DETOXICATION MECHANISM OF GLUCURONIC ACID WITH SPECIAL REFERENCE TO ITS RELATION TO LIVER FUNCTION

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I. INTRODUCTION

That glucuronic acid first reported by Jaffe in 1878 (hereafter termed G-acid) plays an important role in combined detoxication has been clarified by Fischer, Oberst, Gross and others. Further it has been demonstrated by Embden, Persona, Sauer, Boku, Nasarijans, Bueding and Nsihimura that the liver is the most important organ for the production and combination of G-acid. However, no method had hither to been available for preparation of G-acid other than from combined G-acid excreted, until Ishidate in 1951 succeeded in synthesizing this acid, since when it has become possible to administer large amounts of G-acid. But it has been questioned by Lipschitz whether G-acid so administered is utilized effectively as in the case of body G-acid, in production of combined G-acid in the liver. In 1954 however, Douglas and Packham undertook experiments with radio-active G-acid, and found that some of the sodium salt of this acid is directly utilized in the combination involved. However in this combination of G-acid the liver plays an important role, and it is difficult to believe that G-acid administered from outside the body is utilized unconditionally in combined detoxication and it is supposed that the liver function has some influence. Hence the writer investigated the detoxication mechanism especially in relation to liver function, of G-acid, with the fate of blood phenol, a substance most generally subjected to combined detoxication by G-acid, as an indicator.

II. METHOD OF QUANTITATIVE ESTIMATION

1. Estimation of blood phenol

Theis and Benedict's method was followed.

Testing reagents:

1. Reagent for removal of proteins: 10% solution of the sodium salt of Wolfram acid, 2/3 N H_2SO_4.

2. Phenol test reagent: Basic solution consisting of 1.5 g para-nitroanilin dissolved in dilute HCl (50 ccm water added to 40 ccm of concentrated HCl). This solution withstood preservation.

Diazonation: to 10 ccm of above solution was added 3 ccm of a 10% sodium nitrite solution, when the need arose.

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3. 1/10 N iodine solution: to 1.2692 g of iodine and 5.0 g of potassium iodide was added water to make a volume of 10 ccm.

4. Basic solution: about 1 g of phenol crystals was dissolved in 1.01 of 1/10 N HCl, and the concentration assayed by Messinger and Voltman's method; namely, to 25 ccm of the above solution contained in a flask of about 250 ccm capacity was added 50 ccm of 1/10 N NaOH, and after heating to 65° C, 25 ccm of a 1/10 N iodine solution was added. The whole was tightly closed and after standing for 30 minutes at room temperature, 5 ccm of concentrated HCl was added and titrated with 1/10 N sodium thiosulphate solution ($Na_2S_2O_7 \cdot 6H_2O$), employing 2-3 drops of starch solution as indicator.

Computation. If the amount of sodium thiosulphate required in the titration is taken to be A, then $(25-A)\times 1.567$ will be the amount of phenol contained in 25 ccm.

Experiment:

1. Free phenol. 5 ccm of blood was placed in a test tube containing 10 ccm of water, and after hemolysis by immediate shaking, was filtered after addition of 5 ccm of a 10% solution of sodium wolframate and 5 ccm of 2/3 N H_2SO_4 (to remove the proteins). To 5 ccm of the filtrate was added 0.5 ccm of a 50% solution of sodium acetate (to make the reaction weakly acid) and 1% arabic gum (protective colloid), and after shaking, 0.5 ccm of diazo para-nitroanilin was added. After one minute 1 ccm of 20% Na_2CO_3 was added to droduce a color, which was examined with a Pulflich's colorimeter using 0.5 ccm cubett and a S 53 filter.

2. Total phenol. To 5 ccm of the filtrate with the proteins removed was added 0.13 ccm of concentrated HCl (S.G. 1.19) and heated in a boiling water both for 10 minutes. After cooling the mixture was neutalized with 10% HaOH (about 7 drops) and titrated in a manner similar to the above for free phenol.

