clouding of consciousness as they do on the presence of an actual focal lesion in the parietal area or elsewhere in the brain.

Summary

In later life, among the reversible toxic and biochemical causes apt to provoke confusional symptoms, dehydration, alkalosis, anoxia, and hypoglycaemia deserve particular emphasis. Anoxia or repeated hypoglycaemia may lead to ultimate dementia, although as a rule only reversible acute symptoms result.

Cerebral tumour in the elderly may be overlooked because the symptoms simply resemble those of growing old, because headache and papilloedema are absent, and because progressive intellectual deterioration may be wrongly attributed to cerebral softening from vascular disease.

Parieto-occipital and parieto-temporal vascular lesions especially give rise to clinical pictures resembling post-traumatic psychosis and post-anoxic encephalopathy. The occurrence of so-called parietal signs is closely related to general clouding of consciousness, some indications of which are usually present.

TESTOSTERONE THERAPY FOR THE PRURITUS OF OBSTRUCTIVE JAUNDICE

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Pruritus is a most distressing symptom in obstructive jaundice and its treatment has hitherto been very unsatisfactory. Methyltestosterone has been successfully used to relieve this symptom in two patients suffering from primary biliary cirrhosis with intrahepatic obstruction to bile flow (Ahrens *et al.*, 1950). We have extended these observations and have used methyltestosterone to treat chronic pruritus in seven patients suffering from obstructive jaundice.

Selection of Cases.—All the patients had chronic jaundice of obstructive type. Three suffered from primary biliary cirrhosis, two from inoperable carcinoma of the main hepatic ducts, one from a gall-stone impacted in the common bile duct, and one from a traumatic stricture of the common bile duct. All the patients spontaneously complained of itching and showed excoriations on the skin due to scratching. Patients with other skin diseases were excluded from this study. Pruritus had lasted for at least six weeks.

Case Reports

Case 1.—A 54-year-old woman with primary biliary cirrhosis began to have itching of the palms in June, 1950, followed by jaundice which had persisted. Examination showed skin xanthomas and hepatosplenomegaly. The faeces were usually pale but occasionally contained bile pigment. Laparotomy showed no obstruction to the extrahepatic biliary system. Pruritus increased, and by December was interfering with her sleep and making her life miserable. Phenolic skin lotions, antihistaminic drugs, and

phenobarbitone were ineffective in controlling the itching. In July, 1951, she was started on methyltestosterone, 25 mg. daily sublingually. After one week's treatment she reported great relief of the itching, which completely disappeared after one month. The drug was continued for three months and the pruritus did not recur. In October sublingual therapy was replaced by a subcutaneous implant of 450 mg. of testosterone propionate. Pruritus returned within seven days and within one month was as severe as before the treatment started in July. Sublingual methyltestosterone in 25-mg. daily dosage again relieved the itching, and the drug has been continued to May, 1952.

Case 2.—A 54-year-old accountant with primary biliary cirrhosis first had jaundice in September, 1948, which has persisted. In December pruritus became troublesome. Examination showed skin xanthomas and gross hepatosplenomegaly. The stools were usually pale. The urine contained both urobilin and bilirubin. Laparotomy revealed no extrahepatic biliary obstruction. Pruritus was intractable and unaffected by phenolic lotions, antihistaminic drugs, or phenobarbitone. In December, 1951, a daily sublingual dose of 25 mg. of methyltestosterone was started and within five days the itching was less. Sublingual therapy was continued for three months and the pruritus did not recur. In March, 1952, oral therapy was stopped and 600 mg. of testosterone propionate in pellets was implanted subcutaneously. For two months the anti-pruritic effect was excellent, but it gradually became less effective in the third and fourth months after implantation. The pellets were then removed and weighed: 495 mg. of testosterone propionate had been absorbed in 127 days. Sublingual therapy with 25 mg. of methyltestosterone daily was then resumed, and this successfully controlled the pruritus for the succeeding two months.

Case 3.—A 69-year-old woman with an inoperable carcinoma of the hepatic common duct began to have progressive jaundice, pruritus, and loss of weight in November, 1951. Examination showed deep jaundice and gross enlargement of the liver. The stools were constantly acholic and the urine did not contain urobilin. Surgical exploration showed a primary neoplasm of the common hepatic duct, causing complete obstruction to bile flow. The patient was treated daily for eight days with linguets identical in shape, size, and taste with those containing methyltestosterone, but having no active substance. These inert "dummy" tablets had no effect on the itching. Methyltestosterone tablets were then substituted, and pruritus was relieved in six days; it recurred five days after stopping the testosterone. The patient was questioned about the pruritus by a physician who had no knowledge whether or not an active tablet was being given.

