Diagnosis of Constitutional Hyperbilirubinemias by Sequential Scanning with I-131-BSP

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Sequential liver scanning was introduced for the diagnosis of medical and surgical jaundices by Yamada and Taplin(1) using I-131-Rose Bengal. Following this trial authors have reevaluated the I-131-BSP (monoiodide)(2) and applied this dye successfully for the same purpose as well as for hepatic function study(2).

In this paper, taking note of the fact that I-131-BSP sequential scanning method makes visible the mechanism of liver uptake, intrahepatic transport and biliary excretion of this dye, the authors aimed to make clear the classification of constitutional hyperbilirubinemias and the pathophysiology of this disease subjects, which are still controversial among researchers.

Materials and Method

The subjects, as shown in Table 1 and 2, were 30 patients of the University of Tokyo Hospital—11 cases of Dubin-Johnson syndrome, 8 Rotor-type, and 11 of Gilbert disease—and three Dubin-Johnson patients at Kofu Municipal Hospital. From this group of cases 2 Dubin-Johnson, 1 Rotor and 1 Gilbert were selected for the following study.

A dose of 400 uCi of I-131-BSP was intravenously injected into the subjects two hours after breakfast. Blood samples were taken at intervals of 5, 7, 10, 15, 30, 45, 60 and 120 minutes, while scanning of liver and intestine was simultaneously undertaken at 10, 30, 60 and 120 minutes and 3～5, 6～8, 20～24 and 30～36 hours. The subjects took ordinary meals during these procedures.

Patients were subjected to an additional BSP 5 mg/kg loading test, S-35-BSP (0.1 mg) clearance and I-131-Rose Bengal (I-131-RB) clearance and continuous scanning.

Case 1 was a 45 year-old male (Table 1(1)—3) who showed jaundice and had been admitted to Tokyo University Hospital 14 years earlier. Laboratory data on this patient were: total protein 7.5, A/G 1.3, total bilirubin 2.4 mg/dl (direct 1.6mg/dl and indirect 0.8mg/dl), TTT 3, Kunkel's test 8, SGOT 22, SGPT 19, Hb 14.8, RBC 4,670,000, WBC 4,800, urine urobilinogen (±), bilirubin (—). Conjugated bilirubin level in the blood was elevated. Blood clearance of BSP (5 mg/kg) showed marked rebound between 45 minutes and 2 hours, as shown in Figure 1. Clearance of I-131-BSP showed

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Table 1. Constitutional hyperbilirubinemias in the 2nd Department of Medicine, University of Tokyo

No.	Name	Age	Sex	Clinical Appearance	Serum Bilirubin			BSP (45')	ZnTT	Urinary Bilirubin	Cholecystogram	Peritoneoscope Black Liver	Granule by Biopsy
					Total	Direct	Indirect						
(1) Dubin-Johnson syndrome													
1	E. N.	22	F	+	2.9	2.1	0.8	9	9.6	±	−	+	+
2	T. N.	16	M	+	3.0	2.1	0.9	7.5	9.2	+	−	+	+
3*	J. Y.	31	M	−	2.8	2.1	0.7	15	11.6	−	−	+	+
4	S. A.	20	M	+	2.5	1.0	0.9	10	6.4	−	−	+	+
5	A. O.	20	M	−	2.6	1.8	0.8	10	8.5	+	−	+	+
6	T. S.	23	M	−	4.2	3.2	1.0	15	9.4	+	−	/	+
7	T. S.	25	M	+	1.8	1.2	0.6	17.5	11.6	−	−	+	+
8	M. N.	15	M	−	4.2	1.9	2.3	12.5	5.6	±	−	+	+
9	Y. U.	23	M	+	6.0	3.7	2.3	2.5	7.7	±	+	+	+
10	T. K.	16	M	−	4.2	3.1	1.1	19	4	−	−	+	+
11	O. S.	23	M	−	4.5	3.2	1.3	/	/	−	/	+	+
(2) Rotor-type													
1	T. T.	20	M	+	14.8	9.2	5.6	35	5.3	+	±	normal	−
2	Y. K.	18	M	−	7.6	5.5	2.1	27.5	8.7	+	−	/	−
3	T. N.	16	F	−	5.1	2.5	2.6	40	7.0	−	±	normal	−
4	S. K.	45	M	−	4.3	2.5	1.0	30	8.4	−	+	normal	−
5	N. K.	21	F	−	4.5	4.1	1.4	30	12	±	±	/	−
6	K. W.	38	M	−	7.2	4.9	2.3	22.5	7	−	±	normal	−
7	K. H.	16	M	−	6.1	4.2	1.9	20	7	−	±	normal	−
8*	H. A.	55	M	−	8.1	5.5	2.6	40	8	+	+	normal	−
(3) Gilbert Disease													
1	M. A.	18	M	+	16.3	1.5	14.8	7.5	10.5	−	+	/	−
2*	Y. O.	22	M	−	5.6	0.7	5.0	6	7.6	−	+	/	−
3	Y. T.	32	M	−	5.3	1.7	3.6	10	10.4	−	+	/	−
4	S. Y.	36	M	+	3.6	0.5	3.1	0	9.8	−	+	/	−
5	K. A.	29	M	−	2.6	0.4	2.2	0	8.8	−	+	/	−
6	O. W.	36	M	−	2.4	0.5	1.9	0	7.7	−	+	/	−
7	H. K.	17	M	−	2.1	0.4	1.7	5	6	−	+	normal	−
8	K. M.	20	M	−	2.1	0.3	1.8	2.5	8.4	−	+	normal	−
9	M. T.	24	M	−	1.6	0.1	1.5	2.5	9	−	+	normal	−
10	T. Y.	16	M	−	11.6	0.8	10.8	2.5	8	−	+	normal	−
11	T. S.	39	M	+	4.9	0.5	4.4	2.5	8	−	+	normal	−

