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THE RESTORATION OF THE LIVER

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A thesis in partial fulfillment of the requirements for the course in Physiology. College of Physicians and Surgeons, Columbia University. 13 May 1945.

'The main factor that determines the weight of the heart, kidneys, and liver protein is the amount of work these organs are required to perform...' (Walter & Addis '39). This doctrine, while a convenient mnemonic for the experimentally discovered fact of the regulation of the size of these and other organs, unfortunately provides no insight into the mechanisms by which this weight regulation is accomplished. The study of the phenomenon of compensatory hypertrophy of the thyroid and adrenal glands has resulted in the discovery in the last 15 years of the elaborate mechanism by which the size and function of these organs are under the endocrine control of the pituitary body. It is hoped that a similar study of the regulation and restoration of the liver might lead to some elucidation of the means by which this important organ is maintained in its typical proportion to the body as a whole, and to the more fundamental problem of the control of growth processes in general.

The operation of this control is perhaps nowhere more dramatically illustrated than in the phenomenon of the restoration of the liver after partial surgical ablation. This process is the more immediate subject of this review.

This history of liver restoration, and the polemics on certain histological aspects of it have been reviewed elsewhere in some detail; space does not permit a review of this interesting historical study. (Podwyszozy '86, Fishback '29.)

The anatomical arrangement of the lobes of the rat liver permits of the ready removal of $70 \pm 3\%$; the median and left lateral lobes constituting this proportion of the total liver mass.

Within 10 days after partial hepatectomy, the rest (i.e., the intact liver mass) grows to reach the original weight of the entire liver! (Higgins & Anderson '31a.) In the rabbit, 20% of the liver can restore the whole (ponfick '90). Fig.1,2 from Higgins and Anderson's and Brues' (Brues et al 36a) data respectively demonstrate the rate of weight restoration of the liver. The most generally used basis of measurement is the ratio of liver-weight to body weight. This standard assumes that the 'normal growth' of the organ is an automatic process that is independent of the phenomenon under study, a conception that is perhaps erroneous. The variation of the body weight over the duration of most experiments or as a result of operation is too slight, however, to vary the picture of what happens.

These observations indicate that there is a rapid increase in weight after operation which is negatively accelerated, the wt. increase tapering off rather markedly after 5-7 days. In Higgins' series, the wet-weight overshoots the normal level, while the dry-weight remains on a plateau at the normal weight. Brues, however, report a slightly lower plateau. These differences are probably not statistically significant. While Higgins claims that there is a cyclic variation in the rate of restoration, the data again are not sufficiently refined to allow of such interpretations of deviations of individual points on the weight-time curves, although the results as a whole are unassailable.

The bugaboo of all growth measurements is the problem of what index to use. While perhaps most convenient, weight changes do not adequately demonstrate our intuitive concept of growth.

The weight of the liver is extraordinarily labile under different

dietary conditions, and has furthermore a highly variable fat content. (Addis et al '36, Luck '36) Furthermore, calculations from data on liver weights and fat content under different dietary conditions including choline deficiency (Handler & Bernheim '43) indicate that the deposition of one gm. of fatty acid is associated with an increase in liver weight of three grams. Yet, the deposition of fat is not ordinarily regarded as 'growth'. The role of the liver as the 'commisariat' of the body' makes particularly difficult an estimation of what constitutes its growth. A criterion that has been used is cell-increase, a process that is, as we shall see, not always correlated with weight-increase.

Brues, et al ('36) have made direct studies on cell number in restoring rat livers. Their results are summarized in Fig. 3. Except that there is no appreciable increase in cell number during the first day after operation, the cell increase parallels the weight restoration of the liver. In starved animals, however, the weight plateaus at about the second day, whereas the cell-increase is not appreciably different from the fed controls. (fig. 3) This suggests the greater suitability of this criterion. In this paper analyses are reported which indicate that the material taken in during the first day of restoration is low in nitrogen. This material has been shown to be lipid (Handler and Bernheim '43) Female rats, in particular are prone to develop fatty livers after partial hepatectomy. The basis of this condition has not been established. Brues reports that a fatty diet retards cell-restoration well below that of fasted controls, a fact of some clinical significance. (Ravdin et al '43.) The importance of diet in restoration will be discussed in more detail below.

