SOME ENDOCRINE CHANGES IN LIVER DISEASE

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AMONGST the numerous metabolic functions of the liver are those concerned with the catabolism or inactivation of hormones. One would therefore expect to find liver disease frequently accompanied by endocrine disturbances; and attempts to correlate certain liver disease with disturbances in endocrine function are not new. In addition, there are certain features of liver disease such as the 'characteristic' skin changes which are attributed to altered hormone metabolism.

The close relationship between liver disease and the gonads appears to be obvious. In the male there is gynæcomastia and an alteration in the secondary hair distribution with loss of axillary and chest hair and a female distribution of pubic hair. Loss of libido, impotence and testicular atrophy complete the characteristic picture of hormonal disturbances in the human male with chronic liver disease. Oligospermia is common (Voegt and Weller, 1959). Prostatic hypertrophy in men with chronic liver disease is rare (Stumpf and Wilens, 1953). The incidence of these endocrine disturbances varies remarkably as between different countries. Gynæcomastia and testicular atrophy, a combination also known as the Silvestrini-Corda syndrome after the authors who first described it (Corda, 1925; Silvestrini, 1926), was found by Lloyd and Williams (1948) to occur in 42% of 55 men with cirrhosis of the liver. The same workers reported 75% incidence of testicular atrophy in their patients. However, the incidence of gynæcomastia in our own cases and in others, as for instance in England, is distinctly low. The same applies to other signs of chronic liver disease such as parotid swelling and Dupuytren's contracture (Davidson, Sherlock, Summerskill, Turner and Wolfe, 1960). It is quite possible that alcoholism alone, or rather the accompanying malnutrition, like that in prisoners of war during the period of nutritional re-feeding (Klatskin, Salter and Humm, 1947; Kark, Morey and Paynter, 1951), plays a decisive part in the development of these signs. 'Alcoholic' cirrhosis predominates in the American cases, but is not nearly so common in England or in Germany.

Moreover it is difficult to determine whether

the altered distribution of secondary hair is constitutionally conditioned or whether it is the result of liver disease. Since Chvostek described the 'habitus' known by his name it has not been possible to determine whether or not men with this type of constitution are more susceptible to the development of cirrhosis. It is therefore very important to question patients about their hair distribution in the 'pre-cirrhotic' phase. Many patients can provide evidence and often photographs to prove that they never had a heavy growth of pectoral, axillary or pubic hair before developing cirrhosis.

Women with chronic liver disease usually have amenorrhœa or dysmenorrhœa and may have cystic mastitis or acne. Sterility is the rule and conception is very rare. In certain age groups, about puberty (Bearn, Kunkel and Slater, 1956; Waldenström, 1952) and after the menopause (Alsted, 1947; Cattani, Vesin and Bodin, 1957; Martini and Dölle, 1960), women are prone to develop a peculiar form of hepatitis of unknown aetiology with a chronic course and with 'post-necrotic' cirrhosis. Altogether the sex ratio of postnecrotic cirrhosis in women to men is 3 : 1, in contrast with Laennec's cirrhosis, which is preponderant in men. Women who develop virus hepatitis during the menopause are especially susceptible to the development of postnecrotic cirrhosis.

Both men and women with chronic liver disease develop certain vascular changes in the skin, such as arterial spiders, 'white spots' (Martini and Staubesand, 1953; Martini, 1955) and palmar erythema. These skin changes occur with almost equal frequency in pregnant women and disappear again soon after parturition. These observations led Bean, (1945) to regard the vascular changes as a manifestation of 'hyperœstrogenism'. An increase in œstrogens is a normal feature of pregnancy. In chronic liver disease the liver is said to be incapable of inactivating œstrogens; hence the œstrogen level in the blood rises. This interpretation is disarmingly simple. It was indeed possible to induce the development of arterial spiders and palmar erythema in one third of 30

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patients with cirrhosis by the administration of oestrogenic substances, but two thirds of the patients showed no such response (Bean, 1958). Nor have such phenomena been observed in patients with carcinoma of the prostate who have received very large doses of oestrogens. In any case a purely hormonal factor would not explain the localisation of the spider naevi and their distribution. They are practically confined to the so-called exposed parts of the skin (face, neck and arms). This localization suggests that beside the hormonal or 'internal' factor in the production of arterial spiders, an 'external' factor may be operating: the structure and function of the affected portion of the skin and of its smallest vessels and their altered reaction to the action of sunshine, wind and light (Martini, 1955).

