unchanged; the B.P. had fallen to 170/95; and the cholesterol was 210 mg. per 100 ml. However, the patient did not feel so well. Treatment was then stopped, and after four weeks the tracing had returned almost to its original normal pattern, the B.P. had risen to 210/105, and the cholesterol to 300 mg. The patient felt better for a time but then deteriorated; she finally improved on a smaller dose of thyroid.

The blood pressure, especially the diastolic, was slightly raised in mild cases. In the severe spontaneous cases it was very high in one half. Nearly always it fell to near normal as the myxoedema was corrected by thyroid hormone. The possibility that the disappearance of the electrocardiographic abnormalities under treatment could be due to fall in blood pressure might be put forward. This cannot be accepted, however, because the T-wave changes in myxoedema are more widespread than in hypertension; they can be corrected very much more quickly than in primary hypertension; and, moreover, they revert just as readily when an initially low blood pressure rises with treatment.

To test the effect of thyroid hormone on the electrocardiogram of patients with normal thyroid function, nine subjects were given triiodothyronine in doses of 40 to 90 μ g. daily. The results are given in Table V. In those with a left ventricular predominance pattern there was some lessening of the depression of the ST segment and increase in the voltage of T; there were similar effects on the tracings of two patients with old coronary thrombosis. In one with a normal tracing thyroid hormone had no effect beyond a slight increase in rate. These effects are in keeping with the usual high T voltage in toxic goitre, for when thyroid hormone is given to a subject whose thyroid is functioning normally a mild degree of hyperthyroidism is produced. This raises the T wave and, with it, lessens the depression of the ST segment. The changes are, however, trivial in comparison with what occurs in myxoedema using the same dose of hormone.

Arrhythmia.—Abnormal rhythms are conspicuously absent. Apart from heart-block, the only one recorded was an occasional extrasystole, either ventricular or auricular. While an excess of thyroid secretion promotes auricular fibrillation, lack of this seems to prevent it.

Heart Size.—There was no enlargement in 14 out of 36 cases. However, pulsation was small even in these. Enlargement when present varied from slight to very great. Its amount was not always proportional to the severity of the hypothyroidism as judged by clinical, cardiographic, blood pressure, or cholesterol findings. It is probable that great enlargement is always due to pericardial effusion (Figs. 8 to 13). This is suggested by the shape of the very large heart and by the rapid shrinkage with treatment; as the face and body lose their puffiness the heart goes down at the same time.

Simulation of Congestive Heart Failure.—In a severe case with cardiac enlargement there is pitting oedema of the feet and legs and engorged cervical veins. Yet the x-ray picture of the lungs does not show congestion, and the patient can lie flat in bed and walk at her ordinary slow pace without dyspnoea. There are usually no cardiac murmurs, the pulse rate is slow, and digitalis is of no value. It is probable, therefore, that there is no congestive failure, the oedema and cervical vein engorgement being accounted for by anaemia, fluid retention, immobility, and pericardial effusion. There was no instance of cardiac pain before treatment was started, and in the two necropsies obtained the coronary arteries were entirely free of atheroma.

ORAL METHYLTESTOSTERONE AND JAUNDICE

BY

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Androgen therapy can be given by injection using single esters of testosterone such as the propionate, phenylpropionate, or oenanthate, or mixtures of esters such as the propionate, valerianate, and undecylenate; by injection of microcrystalline suspensions of testosterone or of testosterone isobutyrate; and by implantation of pellets of fused testosterone or testosterone propionate. Treatment can thus be planned to give temporary high-level doses with an injection every three to four days, or a long-lasting action for three to four weeks, using the oenanthate. After implantation, continuous absorption of small amounts of hormone will last for three to six months.

However, oral therapy is efficient, simple, rapid in action, and can obviously be stopped at once, if necessary. Methyltestosterone was introduced to clinical medicine by Foss in 1939, and since that time must have been used for its androgenic and protein anabolic effects in thousands of cases.

The effect of methylating testosterone was to protect it from deactivation in the liver after its absorption into the portal system, whereas free testosterone was largely inactivated by the liver.

By using the route of oral absorption, steroid hormones are absorbed through the buccal mucosa, when held either under the tongue or between the upper lip and the gum. Much of the hormone is then absorbed direct into the systemic circulation, thus bypassing the liver. When applied in this manner, methyltestosterone is, in fact, hardly more effective than by ingestion (Foss, 1956). Testosterone is of little value when swallowed, but is effective by buccal mucosal absorption (Escamilla and Gordan, 1950).