To explain the phenomenon of restoration, Higgins, Mann and their coworkers at the Mayo Foundation have suggested that the portal blood plays an important role. On the assumption that the influx through the mesenteric arteries is relatively constant, 'the volume of blood which is delivered to any hepatic remnant after partial hepatectomy determines largely the extent of its restoration.' (Higgins, et al., '32.) They propose that the diminution in the size of the liver increases the flow to the remnant, which is responsible for the hyperplasia. More recently, Mann ('40) has suggested that the presence of some substance in the portal blood only, or vascular pressure in the sinusoids may be factors. In support of this hypothesis, the Mayo group have reported a number of interesting experiments.

Stephenson ('33) placed a loose ligature around the portal vein in the rat, partially obstructing it, and determined the weight restoration after partial hepatectomy. Only two-thirds of the amount reported above by Higgins and Anderson was found. Where large collateral vessels were apparent, the extent of restoration was normal. From this one may conclude that a normal portal circulation is necessary for restoration. In dogs, partial hepatectomy two months after the establishment of an Eck fistula resulted in no signs of weight restoration. The effect of the Eck fistula in the dog is a 50% atrophy of the liver with central fatty accumulation. (Mann et al '31a)

The venous anatomy of the domestic fowl is unique in the existence of a large anastomosis between the portal and caval drainages via the ^{colic}colocygeo-mesenteric vein. Studies on this animal indicate a slight, if any, degree of weight restoration after the

partial hepatectomy. (Higgins et al '33.) This is ascribed to the drainage away from the portal vein through this anastomosis of excess blood after partial hepatectomy. If the vena cava is ligated above the renal veins, the extent of weight restoration is increased considerably (60%) over controls. In fact, the ligation alone, which would deliver an increased volume of blood to the liver is reported to induce a size increase in four cases. These studies were, unfortunately, based on weight determinations alone, subject to the criticisms above. Furthermore, transference of concepts from the fowl to the mammal is not immediately justified. In conflict with these results, (Crechowitsch '36). complete restoration in the fowl and dove after partial hepatectomy has been reported but the published data here are particularly inadequate.

Finally, Mann has succeeded in establishing an open portal-caval lateral anastomosis in the dog. (Mann '40). In five cases, wt. restoration was reported to be less than in the control animals. The basis of comparison is, as usual, liver weight, body weight, and the assertion is made that for 200 animals, this ratio was .0345. The variance of this mean value is not given, however, so that statistical evaluation of his results is impossible.

It would be most desirable to have a demonstration in the rat of the effect of an increased hepatic portal blood flow on mitotic rates or cell-increase in the liver. Apparently for obvious technical reasons, a reverse Eck fistula has not been reported for this (small) animal.

While the Mayo group has undoubtedly demonstrated a close relationship between the weight of the liver and an intact portal supply, the latter being a necessary condition for weight restoration

measurements on blood flow in partially hepatectomized animals have not been reported, and the proportional increase to the hepatic remnant is entirely suppositious. Ponfick (190) observed the temporary mesenteric congestion that follows partial hepatectomy, but rejects this as a cause of restoration on the basis of its transience. On the other hand, the liver is no passive container of blood, but Wakim and Mann ('42) have themselves demonstrated, by the translumination technique of Knisely, that circulatory activity in the liver is intermittent, and apparently under some degree of active control. Thermo-Stromuhr measurements indicate a reciprocal relation between flow in the portal vein and hepatic artery, and that the liver may alternately store and discharge blood. (Grindley, Herrick & Mann '41.) An elaborate 'sluice-valve mechanism has been shown to regulate portal flow in the liver (Deysach '41.), and the hepatic flow can be influenced by sympatho- and parasympathomimetic drugs (Wakim '44) as well as by sympathetic stimulation (Griffith and Emery '30) In view of these researches, the statue of the liver circulation in partial-hepatectomized animals, and its relation to restoration must still be regarded as unsettled. Further studies also show the unreliability of weight data.

As a basis for a hypothesis of liver restoration, its modification and simulation by experimental techniques must be considered. Such influences as diet and hormonal regulation have been studied.