The most important question, however, is whether there is actually an oestrogenic excess in patients with chronic liver disease and if so, whether there is any correlation between the oestrogen levels and the clinical signs such as gynæcomastia, altered hair distribution and skin changes.

The Metabolism of Oestrogens

Our knowledge about the nature and quantity of circulating oestrogens in the plasma of patients with liver disease is scanty, and therefore the evidence in favour of the before mentioned 'hyperoestrogenism' in liver disease remains circumstantial (Diczfalusy, 1962). In pregnancy the ratio unconjugated (free) to conjugated 17- β -oestradiol was higher than similar ratios for oestrone and oestriol. If this could be confirmed in patients with liver disease it could well be that this shift towards free oestradiol accounts for the 'hyperoestrogenism' (Diczfalusy, 1962).

Since Zondek's work (1934) it has been known that the healthy liver plays an important part in the inactivation of oestrogenic hormones. In this process conjugation of the hormones with glucuronic acid or sulphuric acid is particularly important. However, it is still not decided whether conjugation and inactivation are one and the same thing or not (Cameron, 1957 a & b). It has been found that under certain conditions the glucuronic acid ester of the hormones is apparently as active as the free hormones. Some conjugates, when administered, are easily hydrolyzed in the body. In contrast to other steroid hormones which are inactivated by enzymatic reduction before conjugation, oestrogens are conjugated in the active form.

It seems doubtful whether the estimation of free and conjugated oestrogens can in any way yield more information about disturbed liver function. Even if this particular liver function of conjugating

oestrogens were disturbed there would still be the intestine to compensate for it. According to Sandberg and Slaunwhite (1957), there exists an entero-hepatic circulation of oestrogens not only in animals but also in man. When radioactive oestrogens were given, 50% of the radioactivity was recovered in the bile, but only 7% excreted in the faeces. Up to 80% was excreted in the urine. It is not yet decided whether oestrogens are absorbed as free oestrogens after hydrolyzation in the intestine or in conjugated form. It was shown recently that in man the intestine is able to conjugate free oestrogens which were brought into the intestinal lumen at operation (Diczfalusy, Frankson and Martinsen, 1961). A retardation in this bilio-entero-hepatic cycle was postulated by Rupp, Cantarow, Rakoff and Paschkis (1951) and Dohan, Richardson, Bluemle and György (1952), to account for the disturbed oestrogen metabolism in patients with cirrhosis.

A further difficulty arises from the indecision about which of the various known oestrogenic hormones is to be regarded as the primary hormone. Oestradiol, oestrone and oestriol have all been nominated. But these three represent only 20% of all oestrogens. Brown and Marrian (1957) suggested the following metabolic pathways for these oestrogens:

In addition, until the last few years the only method available for estimating oestrogens was the biological method of the Allen-Doisy test; this was the method used in most of the reported studies of oestrogen excretion in liver disease. Since then new biochemical methods have been developed, and it is expected that they will provide more accurate quantitative information. Comparison of the two methods is rendered even more difficult by the fact that they estimate different oestrogenic fractions. The Allen-Doisy test estimates oestradiol rather than oestrone or oestriol, whereas Brown's biochemical method estimates all three hormones, (1955). Although much work has been done in the past there is no clear answer yet to the question whether the excretion pattern of oestrogens differs quantitatively and qualitatively in patients with liver disease from that in normals.

The results obtained with the biochemical method are in direct contrast with those obtained by means of the biological assay (Bennett, Baggenstoss and Butt 1950; Dohan and others,

1952; Glass, Edmonson and Soll, 1944; Rupp and others, 1951), which had shown an increase in total oestrogen excretion in nearly half of the patients with cirrhosis, the hormones appearing in the urine mainly as free oestrogens. This was also shown by Müller (1958) using a fluorimetric method. Cameron (1957) was not able to confirm these results using Brown's method. He found, as others had done before him, (Pincus, Rakoff, Cohn and Tumen, 1951) that there was no increase in free oestrogen excretion in his group of 12 patients with cirrhosis, except in 2. His most remarkable finding in half of his patients was an increase in the proportion of oestriol excreted with a corresponding reduction in the amounts of oestrone and oestradiol. This was the result in measuring the excretion of endogenous oestrogens. When larger amounts of oestradiol were administered in patients with severe liver disease a 'shift' towards increased oestradiol excretion took place (Lyngbye and Mogensen, 1961).

The discrepancy between the results of the biological and the biochemical assays can be explained by postulating that certain of the newly identified oestrogenic hormones, such as epicestrol or 16α -hydroxyoestrone, are responsible for the endocrine stigmata in patients with cirrhosis: the oestrogenic activity of these substances would be apparent in the biological assay, but not in the biochemical method employed.