The metabolism of testosterone and methyltestosterone is different. Both hormones are powerfully anabolic and androgenic, but after mucosal absorption in the mouth testosterone produces an increased excretion of 17-ketosteroids, but has no effect on the excretion of creatine in the urine. Methyltestosterone, however, does not materially alter the excretion of 17-ketosteroids, but it does cause creatinuria.

Creatinuria can be produced also by other methylated steroids such as methylandrostenediol and methylandrostenediol. Methyltestosterone causes an increased excretion of glycochamine along with creatinuria, which suggests that the synthesis of creatine is increased (Dorfman and Shipley, 1956). Samuels, Sellers, and McCauley (1946) believe that the kidney is the primary site of action of methyltestosterone on creatine metabolism. In severe liver disease methyltestosterone was able to produce increased quantities of creatine, but this was not possible in nephrosis.

From the practical point of view, patients who have to continue substitution treatment for many years dislike the sublabial route. Designed for slow absorption, the

tablets may in fact last from one to several hours in the mouth, and their unpleasant taste sometimes causes nausea. Thus methyltestosterone is generally to be preferred, as it is almost as effective when swallowed, unlike testosterone, which is relatively useless by ingestion.

Cases of Jaundice Attributed to Methyltestosterone

Eight years after its introduction to clinical medicine, Werner (1947) suggested that methyltestosterone might cause jaundice in some patients, and reported four cases showing this apparent complication, in one of which jaundice did not recur after a retreat of the drug. There was a protracted clinical course with bile in the urine, and pale stools, the flocculation and turbidity tests were negative, and the alkaline phosphatase was low. In this preliminary account he quoted six other cases, reported to him by other doctors, but in only one of these had methyltestosterone been given again, and it was then followed by recurrence of jaundice. Other reports followed. Kinsell (1948) mentioned that in his experience methyltestosterone had occasionally resulted in jaundice and that this was not known with testosterone or testosterone propionate therapy. Without giving further details, he stated that the use of methyltestosterone should be contraindicated in patients with liver disease. He was later reported to have seen four cases (Brick and Kyle, 1952).

Werner, Hanger, and Kritzer (1950) published seven cases of jaundice following treatment with methyltestosterone for periods of eight days to five months. In all these cases there was considerable bilirubinaemia, negative flocculation tests, and normal or slightly raised alkaline phosphatase. In some of the patients the liver was palpably enlarged, and biopsies showed the same picture of the bile canaliculi in the central zones dilated and plugged with bile pigment, and there was minimal or no liver-cell damage. The bile ducts were not dilated and contained no bile. None of these cases had received blood or plasma or had been exposed to any other hepatotoxic agent. In three of these cases, however, there was no recurrence of jaundice after it had disappeared, when methyltestosterone therapy was resumed.

Thorn, Forsham, Frawley, Hill, Roche, Staehelin, and Wilson (1950) quoted another case of jaundice following methyltestosterone which was treated with corticotrophin with some subjective improvement but no benefit to liver function.

Brick and Kyle (1952) reported two cases and one in an addendum. The first of these showed positive flocculation and turbidity tests, and a moderate rise in alkaline phosphatase. The second case showed negative flocculation tests and moderately elevated alkaline phosphatase, and the biopsy picture was similar to that found in the cases described by Werner *et al.* (1950), although there was also some liver-cell damage. The third case was similar.

Wood (1952) described another case after two months' therapy with methyltestosterone. The clinical, biochemical, and histological findings were identical, and electrophoretic studies of the serum proteins showed a γ -globulin-2 fraction below the normal value, unlike that seen in viral hepatitis, where the value is elevated.

Almaden and Ross (1954) reported the case of a woman aged 45 with Sheehan's syndrome who developed jaundice after 178 days' treatment with methyltestosterone (3.36 g. in 230 days). The same biochemical and histological picture was seen.

Following these reports of jaundice which appeared to implicate methyltestosterone, and since it was stated that testosterone was completely free from such toxic effects, some pharmaceutical literature gave this as a reason for discontinuing methyltestosterone therapy and substituting sublabial absorption of testosterone instead. It was also claimed that it was as effective by this route as when parenterally administered as esters.