3. Combined phenol: Total phenol minus free phenol.

2. Quantitative estimation of urinary glucuronic acid

A modified method described below was adopted from Fischman's method[18] and those of Ratisch, Kertesz, Sawada and Machida.

Reagents:

1. Naphthoresorcinol solution. 0.1 g of naphthoresorcinol (Bayer) was dissolved in 50 ccm of distilled water and stored in an incubator at 37° C for 24 hours. The filtrate obtained after filtration was used as a testing reagent. When not needed it was stored in a refrigerato protected from light when it remained effective for 4-5 days.

2. Concentrated HCl (S.G. 1.18).

3. 95% ethanol.

4. Purified ether, with peroxidases completely removed by double distillation.

Materials to be examined: To 5 ccm of urine was added a platinum loopful of yeast (product of Toyo Brewery Co.) and mixed. After incubation for 24 hours at 28° C the supernatant obtained after centrifugation at 2000 RPM for 30 minutes was examined. In general this supernatant was diluted 50 times, but when concentrated was diluted 100 times. There was in general no need to remove the proteins.

Operation: to 2 ccm of the treated urine was added 2 ccm of naphthoresorcinol (testing reagent) and 2 ccm of concentrated HCl and mixed. The mixture was heated in a boiling water both for 45 minutes, and placed in ice for 10 minutes after cooling. Next, 2 ccm of 95% ethanol and 15 ccm of ether were added and vigorously shaken for 60 seconds. When allowed to stand a beautiful violet blue ether and water layers separated out. The ether layer was pipetted off carefully and 1 ccm of it placed in a cubett and examined in a Pulflich's colorimeter, using a S 35 filter.

Recently Fishman's method has received reconsideration, and Ishidate has reported that the method using naphthoresorcinol picrate is comparatively good.

III. EFFECT OF G-ACID IN THE NORMAL STATE ON THE BLOOD PHENOL, AND EXCRETION OF G-ACID ADMINISTERED IN THE URINE

1. Introduction

In the normal state there is found 1.3–1.5 mg% of free phenol in the blood but when G-acid administered partakes directly in combined detoxication there will arise the probability that a large quantity of G-acid administered will either lower considerably the normal free phenol in the blood or entirely. But no literature is available regarding this at present. Again regarding the excretion of G-acid administered in the urine, Mayer and Baumgarten stated that the majority is decomposed in the body, while Huerthle and Quick stated that the majority is excreted in the urine without being decomposed. The views being thus divided, the writer undertook investigations firstly regarding this problem.

2. Effect of G-acid on the normal blood phenol (Table 1)

a. Experimental method

Healthy male adult white rabbits of body weight 2.5 kg received intravenous injections of large amounts of G-acid (Guronsan prepared by Chugai Seiyaku Co. and consisting mainly of sodium glucuronate, and hereafter used throughout the present series of investigations as G-acid) on an empty stomach in the morning. The dose was 500–1 500 mg per kilogram of body weight. Blood was removed from the ear vein at intervals of 30 minutes for a period of 90 minutes, and the free phenol in blood was estimated.

b. Experimental results

In all cases no significant changes were found.

TABLE 1. Variation of Free Phenol in Blood after Intravenous Injection of Glucuronic Acid to Normal Rabbits

Case No.	Weight (kg)	Amount used mg (ccm)		Free phenol in blood mg%			
		Per kg	Total	Before	30 min.	60 min.	90 min.
11	2.470	500	1 300 (5.2)	1.63	1.59	1.60	1.65
12	2.890	1 000	2 900(11.6)	1.70	1.73	1.68	1.68
13	1.500	1 500	3 700(14.8)	1.28	1.28	1.30	1.32

3. Urinary excretion of G-acid administered under normal conditions (Table 2)

a. Experimental method

Healty male rabbits of body weight 1.6–2.0 kg were fixed by the four limbs in the supine position, and 100–200 mg of G-acid was injected into the thigh muscles. Urine was collected with a Nelaton's catheter fixed in position and the urinary G-acid excreted was estimated at 1 hour intervals.

b. Experimental results

For 1 to 2 hours after injection intramusculaly of G-acid there was a marked rise in urine excretion while the concentration of urinary G-acid showed a conspicuous rise. Thus there was noted great increase in G-acid excretion, the total excreted in the first 3 hours accounting for 15–26% of the amount administered.