In fact, 16α -hydroxyoestrone seems to be just as active as oestriol (Loraine, 1958), and has been demonstrated in considerable amounts in the urine of pregnant women (Brown and Marrian, 1957). An inhibition of the conversion of oestradiol into oestriol was demonstrated by Lyngbye and Mogensen (1961). If such an inhibition occurred in the conversion of 16α -hydroxyoestrone into oestriol the former substance could accumulate without being estimated in the urine by the biochemical method.

It is important, however, not to seek facile explanations until reliable quantitative results about oestrogen excretion have been obtained. It may then perhaps be possible to establish that a definite correlation exists between the particular endocrine features in liver disease and both the quantity and the quality of oestrogens excreted. The morphological changes in the endocrine organs of patients with cirrhosis nevertheless suggest a strong oestrogenic effect (Bennett and others, 1950; Barr and Sommers, 1957): approximately half of 30 female patients had adenofibrosis of the breast or cystic mastitis and endometrial hyperplasia. Two thirds of 70 male patients examined showed the 'characteristic' changes in the prostate and testis. Other remarkable findings in these male patients were a marked

increase in the basophil cells of the pituitary and adrenal atrophy.

Again it will be necessary to consider the variety in 'normal' levels, depending on race, nutrition, age etc. For instance normal Bantu males are reported to have a much higher oestrogen excretion than normal white males in South Africa. The oestradiol fraction was particularly increased in these Bantus. In Bantus with chronic liver disease the oestradiol fraction further increased.

In white men with liver disease it was the oestriol fraction which increased. One can speculate whether malnutrition causes an increase of 'normal' oestrogen levels and/or changes its pattern and moreover, if this increase in turn causes liver disease and cancer with breast changes which are so frequent in Bantus (Bloomberg and others, 1958; quoted in Diczfalusy and Lauritzen, 1961).

The Metabolism of Androgen

The original findings of Fraser, Forbes, Albright, Sulkowitch and Reifenstein (1941), that the excretion of 17-ketosteroids is diminished in the urine of patients with chronic liver disease have repeatedly been confirmed and are considered firmly established (Peterson, 1960). Birke and others found the urinary output of 17-ketosteroids in cirrhotics both male and female as low as in adrenal cortical insufficiency (Birke 1962). Even after testosterone administration the urinary output of 17-ketosteroids is much decreased in patients with liver disease. Whereas some authors (Williams, Cantarow, Paschkis and Havens, 1951; Birke, 1962) found no decreased ability to convert testosterone to 17-ketosteroids, some others thought it to be disturbed (West, Tyler, Brown and Samuels, 1951). Both the conjugation with glucuronic acid and sulphuric acid are disturbed (Birke, Diczfalusy and Plantin, 1959), but no free 17-ketosteroids were excreted (Bongiovanni and Eisenmenger, 1951). Apparently both the 17-ketosteroids originating in the adrenal cortex and in the testis are diminished (Cameron, 1957). However, this diminution is probably not alone due to faulty conversion of testosterone to 17-ketosteroid, but to reduced androgen production as well. The resultant imbalance between androgens and oestrogens could also account for the 'hyperoestrogenism' even in those males who have a normal oestrogen output in the urine. For there is an undoubted antagonism between oestrogens and the other steroid hormones (Szego and Roberts, 1953). The diminution in androgen production still requires explanation. An excess of oestrogens might depress androgen production by inhibiting the production and release of gonadotropin from the pituitary gland. The

urinary gonadotropin excretion has been found to be greatly reduced in some cases (Voegt and Weller, 1958). Or, there could be a primary reduction in androgen production owing to malnutrition with protein deficiency which frequently accompanies alcoholic cirrhosis. Reduced pituitary function in malnutrition was reported by Fletcher and Brown (1959). Another possibility is the direct damaging effect of alcohol on the endocrine system; for the 'endocrine stigmata' are undoubtedly more common in alcoholic cirrhosis than in posthepatic cirrhosis. But this is speculation.