In inanition, the liver loses more weight proportionally than any other organ, or than the body as a whole. While it has been suggested that this represents a utilization of the liver materials for the rest of the organism, experiments have been reported which may indicate that the situation is not so simple. (Jackson '15,

Addis, et al '36)

In the rat, the weight of the liver can be reduced to 40 % of its normal size by fasting (10 days). If a partially hepatectomized animal is fasted, the remnant, in this 30 %, increases to the 40 % of the intact, starved animals. These authors conclude that the reduction in mass of the liver in starvation is due primarily to a reduced liver requirement in the starved animal. The particular function of the liver that is to be maintained is not indicated, nor the mechanism by which a changed 'functional demand' can modify liver size. (Rous & McMaster '24.) Brues et al (loc.cit.) have shown that the cellular increase is not diminished in these starved animals, so that the functional demand that controls liver size and that controls cell-increase are not identical. This multiplication of hypothesis perhaps calls for Occam's Razor. Rous' results can perhaps be interpreted by postulating that partial hepatectomy induces some stimulus to hepatic growth, irrespective of nutritional condition. In order to demonstrate that the relation of liver size to portal flow is not comparable to its dependence on food intake, cytological studies or cell counts must be reported from rat livers in which the portal blood has been diverted, and this has not been done.

The liver can be enlarged by various dietary conditions, such as casein refeeding (Luck '36). Since no particular fraction of the liver has been shown to be increased, it has been assumed that an actual 'protoplasmic' increase has occurred. While cell counts have not been made, it appears that there is a hypertrophy rather than a hyperplasia of the liver cells. Weight increases are most marked on feeding dried liver or kidney, which has been

interpreted as due to nucleic acid content, a conclusion of particular interest in view of Marshak's recent observations (see below.) (Walter and Addis '39)

The optimum diet for liver weight restoration is one 'high in caloric content, high in carbohydrate, adequate in protein, supplemented with vitamins and low, but not lacking in fat.' (Mann '43a).

Other local conditions can modify the rate of restoration. Of these, the effect of obstructing the hepatic duct is perhaps of the greatest clinical interest. Ligation of the duct in the rat (where there is no gall bladder) leads to an enlargement of the liver, which may subside if the patency of the duct is reestablished with solution of the ligature. Otherwise the animals do not survive longer than four weeks. If partial hepatectomy is performed immediately after the obstruction, there is an apparent hypertrophy, even more rapid than in normally restoring livers. Microscopic examination reveals, however, that this hypertrophy is due to a distension with RBC and retained bile. This is accompanied by fibrotic changes, a pathological picture accepted by some as 'biliary cirrhosis.' There is no evidence of cell-proliferation as in normal restoration. (Higgins & Anderson '33.) In the dog, survival after cholecystectomy and obstruction is much longer—probably indefinite if the animal is properly nursed. One to seven weeks later there are no marked histological changes, but restoration does not occur (on a weight basis) after partial resection. However, the presence of an increased number of mitotic figures in the parenchyma is reported. Concurrently there was apparent engorgement of the sinusoids. (Mann '31b.) In this animal there is evidently less damage to the liver parenchyma after obstruction than in the rat. The nature of this 'damage' is

not sufficiently well understood to allow this effect to be fitted in to any of the theories of liver restoration. That biliary obstruction does limit the 'growth potentialities' of the liver parenchymal cells is indicated by work on transplants. At best, autotransplanted liver cells do not survive very well. Although the graft may take for a time, the parenchymal cells typically disintegrate after 1-2 weeks, leaving a branching network of bile-duct cells which may persist considerably longer. (Cameron '36, Loeb '18, Otsuka '39.) If the transplants are taken from livers that have already been obstructed, survival of the graft is very much curtailed, an obstruction of more than three days being critical. If the liver is obstructed after the graft is taken from the liver, the resulting jaundice does not influence the hepatic transplant. (Cameron '35.) Bile duct cells proliferate in all circumstances.

