STUDIES OF COPROPORPHYRIN. IV. THE PER DIEM EXCRETION AND ISOMER DISTRIBUTION IN THE URINE IN INFECTIOUS HEPATITIS, INFECTIOUS MONONUCLEOSIS, AND MECHANICAL JAUNDICE [1]

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(Received for publication December 29, 1948)

The occurrence of increased amounts of porphyrin in the urine in cases of liver disease was first duly emphasized by Archibald Garrod (1, 2). Garrod believed this to be hematoporphyrin, a confusion with coproporphyrin which was corrected by H. Fischer and Zerweck (3), and which undoubtedly depended upon the very close similarity of the absorption spectra of the two porphyrins. When examined with the relatively crude spectroscopes available at the time of Garrod's study, these porphyrins were indistinguishable. The investigations of H. Fischer, however, made it clear that hematoporphyrin does not occur in the urine, if, indeed, it occurs as a natural product at all. Studies of urinary porphyrin excretion in liver disease, subsequent to that of Garrod, have been for the most part of rather fragmentary nature, consisting of one or not more than a few examples of any one affection. The pertinent literature has been reviewed within recent years (4, 5) and need not be considered here. Attention may be drawn, however, to the papers of Nesbitt and Snell (6, 7) and Localio and co-workers (8), in which considerable data were reported on the feces-urine ratio of coproporphyrin both in obstructive jaundice and liver disease. The papers of Watson (9, 10) and Dobriner (11) present limited data on the urinary isomer distribution (ratio of types I and III) in these conditions. Dobriner made several important observations in cases of catarrhal jaundice, obstructive jaundice, and cirrhosis of the liver, to which reference will be made again, in this and subsequent papers of this series. Studies of isomer distribution have been generally discouraged, however, by the lack of a method of isomer analysis applicable to small volumes of urine, and as a corollary of this, the lack of exact knowledge of the isomer distribution in normal urine. In previous papers a suitable method has been described (12, 13) and in paper I of this series (14) the results of the application of this method to normal urine have been given. The purpose of the present investigation was to determine the total urinary coproporphyrin (UCP) as well as the isomer distribution in 24-hour samples from cases of infectious hepatitis at various stages of the disease, and also, for purposes of comparison, from cases of infectious mononucleosis and of mechanical jaundice, the latter term being used to designate jaundice due to extrahepatic biliary obstruction, or obstruction of the main hepatic ducts in the liver. It was also desired to assay the value of the UCP determination, relative to other methods of studying liver function, as an indication of residual hepatic functional impairment in cases of hepatitis at various periods after the disappearance of jaundice.

MATERIAL AND METHODS

The method of Schwartz and associates (13) was used to determine the UCP and the isomer distribution. Recent evidence indicates that the true value for the UCP is approximately 20 per cent higher than that obtained with this technique. Nevertheless, all of the data given in the following may be compared directly with the normal data given in paper I (14).

The fractional serum bilirubin was determined according to the modification of the Malloy-Evelyn method

[1] Aided by grants from the John and Mary R. Markle Foundation, New York City; the Division of Research Grants and Fellowships, U. S. Public Health Service (Research Grant No. 345); and the Medical Research Fund of the Graduate School, University of Minnesota, Minneapolis.

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described by Ducci and Watson (15). The bromsulfalein retention in the blood was determined according to Mateer (16), 45 minutes after injection of 5 mg. of the dye per kilo of body weight. The cephalin cholesterol flocculation test was performed according to Hanger (17). Cholesterol and cholesterol esters were determined by the method of Sperry and Schoenheimer (18). In some instances the urine urobilinogen was determined in 24-hour urine samples (19); in others the quantitative urine Ehrlich reaction (20, 21) was carried out on individual or two-hour samples. The number of coproporphyrin determinations and the cases which were studied are given in Table I.

As noted in Table I, the determinations were often repeated, either with relation to stage of the disease or fluctuation of the jaundice, or in some instances within a brief interval, for purposes of corroboration. The majority of determinations in the infectious hepatitis group were in the period after the disappearance of jaundice.

TABLE I

Composition of clinical material and number of determinations

Group	Diagnosis	Number of cases	Number of determinations of UCP	Isomer analyses
1	Infectious hepatitis*	96	172	53
2	Infectious mononucleosis†	25	25	16
3	Cancer of pancreas or bile ducts	41	46	38
4	Common duct stone or stricture	30	49	30
5	Cirrhosis (all types)‡	48	95	53

* This group includes cases of epidemic hepatitis and homologous serum jaundice, some of which were studied in Minneapolis, and some at the Schick and DeWitt General Hospitals of the U. S. Army, at Clinton Ia., and Auburn, Cal., respectively; the urine porphyrin studies were carried out in all instances in Minneapolis. The group also includes cases of epidemic and homologous serum jaundice, and of sporadic hepatitis studied in Minneapolis.

† These cases were studied on the Health Service of the University of Minnesota Hospital, Dr. Ruth Boynton, Director. Liver function studies in this group have been reported elsewhere by Dr. Ralph Peterson (26).

‡ The cirrhosis data will be considered in detail in the ensuing paper of this series, but are included in the present communication for purposes of comparison, with particular respect to the differential diagnosis of jaundice.

RESULTS

The data obtained in the five groups of cases (as noted in Table I), are given in Tables II–VI, respectively. The data in Table II permit some comparison of the UCP in cases of hepatitis, with the results of other tests of liver function, as well as

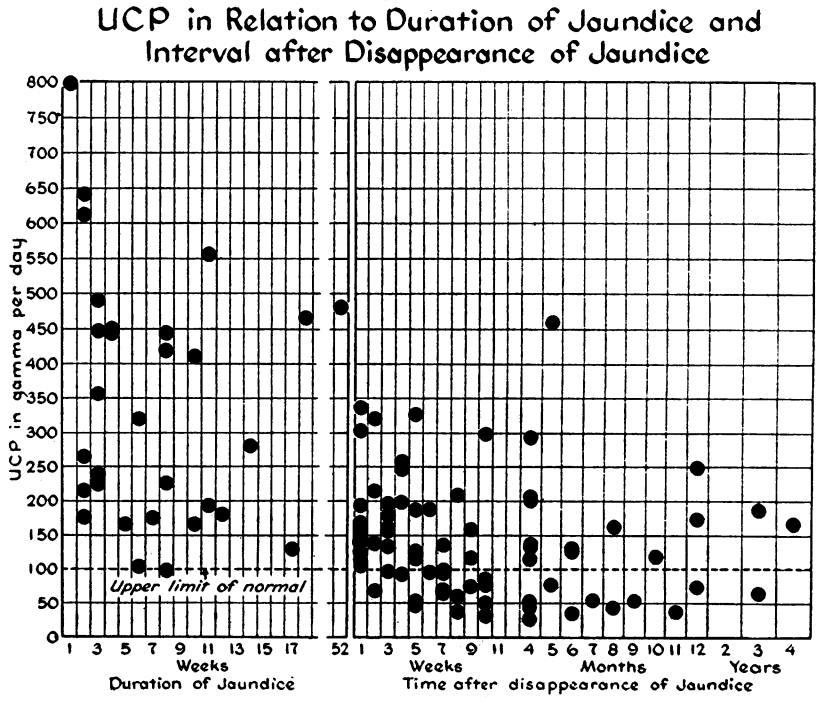

FIG. 1

TABLE II

UCP in cases of infectious hepatitis, compared with stage of disease, symptoms, and status of the liver

