

## FURTHER QUANTITATIVE STUDY OF THE DUODENAL BLOOD-DERIVED PIGMENTS \*

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In this, our second year's work, we have entertained with reference particularly to pernicious anemia a twofold objective, namely, the determination of pigment values after splenectomy in cases estimated quantitatively prior to operative interferences, and a critical study of the relationship between the pigment output and red cell count in parenteral anemias. It would seem that a study of the blood-derived pigments before and after splenectomy as undertaken above might shed some light on the reasonableness of the hypothesis of hypersplenism; whereas the latter analyses would serve to demonstrate indirectly the state of the bone marrow. Incidentally a variety of non-hemolytic diseases have been studied, including enteral-bleeding anemias with pernicious-like blood pictures.

Following precisely the technic elaborated in our previous work<sup>1</sup> we made a total of fifty-seven determinations in forty individual patients, which are here recorded. Of these, twenty-one are cases of pernicious anemia and one hemolytic icterus. A total of seven patients with pernicious anemia of this series and one with hemolytic icterus have been splenectomized. Three of the former have been studied both before and after the operation. Two patients are included in whom splenectomy had been performed a year previous.<sup>2</sup> The material for this study has been drawn largely from the University Hospital and outpatient clinic, ten are referred patients and six were studied at the Rochester Clinic.

In Table 1<sup>3</sup> are grouped together the determinations made in cases of pernicious anemia and hemolytic icterus with spleens retained. A

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<sup>1</sup> Read at the April, 1916, meeting of the Minnesota Pathological Society.

1. Schneider, J. P.: The Splenic Pathology of Pernicious Anemia and Allied Conditions, *THE ARCHIVES INT. MED.*, 1916, **17**, 32.

2. In no instance is a determination included in which the slightest variation in technic obtained, or such as not strictly fresh duodenal contents were used. The Kirchoff and Bunsen large model spectroscope was used in all of these determinations, diluting the original contents as indicated in our previous paper. A handy-sized instrument, so constructed as to lend itself to a reading of the values of urobilin and urobilinogen on a micrometer scale without the necessity of diluting the original solution, is in the course of construction.

3. The term "H.-H. Index" heading the last column is an abbreviation for the proposed designation, "hematopoietic-hemolytic index," the nature and meaning of which will appear subsequently in the text.

mere glance at the table will serve to show, as we demonstrated in our last year's work, the striking values of urobilin and urobilinogen in the hemolytic anemias. Urobilinogen, which is normally absent or present as a mere trace, may and at times does exceed in value that of urobilin. In no undoubted case of pernicious anemia has the total value of the two pigments been less than 2,000.