Case 4.—A 79-year-old woman with carcinoma of the main hepatic ducts developed rapidly progressive painless jaundice with pruritus in January, 1951. The liver was enlarged, the stools were usually pale, and the urine contained both urobilin and bilirubin. Phenobarbitone, antihistaminic drugs, and the local application of a phenol-containing lotion did not relieve the pruritus. In November she was started on sublingual methyltestosterone, 25 mg. daily. In six days the itching was completely relieved. On stopping the drug, the pruritus returned in three days and was allowed to become severe before sublingual methyltestosterone was again given, with further relief of the symptoms. In January, 1952, sublingual therapy was stopped and a subcutaneous implant of 450 mg. of testosterone propionate given. This was ineffective in controlling the itching, which returned in six days. Thirty-three days after the insertion the implant was removed and only 56.9 mg. had been absorbed. Sublingual testosterone treatment was once more effective. Intramuscular testosterone propionate in a dose of 25 mg. twice a day was tried, but proved of little, if any, value in controlling the pruritus. The patient died in April, and necropsy showed a carcinoma of the main hepatic ducts in the porta hepatis.

Case 5.—A 45-year-old woman, with a gall-stone in the common bile duct, began to have upper epigastric pain, nausea, and vomiting six weeks previous to admission. Jaundice and pruritus quickly followed, and the jaundice progressively deepened. Examination showed only hepatomegaly; the gall-bladder was not palpable or tender. The faeces were acholic. The urine showed bilirubin and a persistent absence of urobilin. Control pharmacologically inert linguets were started, and seven days later the pruritus was still very distressing to the patient. The inert linguets were then replaced by daily sublingual administration of a tablet containing 25 mg. of methyltestosterone. Within four days the itching was much less severe, and seven days after starting the drug pruritus had ceased. Operation showed a gall-stone impacted in the lower end of the common bile duct.

Case 6.—A 41-year-old woman with primary biliary cirrhosis started to have skin irritation in November, 1950. Although the urine was dark in colour jaundice was not noticed until December, 1951. Examination showed hepatosplenomegaly. The faeces varied in colour, and, although usually acholic, occasionally their colour was almost normal. Urine contained urobilin and bilirubin. Laparotomy failed to demonstrate any extrahepatic biliary obstruction. Pruritus continued severe and persistent, and in May, 1952, the patient was given daily 25 mg. of methyltestosterone sublingually. Itching lessened in five days, and within two weeks had completely disappeared. The pruritus remains controlled by 25 mg. of methyltestosterone four times a week.

Case 7.—A 48-year-old woman suffering from post-operative stricture of the common hepatic duct was operated on in September, 1948, for the removal of a cyst of the cystic duct. In May, 1949, she first experienced attacks, lasting about a day, of sudden epigastric pain with rigors, fever, and jaundice. These recurred every two to three weeks. Pruritus developed which was maximal during the attacks but was also experienced during the intervening periods. The patient was again operated on in June, 1951. A stenosis of the common hepatic duct was discovered, and an attempt to reconstruct the duct was only partially successful. The attacks continued and were still associated with pruritus, which caused her the acutest distress. In June, 1952, she was started on daily sublingual methyltestosterone, 25 mg., and in four days the pruritus ceased. Although the attacks of jaundice, rigors, and fever continue, there has been no recurrence of pruritus.

Comment on Cases

The subjects treated and the results obtained are summarized in the Table. Some side-effects of testosterone were recorded.

Effect of Sublingual Methyltestosterone (25 mg. daily) on Pruritus in Obstructive Jaundice

Case No.	Sex and Age	Diagnosis	Duration of Pruritus	Time Taken for Relief	Serum Bilirubin mg./100 ml.		Serum Total Cholesterol mg./100 ml.	
					Initial	Rise*	Initial	Fall*
1	F 54	Primary biliary cirrhosis	14 mths	7 days	10.0	8.5	600	180
2	M 54	Hepatic duct carcinoma	3 years	5 "	12.2	2.0	290	90
3	F 69	" "	3 mths	6 "	3.7	9.3	550	220
4	F 79	Stone in common bile duct	7 "	6 "	18.0	4.0	800	380
5	F 45	" "	6 weeks	4 "	—	—	—	—
6	F 41	Primary biliary cirrhosis	18 mths	5 "	7.8	6.0	640	220
7	F 48	Stricture of bile duct	46 "	4 "	—	—	—	—

* Values six weeks after beginning of methyltestosterone therapy.

