Progress report

Mechanism of hypogonadism in cirrhotic males

For many decades, the pathogenesis of the testicular atrophy and overt feminisation that occur in some men with chronic liver disease has fascinated both clinicians and biochemists. A widely accepted explanation for these changes was first proposed by Edmondson and colleagues in 1939, who suggested that in these patients the diseased liver was unable to inactivate endogenously produced oestrogens. Inadequate methodology has for many years prevented the confirmation or refutation of this hypothesis but recent major advances in biochemical and endocrinological techniques have stimulated a renewed interest in the problem. The purpose of this report is to review some of the more recent studies and to re-examine some of the theories of the pathogenesis of these changes. The specific problem of haemochromatosis will not be discussed.

Clinical features of hypogonadism and feminisation

It is claimed that Koechling (1835) (cited by Bergonzi (1934)) was the first to recognise the association of gynaecomastia and liver cirrhosis in men, but the clinical triad of gynaecomastia, testicular atrophy, and liver cirrhosis became widely acknowledged only after Italian hepatologists had redescribed these features in the mid-1920s.

HYPOGONADISM
Clinical hypogonadism in cirrhotic men is manifested by reduced testicular size and the clinical features of inadequate testicular function. Between 50-75% of cirrhotic men have both macroscopic and histological testicular atrophy. Associated with this, 80-90% of cirrhotic men are impotent and seminal fluid characteristics are grossly abnormal in the small minority of patients who are able to produce an ejaculate. Other signs of hypogonadism include reduced body hair, decreased beard growth, and reduced prostatic size. Histologically, cirrhotic men have a decreased incidence of benign prostatic hypertrophy.

FEMINISATION
Gynaecomastia, the hallmark of feminisation, may be found uni- or bilaterally in about 40% of cirrhotic men. It is caused by hyperplasia of glandular tissue elements. Less dramatic signs of feminisation include a female escutcheon, female body habitus, and cutaneous arterial spider naevi which are said to be related to a hyperoestrogenic state.

A differential incidence of some of these endocrine signs has been found depending on the aetiology of the liver disease. Thus, three groups find
gynaecomastia to be more common in alcoholic cirrhotics\textsuperscript{7,14,15} but others\textsuperscript{6,12} could not confirm this. Similarly, testicular atrophy has been reported as being more common in alcoholic cirrhotics\textsuperscript{6,7}, although this finding is not universal either\textsuperscript{18}. It has been suggested that the more frequent occurrence of endocrine signs in alcoholic liver disease is attributable to greater liver dysfunction in these patients\textsuperscript{7}, but there is, in fact, no clear relationship between the degree of liver dysfunction and the incidence of endocrine changes\textsuperscript{18}.

**Biochemical basis of hypogonadism**

Biochemical hypogonadism is well established in cirrhotic men. Total plasma testosterone concentrations are lower than normal\textsuperscript{11,19–22}. This modest decrease masks a far greater fall in the non-protein bound (biologically active) fraction of plasma testosterone\textsuperscript{12,16,20} caused by the increased concentrations of sex-hormone binding globulin (SHBG) in cirrhotic men\textsuperscript{23–25}. SHBG is the most important plasma protein in determining the protein-binding of plasma testosterone\textsuperscript{26}.

The low plasma testosterone in cirrhotic men is caused by a reduced production of testosterone by the testes. Kinetic studies have shown that the atrophic testes of cirrhotics produce only one-quarter of the normal amount of testosterone\textsuperscript{27,28}. Furthermore, 15% of testosterone produced in these men is derived not from the testes but from peripheral conversion of circulating androstenedione\textsuperscript{28} (Fig. 1). Testosterone production by the testes of cirrhotic men is therefore grossly inadequate.

**Biochemical basis of feminisation**

The three principal unconjugated oestrogens (oestrone, oestradiol, and oestriol) are found in the plasma of normal men. They are derived both from

![Diagram](Fig. 1) Potential pathways for androgen-oestrogen interconversion. In normal men significant androgen-oestrogen interconversion occurs at sites other than in the liver or endocrine glands.
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direct glandular secretion (for example, by the testes—25% of oestradiol29; by the adrenals—5-10% of oestrone30) and from peripheral conversion of the major circulating androgens (for example, 50% of oestradiol originates from circulating plasma testosterone31; 25% of oestrone originates from circulating androstenedione31—Fig. 1).