Case no.	Initials	Sex	Age	Date	Week of disease	Week after disappearance of jaundice	Symptoms*	Liver enl.†	Tenderness	SB 1′	SB T	Brom	CC	CE per cent	UE	UU 24 hr.	UCP γ/24 hrs.
1	T. M.	♂	30	10–10	10	2	0	10	+	0.7	1.1		3+	52	0.6		320
				11–21	16	8	0	3	0				2+	66			60
2	J. R.	♂	28	10–20	4	Never j	I	0	+	0.0	0.03	0	1+	40			143
				11–21	10	Never j	0	1	+			0					86
3	F. F.	♂	31	10–9	34	5	I	3	+	0.0	.44	3	0		.25		47
				11–15	39	10	I	3	++			0	0	54			77
4	R. V.	♂	27	10–10	11	8	I	1	0								209
				11–20	17	14	I	1	0	.03	0.1	4		80			115
5	H. M.	♂	23	11–16	22	14	0	4	0	.2	.65	24	3+	67	3.8		208
6	F. R.	♂	26	10–9	6	j	0	3	+	3.7	4.1		1+		0.7–3.0		319
				11–16	11	j	0	3	+	5.8	9.2			33			193
7	M. D.	♂	23	10–1	13	7	I	4	+	0.0	0.17	1	0	57			65
				11–15	19	13	I	5	0						1.8		292
8	J. T.	♂	35	10–7	5	1	++	4	0	0.3	0.7	4	0	63			193
				11–16	11	7	++	6	++								99
9	H. C.	♂	37	9–20	25	9	++	2	+	0.1	0.2	0	0	45			159
				10–27	30	14	0	1	0				0	56	2.5		133
10	R. C.	♂	28	9–27	11	7	I	3	0	0.5	1.1	9	0		1.5		138
				11–21	18	14	+	2	0			5					28
11	P. U.	♂	21	10–2	4	j	+	2	0	2.7	4.3		4+		2.3		444
				11–16	10	5	0	0	0			0			0.5		115
12	J. R.	♂	21	10–8	3	j	++	4	+	3.1	5.5	0	1+	36	3.8		448
				11–15	8	sl j	I	1	+								99
13	A. M.	♂	21	10–1	24	4	0	0	0	0.1	0.2	8	0	47	1.8–4.6		92
14	C. M.	♂	37	9–20	36	30	++	5	++	0.3	0.6		0	69	2.0–2.7		161
				11–15	39	33	I	0	0								52
15	W. W.	♂	40	9–24	56	46	I	1	0	0.0	0.3	0	0	61	0.7		172
16	F. H.	♂	40	9–20	3 yr. 10 wk.	Approx. 3 yr.	+	0	0	0.2	0.44	0	0	49	1.1–3.3		187
				11–15	3 yr. 14 wk.	Approx. 3 yr.	+	0	0								63
17	M. H.	♂	21	9–28	4	2	0	4	0	0.5	0.65	15	0		0.5		213
18	J. H.	♂	23	9–20	1 yr. 3 wks.	6	+	3	+	0.0	0.2	0		60	2.0		189
19	W. M.	♂	22	9–28	10	3	0	2	0	0.2	0.58	5	0		1.0		96
20	J. D.	♂	32	10–2	19	17	0	0	0	.23	.44		0		2.3		76

* Symptoms: I = Indefinite or questionable; +, ++ mild or moderate weakness, fatigue, anorexia; +++ severe anorexia and weakness, patient very sick but not comatose.

† Enl.: Cm. below costal margin in midclavicular line. Tenderness: + = slight, ++ = moderate, +++ = marked.

Key: SB = Serum bilirubin
1′ = prompt direct
T = total
CE = Cholesterol ester %
Brom = % retention of Bromsulfalein in blood 45′ after 5 mg. per kilo body weight
UE = Urine Ehrlich units per 2–4 P.M. urine sample
CC = Cephalin cholesterol flocculation at 24 hours
UU = mg. urobilinogen in 24 hr. urine

TABLE II—*Continued*

Case no.	Initials	Sex	Age	Date	Week of disease	Week after disappearance of jaundice	Symptoms*	Liver enl.†	Tenderness	SB 1′	SB T	Brom	CC	CE per cent	UE	UU 24 hr.	UCP γ/24 hrs.
21	P. B.	♂	30	10–1	8	1	I	6	+	0.1	.52				1–2.2		159
				11–15	14	7	I	5	+	0.1	.38	0	0	56	0.5		94
22	R. G.	♂	28	9–28	10	sl j	0	10	0	1.7	3.3	9	3+	22	1.8		167
				11–16	16	5	0	0	0	0.2	0.7	5	0	74	0.6		52
23	D. H.	♂	26	9–26	18	10	0	0	0	.03	.4	1	2+		4.6–1.2		150
24	J. M.	♂	23	10–2	13	2	+++	4	+++	0.3	.8	5	0	52	1.9		67
				11–15	19	8	0	0	0	.17	.52	2.5	0	58	1.2		37
25	V. N.	♂	24	10–1	9	7	0	0	0	.03	.23						69
				11–21	15	13	0	0	0								51
26	W. R.	♂	24	10–1	28	24	+	0	+	.03	.44		0		.8		127
					34	30	0	0	0								43
27	J. S.	♂	33	9–28	12	4	0	0	0	0.1	.23	12	0	49	1.4		256
				11–15	18	10	0	0	0			0					32
28	J. W.	♂	24	9–28	28	2–4	+	3	0	0.5	1.5	10	0	51	5.0		197
				11–16	34	8–10	I	0	0						.3–1.6		116
29	R. F.	♂	25	11–15	52	28	0	2	0	0.01	0.41				0.97		53
30	E. P.	♂	28	2–16	4	j	+++	6	+++	17.0	30.7		3+	15	1.8–5.0	15	450
				3–26	10	j	I	5	0	2.13	5.13		1+	62	2.8		410
				4–14	12	1	0	5	0	0.5	1.75				4.95		336
31	E. C.	♂	22	2–16	13	3	+	0	0	0.5	1.6	1.5	0		0.5		132
32	R. B.	♂	24	2–17	3	j	I	0	0	1.0	3.2	7	1+	79	1.2		240
				3–20	7	3	0	0	0	0.4	1.2	0.5	2+		1.7		160
33	W. M.	♂	23	4–4	5	2	0	2.5	0	0.5	1.6	4	0	74	2.7		139
34	R. B.	♂	30	2–16	3	j	+++	5	0	10.9	19.5		3+		4.5		490
35	R. R.	♂	35	4–4	28	16	+	3	++	0.1	1.1	0	0	76	1.8		47
36	C. M.	♂	37	2–16	4	1	0	0	0	0.6	1.3	0	0	71	2.2		150
37	L. H.	♂	25	3–4	23	10	++	8	++	0.1	0.99	0.5	0	63	0.73		86
38	H. J.	♂	25	4–4	26	15	0	0	+	0.25	1.1	3.5	0	76	.96	1.5	136
39	W. C.	♂	25	4–4	10	1	I	1	0	0.65	1.65		1+		2.1		152
				4–14	12	3	0	0	0	0.4	0.95	1	0		1.0		180
40	C. R.	♂	27	3–26	1 yr.	j	+++	5	0	8.0	16.0		3+	39	8.0		480
41	J. B.	♂	45	2–5	6	4	I	0	0	0.5	1.0	12	1+	53	12.0		198
				2–16	7	5	I	0	0	0.5	1.1	15	2+		2.2		328
				3–13	11	9	0	0	0	0.2	0.8		1+	70	0.9		75
42	F. D.	♀	44	11–9–46	5	j	++	2	0	12.8	22.2		4+	25	0.1		164
				11–14	6	j	++	2	0	12.8	24.3		4+	31			104
				11–24	7	j	++	2	0	13.5	25.6		4+	25	0.4		156
				11–27	8	j	++	2	0	12.7	25.1		4+	20	1.2		225
43	E. G.	♂	48	8–9–46	12	j	+	0	+	2.5	4.8		0	68	1.6		180
				8–22	14	j	+	0	+	1.4	2.8	1.4	1+	69	0.5		280