The depth of jaundice tended to increase. Patients with continuing unrelieved bile-duct obstruction would be expected to show a steady deepening of icterus. How-

ever, with one exception (Case 5), the patients studied had been jaundiced for so long a time that the rate of increase had become very slow. In all the five subjects in whom serial serum bilirubin values were available testosterone seemed to increase the rate of rise of serum bilirubin. Patients should be warned that the testosterone therapy may make them more yellow and that this does not indicate a worsening of their liver function.

The serum total cholesterol tended to diminish. This was particularly so when the pre-treatment values were very high. A patient with a normal initial value (Case 2) showed only a slight fall with testosterone therapy.

Masculinization was noticed in three patients. Case 1 developed hirsuties nine months after starting daily sublingual therapy. The voice deepened. This necessitated stopping the drug. Treatment was resumed with 25 mg. sublingually every other day. Pruritus remained controlled and the masculinization has not progressed. Case 6 noticed a few hairs appearing on the chin within 11 weeks of beginning sublingual testosterone, 25 mg. daily. Dosage was reduced to 25 mg. three times a week, and the hirsuties has not progressed; itching has not recurred. Case 4 also developed some hirsuties three months after starting sublingual therapy. This did not distress the patient, and the testosterone was continued. The three other female patients in this series did not receive testosterone long enough for endocrine complications to develop.

Discussion

Pruritus cannot be evaluated objectively, and the value of any drug used in its treatment is very difficult to assess. The failure of "dummy" inert tablets to relieve the pruritus in two of our patients and the use of a "neutral" observer to assess the results helped to circumvent this difficulty. Pruritus may disappear spontaneously during the course of obstructive jaundice, even though the bile-duct occlusion is not relieved. This is usually associated with failure of liver-cell function. This could hardly explain the relief from pruritus in all of the patients treated in this series, particularly as in three subjects the itching recurred when the testosterone was withdrawn.

Testosterone propionate has been successfully used in the treatment of senile pruritus (Feldman *et al.*, 1942). There are few reports of its use in jaundice. Ahrens and his group gave 25 mg. of methyltestosterone daily by mouth to three patients suffering from the itching of primary biliary cirrhosis: in two there was conspicuous relief; in the other the testosterone had little effect. Parkinson (1952) was successful with oral testosterone in treating pruritus in a patient suffering from biliary cirrhosis.

The seven cases reported above all made a dramatic response to oral testosterone. The rationale of this therapy is not known. Pruritus in jaundiced patients is often attributed, on rather slender evidence, to irritation of cutaneous sensory nerves by retention of bile salts in the blood. Blood-bile-salt levels, however, do not correlate with the incidence of pruritus (Snell and Keyes, 1933; Sherlock and Walshe, 1947), and attempts to initiate or aggravate pruritus by giving bile salts have usually failed (Brulé and Cottet, 1942; Sherlock and Walshe, 1947). Moreover, bile salts incorporated in a lotion have been successfully used in the treatment of pruritus due to primary skin disease (Brulé and Cottet, 1942). Flink and Williams (1952) relieved pruritus with corticotropin in five patients with obstructive jaundice, and related this to a small fall in the blood-bile-salt level. The subjective improvement could equally well be correlated with the feeling of well-being induced by corticotropin. Other steroids have had limited trials for anti-pruritic effect. Ahrens and his co-workers, using progesterone and oestradiol, failed to influence pruritus in four patients suffering from primary biliary cirrhosis, but further trials are needed with other steroid drugs.

A high serum cholesterol and serum lipid level develops in prolonged obstructive jaundice of whatever cause. The

extent of the elevation can be correlated with the occurrence of skin xanthomas (Ahrens *et al.*, 1950). Testosterone lowers the total serum cholesterol level in primary biliary cirrhosis (Ahrens *et al.*, 1950; Parkinson, 1952), and we have confirmed this finding. This further action of testosterone in obstructive jaundice may therefore prevent or ameliorate the xanthomatous skin lesions.

Absence of bile from the intestines leads to steatorrhea with imperfect absorption of calcium and the fat-soluble vitamins. Patients with prolonged obstructive jaundice develop secondary changes in the bones with kyphosis, spontaneous fractures, and radicular pain. Androgen administrations result in a diminished urinary loss of calcium and phosphate and a conspicuous fall in urinary nitrogen (Reifenstein and Albright, 1947). Testosterone may therefore have an additional beneficial effect on the bone lesions of obstructive jaundice.