In a fairly extensive use of methyltestosterone since 1939 with doses of 5–150 mg. daily for prolonged periods up to ten years, it so happens that we have encountered only one instance of jaundice which might possibly have been attributed to methyltestosterone (Foss and Simpson, 1957).

Since, for practice purposes, it would be a pity to withhold the use of methyltestosterone unless its association with jaundice was proved to be a direct sequence and not merely coincidental, we felt we should try to ascertain whether any other physicians had noted this association. Following letters to the *Lancet*, *British Medical Journal*, and *Journal of the American Medical Association* (Foss and Simpson, 1956a, 1956b, 1957), we received information about 13 further cases in which there appeared to the observer to be an association between the taking of methyltestosterone and the appearance of jaundice. More recent reports have also been published, and Koszalka (1957) described the first death.

The patient, a man aged 60, had had jaundice in childhood, and had lost much weight after an abdomino-perineal resection for carcinoma of the rectosigmoid. He was given 10 mg. of methyltestosterone three times daily for its protein anabolic effect. After six weeks he developed jaundice, and two months after its onset died, with progressive dehydration and metabolic acidosis. The liver showed no evidence of carcinoma, and there was some degeneration of the liver cells in the central parts of the lobules associated with numerous intracanalicular plugs of bile. The unusual degree of central hepatocellular degeneration and atrophy was attributed to terminal changes.

Furman, Howard, Norcia, and Keaty (1958), in a study of the effects of androgens on the serum lipids and lipoproteins, mention the case of a male who became deeply jaundiced during a course of methyltestosterone. This cleared on stopping the hormone and did not recur when a second course was given.

This makes a total of 42 cases, the essential details of which are shown in the Table. It is unlikely that the two cases showing primary biliary cirrhosis and one with liver metastases were directly attributable to methyltestosterone.

Other experienced observers have, however, never seen a case of jaundice following methyltestosterone therapy (Gordan, 1956; Palmer, 1957; Spence, 1958; Bishop, 1958; Greene, 1958; Swyer, 1958).

In the cases described, the onset of jaundice varied from eight days to a year after starting treatment, but usually began after about three to four months. Some patients had been taking as little as 10 mg. daily, and others as much as 100 mg. daily. There does not seem to be any relationship between the size of the dose and the latent period before the onset of jaundice. It has not been reported in children and there are only two cases (in patients aged 15 and 17 years) below the age of 24, and the oldest was a man of 74.

The clinical picture was that of anorexia and nausea, listlessness and lethargy, and upper abdominal

discomfort, followed a few days later by vomiting and jaundice, of slight to moderate intensity, with bile in the urine and pale stools. Sometimes urobilin was detected. In early cases the patients were thought to have an obstructive jaundice and some were submitted to laparotomy. There were no reports of pyrexia.

When methyltestosterone was withdrawn the jaundice cleared in some cases in a few days, but in others it lasted one to three months, again without any relation to dosage. In three cases of Werner *et al.* there was no recurrence after giving further treatment, but in three other cases (Fearnley *et al.*, 1957; Taverner, 1957; Higgins, 1957), where methyltestosterone had been given for pruritus, the jaundice waxed and waned according to whether this steroid was being given or withdrawn. The case of Fearnley *et al.* had pruritus of pregnancy, and those of Taverner and Higgins were both shown to have primary biliary cirrhosis at biopsy. Although the onset of jaundice occurred during the administration of methyltestosterone in these cases of primary biliary cirrhosis, it is not fair to claim that this steroid was primarily responsible.

The main biochemical findings were as follows. (1) Bilirubinaemia of slight to moderate degree (range 1.2-37 mg./100 ml.). In one of Oliver's cases (1956a, 1956b) blood was not taken till after jaundice of one day's duration had subsided, and the figure was only 0.9 mg./100 ml. (2) Moderate elevation of the serum alkaline phosphatase. The figures are not all comparable, as different units were quoted in English and American reports. (3) In all except one case, where records are available, the thymol turbidity, thymol flocculation, colloidal gold, and zinc turbidity tests were negative.

Electrophoretic studies were reported in four cases: three were normal, and in the other γ -globulin-2 was below normal. Liver histology was examined in 18 cases. Thirteen of these showed a picture of bile plugging of the intercellular canaliculi (cholestasis) without any notable inflammatory reaction or parenchymal cell necrosis. In two there was in addition some liver-cell damage; in another the liver was full of metastases from breast carcinoma, and two showed primary biliary cirrhosis.

