CORTICOSTEROIDS AND BILIRUBIN METABOLISM

Despite considerable advance in the understanding of bilirubin metabolism in recent years, surprising little is known about the manner in which adrenal corticosteroids lessen the hyperbilirubinemia of jaundiced patients. Anyone who has given corticosteroids to patients with liver disease cannot fail to be impressed with the dramatic reduction in jaundice that can occur. A fall in the serum pigment concentration is seen particularly in patients with viral hepatitis; after 4 to 6 days of steroid administration a drop to less than one-half of the original serum level is not unusual. This remarkable action of steroids is not limited to patients with viral hepatitis. Corticosteroids also can lower the serum bilirubin concentration of patients with complete extrahepatic biliary obstruction, although the rate of fall is usually of lesser magnitude than that observed in hepatitis. It is no wonder, then, that the mechanism or mechanisms responsible for this action of steroids have been the subject of active investigation since it was first recognized in the early 1950's.

Theoretically, corticosteroids could lower the serum bilirubin concentration of jaundiced patients by one or more of the following ways: (1) increase the excretion of bilirubin into the bile, (2) reverse or ameliorate the underlying disease process, (3) promote the renal loss of bilirubin, (4) change the apparent serum concentration of pigment by expanding plasma volume, (5) favor the extravascular distribution of bilirubin, and (6) alter the metabolic processes involved in the breakdown of heme or bilirubin.

One of the earliest hypotheses advanced was that corticosteroids augmented hepatic excretory function; i.e., reduction of hyperbilirubinemia was the result of choleretic properties of the hormone. The report of Patterson in 1954 that cortisone increased bile flow and bilirubin excretion in normal subjects supported this explanation, but more recent and better controlled studies of the excretion of bile following corticosteroids have failed to demonstrate either a choleretic or hydrocholeretic effect. These investigations were performed on patients without overt liver disease. Therefore, they do not exclude the possibility that a therapeutic effect of steroids increases biliary excretion in patients with active liver disease (e.g., hepatitis).

A great deal has been written during the past 15 years as to whether corticosteroids actually can reverse the primary derangements underlying any of many hepatic disorders for which the agents have been given. The rapid improvement in the clinical status and laboratory tests of hepatitis patients given steroids at first glance suggests such an effect. Yet although there is abundant information about the action of corticosteroids on biochemical processes, there is essentially no convincing evidence that they possess specific salutary properties with respect to "sick" hepatic parenchymal cells. In this regard the findings of Pagliaro that hepatitis renders hepatic lysosomes more labile is of particular interest, for Weissman has reported that corticosteroids stabilize lysosomal membranes. Prevention of lysosomal rupture with resultant cell death by autodigestion is a possible action of corticosteroids which has not been studied. Other mechanisms postulated for improvement in hepatic cellular function following steroids have included their anti-inflammatory activity with consequent diminution in intrahepatic edema and cellular infiltrate, and the suppression of autoimmune activity in "chronic active hepatitis." Whatever the mechanism, if steroids exert a beneficial effect on hepatic function, it is plausible to as-
assume that a return toward a normal pattern of bilirubin excretion should ensue. A fall in the hyperbilirubinemia should be accompanied by a sharp rise in the amount of bilirubin excreted into the bile. This in turn should be reflected by a detectable increase in the excretion of bilirubin derivatives, such as urobilinogen, into the urine and stool. Actual measurements of fecal and urinary urobilinogen coincident with steroid therapy have shown only a slight increase but the values still fall within the normal range. This amount is insufficient to account for the observed changes in the serum level of bilirubin. Therefore, while increased biliary excretion pigment cannot be excluded as a possible mechanism of steroid action in patients with hepatocellular disease, it could play only a relatively minor role in the reduction of hyperbilirubinemia. However, even if corticosteroids do promote increased biliary excretion, that cannot explain the clearing of jaundice in patients with complete extrahepatic obstruction. Clearly, some other mechanism must be operative in these patients.

A substantial increase in the renal loss of bilirubin could lower the serum bilirubin level whatever the cause of jaundice. Such an effect has been looked for and not found in either patients with hepatitis or complete obstruction. In fact, decreased renal excretion of bilirubin has been observed in patients with hepatitis, presumably the result of the diminished serum concentration of pigment.

An expanded plasma volume could reduce the serum bilirubin level as a result of dilution but this is highly improbable. The increase in plasma volume would have to be enormous (to the point where it could hardly escape notice) to account for the substantial drop in the bilirubin level brought about by steroids.

A change in the intravascular to extravascular distribution of bilirubin is a possible explanation which has not been specifically investigated. Steroids can alter membrane permeability and increased affinity or binding of pigment as a result could produce a fall in the serum bilirubin level. However, this explanation is not likely since clinical jaundice in this circumstance would probably be intensified rather than diminished following steroid administration.