TABLE 2. Glucuronic Acid Excreted in Urine after Intramuscular Injection of It to Normal Rabbits

Case No.	Amount used	Amount of urine and excreted G-acid	Before	1 hr.	2 hr.	3 hr.	Total of excreted G-acid / Amount used %
7	200 mg 4 ccm	Urine (ccm)	5.0	11.0	12.0	3.8	15%
		G-acid (mg%)	20	114	134	130	
		G-acid (mg)	1.00	12.54	16.08	4.94	
8	200 mg 4 ccm	Urine (ccm)	7.0	15.0	11.5	6.0	20%
		G-acid (mg%)	16	124	148	140	
		G-acid (mg)	1.20	18.60	17.02	8.40	
9	100 mg 2 ccm	Urine (ccm)	6.5	21.0	7.5	6.0	26%
		G-acid (mg%)	15	46	116	141	
		G-acid (mg)	0.98	9.66	8.70	8.46	
10	100 mg 2 ccm	Urine (ccm)	5.5	12.0	10.5	40	23%
		G-acid (mg%)	18	96	100	110	
		G-acid (mg)	0.99	11.52	10.50	4.40	

4. Summary and considerations

In the normal state when a large quantity of G-acid is administered no significant change is noted in the blood free phenol, but there is seen a marked rise in the amount of urinary G-acid excreted. In other words under normal conditions most of the G-acid administered do not pertake in combined detoxication, and all seem to be excreted in the urine.

IV. DETOXICATION EFFECTS OF G-ACID DURING PHENOL LOADING UNDER NORMAL LIVER FUNCTION CONDITION (Table 3, Photographs 1 and 2)

1. Introduction

In the previous pages it was made clear that most of the G-acid administered under normal conditions do not partake in detoxication. However Packham has shown that in normal rats, when radioactive G-acid is administered during naphthol loading some of the sodium glucuronate is utilized directly in combined detoxication. Therefore the writer investigated the state when G-acid

is administered during phenol loading, and indirectly tested the results of Packham by examining the conditions necessary for the G-acid administered to partake in detoxication.

2. Experimental method and results

a. Experimental method

Into healthy white male rabbits weighing about 2 kg, 6 ccm per kg (0.3 g) body weight of a 5% aqueous solution of phenol was given orally with a gastric sound. Immediately after, a similar quantity of G-acid was injected intravenously, and the blood free phenol before and after phenol loading and the histology of the liver at the end of 24 hours (after fixation with 10% formalin and staining with hematoxylin eosin) were examined and compared with the controls not receiving G-acid.

b. Experimental results

In the G-acid administered group there was seen no increase in blood phenol content and practically no liver impairment. In contrast, in the control group

TABLE 3. Effect of Glucuronic Acid on Free Phenol in Blood of Rabbits, Administered Phenol

	Case No.	Weight (kg)	Amount of phenol administered and G-acid used (mg)	Free phenol in blood (mg%)	
				Before	After 60 min.
By injection of G-acid	1	1.910	573	2.70	2.40
	2	2.670	801	3.30	3.25
	3	2.200	660	2.10	2.20
No injection	4	2.140	642	2.00	2.85
	5	1.850	555	1.95	2.30
	6	2.300	690	2.50	3.00