* Cases examined in the present report

rapid decline (Fig. 1), and clearance of ICG showed also fast decay (k=0.278).

The result of I-131 BSP sequential scanning is shown in Figure 2: a notable delay in excretion into the intestine is observed as compared with a normal control in Figure 2 (where most of I-131-BSP is excreted into the intesitne in two hours). Even four hours later, only a sligh excretion into the intestines is observed. Twe nty-two hours later, liver radioactivity decrease along with marked excretion into the intestine

The result of I-131-RB sequential scanning i shown in Figure 3. Here it is noted that biliar excretion is retarded, but most has been exc

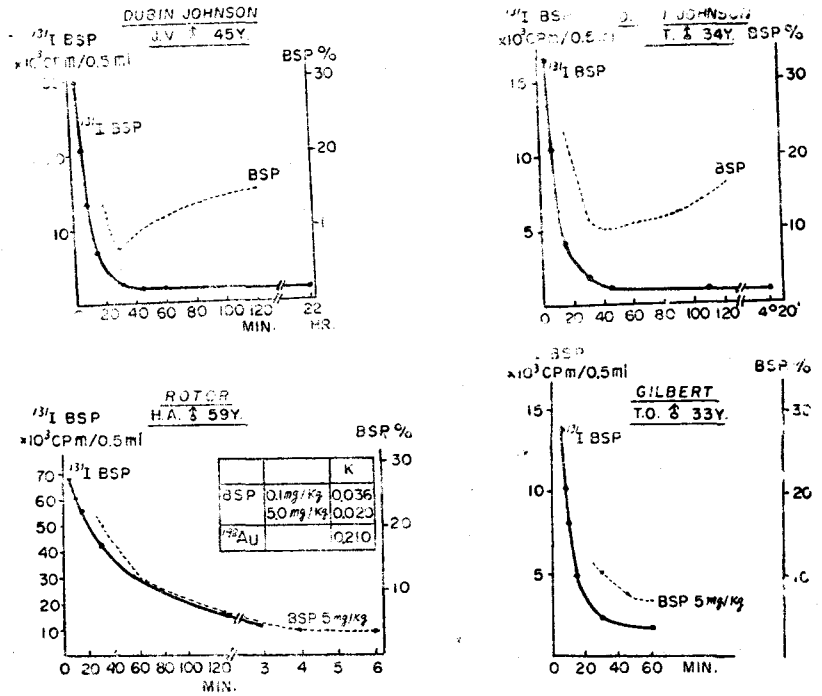
DUBIN JOHNSON
BSP %
BSP
MIN.
HR.
ROTOR
H.A. ♂ 59Y.
K
0.1mg/Kg 0.036
5.0 mg/Kg 0.020
0.210
BSP 5 mg/Kg
GILBERT
T.O. ♂ 33Y.
BSP 5 mg/Kg
MIN.

Fig. 1.