TABLE II—*Continued*

Case no.	Initials	Sex	Age	Date	Week of disease	Week after disappearance of jaundice	Symptoms*	Liver enl.†	Tenderness	SB 1′	SB T	Brom	CC	CE per cent	UE	UU 24 hr.	UCP γ/24 hrs.
44	B. K.	♂	32	5–15–46	18	j	+	5	+	1.9	4.5						465
				6–1	20	1	+	3	+	0.9	1.8		3+	76			134
				6–2	20	1	+	3	+						0.9		164
				7–10	25	6	+	3	0	0.2	0.5		1+	67	0.6		94
45	A. G.	♂	21	3–12–46	19	16	+	2	+	0.2	1.0	3	0	73	0.7	10.4	203
				3–17	20	17		2	+								460
				5–2	26	23		0	+	.06	0.8		0	74		1.0	129
				10–16	48	45		0	0	0.1	0.7		0		0.5		249
46	A. G.	♂	40	4–16	1	j	+	2	0	4.1	7.1		4+	75		22.3	779
				4–24	3	sl j		0	0	0.9	1.7	9.5	4+				356
47	A. C.	♀	28	4–13	3 yr.	1 yr. 2 mo.	+	1	++	0.1	0.7	3%	0	75	1.7		72
48	C. M.	♂	30	5–26	8	j	I	1	+	26	37.9		0		4.6		420
49	V. A.	♂	41	2–24	8	j	+	2	+	5.9	10.1		0	55		11.1	445
				3–15	11	j	+	2	0	2.6	4.6					26	554
				4–8	14	1	0	0	0	0.6	1.5		2+	69		2.7	302
				5–6	18	5	0	0	0	0.3	0.8		0			2.9	188
				6–17	23	10	0	0	0	0.2	0.6		0			0.7	259
				8–8	30	17	0	0	0	0.2	0.6	3%	0			1.2	253
50	M. B.	♀	30	12–1	1 yr.	About 11 mo.	I	0	0	0.2	2.1	2%	1+	74	0.6	1.0	36
51	L. H.	♀	32	9–4	2	j	+	1	+	1.8	3.0	30.5	4+	35		20.0	265
				9–7	2	j	+	1	+								642
				9–24	3	1	0	0	0	.16	0.7	3	4+				148
52	M. H.	♀	27	2–28	16	1	+	1	+	0.8	1.7	12.5	3+	60		2.6	116
53	I. S.	♀	52	12–4	17	j	+	0	0	1.2	2.2		2+	67		0.7	130
54	G. B.	♂	30	5–20	31	13	+	+	0	0.2	2.0	2.4	0			4.2	143
				7–8	37	19	0	+	0	0.2	1.8	2.0	0			0.3	135
55	A. B.	♂	40	4–30–46	28	22	+		0	0.2	2.8	5.0	1+		1.9		35
56	P. T.	♂	54	4–28–46	2	j	+	+	+	15.4	26.7		3+	26	10.0		611
				6–7–46	7	1	+	0	0	0.6	1.2		0	67	3.2		105
57	G. T.	♂	50	4–19–48	2	j	+	2	+	4.6	7.7		4+	50.5	11.2		224
				5–8–48	4	4	+	2	+	14.7	31.7		4+	21		1.0	245
58	M. S.	♀	19	7–17–47	2	Never j	+	+	+	0.2	0.5	2	1+			1.5	45
59	H. F.	♀	37	7–2–47	4 yr.	4 yr.	+	0	0	0.2	1.1	3	0		4.5		153
60	L. S.	♀	47	5–2–45	2	j	+	1	+	9.0	13.0		3+	17			178
61	R. G.	♂	21	7–1–45	12	10	+	1	+	0.1	0.5		0			0.3	119
62	H. H.	♂	50	3–18–48	3	j	+	2	+	1.3	2.5		3+	67		1.3	222
				3–29–48	5	1	+	1	+	0.4	1.1		0			1.0	141
				4–11–48	7	3	+	1	+				0			1.0	158
				4–25–48	9	5	0	0	0				0				125

with the patients' symptoms, approximate liver size, and degree of tenderness, at various stages of the disease. Table IIA includes supplementary data on the UCP; in these instances additional information as to hepatic function was lacking or fragmentary.

In Figure 1, the values for UCP in the cases of hepatitis are plotted with relation to the duration of jaundice or the interval from the disappearance of jaundice. This figure includes all of the determinations in all cases in which there had been jaundice. As a matter of fact, the present mate-

TABLE IIA

Additional UCP determinations in cases of infectious hepatitis

Case no.	Initials	Age	Sex	Presence or absence of jaundice	UCP in γ/24 hrs.
63	J. B.	67	♀	+	257
64	A. P.	29	♀	−	206
65	E. S.	30	♂		739
					448
					425
				+	472
					220
					155
					134
				−	91
					158
66	C. R.	31	♂	−	197
67	E. R.	24	♂		39
					42
				−	77
					120
					37
68	J. M.	59	♂	+	432
69	L. S.	42	♂	+	451
70	I. N.	24	♂	+	252
71	C. L. F.	23	♂	+	346
72	O. D.	54	♂	+	205
73	L. F.	45	♂	+	242
74	S. S.	55	♀	+	265
				−	235
75	M. A.	25	♂	−	151
76	J. M.	21	♂	+	170
77	W. S.	23	♂	+	312
78	N. T.	21	♀	+	197
79	J. O.	34	♂	+	222
80	H. W.	42	♂	+	505
81	D. W.	27	♂	−	150
82	R. S.	23	♀	+	241
83	R. K.	24	♂	+	314
84	B. R.	30	♂	+	296
85	P. T.	21	♂	+	210
86	C. S.	26	♂	−	160
87	J. G.	27	♂	−	208
88	F. W.	4	♂	+	179
89	M. G.	25	♂	−	141
90	R. F.	25	♂	−	540
91	B. R. K.	22	♀	+	177
92	H. F.	53	♂	−	145
93	G. G.	23	♂	−	210
94	T. C.	40	♂	+	304
95	C. B.	74	♂	+	279
96	E. E.	20	♀	+	182

TABLE III

Coproporphyrin isomer distribution in 24-hour urine samples from cases of hepatitis

Case no.	UCP in γ/24 hrs.	Isomer distribution in per cent		Type III γ/24 hours
		I	III	
4	209	88	12	25.1
6	319	92	8	25.5
8	193	92	8	15.4
10	138	84	16	22.1
12	488	96	4	19.5
14	161	81	19	30.6
15	172	80	20	34.4
19	96	90	10	9.6
23	150	90	10	15.0
26	127	87	13	16.5
27	256	93	7	17.9
30	450	98	2	9.0
32	160	93	7	11.2
34	490	99	1	4.9
36	150	93	7	10.5
38	136	92	8	10.9
39	152	91	9	13.7
40	480	96	4	19.2
41	198	88	12	23.8
	328	90	10	32.8
	75	87	13	9.8
42	164	92	8	13.1
	106			
	156			
	225	89	11	24.8
43	180	90	10	18.0
	280	86	14	39.2
44	465	95	5	23.3
	134			
	164	89	11	18.0
	94			
45	203			
	460	93	7	32.2
	129	90	10	12.9
	249			
46	779	96	4	31.2
	356			
47	72	86	14	10.1
48	420	91	9	37.8
49	445	90	10	44.5
53	130	91	9	11.7
54	143	91	9	12.9
67	120	85	15	18.0
69	415	89	11	9.8
72	205	80	20	41.0
75	151	79	21	31.7
79	222	90	10	22.2
84	296	90	10	29.6
86	160	91	9	14.4
87	208	94	6	16.5
88	179	83	17	30.4
89	141	86	14	19.7
90	540	96	4	21.6
91	177	92	8	14.2
92	145	85	15	21.8
93	210	95	5	10.5
94	304	89	11	33.4
95	279	98	2	5.6
96	182	86	14	25.5

rial includes but one instance of what was believed to represent hepatitis without jaundice (Case 2 in Table II). The upper limit of normal of 100 γ, as indicated in Figure 1, was established with relation to the value of the mean plus two standard deviations, or 97 γ. One instance of the 53 in the normal group was above this value, with 99 γ (see paper I of this series [14]).