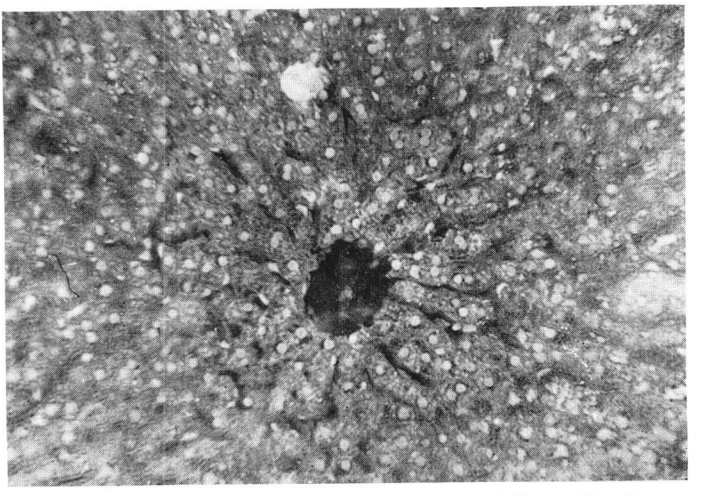

PHOTO. 1. Histological appearance of liver, G-acid given when phenol was administered.

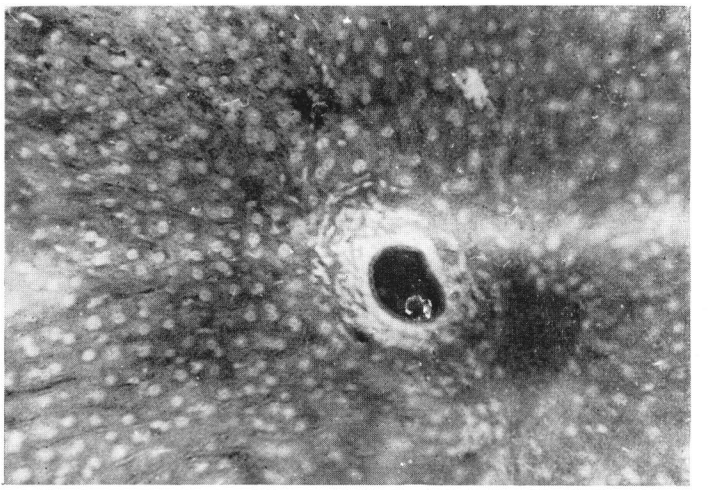

PHOTO. 2. Histological appearance of liver, G-acid not given when phenol was administered.

the blood free phenol rose at the end of 60 minutes and the liver showed signs of impairment at the end of 24 hours. Thus G-acid administered during phenol loading seemed to act beneficially in the detoxication of phenol.

3. Summary and considerations

From the investigations carried out so far it was noted that G-acid administered under normal conditions when the need for G-acid is not present in the living body, does not partake in the process of detoxication and is excreted in the urine. But when a toxic substance such as phenol enters the living body and the need for G-acid arises the administration of this G-acid causes it to be taken up by the liver and utilized in combined detoxication, thus contributing to protection of the liver.

V. DETOXICATION EFFECTS OF G-ACID DURING LIVER FUNCTION IMPAIRMENT, AND INFLUENCE ON LIVER FUNCTION (Table 4-6)

1. Introduction

The normal liver is the most important organ of detoxication, and it has been reported by Nango that when hepatic impairment exists the amount of free phenol in the liver increases. Again according to Iwanami, when no liver impairment is recognized and signs of autointoxication arise there is seen an abnormal increase in urinary G-acid excretion and abnormal fall in blood G-acid content, while in cases where liver impairment exists there is seen an abnormal decrease in both urinary and blood G-acid contents. The above seems to indicate that an increase in toxic substances in the body produces a rapid insufficiency of G-acid. Thus it would seem that the administration of G-acid during liver impairment is necessary from the aspect of detoxication, but in this case, to what extent the G-acid administered is utilized by the impaired liver

in combined detoxication remains unknown. In order to clarify this the writer administered G-acid under various degrees of liver impairment and observed the fall of phenol in blood, together with the transitions in liver function by noting the quantitatively the values of urinary millon excreted.

2. Experimental method and results

a. Experimental method

Healthy white male rabbits of body weight 1.5–2.0 kg were employed, and liver impairment was induced by oral administration with a sound, of 0.3 ccm per kg body weight of a 25% solution of carbon tetrachloride in olive oil. The grade of liver impairment was determined by Imanaga's method of quantitative estimation of urinary millon, and impairment of the desired grade induced by continuing the administration of CCl_4 to the necessary degree. Two rabbits with approximately equal liver impairment were next selected, and to one, daily injections of G-acid subcutaneously were given, while the other received no such treatment. The materials for examinations were collected in all cases 5 hours after the injection of G-acid, the blood from the ear vein and the urine by means of a Nelaton's catheter.

