patient developed diabetes comparatively early in life, that he requires moderately large doses of insulin, and that he is in satisfactory control under the present regimen, all discourage any such change.

SUMMARY

A case is reported of Addison's disease occurring in a diabetic, maintained on various forms of therapy for 13 years.

The main items in his present regimen of treatment are cortisone, insulin and salt.

Recent literature concerning this combination of diseases is reviewed and the present forms of treatment are discussed.

This appears to be the 81st case of coexisting diabetes and Addison's disease reported in the literature.

The authors wish to record their appreciation of the co-operation and assistance of the various consultants who have aided in the maintenance and study of this patient over so many years, namely Drs. R. C. Bennetts, R. A. Cleghorn, Allen Gold, G. W. Halpenny, E. A. MacNaughton, E. S. Mills, A. E. Moll, C. J. Pattee, and I. M. Rabinowitch. Special thanks are due to Dr. Guy Joron, of the Division of Metabolic Diseases, Department of Medicine, Montreal General Hospital, who has been consulted during this patient's hospitalizations during the past 11 years, and who kindly reviewed the manuscript.

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# Jaundice Associated with Methandrostenolone (Danabol) Administration

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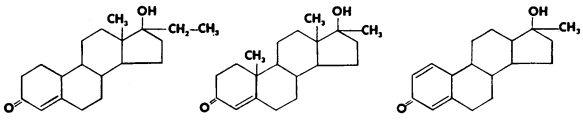
A NEW anabolic agent, methandrostenolone (Danabol), has recently been introduced for clinical use as a "tissue building" agent with an unusually favourable anabolic to androgenic ratio. The drug is used to stimulate appetite and decrease protein catabolism. It is closely related in structure to norethandrolone (Nilevar) and methyltestosterone.



Norethandrolone Methyltesterone Methandrostenolone

Jaundice due to intrahepatic cholestasis[1] with or without cholangiolitis[2] has become more common in recent years. It has been reported following administration of arsenicals,[3] methyl testosterone,[4, 5] para-amino salicylate,[6] methimazole,[7] sulfadiazine,[8] thiouracil,[9] chlorpromazine[10, 11] and norethandrolone.[12-14] It is the purpose of this paper to present the findings in a case of jaundice apparently due to methandrostenolone.

From the Department of Medicine, Toronto Western Hospital.

A 54-year-old white man fell from a scaffold while at work in April 1961. He sustained fractures of the right femur and of the supracondylar region of the right humerus. He was admitted to hospital in another town and underwent an open reduction of both fractures. He subsequently developed osteomyelitis, due to *Staphylococcus aureus haemolyticus*, in the right elbow and right hip.

He was first admitted to the Toronto Western Hospital in July 1961 for treatment of osteomyelitis and unhealed fractures. Extensive débridement of both areas, as well as removal of the head of the right femur, was carried out. In July he was given two bottles of blood during the operation on his hip. No further transfusions were given. Various antibiotics were administered throughout his long hospital admission, including intramuscular penicillin and streptomycin. He received eight injections prior to his discharge in December 1961 of a preparation (Dicrysticin) containing 300,000 units of procaine penicillin G, 100,000 units of potassium penicillin G and 0.25 g. of dihydrostreptomycin sulfate.

While in hospital his hemoglobin level remained about 12 g. %, and his white blood cell count ranged from 8000 to 12,000 per c.mm. His alkaline phosphatase value was 21.1 King-Armstrong units in November 1961. At the same time, estimation of his serum proteins revealed a total of 6.7 g. % with an albumin level of 3.65 g. % and a slightly raised beta-2 globulin level of 0.70 g. %, his other globulins being in the normal range.

About October 1961 it was noted that this man was becoming quite depressed. His right arm had healed but he had a permanent disability and marked limitation of movement. He continued to have a draining sinus from the right hip and quite a lot of pain and discomfort in the right leg and hip. His appetite decreased, he lost considerable weight, cried very easily and lost interest in his rehabilitation program. He was discharged to the Workmen's Compensation Board Hospital and Rehabilitation Centre at Downsview, Ontario, in December 1961.

Methandrostenolone, 10 mg. daily, was started on January 4, 1962, with the hope that it would increase the patient's appetite. In addition, he was given the antidepressant etryptamine acetate (Monase), 15 mg. daily, starting on January 9. Jaundice was first noted on January 19, and increased rapidly. He was readmitted to the Toronto Western Hospital on January 25, 1962, having received a total of 200 mg. of methandrostenolone.

The jaundice had developed suddenly and increased rapidly, without nausea, vomiting, pain, pruritus or malaise. The patient did not notice any change in his general condition apart from the yellow discolouration of his skin and sclerae. He had no history of previous jaundice, biliary tract disease or alcoholism.