Experimental cirrhosis induced in the rat by administration of CCl_4 per os also limits the extent of restoration, few restorative signs being seen if a fibrotic atrophy has already occurred. (Mann et al '31c.) That the mechanism of liver restoration has broken down in the cirrhotic animal is fairly clear, since in the early course of experimental cirrhosis, destruction by chemicals of masses of liver parenchyma is followed by their replacement by the mitotic proliferation of undamaged cells, a process that is analagous to restoration after surgical resection. When this replacement does not occur, cirrhosis is established. (Schultz et al '23, Mann '43). The newly restored liver is less sensitive to the administration of CHCl_3 and CCl_4 , and more sensitive to Phosphorus poisoning than is the normal rat liver. The pathology of the lesions is however the same. (Anderson '33, Lacquet '33, Love '33.)

Some attempts have been made to demonstrate an endocrine control of restoration, but they have so far been quite inconclusive. The effects of hypochysectomy have been investigated by the Mayo workers in relation to weight restoration, and by others with cell-counts, in the rat. (Higgins & Ingle '39, Franseen et al '38.) The weight restoration is markedly diminished by hypophysectomy performed 1 week prior to the liver operation. This may be largely a matter of appetite. Hypophysectomized animals regenerated '27% of the weight of the liver which regenerated in the adequately fed controls.' Animals which were paired-fed with the hypophysectomized rats regenerated '40% of that which regenerated in those animals which ate as much as they wished.' The significance of this difference is not clear, but it is apparent that anorexia is the major factor in diminishing weight restoration. Franseen restricted the diet of his controls so that their weight was comparable to the hypophysectomized animals, and found no significant difference in the weight restoration. Furthermore, mitotic rates and cell-counts were not variable between hypophysectomized, semi-starved and normal rats after hepatectomy. The results of these independent observations demonstrate that, unlike the control in other glands such as the thyroids and gonads, the hypophysis does not play an important role in mediating the compensatory hypertrophy of the liver. One week, however, is not long enough to allow involution of the pituitary-controlled glands in the rat, so that these experiments do not disallow endocrine control by other organs.

In contrast to the lack of effect of removal of the pituitary, the administration of pituitary extracts has been shown to cause a marked increase in the size of the liver. There is some evidence that this is mediated through the thyroid. The administration

of a growth-hormone preparation, 7 units daily for 1-16 days led to an increase in liver weight, absolutely and proportionately of about 20%. This was accompanied by increase in cell-count of about 18%, which was statistically significant. Feeding influenced the size of the liver cells, and of the total liver weight, but did not affect liver cell number. The magnitude of this increase was not such as could be reflected in mitotic rates, and colchicine was not used. This observation is important because it demonstrates that a 'true growth' has taken place, and that the increase in liver weight is hyperplastic, comparable to the regenerating liver. Since cell-increase will occur in hypophysectomized restoring livers, this effect of APL either plays no role in normal restoration, or plays on some other step in the chain of events that controls restoration. (Lee & Freeman '40.)

Fraenkel-Gonrat (et. al. '42) have examined the effects of a series of relatively purified pituitary preparations on the liver weight of hypophysectomized rats. The fractions used had: lactogenic, ACT, Somatotrophic, Thyrotrophic, ICSH and FSH activities. Of these fractions, only the growth and thyrotrophic hormone active ones caused significant increases in liver weight. The growth hormone fraction, furthermore, had an hepatotrophic activity comparable to its thyrotrophic action, so that these authors postulate that the thyrotrophic action, is that which is responsible for the increase in liver weight. The N contents of the hypertrophied livers did not vary significantly from the controls, 'so that they must be regarded as actual changes in the amount of liver substance.'

Observations reported incidentally to the renotropic effects of pituitary extracts (Selye & Nielson '44) indicate that the prolonged

administration of crude alk. extracts of APl over a period of two months can induce an absolute increase of liver size over controls of almost 100%, and relative to body weight of 40 %. The cytological basis of this increase was not studied. While there are very numerous reports of changes in visceral size under pituitary variation, they will not be reported here because of the ambiguity of their interpretation in the absence of cytological information.