TABLE 4. Case of Slight Liver Damage Caused by Carbon Tetrachloride in Rabbits (100 mg of G-acid per Day Injected Subcutaneously)

Days after G-acid administration→ / Experiments↓			0	1	2	3	4	5	6	7
Phenol in blood (mg%)	G-acid used	Total	2.64		2.55		1.83			1.92
		Free	2.40		2.10		1.50			1.65
		Conjugated	0.22		0.45		0.33			0.27
	Control	Total	2.42		2.55		2.37			2.32
		Free	2.10		2.30		2.00			1.80
		Conjugated	0.32		0.25		0.37			0.52
Millon values of urine (mg%)	G-acid used		20.5	21.0	20.0	18.5	17.0	13.5	10.0	11.0
	Control		22.0	19.5	20.0	23.0	19.0	19.0	17.0	16.5

TABLE 5. Case of Medium Grade Liver Damage Caused by Carbon Tetrachloride in Rabbits (100 mg of G-acid per Day Injected Subcutaneously)

Days after G-acid administration→ / Experiments↓			0	1	2	3	4	5	6	7	8	9
Phenol in blood (mg%)	G-acid used	Total	3.85			3.90		3.37		2.05		1.77
		Free	3.40			3.40		3.00		1.60		1.45
		Conjugated	0.45			0.50		0.37		0.45		0.32
	Control	Total	3.20			3.35		3.48		3.00		2.64
		Free	2.70			2.90		2.90		2.70		2.30
		Conjugated	0.52			0.45		0.58		0.30		0.34
Millon values of urine (mg%)	G-acid used		25.0		26.0	28.0	22.0	19.0	12.0	13.5	8.5	5.0
	Control		26.5		27.0	27.5	25.0	25.0	23.0	18.5	15.0	13.0

TABLE 6. Case of Serious Liver Damage Caused by Carbon Tetrachloride in Rabbits (300 mg of G-acid per Day Injected Subcutaneously)

Days after G-acid administered→ Experiments ↓			0	1	2	3	4	5
Phenol in blood (mg%)	G-acid used	Total	6.05		6.60		7.60	Death
		Free	5.40		6.30		7.60	
		Conjugated	0.65		0.30		0	
	Control	Total	5.85		7.40			
		Free	5.30		7.20	Death		
		Conjugated	0.55		0.20			
Millon values of urine (mg%)	G-acid used		175	190	210	290	350	420
	Control		170	190	250	Death		Before of death

b. Experimental results

In animals with low to medium degrees of liver impairment, injection of G-acid produced a rapid decrease, when compared with the controls, in both free blood and total phenols. The urinary millon value also showed an almost parallel decrease. But incases of high liver impairment, inspite of injections of large quantities of G-acid, there was noted a daily increase in free and total phenols, and in the terminal stages practically no combined phenol could be demonstrated in the blood and a fall in urinary millon value was also not noted.

3. Summary and consideration

From the above results it will be noted that in low to medium grades of liver impairment the administration of G-acid results in its utilization in the process of combined detoxication, and as a result the free phenol in the blood decreases rapidly, and from the decrease in toxins of the phenol the liver is protected and the urinary milon value rapidly falls. That no marked difference was noted in the combined phenols in blood of the two is believed to be due to the fact that combined phenol does not remain in the blood but is rapidly excreted in the urine. In cases of high liver impairment combined phenols in the blood are practically not found and the detoxication effects of G-acid are lost. Again no effects are noted for liver function. This is believed to be due to the liver being an important organ of combination, and with serious liver impairment there results a marked fall in combining ability. From the above findings it will be noted that G-acid when administered during liver impairment, is utilized in combined detoxication when the imapirment is not serious, and thus helps to improve the liver function, but in high grade liver impairment it is believed that it cannot be utilized in combined detoxication and thus not produce a significant influence on the liver function.