TABLE 1.—DETERMINATIONS IN CASES OF PERNICIOUS ANEMIA WITH SPLEENS RETAINED

Case No.	Date	Name	Blood Count	Hemo-globin	Index	Bilirubin	Urobilin	Urobilin-ogen	Total	H.-H. Index
1	5/24/15	J. A.	2,800,000	70	1.3	+++	1,400	1,600	3,000	0.97
1	6/ 3/15	J. A.	3,200,000	62	1—	+++	1,200	1,400	2,800	1
1	7/22/15	J. A.	4,000,000	65	0.8	+++	1,400	1,200	2,600	1.1
2	5/ 3/15	Mr. S.	2,000,000	37	0.92	+++	1,800	2,000	3,800	0.97
2	6/22/15	Mr. S.	Not recorded	..	.....	+++	2,000	3,600	5,600	....
2	6/22/15	Mr. S.	3,600,000	60	0.83	+++	1,400	1,600	3,000	1.1
3	6/10/15	Mr. B.	1,700,000	30	0.9	+++	2,200	3,200	5,400	1.1
3	10/23/15	Mr. B.	1,000,000	25	1.2	+++	2,000	2,200	4,200	0.86
4	9/16/15	Mrs. B.	2,500,000	45	0.9	+++	1,400	1,200	2,600	0.85
5	10/ 6/15	C. S.	1,300,000	36	1.4	+++	1,400	1,000	2,400	0.61
6	3/ 1/16	Mrs. T.	1,600,000	36	1.1	+++	2,200	600	2,800	0.73
7	3/ 2/16	Miss G.*	2,840,000	47	0.8	+++	4,600	1,000	5,600	1.4
8	3/ 2/16	W. H.	1,960,000	38	0.9	+++	2,000	600	2,600	0.75
9	3/ 3/16	Miss L.	2,940,000	50	0.8	+++	5,000	1,000	6,000	1.4
10	3/14/16	Mrs. S.	4,000,000	78	0.98	+++	1,000	1,000	2,000	1
11	3/16/16	Mr. P.	2,000,000	48	1.2	+++	2,400	800	3,200	0.87
12	3/19/16	W. M.	1,500,000	31	1 *	+++	1,600	600	2,200	0.61
13	3/22/16	Mr. M.	2,500,000	48	0.9	+++	1,800	800	2,600	0.85
14	3/28/16	Mr. H.	1,300,000	20	0.8—	+++	2,800	800	3,600	0.81
15	4/10/16	Mrs. S.	1,500,000	25	0.83	+++	3,600	2,000	5,600	1.1
16	6/14/16	Mrs. F.	2,400,000	43	0.9	+++	1,400	1,600	3,000	0.9
17	5/20/16	J. B.	1,750,000	35	1	+++	1,600	800	2,400	0.7
18	3/12/16	Dr. M.	1,500,000	32	1	+++	1,400	600	2,000	0.6
19	4/20/16	Mr. H.	1,270,000	20	0.8	+++	2,400	800	3,200	0.73
20	5/20/16	Mrs. H.	1,970,000	30	0.8	++	1,200	400	1,600	0.6

\* A case of hemolytic icterus.

Case 38 would appear to be an exception; but while it is listed as a case of pernicious anemia, there are several other features not in accord with the findings generally observed, namely, the lack of pleochromia in the bilirubin values and the physical findings of emaciation, certainly rare in pernicious anemia. Case 1 is a continuation study of a last year's patient, dealt with fully in Curve 1.

Table 2 embraces five of the seven cases of splenectomized patients. Of these, three were observed over a long period of time, repeated duodenal estimations having been made after the operation in order to establish the nonaccidental nature of the findings. It will be observed that the pigment values suffer a definite reduction to a normal level as soon as two weeks after ablation of the spleen and remain at that level as long as studied, in Case 5 during the ensuing five

TABLE 2.—DETERMINATIONS IN FIVE CASES OF PERNICIOUS ANEMIA  
BEFORE AND AFTER SPLENECTOMY

Case No.	Date	Name	Blood Count	Hemo-globin	Index	Bilirubin	Urobilin	Urobilin-ogen	Total	H.-H. Index
Before splenectomy 4	9/16/15	Mrs. B.	2,500,000	45	0.9	+++	1,400	1,200	2,600	0.85
After splenectomy 4	11/16/15	Mrs. B.	3,900,000	70	0.9	++	400	0	400	
4	12/22/15	Mrs. B.	3,500,000	65	0.92	++	1,200	200	1,400	
4	2/23/16	Mrs. B.	4,300,000	71	0.92	++	1,200	0	1,200	
Before splenectomy 5	10/ 6/15	C. S.	1,300,000	36	1.4	+++	1,400	1,000	2,400	0.61
After splenectomy 5	11/ 1/15	C. S.	1,900,000	30	0.8	++	1,000	200	1,200	
5	11/26/15	C. S.	3,000,000	70	1.3	++	1,000	0	1,000	
5	12/ 8/15	C. S.	4,000,000	70	0.87	++	800	0	800	
5	1/14/16	C. S.	3,500,000	70	1	++	1,400	0	1,400	
5	3/ 7/16	C. S.	4,700,000	83	1	++	800	0	800	
Before splenectomy 15	4/10/16	Mrs. S.	1,500,000	25	0.88	+++	3,600	2,000	5,600	1.1
After splenectomy 15	4/30/16	Mrs. S.	2,500,000	39	0.8	++	1,200	200	1,400	
After splenectomy 21	3/ 2/16	M. S.	*	..	.....	++	400	0	400	
22	5/ 1/16	Mr. S.	1,750,000	Not re- corded	.....	++	1,200	2,000	3,400	