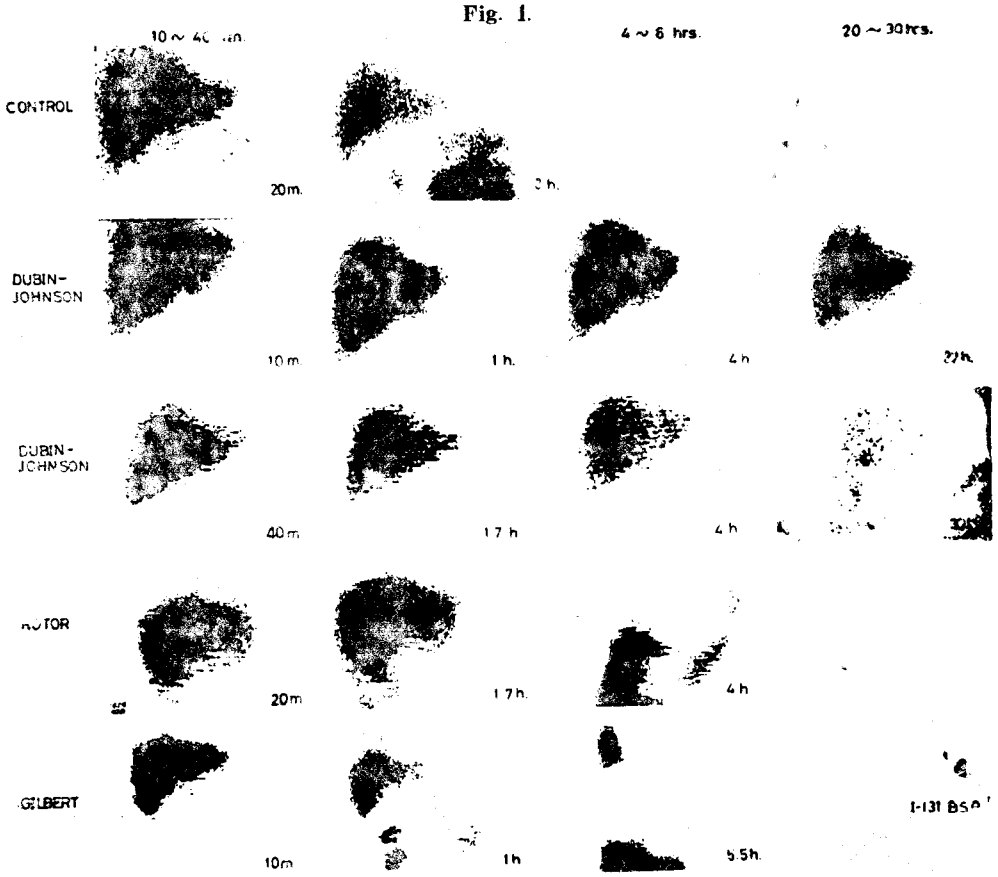
4 ~ 6 hrs.
20 ~ 30 hrs.
CONTROL
20m.
DUBIN-JOHNSON
10 m
1 h.
4 h
DUBIN-JOHNSON
40 m
1 7 h
4 h
ROTOR
20m
1 7h.
4 h
GILBERT
10m
1 h
5.5h.
I-131 BSP

Fig. 2.

eted 8 hours later, showing less disturbance of excretion than in the case of I-131-BSP. The interval between these two sequential scanning procedures was one month.

Case 2 was a 34 year-old male, admitted to Kofu Municipal Hospital (Table Ⅱ-1). Before his referral to the Hospital he complained of epigastric pain. A negative cholecystogram lead the private surgeon to make an exploratory operation, and it was observed that his liver was black. On admission his laboratory data were: jaundice index 20, total bilirubin 2.6 mg/dl (direct 1.8 mg/dl, indirect 0.8 mg/dl), alkaline phosphatase 1.2, SGOT 6, SGPT 12. As in the previous case, direct bilirubin showed an increase, and a BSP (5 mg/kg) load caused a rebound of BSP between 45 minutes and two hours (Fig. 1). Thus, the diagnosis was Dubin-Johnson syndrome. In this case, I-131-BSP showed rapid clearance as well as ICG(k=0.231). Rebounding of I-131-BSP was not observed.