Details of Cases

[illegible]

There seems to be little doubt that jaundice may follow methyltestosterone therapy, but that this complication is rare. Clinically the jaundice is of obstructive type with bile in the urine and pale stools. Malaise is of varied duration, and sometimes the icterus is protracted. In several cases some pre-existing liver disease has been recognized, and it would seem that methyltestosterone has then precipitated rather than caused the jaundice. Methyltestosterone must have been given to numerous patients with pruritus associated with obstructive jaundice following the report of its value by Lloyd-Thomas and Sherlock (1952), and in many of these, often with serious liver disease, jaundice has been increased, but it has not been regarded as of sufficient importance to withdraw therapy.

Pathogenesis

The pathogenesis of the condition under consideration is doubtful. Wood (1952) wondered whether it is related to the known creatinuria associated with therapy with methyltestosterone, or whether it is due to defective transmethylation or to disturbed hydration of the bile, with consequent inspissation of thick plugs in the canaliculi.

Free testosterone or testosterone propionate is not believed to cause jaundice, but Hanger (1957) reported one case following oral administration of non-methylated testosterone, and suggested that it might in some way be due to the large amount of hormone in the portal blood. Sublabial absorption of testosterone would not exclude this, because quite a moderate amount of the hormone is bound to be swallowed in the saliva, and, further, many of the reported cases of methyltestosterone jaundice have followed sublabial absorption.

From the original reports, it seemed that methylation of testosterone was a likely factor, although we have no knowledge of jaundice following methylandrostenediol or methylandrostanolone, and it has not been noted with fluoxymesterone (Skillern, 1957). Peters *et al.* (1958) reported the occurrence of jaundice in 2 of 10 patients during trials of 17-methyl-19-nortestosterone. Histologically the appearances were identical to those seen after methyltestosterone jaundice. No cases of jaundice, however, were reported by Ferin (1956) in a similar series. However, Nabarro (1958) has informed us of a man who developed jaundice after 14 days on 17-ethyl-19-nortestosterone (norethandrolone), 50 mg. daily, with a serum bilirubin value of 3.4 mg./100 ml. and alkaline phosphatase 20 units. This case is perhaps complicated by the fact that the patient had been taking methyltestosterone up to three months previously. This non-methylated anabolic hormone with relatively slight androgenicity has of late excited considerable interest.

At an American conference on the effect of norethandrolone on the liver, the opinion was expressed that it produced a cholestasis similar to that following methyltestosterone therapy and various other drugs, and that there was no *prima facie* evidence of liver-cell damage (Popper, 1958). Plum and Dunning (1958) and Dunning (1958) reported the cases of two out of seven patients with poliomyelitis treated with norethandrolone who developed mild cholestatic jaundice after taking 20 mg. three times daily for 19 and 20 weeks. Venning (1958) stated that about a dozen cases of jaundice following norethandrolone had been reported to the manufacturers. It is probable that, in fact, the incidence of jaundice from cholestasis is a relatively much commoner complication of therapy with norethandrolone

than with methyltestosterone. Sherlock (1958) abandoned methyltestosterone for relieving pruritus associated with jaundice and found norethandrolone effective for this (and less androgenic), but it consistently produced further elevation of the serum bilirubin in these patients.

Cameron (1958a) states: "After excluding cases of obstruction of the extrahepatic bile ducts, cholangitis of medium and small bile ducts, with or without pericholangitis, there remain unexplained instances of acute and chronic jaundice of hepatic origin. They share one constant feature in the form of biliary thrombi located in the centrolobular zone and signs of biliary canicular stasis. . . . Liver-cell degeneration is not prominent and may even be absent." Later he says: "Liver-cell damage . . . is not an essential factor, for thrombi form regularly during the jaundice produced by certain drugs such as toluylenediamine, methyltestosterone (Werner *et al.*, 1950), and chlorpromazine (Menguy *et al.*, 1955). In none of these instances is there definite structural change in liver cells." One must always be cautious in attributing jaundice to drugs which have been given to a patient, and every effort must be made to eliminate the possibility of virus infections. Although usually the histological picture of canicular stasis due to drugs shows no associated liver-cell degeneration or necrosis and is distinct from that of viral hepatitis, from time to time an undoubted case of the latter may show very minimal cell infiltration (Cameron, 1958b).

