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Itch in Liver Disease: Facts and Speculations

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"In both [types of icterus] . . . the whole body is itchy . . . the bilious particles being prickly" [1].

Pruritus in hepatobiliary disease is commonly believed to be caused by retention of bile acids with their sequestration in the skin. However, we have recently demonstrated that skin levels of bile acids in patients with cholestasis correlate poorly with pruritus. In this report, we present additional data concerning the relationship of pruritus to bile acid retention: (1) the urinary excretion of sulfated and nonsulfated bile acids was not significantly different in patients with cholestasis who itched compared to those who did not; (2) one patient with itch associated with a liver abscess had normal levels of bile acids in serum, skin, and urine; (3) patients with primary biliary cirrhosis who itched had lower serum bile acid levels than patients with mechanical biliary obstruction who did not itch.

These studies support our premise that pruritus in hepatobiliary diseases is not directly related to bile acid retention. They suggest that the type of cholestatic disorder, and not simply the magnitude of the cholestasis, as estimated by the elevation of serum bile acids, is important. We propose that the agent responsible for pruritus is produced in response to cholestasis, possibly through activation of the alternate pathway of bile acid synthesis. Properties of the hypothetical pruritogen are discussed.

INTRODUCTION

Itch is a frequent and very troublesome symptom in many types of liver disease, particularly those with prominent cholestatic features, such as biliary obstruction, primary biliary cirrhosis, and congenital cholestatic syndromes [2]. It is rare however in other types of liver disease, most notably alcoholic liver disease, even when severe cholestasis is present.

Since the demonstration in 1960 that the bile salt binding agent cholestyramine effectively relieves the itch of cholestasis, and concomitantly lowers serum bile salt concentrations [3], it has been widely assumed that retention of bile salts, with their deposition in the skin, is related in some way to the development of the pruritus. Although this assumption has several inconsistencies and has been seriously chal-

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lenged by the demonstration that skin levels of bile acids in patients with cholestasis correlate poorly with pruritus [4], there has been no reasonable alternative candidate for the role of cholestatic pruritogen.

The evidence for and against a role for bile acid retention as a cause of cholestatic itch is summarized in Table 1. Theoretical objections to assigning the role of cholestatic pruritogen to bile salts have been previously stated [4]. Some further considerations will be given here.

Although purified bile acids have produced itch when injected into skin blisters [8], or applied to dekeratinized skin at acid pH [9], in both studies unconjugated bile acids were found to be more pruritogenic than conjugates, and dihydroxy bile acids more frequently produced itch than did cholic acid. Based on these considerations, one would expect to see pruritus predominantly in diseases associated with retention of unconjugated bile acids, and those with a predominance of dihydroxy bile acids. These conditions are found in the stagnant loop syndrome [15], but these patients do not itch. In cholestatic liver disease, unconjugated bile acids are seldom detectable in serum [4,7]. Dihydroxy bile acids predominate in the serum in those liver diseases infrequently associated with pruritus, most notably alcoholic liver disease in all stages [16], and in advanced cirrhosis of all types [17]. Therefore, the experimental production of pruritus with bile salts must be interpreted with caution.

The effect of cholestyramine may not be mediated by its effects on bile acid metabolism, since it also relieves the pruritus of polycythemia rubra vera [18], and uremia [19].

We have studied further the possible relationship between bile acid retention and itch by measurement of serum and urinary bile acid concentrations, including separate quantitation of sulfated and nonsulfated bile acids in the urine, and could not demonstrate a relationship between pruritus and serum or urinary levels of any major bile acid.

METHODS AND PATIENTS

All patients were evaluated at Yale–New Haven Hospital. Itch was evaluated as previously reported [4], and fasting serum and 24 hour urine specimens were obtained.

Serum bile acids were measured as described previously [4]. For measurement of urinary bile acid excretion an aliqot of 5 to 100 ml of urine was alkalinized to pH 11 with 1 N sodium hydroxide and slowly percolated through a 1 × 10 cm column of SM-2 (XAD-2) [20]. Bile acids were eluted with 100 ml of methanol, which was flash

TABLE 1

Conflicting Data about the Relationship Between Itch and Bile Salt Retention in Cholestasis. For a fuller discussion, see text.

For	Against
1. Relief with cholestyramine [3,5]	1. Poor correlation with serum bile salts [4,10,11,12]
2. Correlation with serum bile salt levels in certain diseases [6,7]	2. Relief with phenobarbital treatment without a decrease in serum bile acids [13]
3. Experimental production of itch with pure bile salts [8,9]	3. Relief with androgen therapy with a rise in serum bile acids [7,14]
4. Correlation with skin surface bile salt concentrations [10,11]	4. Lack of correlation with skin *tissue* levels of bile acids [4]

TABLE 2

Urinary Sulfated and Nonsulfated Bile Acid Excretion (mg/24 hr) in Biliary Obstruction (Mean and Range). One patient with itch had pruritus gravidarum; all of the others had mechanical biliary obstruction.

