 per cent of the original amount before operation.

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