Oestradiol is the most biologically potent oestrogen. Like testosterone, it is bound in the plasma by SHBG29 and albumin. However, the affinity of SHBG for oestradiol is less than that for testosterone, while the affinity of albumin for oestradiol is higher than that for testosterone77. As a result, changes in plasma SHBG exert a far more profound effect on the free testosterone fraction than on the free oestradiol fraction92. The effect of isolated changes in albumin concentration on the relative binding of testosterone and oestradiol has not been specifically studied.

Unlike the biochemical evidence of hypogonadism, biochemical feminisation in cirrhotic men has not been adequately established. Early studies of urinary oestrogens, using biological1,33-36 and biochemical37-39 methods, were contradictory with findings of normal35-37 or high1,33,34,38,39 urinary oestrogens in cirrhotics. Since the advent of more sensitive methods has enabled the measurement of unconjugated plasma oestrogens, most reports have concerned plasma oestradiol. In cirrhotic men, total unconjugated plasma oestradiol has been reported as normal11,15,16,40,41, minimally raised7,22,42,43, or greatly raised20,44,45. There is equal disagreement about unbound (biologically active) plasma oestradiol in cirrhotic men with reports of normal15,41, marginally raised7, or markedly raised20 free plasma oestradiol. The technique of steady-state gel filtration46 is probably the most physiological method of measuring the free fraction and both groups using this technique15,41 found no change in protein-binding of oestradiol in cirrhotic men.

It is difficult to reach firm conclusions in view of all these contradictory reports. It would seem that total plasma oestradiol concentrations may be minimally raised in significant proportion of cirrhotic men, while free plasma oestradiol concentrations appear marginally raised in only a minority of cirrhotic men. Although in the largest single study7 a slight correlation was found between gynaecomastia and total plasma oestradiol concentrations, many patients with gynaecomastia had consistently normal total and free plasma oestradiol concentrations. The significance, therefore, of marginally raised plasma oestradiol concentrations, when they occur in cirrhotic men, is not readily apparent. It may be that there is, in cirrhotic men, increased sensitivity of breast tissue to circulating oestrogens.

There is more agreement about plasma oestrone concentrations in cirrhotic men. Oestrone is the metabolic precursor of oestradiol but it is a weak oestrogen with only about one-twelfth of the feminising potency of oestradiol47. Many groups41,43-45,48 have found raised plasma oestrone in cirrhotic men but only two41,48 have found that this rise correlates with the presence of gynaecomastia. The poor feminising ability of oestrone (as compared with oestradiol) makes the significance of this finding uncertain and a similar conclusion applies even more forcibly to the marginally raised unconjugated plasma oestriol concentrations also found in cirrhotic men41,43.

Kinetic studies have only partially clarified these confusing findings. One group45 have found an increased production rate of oestradiol in cirrhotic
men but this has not been confirmed. The different conclusions from these two studies hinge entirely on their different findings for plasma oestradiol concentration, as both had found a normal metabolic clearance rate for oestradiol in cirrhotic men. The production rate of oestrone has been found to be raised in cirrhotic men in two studies. In one study, the less direct urinary production method was used, while, in the other, the method used was not specified. The findings from these studies would be consistent with raised plasma oestrone concentrations.

Kinetic studies have also shown that, in cirrhotic men, there is increased peripheral conversion of androgens to oestrogens—both of testosterone to oestradiol and androstenedione to oestrone. However, the assessment of the quantitative importance of these interconversions depends on the plasma concentrations of the precursor compound. Since plasma testosterone is low in cirrhotic men, the mass of testosterone converted to oestradiol per unit time is no higher than normal. Similarly, the quantitative importance of the androstenedione-oestrone interconversion is difficult to assess as plasma androstenedione in cirrhotic men has been found to be either increased or normal. Therefore, although there is increased peripheral conversion of androgens to oestrogens in cirrhotic men, the quantitative importance of these interconversions in explaining changes in plasma oestrogens is not clear.