	Itch	No Itch	*p*
No. of Patients	5	6	
Sulfates	9.8 (0.4–15.9)	5.8 (0.8–15.5)	NS
Nonsulfates	9.7 (0.8–23.3)	5.1 (1.9–12.2)	NS
Total (mg/24 hr)	19.5 (1.9–39.1)	10.9 (2.7–17.7)	NS

evaporated. The residue was reconstituted in 2.0 ml of chloroform: methanol 1:1; sulfated and nonsulfated bile acids were separated by column chromatography using 1 × 25 cm columns of Sephadex LH-20 [21]. After addition of internal standard, the bile acids were quantified using the same method as for serum samples.

RESULTS

The urinary excretion of bile acids in patients with cholestasis, in relation to the presence or absence of itch, is presented in Table 2. Although patients with itch had higher mean excretion of individual and total bile acids than those without itch, this was not statistically significant because of the wide range of values.

The percent of total urinary bile acids present as sulfates was similar in all groups (Table 3). As reported by others [21,22] most of the monohydroxy bile acids are sulfated, but cholic acid is mostly unsulfated.

One patient (not included in the above) without cholestasis, but with itch associated with liver disease, was particularly instructive. A 41-year-old diabetic lady presented with a five week history of daily fevers and persistent itching. Investigation revealed no evidence of cholestasis except for a serum alkaline phosphatase of 153 (normal 10–70 I.U.). A leukocytosis of 20,700 was present and a large right lobe defect was demonstrated on liver scan. Three days after surgical drainage of a staphlococcal liver abscess her itching disappeared. Analysis of preoperative serum and a 24 hour urine specimen showed total serum bile acids of 1.6 μg/ml (normal less than 2.0 μg/ml) and urinary excretion of less than 1.0 mg/24 hrs. (normal).

A skin specimen, obtained at surgery [4], contained only traces of bile acids. This patient thus had itch associated with liver disease but no demonstrable bile acid retention.

Analysis of serum bile acid data by disease category in relation to itch is shown in Table 4. Within individual disease categories, the mean level was higher in patients with pruritus. However, patients with mechanical biliary obstruction and no itch had

TABLE 3

Percent of Total Urinary Bile Acid Present as Sulfates (mean ± SD). Numbers in brackets indicate the number of patients studied. Controls were patients without cholestasis admitted for non-hepatobiliary surgery.

	Monohydroxy	Dihydroxy	Trihydroxy	Total
Cholestasis with Pruritus (5)	80.6 ± 33.1	66.8 ± 24.5	24.2 ± 18.4	46.7 ± 13.1
Cholestasis without Pruritus (6)	86.7 ± 15.0	79.5 ± 12.6	20.5 ± 15.1	51.5 ± 16.8
Controls (8)	82.6 ± 28.0	72.5 ± 24.5	24.7 ± 28.8	66.8 ± 26.2

TABLE 4
Serum Bile Acid Levels by Disease Category (μg/ml). The miscellaneous group includes four subjects with pruritus gravidarum, two with alcoholic liver disease, and 5 with congenital cholestatic syndromes.

	Itch		No Itch		
	Number	Mean ± SEM	Number	Mean ± SEM	*p*
Primary Biliary Cirrhosis	34	25.6 ± 4.0	15	13.5 ± 3.7	<0.01
Mechanical Biliary Obstruction	11	90.8 ± 5.2	9	33.2 ± 4.3	<0.005
Miscellaneous Cholestatic Diseases	14	54.1 ± 7.9	—	—	—

higher serum bile acid levels than did patients with primary biliary cirrhosis who itched.

DISCUSSION

The absence of a significant difference in bile acid excretion in patients with cholestasis and itch compared to those without itch (Table 2) makes it unlikely that urinary excretion of bile acids is a protective mechanism with respect to pruritus, as suggested previously [11]. There was also no difference in the fraction of urinary bile acids present as sulfates in the two groups of patients (Table 3). Therefore it is unlikely that large differences in the retention of either sulfated or nonsulfated fractions could correlate with pruritus. Peak serum bile acid levels occur postprandially, but we used fasting levels because they correlate well with skin levels [4].

Since the levels of serum bile acids in different disease categories in which pruritus occurs are quite dissimilar (Table 4), the type of hepatobiliary disease, and not simply the magnitude of the cholestasis, may be an important determinant of itch. It is possible that a pruritogen is produced in cholestasis, and that production of this pruritogen begins at different levels of cholestasis, depending on the underlying disease and the mechanism of the cholestasis.