As shown in Figure 2, sequential scanning of I-131-BSP makes it clear that after initial rapid uptake hepatic radioactivity decreases only slightly 100 minutes and 4 hours later. Excretion of I-131-BSP into the intestine is impaired. I-131-BSP is excreted from the liver into the intestine only 30 hours later. I-131-Rose Bengal scanning (Fig. 3) showed, on the contrary, early excretion into the intestine. Even the gall bladder was visualized 1 hour after injection. The interval between these two sequential sca-

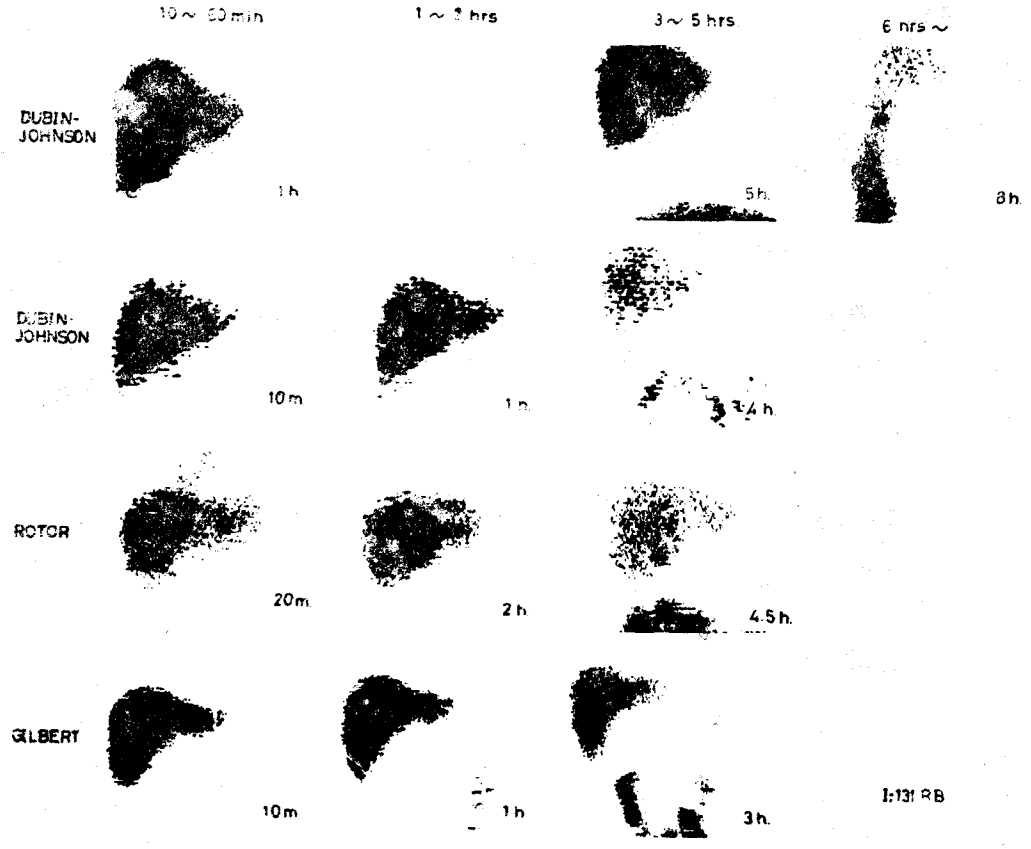

Fig. 3.

Table 2. Constitutional Hyperbilirubinemias in Kofu Municipal Hospital

Dubin-Johnson Syndrome													
1*	K. T.	34	M	−	2.6	1.8	0.8	5.0		+	−	+	/
2	C. K.	25	F	+	5.8	3.1	2.7	27.1	6.2	+	+	+	+
3	J. K.	33	M	+	—	—	—	—	—	+	−	+	+

* Cases examined in the present report.

nning procedures was 1 month. No notable change in laboratory data was found.

Case 3 was a male, 59 years of age (Table I, (2)-8). When admitted to the University of Tokyo Hospital four years earlier, he was diagnosed to be Rotor type based on such data as high direct bilirubinemia, high retention of BSP, liver biopsy and laparoscopy. His laboratory data at the time of re-admission were: total protein 6.8. alkaline phosphatase 2.4, jaundice index 30, total bilirubin 5.7 mg/dl (direct type 3.9, indirect type 1.8) TTT 3, Kunkel's test 8, SGOT 10, SGPT 18, urine urobilinogen (卄), bilirubin (+). Blood clearance of the several dyes is shown in Figure 1: clearance of BSP 5 mg/kg is extremely delayed (k= 0.020), and those of I-131-BSP and I-131-RB are likewise slow. ICG clearance is also extremely delayed (k=0.0153). However, Au-198 colloid clearance shows normal decay (k=0.210).