VI. METABOLISM OF G-ACID IN PORTAL HYRERTENSION

1. Introduction

There is no literature at all on the metabolism of G-acid in cases of portal hypertension, but toxic substances such as phenol produced in the intestinal

canal, are detoxicated in the liver as they are transported via the portal veins, and the combined detoxication by G-acid plays an important role in the detoxicating functional process. Hence in cases where the flow from the portal veins into the liver is obstructed, and in addition there is increase in portal vein pressure accompanied by some impairment of liver function, or when an Eck's operation has been preformed in this disease and the portal blood is shunted off from the liver and flows directly into the general circulation, there will result a big change in G-acid metabolism. The writer therefore examined from the amounts of free phenol in the blood and the urinary excretion of G-acid, the states of G-acid metabolism in this condition. Further an investigation was also made of the detoxicating effects of G-acid administered with phenol as indicator. By such means an aspect of G-acid metabolism in this disease was made clear, and an interesting finding regarding the detoxicating mechanism of G-acid was obtained.

2. Amount of free phenol in blood

a. Before operation (Table 7)

Seventeen cases of portal hypertension (5 of liver cirrhosis, 11 with Banti's syndrome and 1 with occlusion of the hepatic vein) were examined for their free phenols in blood before operation, and the amounts were found to be 1.3–1.85 mg%, and did not differ much from the normal values of 1.30–1.50 mg%.

TABLE 7. Free Phenol in Blood in Portal Hypertension (Preoperation)

Name	Age	Sex	Diagnosis	Phenol (mg%)
Kawamoto ···	27	♂	Liver cirrhosis	1.75
Sasaki ·····	48	♂	〃	1.80
Kōno ·····	63	♂	〃	1.45
Katō ·····	45	♂	〃	1.63
Nagase ·····	51	♂	〃	1.30
Nagano ·····	38	♀	Obliteration of hepatic vein	1.50
Izumi ·····	52	♀	Banti's Syndrome	1.85
Sekiyama ····	54	♂	〃	1.34
Mori·····	45	♀	〃	1.50
Goto·····	45	♀	〃	1.60
Murase ·····	24	♂	〃	1.35
Itō·····	60	♀	〃	1.50
Asano ·····	46	♀	〃	1.47
Kurihara·····	57	♀	〃	1.30
Ōhasi ·····	47	♀	〃	1.54
Ōta ·····	68	♀	〃	1.40
Tuda·····	20	♀	〃	1.36

b. After Eck's operation (Tables 8 and 9)

After Eck's operation the blood phenol in 9 cases (4 of liver cirrhosis, 4 of Banti's syndrome and 1 of liver cancer) showed with the exception of liver cancer, significant rise quantitatively. Next, Eck's operation was performed in 10 dogs and there was noted a transitory rise in content which shortly returned to normal and an increase was not noted.

TABLE 8. Variation of the Free Phenol in Blood after Eek's Operation (Clinical Study)

Name	Age	Sex	Diagnosis	Pre-operation	2 W	1 M	2 M	3 M	4 M
Kikuyama	42	♂	Liver cirrhosis		1.93		1.60	{ Obliteration of anastomosis region	
Kōno(M)	63	♂	〃	1.45	1.75	1.50	1.63		
Katō	45	♂	〃	1.63	1.40	1.55			
Nagase	51	♂	〃	1.30	1.17	1.25			
Itō	60	♀	Banti's syndrome	1.50	1.13	1.35	1.25	1.55	1.75
Ōhasi	47	♀	〃	1.54	1.10	1.25	1.30	1.44	
Ōta	68	♀	〃	1.40	1.25	1.38			
Tuda	20	♀	〃	1.36	1.30	1.45	1.40		
Kōno(K)	54	♂	Liver cancer	1.33	0.95	2.50	2.38		

TABLE 9. Variation of the Free Phenol in Blood after Eek's Operation (Experimental Study, in Dogs)