The inability to show unequivocal hyperoestrogenism in cirrhotic men has led to a search for less direct indices of biochemical feminisation. It has been suggested that increased plasma SHBG is indirect evidence of biochemical hyperoestrogenism. This finding in cirrhotic men, however, has other potential explanations. Increased plasma sex-hormone binding globulin has been reported in male hypogonadism of any cause and also in non-cirrhotic chronic alcoholics. Raised plasma SHBG in cirrhotic men does not therefore constitute strong evidence of hyperoestrogenism in these men, although in other situations hyperoestrogenism is one of the most potent causes of increased plasma SHBG concentrations. Plasma prolactin is to some extent oestrogen-responsive and has been found by one group to be raised in cirrhotics but this finding has not been confirmed (see the section on hypothalamic-pituitary function).

To summarise, there is no clear evidence of increased circulating concentrations of biologically potent oestrogens in cirrhotic men. There is good evidence that plasma oestrone is raised in these patients; this may be partly caused by an increased production of oestrone which might, in turn, be caused by increased peripheral conversion of androstenedione to oestrone in these men. The metabolic importance of the raised plasma oestrone, a biologically weak oestrogen, is not apparent.

Hypothalamic-pituitary function

The contribution of hypothalamic-pituitary dysfunction to the endocrine changes of cirrhotic men has recently been clarified. Figure 2 shows a simplified diagram of the hypothalamic-pituitary regulation of testicular function in normal adult men.

Early studies of urinary gonadotrophins in cirrhotics, using bioassay, had been contradictory with reports that these were low, normal, or high.
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Fig. 2  Hypothalamic-pituitary control of testicular function in normal men. The products of testicular function, spermatozoa and testosterone, in some way exert a negative feedback regulation of the hypothalamic-pituitary control of gonadotrophin (LH, FSH) secretion. (Gn RH = Gonadotrophin releasing hormone; LH = luteinising hormone; FSH = follicle stimulating hormone).

Although there is a similar wide range of reported values for plasma gonadotrophins as determined by radioimmunoassay in cirrhotics, the broad consensus of findings is that plasma gonadotrophins are normal in the majority of cirrhotic men and only a minority have high values. Low values are seen pre-terminally.

There are two implications from this finding of normal plasma gonadotrophins in the majority of cirrhotics with frank testicular failure. The first is that there may be in these patients a primary testicular defect, as the testes are hypofunctional despite a normal trophic drive. The second is that there must also be a hypothalamic-pituitary abnormality because in other causes of primary hypogonadism, where there is a comparable degree of testicular failure, plasma gonadotrophin concentrations are markedly raised. An abnormal plasma gonadotrophin response to clomiphene administration in cirrhotics confirms the presence of a hypothalamic-pituitary defect in these men and this defect has been further localised to the hypothalamus, as the pituitary response to gonadotrophin releasing hormone (Gn RH) in cirrhotics is either normal or supranormal.

The absence of galactorrhoea in cirrhotic men with or without gynaecomastia would suggest that plasma prolactin concentrations in these men are normal. Although one group has reported raised plasma prolactin in cirrhotic men, two other groups have found normal plasma prolactin in cirrhotics, using both bioassay and radioimmunoassay. The latter group has further found a normal plasma prolactin response to stimulation with thyrotrophin releasing hormone (TRH) in cirrhotic men.

To summarise, recent studies have shown that cirrhotic men have defective
hypothalamic-pituitary secretion of gonadotrophins, caused by a hypothalamic defect.

**Aetiology and pathogenesis of endocrine changes**

Many different hypotheses have been proposed to explain the pathogenesis of endocrine changes in cirrhotic men. A number of these will be considered in the light of recent findings.