Adrenal Hormones

The great deal of interest aroused in recent years by the adrenal hormones has also directed attention to the relationship between adrenal cortical hormones and the liver. There are certain clinical observations which suggest disturbances in adrenal hormone metabolism but the exact nature of these disturbances has not yet been defined. Bearn and coworkers (1956) have described signs of 'hypercorticism' especially in the peculiar form of chronic hepatitis which occurs in girls and young women. The signs include acne, moonface, striae, and more rarely hirsutism. These girls often have amenorrhœa and react to œstrogen administration by rise in the bilirubin level. Waldenström (1952) has reported similar findings. The incidence of each of the signs ascribed to adrenal cortical hyperfunction is so variable that there is a good deal of justified doubt about the existence of such a syndrome. (Willcox and Isselbacher, 1961). This group of patients does more commonly share other signs such as polyarthritis and hypergammaglobulinæmia, rarely the LE-cell; and it has therefore been suggested that an autoimmune pathological process may be involved (Mackay, 1961). Incidentally, these patients respond particularly well to cortisone treatment. Further details about the treatment of liver disease with corticosteroids will not be discussed here and the reader is referred to the paper by Goldgraber and Kirsner (1959).

Recent observations have shown the importance of the liver in the elimination of exogenously administered hydrocortisone. Only about 1% of the free form of this hormone appears in the urine. About 3% is excreted as unconjugated metabolites, 80 to 90% appears as conjugated, water-soluble metabolites (Schedl, 1962). In mice about 70% of labelled hydrocortisone was found in the liver within five minutes of administration. Plager, Tyler, Hecht and Samuels (1954) have reported similar findings in man. They detected much less radioactivity in the hepatic venous

blood than in the arterial blood after intravenous administration of radioactive hydrocortisone.

In patients with chronic liver disease the plasma levels of free corticosteroids and its rise after ACTH administration were the same as in normal subjects (Englert, Brown, Wallach and Simon, 1957; Birke and others, 1959). However, hydrocortisone administered to patients with liver disease disappeared much more slowly from the blood stream and appeared in the urine in much lower concentration than in normal subjects. Surprisingly, cortisone, corticosterone and tetrahydrocortisone were found to disappear from the blood stream with equal rapidity in patients with liver disease and in normal subjects (Englert and others, 1957; Peterson, 1960). These findings are best explained by the existence of a specific TPNH dependent enzyme, the Δ -4-hydrogenase, which reduces cortisol to dihydrocortisol. Dihydrocortisol is then further reduced to tetrahydrocortisol. These reduced forms are conjugated in the liver with glucuronic acid or sulphuric acid and then excreted in the urine. Apparently it is only the enzymatic reduction which is disturbed in liver disease and not the conjugation with glucuronic acid. When the 'right' combinations are presented as for instance tetrahydrocortisol conjugation proceeds normally (Brown, 1960). The amount of urinary unconjugated steroids in patients with liver disease seems to be slightly raised above normal and consists mainly of 6 β -hydrocortisol (Katz, Lipman, Frantz and Jailer, 1962).

Thus it appears that the rate of cortisol metabolism is decreased in liver disease. The body pool of cortisol is normal or slightly increased, whereas the turnover rate of the pool is about half normal (Peterson, 1960). This means that in patients with liver disease the physiologic action of cortisol is prolonged. This in turn will inhibit corticotropin secretion and thus consequently lead to the depression of cortisol synthesis and secretion. These patients—although seemingly being 'eucorticot'—actually have an adrenal cortical insufficiency as regards the quantity of cortisol synthesized (Schedl, 1962). Since the diseased liver has partly lost its capacity to inactivate cortisol the plasma level remains within the normal range. It has frequently been noted that the adrenal glands of patients with cirrhosis are small in size with narrow cortices and a decreased lipid content (Barr and Sommers, 1957). We must realise then that the liver together with the adrenal and the pituitary plays an important part in the corticosteroid homeostasis of the organism (Birke, 1962).

These observations are particularly interesting in comparison with rather different recent findings

in relation to the other equally important adrenal hormone, aldosterone (Koczorek and Wolff, 1959). Aldosterone plays a very special role in the pathogenesis of ascites. The patients with cirrhosis lose the ability to excrete sodium and water at some particular point of time. Sodium and water then undergo excessive reabsorption by the renal tubules. Sodium reabsorption is largely influenced by aldosterone which is excreted in the urine in greater than normal amounts in cirrhotic patients with ascites (Luetscher and Johnson, 1954; Wolff, Koczorek and Buchborn, 1958). However, as other patients with œdema but with normal liver function also excrete excessive quantities of aldosterone in the urine, it seems that aldosterone is probably not solely and primarily responsible for the development of ascites.