Case No.	Sex	Weight (kg)	Pre-operation	2 W	1 M	2 M	3 M	4 M
201	♀	5.9	1.40	1.35	1.00			
202	♂	8.5	1.35	1.85				
203	♂	9.1	1.19	1.12				
204	♂	8.0	1.65	1.85	1.30			
626	♀	15.0	1.20	1.36	1.50	1.32		
653	♀	10.0	1.75	2.60	1.53	1.30	1.44	
682	♂	12.0	2.17	2.25	2.00	1.45		
901	♀	15.8	1.33	2.70	2.12	1.35		
902	♀	10.3	1.85	1.34	1.50			
903	♀	13.0	1.20	2.80	2.32	1.11	1.10	1.30

3. Excretion of urinary G-acid in this condition

a. Before operation (Table 10)

In 5 cases with portal hypertension (1 with liver cirrhosis, 4 of Banti's disease) the daily excretion of urinary G-acid was 140–320 mg, with an average of 213.3 mg.

b. After operation (Table 11)

The amount of G-acid excreted in urine one to two months after Eck's operation was examined in one case of liver cirrhosis and 3 with Banti's syndrome, and it was found to be 95–330 mg, with an average of 165 mg. When these were examined individually, it was found to be 220 mg before operation and 160 mg one month after operation in 'Itoh', a female aged 60 with Banti's syndrome, while it was 320 mg before and 175 mg two months after operation in Tsuda, a femal aged 20 with Banti's syndrome. Both cases showed marked falls in value.

TABLE 10. Amount of Glucuronic Acid Excreted to the Urine per Day in Portal Hypertension (Preoperation)

Name	Age	Sex	Diagnosis	G-acid (mg)
Kōno	63	♂	Liver cirrhosis	275
Ōtake	23	♀	Banti's syndrome	165
Itō	60	♀	〃	220
Sekiyama	54	♂	〃	160
Ōta	68	♀	〃	140
Tuda	20	♀	〃	320

M.V. 213.3

TABLE 11. Amount of Glucuronic Acid Excreted to the Urine per Day after Eek's Operation

Name	Age	Sex	Diagnosis	Day's after operation	G-acid (mg)
Kikuyama ·	42	♂	Liver cirrhosis	2 M	95
Itō·····	60	♀	Banti's syndrome	1 M	160
Ōhasi·····	47	♀	〃	1 M	230
Tuda ·····	20	♀	〃	2 M	175
					M.V. 165

c. Normal state (Table 12)

The daily urinary excretion of G-acid under normal conditions has differed considerably according to different reports, but such is believed to be due to differences in the methods employed. The minimum value of 70-140 mg was reported by Kawanishi, and the maximum of 400-600 mg by Mozolowski. The results for 6 normal persons examined by the writer were 215-577 mg, with an average of 395.3 mg, and were close to the figures of 370 reported by Tollens and 300-570 mg reported by Couzen.

4. Detoxication effects for phenol of G-acid (Table 13)

To one case of liver cirrhosis (3 weeks after Eck's operation), one case of Banti's syndrome (2 weeks after operation) and one of hepatic vein occlusion (before operation) 1 000 mg of G-acid were injected intravenously and at intervals of one hour for 3 hours the changes in blood phenol were examined, and there was noted a clear lowering.

5. Summary and considerations

From the above experimental results it would appear that in portal hypertension there is no rise in free phenol both before and after operation, indicating practically no impairment in detoxicating ability. However in

TABLE 12. Amount of Glucuronic Acid Excreted to the Urine per Day in Normal Adult

No.	Age	Sex	mg
1	32	♂	577
2	33	♂	370
3	25	♂	215
4	28	♀	230
5	20	♀	660
6	23	♀	320

(M.V. 395.3 mg)

Literatures of Amount of Glucuronic Acid Excreted to the Urine per Day in Normal Adult

Tollens ·····	370 mg
Sauer·····	220～280 mg
Couzen ·····	300～590 〃
Mozolowski····	400～600 〃
Kawanisi ·····	70～140 〃
Sawada ·····	277～ 98 〃

TABLE 13. Effect of Glucuronic Acid Injected on the Free Phenol in the Blood in Portal Hypertension

