Metabolic Studies in Patients with Cancer of the Gastrointestinal Tract

XVII. The Conjugation of Phenols*

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INTRODUCTION

Hepatic dysfunction in patients with gastrointestinal cancer was found in this hospital to be a relatively frequent abnormality (1). Moreover, the functional derangement of the liver in most instances was associated with an altered chemical composition of the organ (2). Of 18 patients with cancer of the stomach, the livers of 16 had fatty infiltration and all probably had a decreased glycogen content.

One of the several tests used to ascertain the presence of hepatic insufficiency in the patients studied was their ability to synthesize and conjugate glucuronic acid. The formation of and the conjugation of glucuronic acid with aromatic compounds is apparently a function of the liver, and in the presence of hepatic parenchymal disease that function is considerably impaired (4). The daily excretion of abnormally small amounts of glucuronate in the urine was found in 44 of 50 patients with cancer of the gastrointestinal tract (1).

Much of the phenol and *p*-cresol excreted by the body is detoxified by conjugation with glucuronic acid (4). This conjugation, either with sulfuric or glucuronic acid, has been shown to take place primarily in the liver (6). The excretion of total phenols, on the other hand, appears to be a function of the diet ingested and the degree of intestinal fermentation (7). From the evidence it was believed that measurement of the urinary excretion of conjugated phenols should serve two purposes: It would (a) provide an index of hepatic function, and (b) perhaps explain the cause for a low urinary excretion of glucuronates by the patient with gastrointestinal cancer.

CLINICAL MATERIAL AND METHODS

The excretion of free and conjugated phenols by three groups of patients was measured. The first group consisted of 12 normal adults who were used as controls to determine the fraction of the total phenol excreted in the conjugated form. The second comprised 5 patients with hepatic cirrhosis who manifested both clinical and laboratory evidence of hepatic decompensation. The third was composed of 12 patients with cancer of the gastrointestinal tract; all these had a considerable degree of hepatic insufficiency as determined by several different hepatic function tests.

All the persons studied had taken normal diets. During the period of observation all excreted from 1 to 2 liters of urine per day. None received any phenolic compounds.

The free and conjugated phenols were measured in the urine by the method of Folin and Denis (3). The final color developed was read in a Pfaltz and Bauer fluorophotometer. The urinary content of glucuronates was determined by the technic of Maughan and his associates (5).

RESULTS

Normal persons.—The daily excretion of conjugated and total phenols, and that of glucuronate, was measured in the urine of 12 normal persons. Their urines were collected for periods of from 1 to 4 days. The urinary output of total phenol ranged from 228 to 807 mgm. and averaged 461.5 mgm. per day. Of these amounts, the conjugated phenol ranged from 24 to 43 per cent, and averaged 31.4 per cent (Table I).

The urinary excretion of glucuronate by these 12 subjects ranged from 308 to 800 mgm. and averaged 462.2 mgm. per day. These outputs of glucuronates are in agreement with those ascertained for another group of normal subjects in a previous investigation (1).

Patients with hepatic cirrhosis.—In contrast to the findings in normal persons were those obtained for the urinary output both of conjugated phenols and glucuronates by 5 patients with hepatic cirrhosis. The urines of these patients were collected for from 2 to 4 days. Although the daily excretion of total phenols was within normal limits (Table I), the

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conjugated fraction of that substance was lower than that of the lowest normal value in 4 of the 5 instances, and lower than the normal average value in all. The excretion of total phenols ranged from 216 to 945 mgm. and averaged 516.4 mgm. per day, and the conjugated fraction ranged from 9 to 25 per cent of the total and averaged only 15.2 per cent. The urinary output of glucuronates, likewise, was in all instances abnormally low. These ranged from 118 to 186 mgm. and averaged 153.4 mgm. per day.

Patients with cancer of the gastrointestinal tract.— The phenols and glucuronate were measured in the urines of 12 patients with gastrointestinal cancer. The urine specimens were collected for from 1 to 4 days. Of the 12, 9 excreted normal total amounts of phenols, and 10 a normal conjugated fraction (Table I). The total phenol outputs ranged from 134 to 892 mgm. and averaged 422.1 mgm. per day; of these amounts from 19 to 42 per cent were conjugated.