Sequential scanning of this patient is given in Figure 2. Ten to 30 minutes after injection slow blood clearance and delayed liver uptake of I-131-BSP cause visualization of radioactivity remaining in the heart pool. One hundred minutes later, however, delayed liver uptake does not prevent excretion into the intestine. Four hours later practically all the I-131-BSP has been excreted into the intestine.

Sequential scanning of I-131-RB shows a similar tendency. That is, 20 minutes after injection (Fig. 3), radioactivity remains in the blood pool, while the gall bladder appears rapidly one hour later. Excretion into the intestine occurs two hours later and finishes almost completely in four hours.

Case 4 was a 33 year-old male (Table I, (3)-2). The patient had been admitted to the University of Tokyo Hospital 10 years earlier and a diagnosis of Gilbert disease was made. Laboratory data at this time were as follows: total protein 7.6, alkaline phosphatase 1.5, jaundice index 21, total bilirubin 3.3 mg/dl (direct 0.7, indirect 2.6), TTT 1, Kunkel 6, BSP 7.5% (45 min. retention), SGOT 13, SGPT 5, urinary urobilinogen (±) and bilirubin (−). As is shown in Figure 1, BSP (5 mg/kg) and I-131-BSP are cleared rapidly from the blood. Sequential I-131-BSP scanning shows almost normal hepatic uptake and excretion into the intestine (Fig. 2). I-131-RB scanning shows the same result (Fig. 3).

Discussion

Extensive reports have been filed about Dubin-Johnson (4) and Rotor (5) diseases since their discovery along with Gilbert disease (6) and Criegler-Najjar syndrome (7). Both Dubin-Johnson and Rotor type, regarded as constitutional hyperbilirubinemia in the narrow sense, are considered to be related closely as far as bilirubin metabolism is concerned. Sherlock (8) in her textbook grouped them together under the category of the disturbed canalicular excretion. In Japan, there is also no consensus. Some

consider that Rotor type is either a variant or incomplete type of Dubin-Johnson syndrome(9), whereas others reject this view (10).

In this paper, authors have introduced sequential scanning with I-131-BSP to visualize the mechanism of liver uptake and excretion in these disorders. It was found that, in Dubin-Johnson syndrome, blood clearance of I-131-BSP proceeds rapidly, and liver uptake is satisfactory. Once it is transferred to the liver, however, I-131-BSP remains there for a long time, and even diet intake does not facilitate excretion, as is seen in normal subjects. Though it varies with the patient, retention in the liver continues for at least 10 hours and even several times this period. In the Rotor type, I-131-BSP blood clearance and hepatic uptake are both slow. However, once transferred into the liver, I-131-BSP is rapidly excreted into the intestine. Gilbert disease does not show any disturbance by this method.

In other words, as far as the cases observed in this I-131-BSP study are concerned, Dubin-Johnson and Rotor types present distinctively different pathophysiologic patterns in regard to liver uptake and excretion into the intestine. In Dubin-Johnson syndrome, there is no disturbed mechanism in liver uptake of I-131-BSP, but notable impairment in the excretion mechanism. In Rotor type, conspicuous interference with the mechanism of uptake by the liver is seen, but insignificant disturbance of the excrection of I-131-BSP. These facts do not support the theory that disturbance of canalicular excretion constitutes the main cause of Dubin-Johnson and Rotor type diseases. Both types show similar clinical syndromes; however, these results indicate that the two syndromes represent distinctly different disorders.

Previously, observation of the reappearance of conjugated BSP served as one of the major clinical indices to differentiate Dubin-Johnson and Rotor types. Even though the disturbance in these disorders lies in the area of bilirubin conjugation and bilirubin transport into the bile canaliculi, no adequate method is available at this time for the direct observation of hepatic excretion of bilirubin and other dyes such as BSP.

The fact that, in Rotor type, no notable disturbance of canalicular excretion was observed with either I-131-BSP or I-131-RB gives a better basis for interpretation and helps to distinguish Rotor type from similar diseases.

Significant disturbance in I-131-BSP excretion, similar to that in serious cases of medical jaundice, is an important finding for understanding the pathophysiology of Dubin-Johnson syndrome. This fact is in accord with the finding under the electron microscope that pigments deposit in lysozyme in Dubin-Johnson syndrome different than in Rotor type patients. Lysozyme is considered to be related to biliary excretion. (11) Also, the metabolism of I-131-BSP is in harmony with the fact that cholecystographic visualization of the gall bladder is difficult in Dubin-Johnson syndrome and is relatively easy in Rotor type.