Name	Age	Sex	Diagnosis	Before	1 hr.	2 hr.	3 hr.
Kikuyama	42	♂	Liver cirrhosis (3 W after ope.)	1.93	1.60		1.51
Itō·····	60	♀	Banti's syndrome (2 W. after ope.)	1.13	0.70	0.90	1.10
Nagano··	38	♀	Obliteration of hepatic vein	1.50	1.40	1.33	1.40

this condition the excretion in urine of G-acid becomes low and there is a further tendency to decrease after Eck's operation. In other words, there is lowering in production of G-acid in the body, and by the administration of G-acid there results a decrease in quantity of free phenol in the blood, showing utilization of the G-acid administered in combined decomposition. The above view suggests that the apparently normal quantity of free phenol in blood does not actually mean such but indicates a pathologic state. Hence in portal hypertension the administration of G-acid is to be recommended though an increase in phenol may not be noted. This is extremely interesting and calls for further investigations.

VII. SUMMARY AND CONSIDERATIONS

As it has been difficult to secure G-acid, researches on the effects of this acid administered into the living body have so far been rare, and no literature is available especially on the relation between G-acid detoxication mechanism and hepatic function. Based on the fact that the organ for G-acid combination is the liver, and that sodium glucuronate is utilized directly to some extent in combined detoxication as has been reported by Douglas and Packham, the writer undertook investigations on the relationship between such a mechanism and liver function. As a result it was found that most of the G-acid administered under normal conditions do not partake in detoxication, but when a toxic substance such as phenol is introduced into the living body or there is an acute hepatic impairment of not too high a grade, G-acid is found to play a role in detoxication. According to Professor Imanaga the liver plays a most important role in the mechanism of combined detoxication of phenol, and that such is due mainly to the combination of G-acid. Also that when a toxic substance such as phenol appears in the living body there results a change in the normal process of decomposition and synthesis of sugars by the liver, whereby combined G-acid is synthesized from the trisaccharides, and this directly is involved in the detoxication mechanism of the living body. In other words, when the quantity of a toxic substance such as phenol increases in the living body, there results an abnormal enhancement in activity of the mechanism of combined G-acid synthesis by the liver. Thus G-acid which does not partake in detoxication under normal conditions, seems to do so when loaded with phenol, or when phenol is produced in abundance as in acute hepatic impairment. When the grade of liver impairment is high there results no detoxicating effect even when large doses of G-acid are administered, and such is probably due to the marked lowering in combined G-acid synthesis of the liver.

In portal hypertension there is no increase in free phenol in the blood, and no increase was also noted even after Eck's operation whereby the portal blood is made to flow directly into the general circulation without passing the liver. This was an unexpected finding. However in this condition there was deficiency in the body of G-acid, and in such a case when G-acid is administered, despite no increase in free phenol, there was noted activity in combined detoxication. Hence G-acid administered is involved in combined detoxication when there

exists an increase in phenol in the living body calling for a greater demand of G-acid, as well as when there is deficiency in body G-acid as in the case of portal hypertension. This is a very interesting finding, and it is intended to make further investigations regarding the mechanism in the near future.

VIII. CONCLUSIONS

Investigations were made on the detoxicating effects of Glucuronic acid for phenol under normal conditions and in liver impairment, and the following results were obtained regarding the detoxicating mechanism of this G-acid, especially in relation to liver function.

1. When there exists no need for G-acid in the normal living body, G-acid that is administered is not involved in detoxication.

2. However when a toxic substance such as phenol is introduced or when an acute hepatic impairment exists and calls for a sudden high demand of G-acid the administration of G-acid protects the liver by becoming involved in the detoxicating mechanism. In such a case the main combining organ is the liver, but when the grade of liver impairment is high, whatever the amount of G-acid administered there results no utilization of this G-acid in combined detoxication.

3. In portal hypertension there is in general a deficiency in body G-acid, and though no increase in free phenol is seen, the administration of G-acid produces a lowering in free phenols, unlike under normal conditions, and a detoxicating activity is noted.

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