Although chlorpromazine is a relatively frequent causative agent of cholestatic jaundice, modification of the side-chains produces a drug of similar pharmacological properties — "dartialan," a phenothiazine derivative which appears to be completely free from the liver toxicity (Venning, 1958).

What the causative factor is in all these cases remains obscure, but it is evident that methyltestosterone is not alone among the potent synthetic androgenic or anabolic steroids to produce cholestasis and jaundice. Thus, one cannot postulate that methylation and its influence on creatine metabolism can be the responsible cause. Dunning (1958), in a report on two cases of jaundice after norethandrolone, commented that chlorpromazine jaundice usually appears early, and is thought to be a hypersensitivity reaction. This is unlike that due to methyltestosterone, which occurs usually after a prolonged course (three to four months) and may not recur when later methyltestosterone is reinstituted.

Liver Function Tests

Kory, Watson, Bradley, and Peters (1957) reported unexpected retention of bromsulphthalein in about three-fourths of a series of patients treated with norethandrolone. Abnormal dye retention was considerable (up to 51%); other liver-function tests were entirely normal and no clinical signs of liver disease appeared. The effect was reversible with discontinuation of the drug. Liver biopsies in six individuals with high dye retention were normal. Heaney and Whedon (1958) found that both methyltestosterone and norethandrolone in doses of 20–100 mg. a day by mouth in 11 patients caused a retention of bromsulphthalein and reduced clearance, which was not noted after 100 mg. daily of testosterone propionate by injection. There was no evidence of any other change in liver-function tests during a period of 7 to 10 days. The bromsulphthalein clearance returned

to normal within about 10 days after withdrawing therapy. The authors state that there is indirect evidence which indicated that the defect involves the hepatic excretory mechanism rather than the liver dye uptake.

It has also been shown that 30 mg. daily of norethandrolone for six weeks given to six laboratory workers produced a consistent and significant increase in the level of serum glutamic-oxalacetic transaminase, serum lactic dehydrogenase, and serum aldolase, and a marked retention of bromsulphthalein in all subjects. There was no change in thymol turbidity and cephalin flocculation tests and no jaundice (Dowben, 1958).

Conclusion

Although jaundice is a rare complication after methyltestosterone, there is apparently no evidence of liver-cell damage, and recovery of liver function follows its withdrawal. Because of the comparative rarity of this complication and its apparent transient character, we do not feel that there is enough evidence to justify withholding therapy with methyltestosterone, especially in view of its simplicity and efficiency as an oral androgenic and anabolic substance. It is prudent not to give this steroid again to a patient who has developed cholestatic jaundice during a previous course.

We are indebted to Drs. Fearnley, Tomlinson and Balmforth, Hanger, Higgins, Hirsch, Nabarro, Oleesky and Munro, Oliver, Palmer, Priest, Skillern, Taverner, and Westlake for supplying details of further cases in response to our request, and for allowing us to incorporate them in this paper; to Dr. G. R. Venning, of Searle Research Laboratories, for information about norethandrolone jaundice; and to Professor Sir Roy Cameron and Dr. Sheila Sherlock for their helpful criticism.

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CHRONIC BRONCHITIS IN INDUSTRY AN ACCOUNT OF A TRIAL OF H. INFLUENZAE VACCINE

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Chronic bronchitis is roughly five times as common in Britain as in most industrial European countries and ten times more so than in Scandinavia or the United States. Economically the cost in lost working days, production, and health insurance claims is tremendous (Stuart-Harris and Hanley, 1957).

It is difficult to account for this high prevalence, although numerous predisposing factors such as age, heredity, sex, climate, atmospheric pollution, and smoking have been indicted (Oswald *et al.*, 1953). There is wide agreement that bronchial infection is of paramount importance, particularly in determining whether the disease progresses to the disabling irreversible stage (Ogilvie and Newell, 1957).

Attention has therefore been concentrated upon the infective aspect, especially as Mulder (1938), Mulder and Goslings (1948), and May (1953a, 1953b, 1954) have demonstrated that *Haemophilus influenzae* can be found in the sputum of up to 90% of chronic bronchitics. The pneumococcus comes next in frequency. Other pathogens are relatively uncommon. These organisms are rapidly reduced in number by treatment with suitable antibiotics, but they promptly re-establish themselves afterwards (May, 1953b).

Elmes *et al.* (1953) found short courses of various antibiotics only slightly and transiently effective, but they subsequently reported considerable benefit from a