In view of the specificity of TTH in stimulating liver increase, the role of the thyroid gland in restoration seems promising. Attempts to ascertain the effects of hyperthyroidism on restoration are complicated by the fact that animals which have received previous treatment with thyroid 'could not withstand the loss of 70% of the liver.' (Higgins'33). It was necessary to perform partial hepatectomy before commencement of thyroid administration. The administration of this thyroid ration to control animals caused an increase in proportional and absolute body weight, and the restoring livers under the influence of thyroid restored this increased weight (approx. 25% greater.) Appreciable deviation from the normal restoration curves did not occur until the end of the first week of restoration, the rate being most accelerated during the second week. In these animals which were not operated on, the administration of thyroid had no effect on liver weight until the second week of treatment. This lag, compared to the very brief one in normal restoration may indicate that if the thyroid plays a role in normal restoration, it may be indirect. On the other hand, Sternheimer, (Sternheimer '39) has reported a great qualitative increase in mitoses in the liver only 48 hours after the administration of a large dose of thyroxine. This is another instance of a conflict

of cytological and gravimetric interpretations. His data also indicate a more rapid weight response of the liver to thyroxine (in this large dosage: 4 mg/kg.) It has also been reported that there is a diminution of the thyroid glands after partial hepatectomy. (Schmidt & Richter '41, Kellaway, et al, Endocrinology '45, A Relation between Thyroid & Liver.)

This 'crucial experiment' that must be performed clearly is the restorative capacity of the liver after the thyroid has been removed, preferably with the feeding of standard doses of this hormone. This has not been done.

The effects of the administration of male hormones to rats and dogs' livers have been tested. (Hall & Korenchevsky '36, Blackman et al '44.) While relative hypertrophy seems to occur, again no cytological observations have been made, and the possibility of involved indirect effects makes unfeasible an extended analysis. In view of the well-established function of the liver in the inactivation of the estrogenic hormones, the effects of these hormones must be considered, but no conclusive reports have as yet appeared.

A hormonal regulation of liver could be demonstrated in parabiotic pairs of animals, an attempt to do which is in progress in these laboratories. In toad larvae which have been parabiosed at an early developmental stage, the extirpation of the liver in one pair is claimed on the basis of one experiment to cause an enlargement of the liver in the other. (Yamada '33.) The applicability of this observation as a proof of a hormonal mechanism in mammals in the adult phase would be unnecessarily speculative.

Thus far the only agents which will stimulate mitosis in the liver are a) the operation of partial hepatectomy, and b) the

administration of thyroid. One other agent of this sort has been described: the administration of suspensions of homologous liver caused an apparent increase in mitotic rate of the intact liver nearly comparable to that after partial hepatectomy. If given to a partially hepatectomized animal, mitotic rates of 15% those usually found in the restoring liver are seen. Unfortunately, the method of expression of mitoses as average number per section is unreliable to variation in cell size, and in proportion of CT cells, etc., in the areas counted, and the figures published show such variability that a statistical analysis seems desirable. (McJunkin & Breuhaus '31.) The implications that these observations hold for normal restoration is not clear, since it is difficult to conceive how the quantities used of such material could occur normally or after partial hepatectomy. Isolation of the active component would be very interesting. Apparently independently, Narshak ('45b.) has studied the effects of 'chromatin' preparations from liver on the mitotic rates of restoring liver, 24-27 hours after resection. Unfortunately the method of counting is subject to a large error, as demonstrated within the paper itself, and the normal mitotic rate is also quite variable in these restoring livers, so that the statistical justification of his conclusions is at best questionable. It is claimed, however, that the fresh chromatin preparation is the most active component, a large series of other compounds having no effect. Again the bearing that this might have on normal restoration is not clear, although the administration of exogenous chromatin may be increasing the growth rate of the restoring liver by lessening the possible limiting factor of nucleic acid rate of synthesis. Thus while chromatin may be a valuable accessory factor, it has not been shown to be the trigger which sets off mitosis, and unfortunately

data on the effect of these fractions on mitotic rates of intact livers are not presented.

There are several papers on changes in the blood chemistry, and on the chemistry, enzyme content and turnover rates of various components in restoring liver, which cannot be reviewed in detail. The chief alterations appear to be an increased blood globulin, decreased albumin, and a very high turnover in P- and in nucleic acid. A bibliography to this phase of the subject is appended to the list of references cited.

The mechanism of liver restoration is, thus, seen to be in a highly controversial state, and the need for further research evident, particularly in the possible role of humoral intermediates, be they specific hormones, or metabolites ordinarily disposed of by the liver, and accumulating in its reduction. The theoretical and clinical importance of such an advance is obvious.

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