As shown in Figure 1 and Table II, a number of the cases of hepatitis were first seen in a late stage of the disease, weeks or months after the disappearance of jaundice. At least two of these are sufficiently instructive to be given in more detail in the following:

TABLE IV

UCP and isomer distribution in cases of infectious mononucleosis

Case	UCP in γ/24 hrs.	Isomer distribution in per cent		Type III in γ/24 hrs.
		I	III	
1. D. J.	189	88	12	23
2. B. R.	163	81	19	31
3. M. G.	410	96	4	16
4. L. V. B.	147	80	20	29
5. G. B.	364	89	11	40
6. H. S.	111	82	18	20
7. E. S.	425	92	8	34
8. P. C.	123	82	18	22
9. C. M.	282	93	7	20
10. E. B.	133	80	20	27
11. E. F.	249	95	5	12
12. E. W.	113	90	10	11
13. D. S.	219	85	15	33
14. F. K.	113	90	10	11
15. T. G.	143	88	12	17
16. D. E.	152	92	8	12
17. F. S.	46			
18. S. A.	133			
19. R. G.	71			
20. D. D.	45			
21. C. A.	177			
22. A. H.	42			
23. K. M.	73			
24. C. D.	77			
25. G. L.	122			

1. Case 45, A. G., male 21, farmer. The patient was first seen at the University Hospital on March 11, 1946. He stated that about six months earlier he developed nausea and anorexia, shortly followed by jaundice which persisted for two months. During the last four months he felt fairly well and had resumed his work, but was bothered by persistent discomfort and tenderness in the right upper abdomen. Examination revealed an enlarged tender liver and a palpable spleen. Routine laboratory studies were normal. As seen in Table II, the fractional serum bilirubin, thymol turbidity, cephalin cholesterol flocculation, bromsulfalein, cholesterol and ester percentage, were all within normal limits. The serum proteins, hippuric acid synthesis, and prothrombin time were also normal. The urine Ehrlich test on individual samples was normal, but the 24-hour urine urobilinogen was 10.4 mg., in other words, considerably elevated. The UCP was markedly increased, usually above 200 γ/24 hours (see Table II). The liver biopsy revealed evidence of an active hepatitis, *i.e.*, small foci of cellular exudate with occasional necrosis, but no fibrosis.

2. Case 49, V. A., male, 41, illustrator. This case is presented in more detail because of the unusually favorable opportunity for study that was presented during the latter weeks of a prolonged "catarrhal" jaundice or sporadic infectious hepatitis. Following is a brief summary of the salient clinical features:

The first day of observation, Figure 2, was February 24, 1947. At this time the patient had been jaundiced for two months. On December 7, 1946, he experienced an acute attack of diarrhea, nausea and vomiting, of 12 hours' duration. He recovered and felt quite well, but on December 26, he noted fever, malaise, and pain in the muscles. His urine became dark, and he consulted a physician who made a diagnosis of infectious jaundice. When first seen at the University Hospital the liver was moderately enlarged and tender. Within three weeks the tenderness had disappeared and the jaundice had markedly diminished. The liver was still palpable. By April 8, the jaundice had disappeared though the serum bilirubin was still distinctly elevated. Although the patient's appetite had returned, a moderate lassitude persisted throughout the summer. He did not have energy enough to play golf which he ordinarily enjoyed. By November of 1947, however, he believed that he had regained an entirely normal status. As noted in Figure 2, the results of the liver function studies, except the UCP, were normal by the 65th day of observation (corresponding to April 30, 1947). The UCP, however, remained considerably elevated, the value on the 171st day (August 14, 1947), being 253. Later determinations have continued to show abnormally high values, as seen in Table VII. The patient feels quite well (December 15, 1948) but has now developed a number of small spider nevi over the neck, upper chest, and hands. The liver is palpable at the costal margin, not tender.

The total coproporphyrin values together with the percentage and actual amount of each isomer as determined in 46 cases of infectious hepatitis, are given in Table III. Similar data for the infectious mononucleosis group are shown in Table IV. In Figure 3, the initial values obtained for the total UCP and per cent of type III isomer, in the first 40 cases of hepatitis to be studied in this way, are plotted in comparison with the values for the normal (Minneapolis) series previously reported (14), and for 38 cases of acute poliomyelitis.

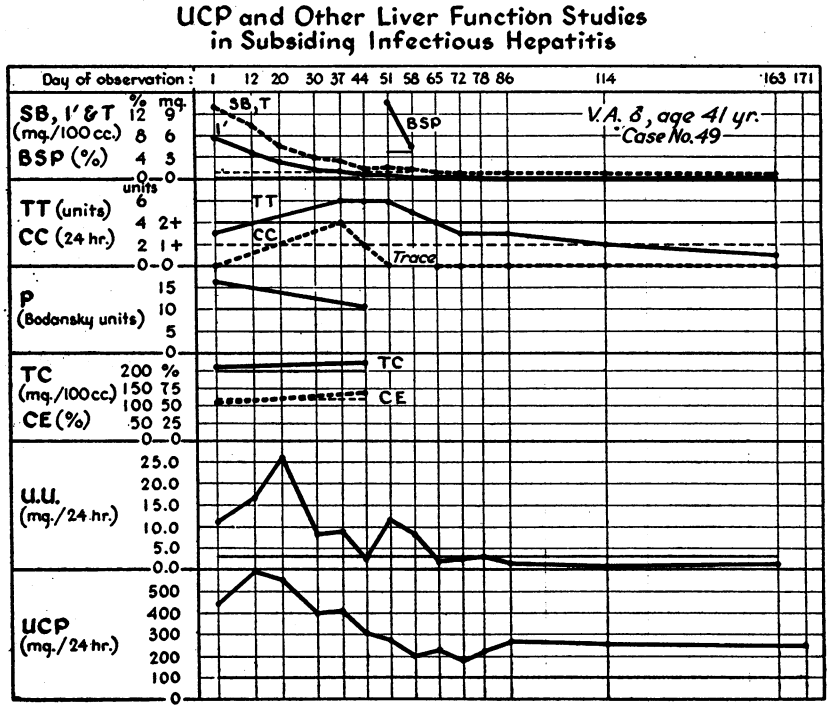
UCP and Other Liver Function Studies
in Subsiding Infectious Hepatitis
Day of observation: 1 12 20 30 37 44 51 58 65 72 78 86 114 163 171
SB, I' & T (mg./100 cc.)
BSP (%)
TT (units)
CC (24 hr.)
P (Bodansky units)
TC (mg./100 cc.)
CE (%)
U.U. (mg./24 hr.)
UCP (mg./24 hr.)
SB, T
I'
BSP
TT
CC
Trace
TC
CE
V.A. ♂, age 41 yr.
Case No. 49

FIG. 2

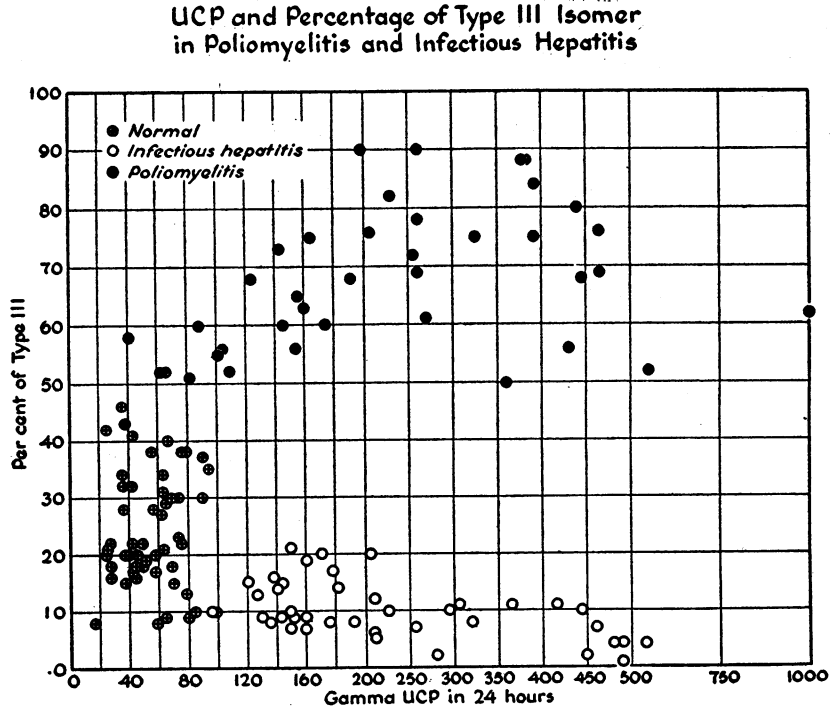
UCP and Percentage of Type III Isomer
in Poliomyelitis and Infectious Hepatitis
Normal
Infectious hepatitis
Poliomyelitis
Per cent of Type III
Gamma UCP in 24 hours

FIG. 3

The latter data have also been reported previously (22) and are included here only for purposes of comparison with the results in the hepatitis cases. One instance was of particular interest because of the likelihood of coexistence of infectious hepatitis and poliomyelitis.