In both disorders I-131-RB and I-131-BSP show parallel metabolism as far as blood clearance and liver uptake are concerned. However, hepatic excretion of I-131-Rose Bengal differs to a considerable degree from that of I-131-BSP. Excretion is relatively rapid in all cases of Dubin-Johnson syndrome studied, and even the gall bladder is visualized both in Dubin-Johnson syndrome and in Rotor type. Therefore, I-131-BSP provides an important contribution to the differential diagnosis of Dubin-Johnson syndrome, which is difficult with I-131-RB. However, further studies are necessary to clarify the interesting difference in metabolism of I-131-BSP

and I-131-RB.

In Dubin-Johnson syndrome, despite the notable disturbance in excretion of I-131-BSP, blood clearance and hepatic uptake of I-131-BSP are faster than in normal cases. This is another point of interest. That is, according to Wheeler et al (12), the transport maximum (tm) of I-131-BSP is practically zero in Dubin-Johnson syndrome while blood clearance is fast, leading us to assume that storage capacity of Dubin-Johnson is increased, or that of Rotor type is decreased.

In Rotor type, as previously pointed out, sinusoidal disturbance of BSP (5 mg/kg) and ICG uptake is notable. However, it is not only with a large dose of BSP or ICG, but trace doses of BSP (S-35-BSP), I-131-BSP and I-131-RB show a disturbance in uptake by the liver. These facts indicate that uptake disturbance in the sinusoidal phase constitutes the core of the pathophysiology of Rotor type disease.

Previous authors have reported that diagnosis of liver cell dysfunction can be easily carried out by loading with trace doses of I-131-BSP or S-35-BSP (2, 15). The adequacy of this method can be also supported by findings in Rotor type, which showed delayed clearance of all dyes studied even though Au-198 colloid clearance remained normal. This fact overcomes the objection that trace dose clearance of dye is only an indication of hepatic blood flow but not of hepatic cell function.

Thus, in addition to the proved usefulness of the application of I-131-BSP to the diagnosis of medical and surgical jaundices the I-131-BSP sequential scanning method is proved in this paper to be important to the differential diagnosis of constitutional hyperbilirubinemias.

Since its introduction by Rosenthal in 1925, BSP has been widely used for clinical and research purposes. In 1961, Tubis labeled BSP with I-131, and hepatic and cerebral monitoring were performed in rabbits and in normal adults after injection of 30 uCi of I-131-BSP. They applied it also for 20-minute retention tests by external monitoring. Romsai et al (18) produced I-131-BSP in their own laboratory and used the preparation for the diagnosis of liver abscess in Thailand. Wood et al (19) used the radioactive diiodide ($BSPI_2$) for liver scintigraphy. Compared with the monoiodide (BSP-I), however, the t-1/2 value for the diiodide was longer. They preferred the diiodide to I-131-RB for liver scanning because of its longer stay in the liver. However, their labeled preparation would be unsuitable for examining the process of liver excretion as described here. As previously mentioned, the authors' scanning agent (monoiodide) has a faster t-1/2 than I-131-RB. When it is applied to normal persons, intra-hepatic transport is considerably shorter than with I-131-RB.

In conclusion, I-131-BSP (monoiodide) has been successfully applied to the differential diagnosis of Dubin-Johnson syndrome and Rotor type by the sequential scanning method. Even though the metabolism of I-131-RB appears to be similar to I-131-BSP, the former failed to differentiate the two disorders.

CONCLUSION

Sequential scanning with I-131-BSP was applied in 2 cases with Dubin-Johnson syndrome, 1 case of Rotor type and 1 case with Gilbert disease, out of a group of 33 cases with constitutional hyperbilirubinemia.

In Dubin-Johnson syndrome, I-131-BSP reveals no disturbance in hepatic uptake, but significant disturbance of the mechanism of excretion into the bile canaliculi. In Rotor type, disturbance of hepatic uptake was seen with I-

131-BSP, but no disturbance of excretion. In Gilbert disease there is no disturbance either of uptake or excretion. DubinJohnson syndrome and Rotor type are regarded as distinct disorders involving different patho-physiological mechanisms.

Unlike I-131-BSP, I-131-Rose Bengal does not cleary differentiate Dubin-Johnson and Rotor type disorders.

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