The pruritogen produced in response to cholestasis must possess certain properties (Table 5). One possibility is that the pruritogen is produced as a result of "activation" of the alternate pathway of bile acid synthesis beginning with 26-hydroxylation of cholesterol (Fig. 1). Bile acid synthetic pathways in man are incompletely understood. However, the major pathway, which begins with 7α-hydroxylation of cholesterol, results in microsomal alterations of the cholesterol steroid nucleus before mitochondrial oxidation of the side chain [23]. The existence of an alternate pathway in man, in which primary oxidation of the side chain precedes changes in the steroid nucleus, is inferred because of the presence in cholestasis of 3-β-cholest-5-ene-24-oic acid, in which the cholesterol nucleus is unchanged [4,24,25]. This pathway is demonstrable in patients with a bile fistula [26].

The known correlates of cholestatic pruritus are compatible with the above hypothesis. Cholestyramine administration enhances bile salt synthesis by the 7α-hydroxylase pathway [27], and perhaps thereby decreases activity of the alternate

TABLE 5
Properties of Hypothetical Cholestatic Pruritogen

1. Excreted in cholestatic bile.
2. Production and/or excretion affected by therapy with cholestyramine, phenobarbital [24], estrogens [25], androgens [26], and possibly thyroxine [28].
3. Dependent on relatively good parenchymal liver function.

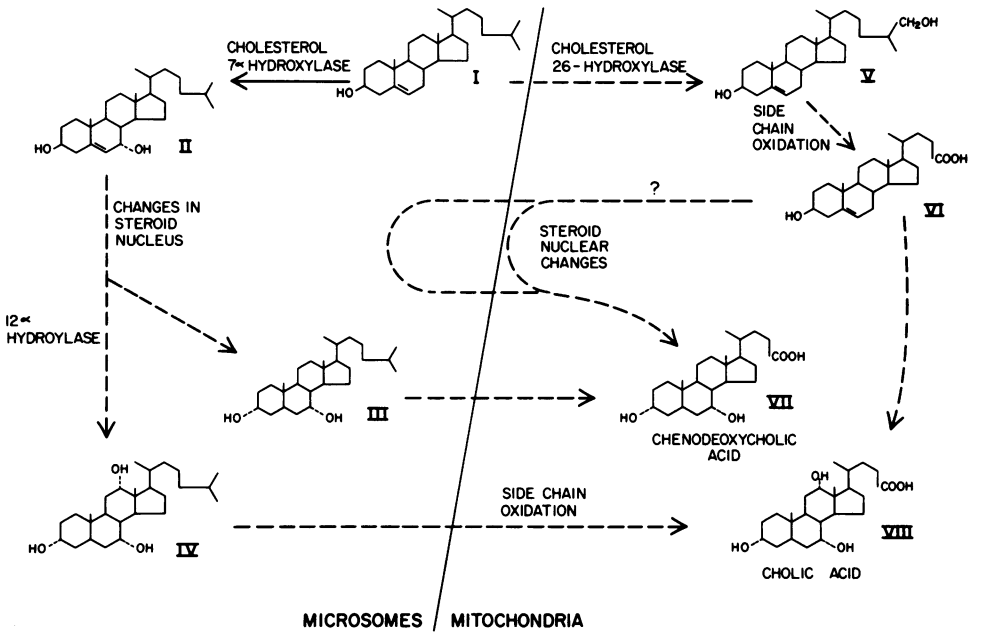

FIG. 1. Simplified schematic diagram of possible bile acid biosynthetic pathways in man. The "alternate" pathway on the right is primarily mitochondrial, and appears to be activated in cholestasis, as evidenced by accumulation of compound VI.

pathway. Alternatively it may enhance biliary excretion of the pruritogen by stimulation of bile-salt-dependent bile flow. Phenobarbital [27,28], estrogens [29,30], and androgens [30] all interact with the bile salt synthetic pathways, although effects of these on the "alternate" synthesis pathway are unknown. The rarity of itch in alcoholic liver disease may also be explained by this hypothesis. Since it requires intact mitochondrial cholesterol side chain oxidation to "activate" the alternate pathway, the pruritogen may not be synthesized in those hepatic diseases where mitochondrial damage is a prominent feature. Alcoholic liver disease is such a condition [31].

Pruritus in thyrotoxicosis is associated with elevations of serum levels of chenodeoxycholic acid [32]. It is of interest that thyroxine also stimulates cholesterol 26-hydroxylase [33], in view of the above hypothesis.

If this hypothesis is correct, then bile acid synthesis by the alternate pathway must begin at a different level of cholestasis in extrahepatic biliary obstruction than in primary biliary cirrhosis (Table 4). The pruritogen should be identifiable as one of the intermediates or products of this pathway. In this, and our previous study [4], we were unable to find a correlation of pruritus with one such compound, 3-β-cholest-5-ene-24-oic acid. Therefore the hypothesis has no direct proof.

Other possibilities can be formulated. For example, it is intriguing to speculate that a final common pathway may exist to cause pruritus in cholestasis, uremia, and polycythemia, since these conditions all respond to cholestyramine administration [18,19]. Similar vascular and/or hormonal changes might occur in all of these conditions, or the same pruritogenic compound might be produced.

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