Case 51, L. H. female, 32, housewife. This patient was seen during the epidemic of poliomyelitis in 1946. She complained of headache and stiff neck, and there was fever. The spinal fluid was found to contain 17 mononuclear cells per cu. mm. When first seen, there was distinct jaundice, in addition to the findings indicative of poliomyelitis. A history was obtained of painless jaundice suffered by her son and several individuals in the neighborhood about six weeks earlier. The patient had observed dark urine at the outset of her own illness. The liver was not palpable or tender at any time. The laboratory data as seen in Table II revealed marked liver functional impairment. The first UCP on September 4, was 265 γ/24 hours; three days later it was 642 γ, and at this time 82 per cent was type I, the remainder type III. This represents 116 γ of type III. In paper I of this

TABLE V

UCP in cases of cancer of the pancreas, bile ducts, or liver

Case no.	Initials	Sex	Age	Diagnosis	Diagnosis by*	Date of determination	SB†		UCP γ/24 hrs.	Per cent I	Per cent III	γ III/ 24 hrs.
							1′	T				
1	C. K.	♀	56	Ca. bile ducts	A	8/27/44 8/29/44 8/30/44	22.0	25.5	330 269 380	95	5	17
2	J. W.	♂	51	Adeno ca. of bile ducts	O	3/2/46	12.8	23.0	314	89	11	35
3	H. A.	♂	74	Ca. C.B.D.	O	12/6/46	16.5	23.2	257			
4	H. A.	♂	59	Ca. C.B.D.	O	7/18/46	24.0	41.6	226	81	19	43
5	G. H.	♀	50	Ca. C.B.D.	O	5/27/46 5/29/46	15.1	31.2	381 172	94	6	23
6	O. O.	♂	53	Ca. head of pancreas	O	4/26/46	3.9	6.5	365	86	14	51
7	E. P.	♂	77	Ca. body of pancreas	O	12/10/45 12/11/45 12/22/45	6.6	9.6	201 180 144	78	22	51
8	G. S.	♂	76	Adeno ca. of bile ducts	O	12/25/46	13.8	24.0	174			
9	W. G.	♂	70	Ca. pancreas	A	4/17/47			196	82	18	36
10	J. D.			Ca. pancreas	A	5/6/47			206	80	20	
11	J. W.	♂	67	Ca. pancreas	O	11/18/44	9.1	15.8	281	91	9	25
12	C. A.	♀	71	Ca. pancreas	C	1/18/48	15.6	27.9	188	82	18	34
13	E. B.	♂	65	Ca. pancreas	A	5/17/47	16.8	31.0	167	85	15	25
14	S. B.	♂	55	Ca. C.B.D.	O	10/9/44	8.0	15.1	282	80	20	56
15	E. C.	♀	62	Ca. G.B.	O	6/14/47	15.3	26.0	364	75	25	91
16	C. C.	♂	75	Ca. liver	O	4/6/47	0.1	0.3	331	74	26	86
17	C. C.	♂	56	Ca. pancreas	O	9/24/47	14.8	28.0	282	62	38	107
18	A. D.	♂	54	Ca. body pancreas	O	2/7/47	0.1	0.4	66	81	19	12.5
19	H. E.	♂	67	Ca. pancreas	A	12/20/44	28.5	43.0	217	74	26	56.5

* A = autopsy
O = operation
C = clinical study only

† SB = serum bilirubin in mg. per 100 cc.
1′ = prompt direct; T = total

TABLE V—*Continued*

Case no.	Initials	Sex	Age	Diagnosis	Diagnosis by*	Date of determination	SBt		UCP γ/24 hrs.	Per cent I	Per cent III	γ III/ 24 hrs.
							1′	T				
20	M. E.	♂		Ca. pancreas	O	6/18/47	9.0	15.8	443	71	29	128
21	A. F.	♂		Ca. C.B.D.	O	10/17/47			294	70	30	88
22	P. G.	♂	74	Ca. pancreas	C	8/23/47	24.2	42.1	198	80	20	39
23	H. G.	♂	65	Ca. liver	O	2/27/47			127	69	31	39
24	N. H.	♂	21	Ca. liver	O	6/30/47	0.1	0.5	79	68	32	25
25	L. H.	♂	69	Ca. C.B.D.	A	10/21/47	7.8	14.5	177	77	23	41
26	R. J.	♀	25	Ca. pancreas	O	10/20/47	6.3	11.1	242	72	28	68
27	A. J.	♂	45	Ca. liver	O	4/24/46	0.1	0.9	61	71	29	18
28	H. J.	♀	66	Ca. C.B.D.	A	8/13/46	0.2	0.4	280	74	26	73
29	M. J.	♀	56	Ca. C.B.D.	C	3/3/48	2.7	3.8	149	72	28	42
30	S. K.	♂	73	Ca. liver	C	9/30/46	16.0	30.0	297	81	19	56.5
31	W. R.	♂	70	Ca. C.B.D.	O	2/1/46	6.6	9.8	272	77	23	62.5
32	F. U.	♂	67	Ca. pancreas	C	2/18/48	10.0	16.5	190	78	22	42
33	C. W.	♀	58	Ca. liver	O	7/13/46	0.1	0.8	137	84	16	22
34	L. W.	♀	61	Ca. C.B.D.	O	3/26/47	8.7	14.5	214	70	30	64
35	J. W.	♂	70	Ca. head pancreas	O	3/2/46	4.6	8.7	314	80	20	63
36	H. K.	♂	65	Ca. bile ducts	O	2/4/47	13.7	24.0	204	75	25	82
37	E. J.	♂	60	Adenoca of ampulla	O	8/14/47	5.6	12.2	208	71	29	71
38	N. P.	♂	60	Ca. pancreas	O	5/10/47	0.4	0.9	113	79	21	24
39	C. A.	♀	68	Ca. bile ducts	O	4/9/48	3.6	6.4	175	70	30	53
40	R. S.	♀	53	Ca. bile ducts	C	7/10/48	0.2	1.1	249	81	19	47
41	B. W.	♀	21	Ca. bile ducts	A	1/30/47	5.6	10.2	300	74	26	79

series, it was noted that 31 γ was two standard deviations above the mean for the normal group. Thus it is evident that there may be a marked increase of one isomer, even though, percentagewise, the other one is preponderant.

Tables V and VI include the data for the biliary tract cancer and the calculous groups respectively. Two exceptional cases included in Table VI deserve individual consideration. Both of these exhibited considerable increases of type III isomer in contradistinction to the other members of the group, in which the increase was mainly of type I. In both, however, there were prominent features serving to distinguish them in other respects as well. In Case 2, gallstones were found in a large sub-hepatic pocket resembling an abscess; the gall bladder and common duct were not identified and the surgeon believed that there had been a severe inflammation with considerable "breaking down of tissue." The spleen, which was removed, weighed 1270 gm., and was diagnosed as splenic hyperplasia or Banti's disease; liver biopsy revealed a definite early cirrhosis. It was impossible to obtain a history of alcoholism or other chemical exposure which might have explained the excessive type III coproporphyrin excretion in this case. The possibility of endogenous chemical intoxication is considered because of the above operative findings.

In Case 12, Table VI, necropsy revealed miliary

tuberculosis. The possible relationship of this condition to an excessive type III coproporphyrin excretion is not clear and is receiving further study. Again one must consider an endogenous chemical intoxication, due to extensive necrosis, as the important factor.