Normally 60% of the endogenous production of aldosterone is excreted as a glucuronic acid conjugate of tetrahydroaldosterone which is biologically inactive; about 20% is excreted as the so-called 3-oxo-conjugate which can be converted to aldosterone by acidification of the urine at pH 1 (the so-called pH 1 extractable conjugate). Only 0.2% of the total is excreted as free aldosterone. About 20% of the excreted metabolites are not yet identified (Koczorek, 1962). Both of the major metabolites of aldosterone are formed in the liver. In patients with chronic liver disease the altered metabolism of aldosterone is characterized by an increased aldosterone secretion rate and a decreased rate of plasma clearance, the plasma half-life time of labelled steroid being 68 minutes against 35 minutes in normals it is further characterized by an increase in the proportion of aldosterone which is metabolized to the 3-oxo-conjugate and a decrease in the proportion which is converted to tetrahydroaldosterone (Coppage, Island, Cooner and Liddle, 1962). The data on aldosterone secretion, however, are somewhat conflicting. Not in all investigations was the secretion rate found to be increased, but sometimes to be decreased. This perhaps could be explained by the different degree of impaired liver function. Thus in patients with cirrhosis and ascites the aldosterone levels in urine are usually markedly increased whereas in patients without ascites normal or only slightly raised levels are found.

In the belief that the adrenals play a dominant role in the development and maintenance of ascites surgeons have undertaken bilateral adrenalectomy on individual patients who had failed to respond to medical efforts at inducing diuresis (Marson, 1954; Giuseffi, Werk, Larson, Schiff and Elliot, 1957). After operation there was a sodium diuresis but no definite water diuresis and the reaccumulation of ascites was prevented only by use of diuretics and a low sodium diet—measures

which had proved ineffective before adrenalectomy.

This operation has been rendered obsolete by the use of aldosterone antagonists. This will not be discussed here but the reader is referred to a recent monograph (Bartter, 1960).

As mentioned before, adrenal factors are not primarily responsible for the disturbances in water and electrolyte balance in patients with chronic liver disease. Preedy and Aitken (1956 a & b) have shown that the administration of œstriol is followed by well marked sodium and water retention in cirrhotic patients with ascites. Cirrhotic patients without ascites behaved like normal subjects and showed no sodium or water retention when given œstriol. They concluded that the salt-retaining action of œstriol depended mainly on the blood-flow through the liver and only secondarily on disturbances in liver cell function. Recently Layne, Meyer, Vaishwanar and Pincus (1962) showed that aldosterone secretion could be increased by œstrogen administration. If the same occurred in patients with liver disease, this could explain the salt-retaining effect of œstrogen.

On the whole, the interdependence of hormones and their metabolites will certainly influence the regulation of steroid metabolism and makes it even more difficult to judge the specific action of one hormone.

In normals, for instance, the œstrogens increase the binding of cortisol to the protein 'transcortin' (an α -globulin) and, if this is saturated, to plasma albumin. This means that less free or active, and more protein-bound or inactive cortisol is circulating (Mills, Schedl, Chen and Bartter, 1960). Œstrogens equally prolong the plasma half-life of cortisol but not of the dihydro or tetrahydro compounds of this steroid; besides they decrease the synthesis rate of cortisol (Peterson, Nokes, Chen and Black, 1960). Thus it appears that this 'œstrogen-effect' in persons with normal livers is very similar to the disturbed cortisol metabolism in patients with liver disease. Could it be that the supposed 'hyperœstrogenism' in patients with cirrhosis accounts for this? Eymer, Schwarz and Weinges, (1961) reported that the 'œstrogen-effect' is missing in patients with chronic liver disease. Cortisol did not increase after administration of œstriol. Bücher suggested that this might be due to the lack of proteins in cirrhosis (discussion of Eymer's paper).

Birke (1962) recently has stressed the fact that different hormones can act differently on the catabolism of steroids by enhancing (œstrogens, hyperthyroidism) or diminishing (androgens, hypothyroidism) the ability of the normal liver to act on the Δ^4 -3-ketosteroids, or, vice versa, on

the side chain. The implication of these observations on the steroid catabolism in disturbed liver function must be awaited, but here certainly is a fascinating field for future research.

The Antidiuretic Hormone

Finally, brief mention must be made of the antidiuretic hormone (ADH) of the pituitary; its significance in the development and maintenance of ascites has not been clarified. Wolff and others,

(1958) found no difference between the antidiuretic hormone plasma level in healthy subjects and in patients with liver disease. Lee and Bisset (1958) on the other hand were able to detect higher levels of antidiuretic hormone activity in blood from the internal jugular vein than in blood from the median cubital vein and they found a distinct elevation of antidiuretic activity in blood from the internal jugular vein in 5 patients with cirrhosis and ascites. The significance of these findings awaits interpretation.

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