**Role of deranged hepatic metabolism of oestrogen**

In the diseased liver of both men and animals, both *in vivo* and *in vitro* studies have shown abnormalities of hepatic metabolism of many oestrogenic compounds (for reviews—Adlercreutz, 197060 and 197461). Despite these, recent *in vivo* studies in cirrhotic men have shown that neither the plasma half-life62 nor the metabolic clearance rate7,48 of plasma oestradiol is significantly different from normal. These findings are strong evidence against the original Edmondson hypothesis1 but do not entirely refute it, as there may still be delayed metabolic clearance of other, less biologically active oestrogens—for instance, oestrone.

Increased peripheral conversion of androgens to oestrogens, shown in cirrhotic men, would not seem to be directly caused by altered hepatic metabolism of these compounds. Preliminary evidence from two studies60,62 indicates that in cirrhosis the transhepatic aromatisation of both testosterone to oestradiol and androstenedione to oestrone is much lower compared with that occurring in extraplanchonic sites. Thus, any role that liver disease may have in causing these metabolic changes must be indirect.

To summarise, it would seem that the original hypothesis of Edmondson and colleagues is now less likely to be correct. Recent studies have failed to show significant changes in the hepatic metabolism of biologically potent oestrogens in cirrhotic men and it is apparent that the role of liver disease in the pathogenesis of such changes as have been shown may only be indirect.

**Role of alcohol (ethanol) consumption**

Although there is no doubt that alcohol consumption can lead to many complex changes in the metabolism of sex hormones, it is not necessary to invoke these biochemical effects to explain the endocrine disturbances of established hepatic cirrhosis. This is because the endocrine changes in cirrhosis are comparable whether caused by alcohol or not6,7,12.

The endocrine consequences of alcohol consumption in non-cirrhotic subjects are, however, of some interest. In general terms, two possible ways in which alcohol consumption might exert a specific effect on endocrine function have been considered. The first is that alcohol consumption might induce specific alterations in the hepatic metabolism of sex hormones and related compounds (other than by non-specific hepatic damage) and the second is that alcohol might be directly toxic to one or more elements of the hypothalamic-pituitary-gonadal axis.

As recent studies have shown that endocrine changes caused by alcohol consumption differ markedly depending on whether consumption is short-term or chronic, these two situations are considered separately.

**Short-term alcohol consumption in non-cirrhotic men**

In a recent study of short-term (four weeks) alcohol consumption63, evidence
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of increased hepatic metabolism of testosterone was found together with an increased metabolic clearance rate of testosterone from plasma. Plasma testosterone fell over the period of study but so, interestingly, did the protein-binding of plasma testosterone. As there was no consistent change in serum luteinising hormone (LH), the authors interpreted these findings as evidence of direct suppression by alcohol of both testicular function and hypothalamic-pituitary function. An alternative explanation is that, although total plasma testosterone was lowered, free testosterone might have remained normal (because of decreased protein binding) and this, together with the normal plasma oestradiol (that was found), would have obviated the need for hypothalamic-pituitary compensation.

Chronic alcohol consumption in non-cirrhotic men
The endocrine changes found in non-cirrhotic chronic alcoholics are quite different from those of short-term consumers. In chronic alcoholics, plasma SHBG is markedly raised\textsuperscript{18,22,64}, which reduces the free fraction of plasma testosterone below normal. There is increasing evidence that many of these patients with fatty livers have raised plasma gonadotrophins\textsuperscript{65} with only marginally lowered concentrations of free testosterone\textsuperscript{18}. This pattern of changes seems similar to that found in men with thyrotoxicosis\textsuperscript{66,67} where the primary abnormality would seem to be an increased plasma SHBG. The recent study by Israel and colleagues\textsuperscript{68}, showing that both thyrotoxicosis and chronic alcohol administration have markedly similar effects on hepatic metabolism, is therefore of interest.

It has been suggested that chronic consumption of alcohol directly reduces spermatogenesis by inhibiting the testicular conversion of retinol to retinal\textsuperscript{69}—the latter being essential for spermatogenesis in animals\textsuperscript{70}. This conversion is unfavourably influenced by high NADH concentrations which might result from intratesticular reduction of ethanol by alcohol dehydrogenase\textsuperscript{69}. Experimental support for this theory is confined to animal studies and further observations are awaited. In another animal study\textsuperscript{71}, chronic feeding of alcohol to developing rats was shown to result in smaller testes at maturity. This does not parallel the human situation, however, in which a secondary atrophy is presumed to occur in a previously normally developed testes.