A third case, not included in the tables, and which we have not been able to classify, was that of an aeronautical engineer, a male, 47 years of age, who was conducting research at very low temperatures. In fact, 24 hours before the onset of his illness, he had spent an hour and a quarter in a cold chamber at − 60° F, wearing a suit specially designed for high-altitude flying. The temperature of his skin, measured by means of a thermocouple, fell to as low as 84° F during the latter part of the experiment. He felt fairly well until the next day when he noticed marked aching in the muscles. This persisted and the next day his temperature rose to 103° C. Two days later he became jaundiced; the urine was dark and the stools light. The jaundice became more marked and persisted about two weeks, the maximum serum bilirubin being 6.8 mg. per 100 cc., of which 3.7 mg. was the prompt direct (one minute) type. The cephalin cholesterol flocculation test was 3 plus. The 24-hour urine urobilinogen was 113 mg. The UCP was 270 γ/24 hours of which 90 per cent was the

TABLE VI

UCP in cases of common duct stone

Case no.	Initials	Sex	Age	Date	SB*		UCP γ/24 hrs.	Per cent I	Per cent III	γ III/ 24 hrs.	Diagnosis by†
					1′	T					
1	M. S.	♀	70	4/5/43	5.8	8.1	230	88	12	28	O
2	C. M.	♀	46	8/18/44	4.4	7.4	260	35	65	169	O
3	M. R.	♀	32	8/28/44	2.7	4.5	120				O
4	H. P.	♀	50	8/7/46 5/5/44	0.9 13.0	1.7 16.3	183 330	87	13	24	O
5	L. C.	♀	78	1/13/47	0.3	1.5	139				C
6	H. B.	♂	46	11/7/44	0.4	1.2	230	93	7	16	C
7	J. R.	♂	58	11/7/44			202	87	13	26	C
8	E. S.	♀	37	12/15/45	2.3	4.8	175				O
9	A. M.	♂	51	9/16/46 9/17/46 9/18/46 9/19/46 9/20/46 9/21/46 9/22/46 9/23/46	2.3 1.0	3.9 2.0	325 302 330 344 264 199 152 109	92	8	26	O
10	M. R.	♀	62	6/25/46 6/26/46 6/27/46 6/28/46 6/29/46 7/1/46 7/3/46 7/7/46	8.9 3.5 	14.2 7.2 	509 223 216 206 180 419 218 238	95 92 	5 8 	25 17 	O
11	B. S.	♂	54	4/2/46	0.3	1.0	248	84	16	40	C
12	F. S.	♂	71	5/23/44 5/30/44	4.3	4.9	180 184	17	83	149	A

* SB = serum bilirubin in mg. per 100 cc.
1′ = prompt direct
T = Total

† A = autopsy
O = operation
C = clinical study only

TABLE VI—*Continued*

Case no.	Initials	Sex	Age	Date	SB*		UCP γ/24 hrs.	Per cent I	Per cent III	γ III/ 24 hrs.	Diagnosis by†
					1′	T					
13	J. M.	♂	72	9/17/47 9/18/47 9/20/47 9/21/47	4.5	10.0	575 512 263 262	83 82 85	17 18 15	97 92 39	O
14	M. S.	♀	59	1/25/48	1.9	3.8	117	90	10	12	O
15	R. B.	♀	61	1/25/48	0.9	1.6	115	88	12	14	O
16	F. G.	♂	81	4/29/47	2.2	3.7	238	93	7	17	A
17	J. W.	♂	72	7/9/46	0.4	1.4	89	91	9	8	O
18	J. J.	♂	58	3/3/46	3.1	6.5	159	81	19	30	O
19	A. H.	♀	74	9/3/46	8.4	12.9	214	77	23	49	O
20	M. H.	♂	46	12/9/45	0.2	2.1	172	85	15	26	C
21	M. C.	♀	30	5/5/46	0.2	1.7	67	82	18	12	C
22	H. H.	♀	37	7/8/46	0.9	2.6	116	86	14	16	O
23	C. F.	♀	68	1/8/47	1.2	3.0	210	91	9	19	O
24	I. R.	♀	40	5/12/47	0.1	0.4	64	79	21	13	O
25	A. F.	♀	58	9/18/47	0.2	1.1	116	83	17	20	C
26	I. M.	♀	66	4/4/48	0.3	1.3	67	79	21	14	O
27	E. M.	♀	38	1/7/48	0.1	0.9	108	80	20	22	C
28	K. H.	♂	71	4/12/48	0.2	1.1	105	90	10	11	C
29	C. H.	♀	73	2/13/48	2.5	4.9	186	94	6	11	O
30	L. C.	♂	41	11/15/48	0.4	1.4	138	88	12	17	O

TABLE VII

UCP and isomer distribution in Case 49 (Figure 2)

Date	UCP in γ/24 hrs.	Per cent Type I
2–25–47	445	90
3–7	593	
3–15	554	
3–25	400	
4–2	413	
4–8	302	
4–15	275	93
4–22	201	
4–29	234	
5–6	188	
5–13	225	
5–20	270	
6–17	259	
8–5	122	
8–14	253	
1–29–48	200	
2–8	232	94
2–8	290*	95
7–16	130	
10–29	266	

* Feces—amount for one day.

type III isomer. The attack was relatively mild and the patient felt quite well six weeks later. This would in all likelihood have been accepted as an episode of sporadic infectious hepatitis if it were not for the curious circumstances at the outset, coupled with the result of the porphyrin determination. The former might be regarded simply as a precipitating factor, but it was then found that there had been considerable alcoholism in the weeks or months preceding the onset of the jaundice, also that there had been moderate exposure to a number of chemicals and heavy metals in connection with the patient's research. Furthermore, the excessive type III coproporphyrin excretion persisted long after the attack of jaundice which has just been described. On March 8, 1946, nearly two years later, the UCP was 208 γ/24 hours with 65 per cent type III; on August 14, 1946, it was 187 γ,

and on November 23, 1946, 175 γ. Thus, while it was impossible to classify this case, it appeared reasonable to believe that it was more likely due to extrinsic chemical and possibly physical factors, and less likely to an infectious hepatitis, although a combination of chemical and viral factors is a distinct possibility.

DISCUSSION

The present results reveal that the urinary coproporphyrin is quite uniformly increased in regurgitation jaundice, whether due to biliary obstruction or to parenchymal hepatic disease. Further study is necessary to determine if this is due only to regurgitation of bile into the blood stream, or to hepatocellular functional impairment, or to a combination. The persistent and often marked elevation of the urinary coproporphyrin long after the disappearance of jaundice points toward an hepatocellular or retention, rather than a cholangiolar or regurgitation factor. The elevated values in obstructive jaundice, however, are perhaps indicative of the latter, particularly inasmuch as they were observed in relatively early cases before one would anticipate significant hepatocellular functional impairment. Van den Bergh (23) was impressed by the coproporphyrinemia and increased coproporphyrinuria in mechanical jaundice, and ascribed them to regurgitation of bile into the blood. Gonzalez-Oddone, working in this laboratory, has observed [5] that intravenously injected coproporphyrin appears in the thoracic duct lymph of dogs having ligated common bile ducts, in this respect behaving like injected bromsulfalein (24). Thus it appears that, in cases of jaundice, the coproporphyrin may appear in the urine in excess as a result either of hepatocellular or cholangiolar impairment, in the first instance probably being retained and in the second, regurgitated from the intrahepatic biliary system into the blood. The fact that the highest values are more likely to be encountered in jaundice due to hepatitis or cirrhosis may indicate a combination of these factors in such cases. This is quite in harmony with the belief that in hepatitis, there is both hepatocellular and cholangiolar injury, varying in severity in different instances and at different stages in the same instance (25).

It is appropriate to ask whether the increased amounts of coproporphyrin I in the urine of the present series of cases represents actual overproduction of this porphyrin, or merely a diversion of that which would normally be excreted in the bile and thence in the feces. There is actually no evidence of over-production. It has already been seen that the factors of retention and regurgitation are probably operative in reducing the biliary excretion of coproporphyrin and increasing its excretion in the urine. The amounts in the urine in these cases do not exceed those of the normal feces in 24 hours. Thus the evidence so far available indicates simple diversion rather than over-production, at least in the majority of cases in which type I is preponderant in the urine. This may be true as well for other conditions in which increased amounts of coproporphyrin I are found in the urine. Simultaneous studies of fecal and urinary excretion are needed, however, before the question can be answered with certainty. The available evidence at the present time (4, 5) indicates that there are but two conditions under which an overproduction of the type I isomer may be anticipated: (*1*) porphyria, a constitutional metabolic fault; (*2*) increased erythropoietic activity following increased blood destruction or blood loss. In the case of the type III isomer, it is clear that there is often marked overproduction and increased excretion from various causes (5).

It appears unlikely that a determination of the total urinary coproporphyrin will frequently be of value in the distinction of parenchymal jaundice from jaundice due to extrahepatic biliary obstruction. Careful study of the data obtained in the present study reveals considerable overlapping of values at various levels of icterus due to biliary obstruction as compared with diffuse liver injury. In Figure 4 the values for UCP in the cancerous, calculous, and hepatitis-cirrhosis groups are plotted against the values for total bilirubin. The data for the cases of cirrhosis included in this figure are considered in more detail in the subsequent paper of this series. It is seen in Figure 4 that while there is no distinct cleavage between the hepatitis-cirrhosis and the other groups, the higher values with lesser degrees of jaundice are more characteristic of the former. It appears from these data that values of 250 γ/24 hours, or higher, with total serum bilirubins less than 6.0 mg., as enclosed

[5] Unpublished observation.