Physical examination at this time revealed a jaundiced man who was chronically ill, with evidence of marked weight loss. The patient was obviously depressed and cried very easily. His pain tolerance was markedly decreased. There was no evidence of petechiae, skin rash or glandular enlargement. His liver and spleen were not palpable. There was no abdominal tenderness. He had a draining sinus in the region of the right hip and evidence of fractures and repeated infection in the right arm and right leg.

The urine was a deep orange colour. Urinalysis revealed the presence of 4+ bile, a negative test for urobilin, and a trace of urobilinogen. The stools were pale. His serum bilirubin showed a total value of 7.4 mg. %, the direct bilirubin being 4.1 mg. %. The serum alkaline phosphatase was 23.3 K.-A. units; thymol turbidity 5.5 units; serum glutamic oxaloacetic transaminase (SGOT) 300 units; hemoglobin 87% or 13.6 g. %. His blood smear was normochromic and normocytic. The platelet count was 350,000 per c.mm.; sedimentation rate, 37 mm. per hour; white blood cell count, 5700 per c.mm. with 40% neutrophils, 2% eosinophils, 41% lymphocytes and 6% monocytes. The prothrombin time was 15 seconds with a control of 15 seconds. The VDRL reaction was negative.

The patient received no further methandrostenolone or etryptamine acetate after admission. The only drugs used at this time were codeine, bisacodyl (Dulcolax) and a preparation containing equal parts of secobarbital and amobarbital (Tuinal). Soon after his readmission to hospital his depression began to improve spontaneously. His appetite returned, he gained weight, his mental outlook improved remarkably and he got out of bed and walked with the aid of a cane. Jaundice faded quite rapidly. The liver was never palpable or tender, and the temperature remained normal. No abdominal tenderness was noted, and the spleen was not enlarged.

By February 1, the serum bilirubin level was 3 mg. %, total, the direct fraction being 1.4 mg. %. The SGOT level rose to 515 units; the alkaline phosphatase level was 11.3 K.-A. units; thymol turbidity 3 units; serum protein 7.2 g. %, total, with an albumin concentration

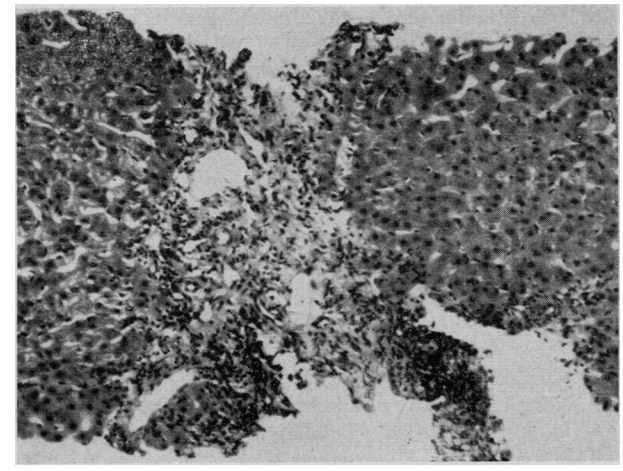


Fig. 1.—Low-power view of liver biopsy showing a portal area (× 120).

of 5.2 g. % and globulin 2 g. %. The urine showed decreasing bile content and the stools returned to normal. On February 11 his serum bilirubin was 1.5 mg. % with a direct fraction of 0.5 mg. %.

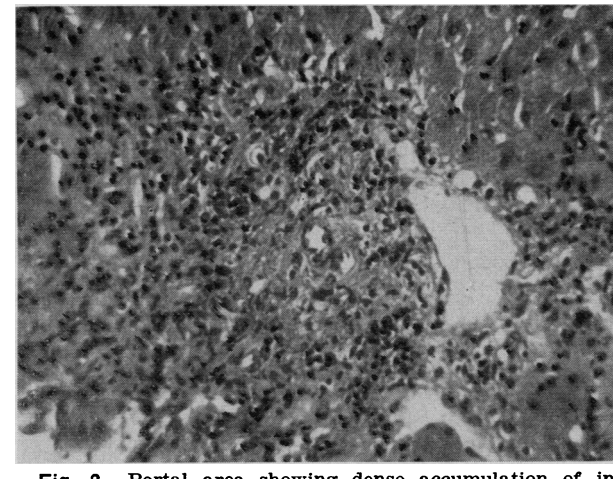


Fig. 2.—Portal area showing dense accumulation of inflammatory cells (× 200).