It is interesting to note that although there appears to be no defect in the capacity of patients with gastrointestinal cancer to esterify phenol, their ability to synthesize or conjugate glucuronic acid is impaired. Among the 12 subjects studied, the daily excretion of glucuronates was abnormally low in 10. The daily outputs of this compound ranged from 75 to 336 mgm. and the average was 207.2 mgm., or less than one-half the normal value.

Table I: The Daily Excretion of Total and Conjugated Phenols and of Glucuronates in the Urine of Normal Subjects, of Patients with Hepatic Cirrhosis, and of Patients with Cancer of the Gastrointestinal Tract

Subjects	Total phenols		Percentage of total phenols conjugated		Glucuronates	
	Range, mgm. per day	Average, mgm. per day	Range	Average	Range, mgm. per day	Average, mgm. per day
12 normal persons	228–807	461.5	24–43	31.4	308–800	462.2
5 patients with hepatic cirrhosis	216–945	516.4	9–25	15.2	118–186	153.0
12 patients with cancer of the gastrointestinal tract	134–892	422.1	19–42	30.2	75–336	207.25

DISCUSSION

The urinary excretion of total phenols apparently is influenced chiefly by the diet and the formation of those compounds in the gastrointestinal tract (7). Accordingly alterations in the output of total phenols by the groups of patients studied cannot be considered as significant, since no attempt was made to standardize their diets.

On the other hand, the esterification of phenols, chiefly with glucuronic and sulfuric acids, presumably occurs principally in the liver (6). When its cells are damaged, as in the livers of patients with decompensated hepatic cirrhosis, the ratio of phenol esters to total phenols would be expected to decrease. This expectation was confirmed by the abnormally low percentage values of conjugated phenols found in the urines of the 5 patients with hepatic cirrhosis included in the present study. Since glucuronic acid normally is used for the detoxication of phenols, it is possible that a limitation in the conjugation of those compounds might have limited the requirement for the synthesis of glucuronic acid. On the other hand, an *inability* of the liver to synthesize or conjugate glucuronic acid might have been the cause of a decreased detoxication of phenols by the patients studied.

The patients with cancer of the gastrointestinal tract have been shown to suffer from a considerable degree of hepatic dysfunction. This dysfunction is manifested in an impaired ability of their livers to fabricate prothrombin and albumin, to esterify cholesterol, to distribute properly vitamin A, to metabolize fat, to excrete bilirubin, to convert that pigment to urobilinogen, and to synthesize or conjugate glucuronates (1, 2). Despite this degree of hepatic insufficiency, it would appear from the present study that these patients still have a normal capacity to esterify phenols, a hepatic function notably decreased in the patients with decompensated cirrhosis of the liver who were studied here. The fact that the esterification of phenols does occur in most instances within normal limits, but that the excretion of glucuronates usually is abnormally low, indicates that other acids, probably sulfuric, now have taken over that function of glucuronic acid. To make this explanation more tenable, it would be necessary to demonstrate in these patients an increased urinary excretion of ethereal sulfates, determinations of which have not been made in the present investigation.

From the data at hand, then, it would appear that the impaired synthesis or conjugation of glucuronic acid by the liver of the patient with gastrointestinal cancer did not limit the capacity of the organ to conjugate phenols. Therefore, it is possible that the association of an abnormally decreased urinary excretion of glucuronates and an impaired ability to detoxify phenols by the patients with cirrhosis of the liver may have no causal relationship, and both might be due to damage of separate hepatic functions. Hepatic damage due to different causes will not always affect the same hepatic function. The fact that pa-

tients with cirrhosis of the liver no longer can conjugate phenols normally, but that patients with gastrointestinal cancer can do so despite the impairment of several other liver functions, may be another example of that phenomenon.

CONCLUSIONS

1. Patients with hepatic cirrhosis have an impaired ability to conjugate phenols. It is possible that the abnormally small amount of glucuronates excreted by these persons might be either the cause or the result of such impairment.

2. Patients with gastrointestinal cancer, who are known to have also a considerable degree of hepatic insufficiency, have a decreased capacity to synthesize or conjugate glucuronic acid. Nevertheless, their ability to esterify phenols remains unimpaired.

3. It is possible that the detoxification of phenols in patients with cancer of the gastrointestinal tract is not dependent necessarily upon the synthesis of glucuronic acid.

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