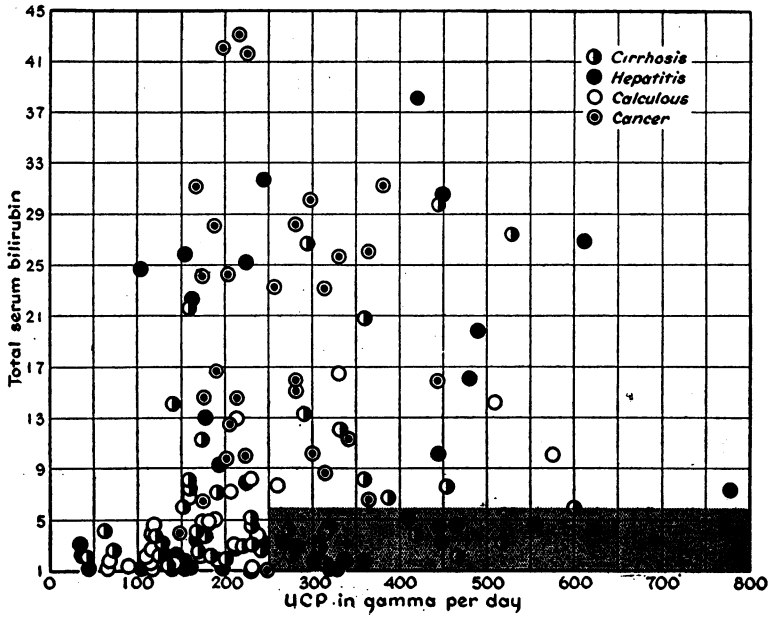

FIG. 4. UCP AND TOTAL SERUM BILIRUBIN IN CASES OF BILIARY TRACT CANCER, COMMON DUCT CALCULUS, INFECTIOUS HEPATITIS, AND CIRRHOSIS

in the shaded area in Figure 4, are much more likely to be associated with hepatitis or cirrhosis, than with extrahepatic biliary obstruction.

Insofar as hepatitis is concerned, the determination of the UCP is of more value in detecting residual hepatic functional impairment at varying intervals after the disappearance of jaundice. In the present series 45 of 95 cases exhibited elevated values at varying intervals after disappearance of jaundice.

In Table VIII, the cases for which data were given in Table II, are subdivided as to whether the increase or lack of increase of the UCP was associated with other abnormalities, either symptomatic, physical or laboratory in character. It is seen that the UCP was elevated in 11 instances (groups 2a and 2c) in which the other laboratory findings were normal. Five of these had significant symptoms or physical findings and six did not. The largest number of cases were in group 2b in which there were symptoms or physical findings together with other abnormal laboratory data. It should be noted that in a number of instances in this group the other laboratory abnormalities

TABLE VIII

Groups with presence or absence of symptoms,* physical findings,* or abnormal laboratory data	Case nos. (as in Table II)	Total
1. Symptoms or physical findings without abnormal laboratory findings	3, 19, 29, 35, 37, 59	6
2. UCP > 100 γ/24 hr. (abnormal)		
a. Without symptoms or abnormal physical findings and without other laboratory abnormalities	4, 11, 15, 38, 49, 61	6
b. With symptoms or physical findings and with other laboratory abnormalities	5, 6, 7, 9, 11, 12, 14, 16, 17, 18, 21, 22, 23, 27, 28, 30, 32, 33, 34, 40, 42, 43, 44, 45, 46, 48, 49, 51, 52, 53, 54, 56, 57, 59, 60, 62	36
c. With symptoms or physical findings but without other abnormal laboratory data	8, 10, 26, 31, 36	5
d. With other abnormal laboratory data, but without symptoms or physical findings	39, 41	2
3. UCP < 100 γ/24 hr. (normal), with other laboratory abnormalities, and with or without physical findings	13, 20, 24, 47, 50, 55	6

* Symptoms > I, liver enl. > 1 cm., liver tenderness + or greater (see key, Table II).

were isolated; thus, in Cases 7, 9, 18, 21, 23, 34, and 59, the only abnormality in addition to the excessive UCP, was an elevated urine Ehrlich reaction; while in Cases 33, 36, 43 and 53 the only other abnormality was in the serum bilirubin level.

It was of particular interest to compare the UCP and the bromsulfalein retention, especially in those cases in which other findings were borderline. As noted in Table II, the bromsulfalein test was carried out 53 times in 43 cases. The UCP value corresponding in time with these determinations, was significantly elevated (> 100 γ/24 hours) in 22 instances in which the bromsulfalein retention did not exceed 5 per cent; conversely, there was but one instance in which the opposite was true. This was Case 13 in Table II, in which the bromsulfalein retention was 8 per cent and the UCP 92 γ/24 hours. Insofar as the UCP and cephalin flocculation tests are concerned, inspection of Table II reveals a negative flocculation in a number of instances in which the UCP was significantly increased; none are found in which the reverse was true.

At present there is no way of determining whether residual functional impairment is synonymous with persistent activity of a virus hepatitis. From a practical standpoint, at any rate, it is probably wise to advise caution as to unusual activity, strain, fatigue, alcohol, etc., at least until the evidence of residual impairment has disappeared. Case 49 in Table II is an example of this problem. Further data for this case are given in Figure 2 and Table VII. This individual was permitted to resume his normal occupation in spite of persistent elevation of the UCP, but at the same time he was enjoined to avoid undue fatigue, irregular hours of sleep and alcohol. One of the problems of the recovery state of hepatitis has been that the individual may complain of persistent weakness and fatigue even though the results of various liver function tests are normal or borderline. In a number of such instances included in the present study, the elevated urinary coproporphyrin gave indication of residual activity or impairment, and appeared to be correlated with the symptoms of fatigue, weakness or nervousness. Conversely, however, we have observed several individuals complaining of one or more of these symptoms yet having normal porphyrin values in addition to normal composite liver function studies. In such instances it has been impossible to decide with certainty whether the symptoms were on a psychic

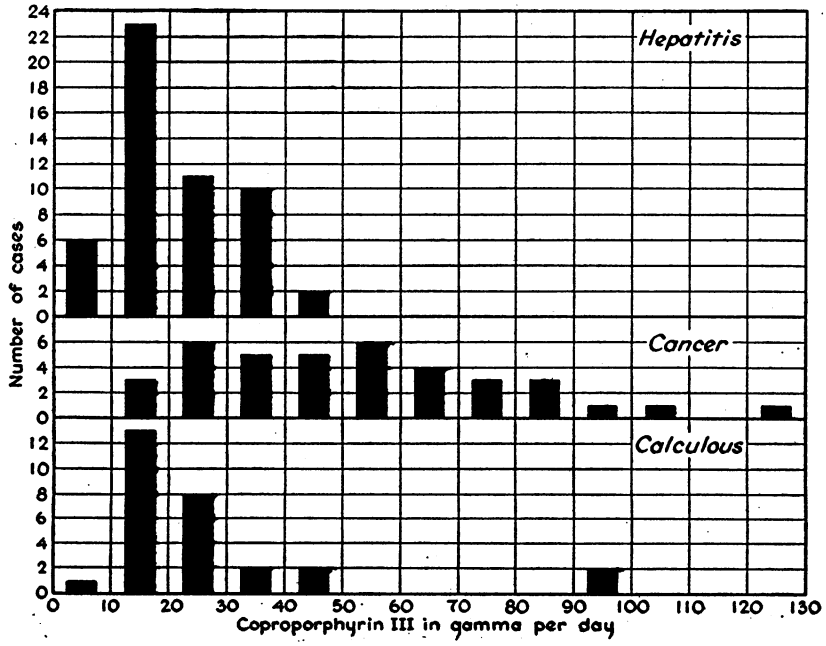

FIG. 5. FREQUENCY DISTRIBUTION OF VALUES FOR URINARY COPROPORPHYRIN III IN CASES OF HEPATITIS, BILIARY TRACT CANCER, AND COMMON DUCT CALCULUS

basis or were in reality due to residual hepatic impairment. Additional studies, including exercise tolerance with relation to coproporphyrin excretion, are desirable in order to determine the degree of assistance one may expect from this determination.