In the absence of evidence for any other mechanism of action, serious consideration has been given in the past few years to the possibility that steroids directly affect the metabolism of heme or bilirubin. Reduction in the serum bilirubin level could result from either diminished conversion of heme, the shunting of heme into metabolic pathways that do not yield bilirubin, or an accelerated breakdown of bilirubin via alternate catabolic pathways. Since most bilirubin is derived from the hemoglobin heme of erythrocytes at the end of their physiological life span, prolongation of red cell survival would temporarily diminish the input of bilirubin and thereby decrease the pigment's concentration in the serum. The rate of red cell breakdown has been found to be increased in both hepatitis and obstructive jaundice, but the rates were not changed by corticosteroids. The input of bilirubin could be substantially reduced if corticosteroids seriously interfered with the production of "early labeled" bilirubin (ELB). Normally accounting for 10 to 20% of the total daily production, ELB is identified by the rapid appearance of isotopically labeled bilirubin in the circulation and bile shortly after the injection of a labeled heme precursor (glycine and δ-aminolevulinic acid). The chief heme sources of ELB are the bone marrow, where it is related in some way to erythropoiesis, and the liver, where it is derived from the heme moieties of rapidly turning over hepatic enzymes and cytochromes. The contribution of ELB to the hyperbilirubinemia of liver disease and extrahepatic obstruction is unknown although there is some evidence to suggest that it may be an important contributing source of bilirubin in extrahepatic obstruction. The effect of corticosteroids on ELB metabolism has been the subject of recent investigations in our laboratory. Studies were conducted on rats with external bile fistula, and with
the aid of a specially designed T-tube which permitted repeated quantitative collections of bile in dogs and human subjects.\textsuperscript{15} When \(\delta\)-aminolevulinic acid-4-\textsuperscript{14}C was the precursor, corticosteroids (cortisone acetate and prednisone) did not significantly alter ELB production in either the laboratory animals or man (R. D. Aach, M. L. Peterson, and J. Fernberg, \textit{in preparation}). Although our results fail to show reduction of ELB synthesis by corticosteroids in normal hepatic function, we have not excluded the possibility of steroids altering ELB synthesis in states of hepatic injury. There is an alternate possibility that corticosteroids "turn on" an alternate metabolic pathway of either heme or bilirubin degradation. There is no direct evidence to support or refute this, but there are several observations which suggest that the stimulation of an alternate catabolic pathway is a tenable hypothesis. These center about the recent documentation of previously unrecognized metabolic pathways for the disposal of heme and bilirubin. Studies of patients with the Crigler-Najjar syndrome and the Gunn rat, who have a deficiency of hepatic glucuronyl transferase,\textsuperscript{16} have shown that a remarkably constant state of bilirubin turnover is maintained even in the absence of this metabolic conversion to the excretory form of bilirubin.\textsuperscript{13} Heme breakdown and bilirubin production occur at normal rates; a steady state is achieved by the catabolism of bilirubin via a pathway which yields colorless diazo-negative polar breakdown products which are excreted in the bile and urine.\textsuperscript{17} Furthermore, evidence was reported very recently for an alternate route of heme degradation which does not involve bilirubin formation. Goldstein found that the heme moiety of hemoglobin contained in Heinz bodies (i.e., hemoglobin which had been modified by oxidation) was primarily converted, not to bilirubin, but to diazo-negative, water- and butanol-soluble metabolites which are excreted into the bile and to a lesser extent into the urine. Finally, there is another example of an alternate catabolic pathway of heme discovered in rats treated with allylisopropylacetamide. This agent is a potent inducer of hepatic heme synthesis but its administration is not followed by a corresponding increase in hepatic ELB.\textsuperscript{19} Since hepatic heme has a relatively short biological half-life, degradation presumably occurs via a pathway which does not yield bilirubin. The limitations of current methodology have not established the identity of metabolites produced by any of these pathways; their number and relationship offer an exciting challenge for future investigations. The existence of alternate routes for disposal of heme and bilirubin can no longer be questioned, but establishing the presence of such catabolic pathways obviously is a far cry from demonstrating that they are responsive to the action of adrenal steroids. There is, however, some precedent for such speculation. The activity of a number of enzymes has been shown to increase substantially as a result of steroid administration. Tyrosine-\(\alpha\)-ketoglutarate transaminase, glutamic-pyruvic transaminase, and tryptophan pyrrolase are but a few examples of enzymes which undergo steroid induction.\textsuperscript{11} Thus, the intriguing possibility that corticosteroids lower the serum bilirubin level in jaundiced patients by enhancing the activity of an alternate metabolic pathway certainly merits further investigation.

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REFERENCES