A percutaneous liver biopsy was performed on January 7. The pathologist's description was as follows. Microscopic examination of the liver biopsy stained

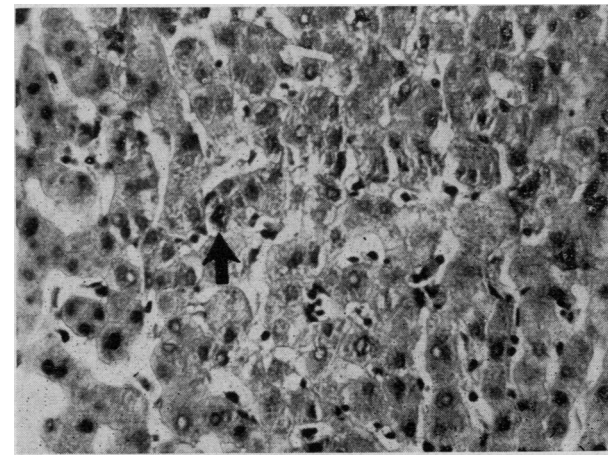


Fig. 3.—Liver biopsy showing bile plug (indicated by arrow) (×200).

with hematoxylin and eosin showed good preservation of the general liver architecture. There was no necrosis, and the liver cells appeared to be moderately well filled with glycogen. The portal areas were conspicuous by the presence of dense infiltrates of lymphocytes and occasional polymorphonuclear leukocytes (Figs. 1 and 2). These cellular aggregations showed no particular orientation within the portal areas and little tendency to infiltrate the adjacent liver parenchyma. In a few areas evidence of bile stasis (Fig. 3) was encountered, but these areas of bile stasis did not bear any constant anatomical relation to the cellular infiltrates. The picture was considered to be compatible with that of toxic or "drug" hepatitis.

A flat plate of the abdomen was negative. An intravenous cholangiogram was carried out on February 13; a normal gallbladder was revealed but the common bile duct could not be visualized. This examination was repeated and the same results were obtained. The patient was allowed to go home on February 14, 1962.

He was recalled for liver function tests on April 4, 1962. At this time his skin and sclerae were normal and there was no evidence of jaundice. His liver and spleen were not palpable. No abdominal tenderness was detected. Laboratory test results were as follows: serum bilirubin 0.4 mg. %, total, the direct fraction being 0.3 mg. %; alkaline phosphatase 10.6 K.-A. units; SGOT 59 units; and thymol turbidity 3 units. The urine was negative for bile and urobilin was present. The serum protein value was 6.6 g. %; the albumin level was 3.61 g. % and the gamma-globulin concentration 1.56 g. %, the values for other globulins being normal. There was a bromsulphalein retention of 20% at 45 minutes.

## DISCUSSION

The absence of fever, nausea, vomiting, malaise, enlargement of the liver and tenderness of the liver makes the diagnosis of viral hepatitis very unlikely in this case. Also, little support is provided by the microscopic appearance of the liver revealed at biopsy. Further, the possibility of serum hepatitis seems remote.

The absence of pain did not completely rule out the presence of cholelithiasis or neoplasm, but the physical findings, clinical course, and radiological evidence of a normal gallbladder lend little evidence to support such a diagnosis. We could not explain the failure of the common bile duct to fill on three occasions after administration of intravenous sodium iodipamide (Cholografin) when the gallbladder filled well. The patient did have considerable gas in his colon, in spite of adequate preparation, and this might have interfered with visualization of the biliary tract.

This man received etryptamine acetate, a monoamine oxidase inhibitor. Jaundice, hepatitis and fatal necrosis of the liver have been reported[15, 16] following the use of iproniazid and β-phenylisopropyl hydrazine (Catron), two other drugs in this group. However, when these drugs caused jaundice, the patients reported to date have been ill, with marked hepatocellular damage and often with acute hepatic necrosis, sometimes terminating in death. No known case of jaundice or evidence of liver dysfunction following the administration of etryptamine acetate has been discovered by the author in the literature to the time of writing.[17, 18] It is true that the drug has recently been withdrawn from the market because of the occurrence of granulocytopenia.[18] Our patient had no evidence of granulocytopenia; he had no malaise with his jaundice, and no evidence of hepatic cellular damage was seen in the biopsy of his liver. Although etryptamine acetate cannot be excluded definitely as the cause of jaundice in this case, on the basis of the present evidence it appears much more likely that methandrostenolone was the cause of this finding.

Methandrostenolone is chemically related to norethandrolone and methyltestosterone, both of which are known to give rise to jaundice of this type. All of these drugs have a common anabolic effect, methyltestosterone having the most potent androgenic effect. The pharmaceutical houses have been striving to produce a drug with a potent anabolic effect with little or no androgenic properties; methandrostenolone is thought to be one of the most favourable drugs in this field.

Wynn and his co-workers[19, 20] studied 30 patients on long-term methandrostenolone therapy and found increased bromsulphalein retention in 70% and SGOT elevation in about 30%. None of their patients developed jaundice, and this may explain why their SGOT levels were usually below 300 units. They concluded, in the light of their investigation, that bromsulphalein retention during administration of an anabolic steroid is not an indication to stop the drug, because bromsulphalein excretion may subsequently return to normal in spite of continued administration. They did, however, advise that it would be a wise precaution to withdraw the drug if the SGOT level exceeded 300 units.