From the present results it is evident that the increase in UCP in hepatitis and mechanical jaundice is due in the main to increased excretion of the type I isomer. Inspection of the data in Tables III, IV, V and VI, reveals, however, that in some instances the amount of type III isomer exceeds the normal upper limit of 34 γ/24 hours reported previously (14). In the hepatitis and infectious mononucleosis groups there are few of these and the excess is slight, probably within the limit of error of the differential precipitation method (12, 13). The two outstanding exceptions were cases in the calculous group which have already been referred to; one of these had a necrotic abscess with marked splenomegaly, and the other had miliary tuberculosis. In one additional instance (Case 13 in Table VI) an unexplained absolute increase of type III coproporphyrin is noted, comprising, however, but 17–18 per cent of the total UCP. In the cancer group, there are quite a number of cases having considerable excesses of type III isomer even though type I is clearly preponderant in each instance. Frequency distribution curves for the three groups are shown in Figure 5. Several cases, already discussed, have been omitted in the preparation of this figure, because of significant peculiarities believed to place them in separate categories. These cases are numbers 51 in Table II, 2 and 12 in Table VI. Figure 5 reveals the relative frequency of increased coproporphyrin III excretion in the cancer group. Nineteen of 39 cases in this group had values above 50 μg. in 24 hours, while all of the 40 in the hepatitis group were below this level. Thus it is evident that the patients with cancer of the biliary tract or liver vary significantly in the composite, from the other groups, and especially from the hepatitis group, in respect to porphyrin metabolism. It appears that an absolute increase of the type III isomer greater than 50 γ/24-hour urine sample, favors the diagnosis of cancer rather than hepatitis, and is much more likely to be encountered with cancer than with calculus, in the presence of regurgitation jaundice. The reason for this difference is not clear, but the possibility may be entertained of an endogenous chemical intoxication, from necrotic or abnormal cells. It is recognized too, that a constitutional factor cannot be excluded.

SUMMARY AND CONCLUSIONS

1. The total urinary coproporphyrin (UCP) is regularly increased above the upper limit of normal of 100 γ/24-hour urine sample, both in infectious hepatitis during the period of jaundice, and in cases of mechanical jaundice. The increase in cases of hepatitis often persists in some measure for considerable periods after the disappearance of jaundice and after the return to the normal range of conventional tests such as bromsulfalein retention and cephalin cholesterol flocculation. In certain instances the increase of the UCP has constituted the only objective evidence of residual hepatic functional impairment.

2. In cases of infectious mononucleosis the UCP is commonly increased, usually in association with other evidence of hepatic functional impairment.

3. Isomer analysis has shown that the increase in UCP in infectious hepatitis, infectious mononucleosis, and mechanical jaundice, is mainly due to the type I isomer. Certain exceptions are discussed and it is shown that in cases of cancer of the pancreas, bile ducts, or liver, the increased UCP, although preponderantly type I, includes an absolute increase of type III with relative frequency. This has not been observed to any significant degree in cases of infectious hepatitis, infectious mononucleosis, or uncomplicated calculous jaundice.

BIBLIOGRAPHY

1. Garrod, A. E., On haematoporphyrin as a urinary pigment in disease. J. Path. and Bacteriol., 1892, 1, 187.
2. Garrod, A. E., On the urinary pigments in their pathological aspects. Lancet, 1900, 2, 1323.
3. Fischer, H., and Zerweck, W., Zur Kenntnis der natürlichen Porphyrine. V. Über Koproporphyrin im Harn und Serum unter normalen und pathologischen Bedingungen. Ztschr. f. physiol. Chem., 1924, 132, 12.
4. Dobriner, K., and Rhoads, C. P., The porphyrins in health and disease. Physiol. Rev., 1940, 20, 416.
5. Watson, C. J., and Larson, E. A., The urinary coproporphyrins in health and disease. Physiol. Rev., 1947, 27, 478.
6. Nesbitt, S., and Snell, A. M., Excretion of coproporphyrin in hepatic disease. I. Correlation of

urinary and fecal excretion with parenchymatous hepatic damage. Arch. Int. Med., 1942, **69**, 573.

7. Nesbitt, S., and Snell, A. M., Excretion of coproporphyrin in hepatic disease. II. Urinary and fecal excretion in biliary obstruction. Ibid., 1942, **69**, 582.
8. Localio, S. A., Schwartz, M. S., and Gannon, C., The urinary/fecal coproporphyrin ratio in liver disease. J. Clin. Invest., 1941, **20**, 7.
9. Watson, C. J., Concerning the naturally occurring porphyrins. I. The isolation of coproporphyrin I from the urine in a case of cincophen cirrhosis. J. Clin. Invest., 1935, **14**, 106.
10. Watson, C. J., Concerning the naturally occurring porphyrins. V. Porphyrins of the feces. J. Clin. Invest., 1937, **16**, 383.
11. Dobriner, K., The urinary porphyrins in disease. J. Biol. Chem., 1936, **113**, 1.
12. Schwartz, S., Hawkinson, V., and Watson, C. J., Quantitative differentiation of minute amounts of the coproporphyrin isomers (I and III) based on fluorescence behavior. Science, 1946, **103**, 338.
13. Schwartz, S., Hawkinson, V., Cohen, S., and Watson, C. J., A micromethod for the quantitative determination of the urinary coproporphyrin isomers (I and III). J. Biol. Chem., 1947, **168**, 133.
14. Watson, C. J., Hawkinson, V., Schwartz, S., and Sutherland, D., Studies of coproporphyrin. I. The per diem excretion and isomer distribution of coproporphyrin in normal human urine. J. Clin. Invest., 1949, **28**, 447.
15. Ducci, H., and Watson, C. J., The quantitative determination of the serum bilirubin with special reference to the prompt-reacting and the chloroform-soluble types. J. Lab. & Clin. Med., 1945, **30**, 293.
16. Mateer, J. G., Baltz, J. I., Marion, D. F., and MacMillan, J. M., Liver function tests; general evaluation of liver function tests and appraisal of comparative sensitivity and reliability of newer tests, with particular emphasis on cephalin-cholesterol flocculation test, intravenous hippuric acid test, and improved bromsulfalein test with new normal standard. J. A. M. A., 1943, **121**, 723.
17. Hanger, F. M., The flocculation of cephalin-cholesterol emulsions by pathological sera. Tr. A. Am. Physicians, 1938, **53**, 148.
18. Schoenheimer, R., and Sperry, W., A micromethod for the determination of free and combined cholesterol. J. Biol. Chem., 1934, **106**, 745.
19. Schwartz, S., Sborov, V., and Watson, C. J., Studies of urobilinogen. IV. The quantitative determination of urobilinogen by means of the Evelyn photoelectric colorimeter. Amer. J. Clin. Path., 1944, **14**, 598.
20. Watson, C. J., Schwartz, S., Sborov, V., and Bertie, E., Studies of urobilinogen. V. A simple method for the quantitative recording of the Ehrlich reaction as carried out with urine and feces. Ibid., 1944, **14**, 605.
21. Watson, C. J., and Hawkinson, V., Studies of urobilinogen. VI. Further experience with the simple quantitative Ehrlich reaction. Corrected calibration of the Evelyn colorimeter with a pontacyl dye mixture in terms of urobilinogen. Am. J. Clin. Path., 1947, **17**, 108.
22. Watson, C. J., Schulze, W. M., Hawkinson, V., and Baker, A. B., Coproporphyrinuria (Type III) in acute poliomyelitis. Proc. Soc. Exp. Biol. & Med., 1947, **64**, 73.
23. H. van den Bergh, A. A., Grotepass, W., and Revers, F. E., Beitrag über das Porphyrin in Blut und Galle. Klin. Wchnschr., 1932, **11**, 1534.
24. Gonzalez-Oddone, M. V., Bilirubin, bromsulfalein, bile acids, alkaline phosphatase, and cholesterol of thoracic duct lymph in experimental regurgitation jaundice. Proc. Soc. Exp. Biol. & Med., 1946, **63**, 144.
25. Watson, C. J., and Hoffbauer, F. W., Liver function in hepatitis. Ann. Int. Med., 1947, **26**, 813.
26. Peterson, R. E., Hepatic dysfunction in infectious mononucleosis; with review of the literature. J. Lab. & Clin. Med., 1948, **33**, 1258.