To summarise, alcohol consumption would appear to play no specific role in the endocrine changes of established cirrhosis, as these changes are seen equally in non-alcoholic cirrhotics. In non-cirrhotic men, both short-term and chronic consumption of alcohol induce a variety of biochemical effects on sex hormone metabolism, but there is as yet no unequivocal evidence of a direct toxic effect of alcohol on either the testes or the hypothalamic-pituitary system in man; many of the endocrine consequences of alcohol consumption in non-cirrhotics may result from changes in hepatic synthesis of SHBG.

Role of primary hypogonadism
The possibility that many, if not all the endocrine changes in cirrhotic men result entirely from a primary testicular defect has recently been reconsidered. In this respect, evidence for a direct toxic effect of alcohol on the testes is unproven (see relevant section) but it has recently been suggested that testicular damage might be mediated by autoimmune mechanisms\textsuperscript{72}, presumably triggered by non-specific hepatic damage.
Although a primary testicular defect would explain the low plasma testosterone\(^\text{11,19-22}\), high plasma SHBG\(^\text{24}\), and possibly the increased peripheral conversion of androgens to oestrogens\(^7\), there are two major objections to this as a unifying hypothesis. The first is that it cannot alone explain the hypothalamic-pituitary suppression found in most cirrhotics or the occurrence of gynaecomastia in only a few (who do not necessarily have the lowest total and free plasma testosterone\(^\text{12}\)). The second, more fundamental objection is that it is far from clear that the undoubted hypogonadism of cirrhotics is of primary origin. Much of the evidence for a primary testicular defect rests on an inadequate plasma testosterone response to human chorionic gondotrophin (HCG)\(^7,11,12\), but the ability of this test to differentiate primary hypogonadism from hypogonadotrophic (secondary) hypogonadism is extremely questionable\(^74,75\).

Therefore, a primary testicular defect in cirrhotic men, if it exists at all, would alone be an inadequate explanation for the endocrine changes seen in these men.

**Miscellaneous factors**

Gynaecomastia is a side effect of many non-oestrogen drugs\(^59\). In particular, spironolactone\(^78\) is often used in cirrhotic men and may contribute to endocrine changes in a proportion\(^7\). The role of this and other agents, however, must be subsidiary in view of the high incidence of endocrine changes observed long before the availability of these drugs\(^5\).

Although knowledge of the pathogenesis of gynaecomastia in other clinical situations might, by analogy, further the understanding of gynaecomastia in cirrhotic men, the pathogenesis of gynaecomastia in other situations remains as obscure as it is in cirrhotic men. The only situation in which the pathogenesis of gynaecomastia appears to be readily understandable is in men with prostatic carcinoma receiving pharmacological quantities of exogenous oestrogens.

**Summary and conclusion**

Men with chronic liver disease frequently develop clinical signs of hypogonadism and overt feminisation. Associated with these features, they have been found to have a reduced production of testosterone with low plasma concentrations, but only a minority of cirrhotic men would seem to have a marginal increase in circulating biologically potent oestrogens. Furthermore, this latter finding does not correlate with the presence of clinical feminisation.

The original hypothesis to explain these changes now seems less likely to be true and no other single hypothesis has, on its own, been found to provide an adequate explanation for all the clinical and biochemical features found in cirrhotic men. It may be that the pathogenesis of endocrine changes in cirrhotic men is multifactorial—for instance, a combination of decreased hepatic clearance of some oestrogenic compounds, an autoimmune mediated primary testicular defect, and a specific potentiation effect by alcohol. Alternatively, it may be that none of these suggested mechanisms is of importance and that the endocrine changes are mediated instead by other mechanisms which remain, as yet, undiscovered or unconsidered.
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The fascination which this problem has held for clinicians and biochemists for many years seems likely to persist for some time to come.

J. R. B. GREEN
Department of Gastroenterology
St Bartholomew’s Hospital
London

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G R Green

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