Kaup and Preston[20] have recently reported a case of jaundice due to methandrostenolone. Their case differs from ours in that the SGOT level did not rise above 132 units, the jaundice persisted for a month unchanged, and liver biopsy at laparotomy showed only minimal mononuclear infiltration around portal areas. Here again there was no evidence of liver cell necrosis, and bile stasis was noted.

The findings in our case are similar to those reported in patients receiving methyltestosterone[4] and norethandrolone.[12] The onset of the jaundice is insidious and occurs after administration of a varying amount of the drug. In the case of methyltestosterone, jaundice is more common after prolonged use of the drug,[4] whereas jaundice due to norethandrolone has been reported after very short courses. The liver is non-tender and usually not enlarged; the bilirubin concentration is raised, especially the direct reacting fraction; SGOT levels may be very high; bile is present in the urine, and flocculation tests are usually normal. Liver biopsy reveals the presence of bile stasis and absence of marked cellular damage with minimal inflammatory cell response around portal areas. Withdrawal of

the offending drug usually results in gradual clearing of jaundice and hepatic abnormalities, although fatalities have been recorded.[21]

The patient described in this report has shown complete clearing of jaundice, but his bromsulphalein retention remains raised until the present and he has slight hypoalbuminemia and hypergammaglobulinemia. The latter two findings could be accounted for, however, by the persisting osteomyelitis of the right hip; this would also explain the raised alkaline phosphatase level in November.

Methandrostenolone is currently being used in the Geriatric Wing of the Toronto Western Hospital, and bromsulphalein retention has been noted to occur in patients so treated.[22] So far no patient has become jaundiced because the drug is discontinued as soon as liver function tests show any abnormality. This study is being continued.

Considering the widespread use of methandrostenolone, jaundice would appear to be a rare complication of its administration. It would, however, be wise to assess liver function frequently while this drug is being used. Bromsulphalein retention and a slight increase in the SGOT level appear to be the first indications of liver dysfunction.

## SUMMARY

A case of intrahepatic cholestasis and cholangiolitis due to methandrostenolone is reported. The similarities between methandrostenolone, norethandrolone and methyltestosterone are noted and discussed. Liver function should be assessed frequently during the course of administration of methandrostenolone. The drug should be withdrawn promptly on the first indication of any abnormality in order to prevent the development of hepatitis and its sequelae.

I am indebted to Dr. Wallace N. Lotto for referring this case to me; to Dr. Frederick A. Jaffe for his interpretation of the liver biopsy, and to Dr. W. Hurst Brown for his helpful comments.

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## PAGES OUT OF THE PAST: FROM THE JOURNAL OF FIFTY YEARS AGO

In this number appears a list of the members of the Canadian Medical Association. . . . It includes the names of thirteen hundred and sixty-six physicians, of whom thirteen hundred and twenty-seven are practising in Canada, the remaining thirty-nine being resident in the United States or abroad. The total number of physicians in Canada, according to the recent edition of the American Medical Directory, is seven thousand two hundred and eighty-seven. Consequently the Association comprises in its membership between eighteen and nineteen per cent. of the physicians of the entire country, or, approximately, one in every five.

This is a satisfactory proportion for the Association to have obtained so soon after its reorganization upon a permanent, national basis, and with the *Journal* just entering upon its third year. It is, however, only a beginning, and the time should not be far off when the Association will be able to claim that only one in every five of the physicians of Canada is *not* a member.

During the year the membership has increased over two hundred, and the work of organization has so far advanced that all but one of the provincial associations have now been brought into affiliation.—Editorial, *Canad. Med. Ass. J.*, 3: 128, 1913.

* * *

An interesting question has arisen through the publication, in a recent issue of a popular magazine, of an article on the Schafer phylacogens. The article is a laudatory one and is intended to make known to the public the benefits to be derived from the use of Dr. Schafer's phylacogens. The point of discussion is, however, an ethical one. Should a popular magazine encroach upon the medical world to the extent of publishing an article—be it non-scientific or otherwise—upon a medical preparation which is as yet in its infancy, in that the research work upon its therapeutic value is still more or less in the experimental stage; and what would be the probable result of such action? Messrs. Parke, Davis and Company protested against the publication, claiming that the result would be detrimental and would tend to prejudice physicians against the treatment. They contended that the publication of matter dealing with any medical preparation in a popular magazine at once opened the door to the suspicion that the remedy was being exploited for advertising purposes among the laity; and that the only legitimate means of expression on any such subject was through the medium of some medical journal. There is something to be said for this line of argument, but readers go too far when they assume that everything that appears in a newspaper or magazine is necessarily false or prejudicial to a new discovery.—Editorial Comment, *Canad. Med. Ass. J.*, 3: 130, 1913.