We have confirmed the rise in the serum bilirubin level in jaundiced patients given testosterone. Methyltestosterone has even been implicated as the cause of an obstructive type of jaundice in seven non-jaundiced patients receiving the drug for its androgenic action (Werner *et al.*, 1950). The mechanism of the jaundice is not known. The increase in the depth of jaundice should not be a contraindication to giving testosterone for its antipruritic action.

Masculinization in female patients is an unfortunate complication of testosterone therapy. Most patients are, however, willing to suffer this disability if the intolerable itching can be alleviated. The exact amount of testosterone needed to prevent itching is still unknown. In some subjects it may be possible to give just enough to relieve the pruritus and yet not induce masculinization. It is suggested that in female patients treatment should be started with 25 mg. of sublingual methyltestosterone daily for three weeks. This dose can then be given three times a week. In some patients it may be possible to reduce the dosage still further and still prevent itching. Male patients with chronic obstructive jaundice show signs of androgen deficiency, and benefit by the full daily dosage of 25 mg. of methyltestosterone sublingually.

Subcutaneous implants of testosterone propionate would seem to be an ideal method of exerting a continuous antipruritic effect. This is true if absorption is adequate (Case 2). However, in some patients absorption is very slow (Cases 1 and 4) and pruritus continues unrelieved. Subcutaneous testosterone propionate implants have therefore proved unreliable, and sublingual methyltestosterone administration is recommended for routine use.

Summary

Methyltestosterone (25 mg. daily sublingually) relieved pruritus within seven days in seven patients suffering from chronic obstructive jaundice. The rationale of this therapy is not known. Testosterone propionate by subcutaneous implant was not so effective, perhaps owing to inadequate absorption.

Other effects of prolonged testosterone therapy were an increase in the depth of jaundice, a fall in the serum cholesterol level, and masculinization in three of the six female patients treated.

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TETANUS SUCCESSFULLY TREATED WITH GALLAMINE TRIETHIODIDE

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The treatment of tetanus falls into two parts—an attack on the infecting organism and control of the muscular spasms. The infecting organism is dealt with by giving toxoid and antitoxin in amounts and by routes which vary widely, but all authorities agree in advising heavy dosage, some recommending intrathecal injection in addition to the intravenous and intramuscular routes; wound toilet is performed.

In the past, control of spasms has been attempted by heavy sedation, and since the introduction of the muscle-relaxing group of drugs D-tubocurarine and mephenesin have both been used in the treatment of tetanus. In this country, Spencer Wells (1858–61) was the first to describe the treatment of tetanus with woorara, which contains an active principle, curarine, isolated by Bous-sangault in 1828; of three cases treated, one recovered. Only two years previously Claude Bernard (1856) had given his original description of curare and discussed its mode of action.

Difficulties in Treatment

During subsequent years the use of curare in the treatment of tetanus has been reported on many occasions, but Cole (1934) and other authors have noted the difficulties for long encountered owing to the lack of a standard preparation. Ory and Grossman (1948) reported two recoveries after the use of curare; they found that the drug caused too much relaxation, the tongue often falling back and causing respiratory obstruction. They also advised the use of atropine to counteract increased bronchial secretion, another troublesome feature in cases receiving curare. Adriani and Ochsner (1947), commenting on five cases treated with curare, stated that one patient died an hour after the administration of a single dose of curare which had been followed by respiratory and circulatory failure; the cause of death was not determined but was probably in part due to curare. They found that the action of curare was extremely abrupt in onset and that the effective response lasted for an average of 20 to 30 minutes. As the dose needed to relieve spasm was too close to that causing complete curarization, they had great difficulty in avoiding respiratory depression and obstruction.

Godman and Adriani (1949), reviewing the management of cases of tetanus, felt that true evaluation was difficult owing to the wide variations between individual cases. They thought that, while the control of rigidity and spasm was essential, no relaxant was entirely satisfactory. For mild cases they preferred a combination of phenobarbitone and "tolserol" (mephenesin), but admitted that though barbiturates were good as sedatives they were of little use as relaxants unless given in doses which would produce anaesthesia. Except in mild cases they recommended early tracheotomy in order to prevent downward spread of upper respiratory infection. Their experience with curare and with curare in oil was unsatisfactory.