\* Not recorded but moderately low count.

months. Ten months have elapsed since patients in Cases 4 and 5 were splenectomized, five since the patient in Case 15 was operated on. All are in good health with the exception of a persistence of the cord changes.

That a reestablishment of pathologic hemolysis with the resulting increased blood-derived pigments does not occur in postsplenectomized cases when a recurrence apparently sets in a year later is strongly probable from the findings in Cases 21 and 22 of Table 2. The patient

in Case 21 had been splenectomized, a brilliant postoperative blood rise recorded, apparently a complete return to good health established, when under the stress of business cares a recurrence took place. A duodenal estimation at this time records nonhemolytic values—on the contrary, oligochromemia. The most plausible explanation would be that the hematopoietic function was below normal delivery at the time of the operative interference and subsequently failed more and more

TABLE 3.—DETERMINATIONS IN VARIOUS DISEASES

Case No.	Date	Name	Disease	Blood Count	Hemo-globin	Index	Bili-rubin	Uro-bilin	Urobl-inogen	Total
1	4/26/15	P. W.	Psychosis.....	5,000,000	100	1	++	900	0	900
1	4/29/15	P. W.	Psychosis.....	5,000,000	100	1	++	1,000	0	1,000
2	4/26/15	Mrs. W.	Pericholecystitis.....	4,200,000	85	1	+	800	0	800
3	5/31/15	Mrs. H.	Liver hydatid.....	4,600,000	90	1	++	600	0	600
4	5/16/15	Mrs. S.	Secondary anemia.....	2,800,000	60	1	++	200	0	200
5	2/ 1/16	Mr. R.	Infectious icterus.....	4,600,000	90	1	+	200	0	200
6	11/ 3/15	Mr. M.	Hemochromatosis.....	4,800,000	75	0.78	++	1,400	0	1,400
7	2/ 7/16	Mr. O.	Gastric carcinoma*.....	8,100,000	50	0.8	+	400	0	400
8	2/12/16	J. H.	Lymphatic leukemia.....	4,000,000	70	0.87	+	1,400	0	1,400
9	3/ 1/16	M. K.	Advanced cirrhosis.....	3,530,000	70	1	+	1,200	Trace	1,200
10	3/10/16	Mrs. M.	Doubtful.....	3,500,000	85	1.2	++	1,000	0	1,000
11	3/11/16	Mrs. D.	Gastric carcinoma.....	1,200,000	20	0.8	+	200	0	200
12	3/12/16	C. D.	Duodenal ulcer.....	3,600,000	40	0.55	+	600	0	600
13	3/14/16	Mr. W.	Gastric carcinoma.....	1,250,000	25	1	+	200	0	200
14	8/ 2/16	Mrs. S.	Gastric carcinoma.....	2,640,000	35	0.7	++	600	0	600
15	6/23/16	Mr. O.	Stone obstruction.....	.....	...	...	+	200	0	200
16	6/22/16	Prof. S.	Neurosis.....	4,800,000	80	0.9	++	1,200	0	1,200
17	6/13/16	O. H.	Unknown.....	4,200,000	69	0.8	+	200	Trace	200
18	4/20/16	Mr. C. C.	Gastric carcinoma*.....	2,000,000	40	1	+	400	0	400
19	5/16/16	Mrs. C.	Secondary anemia.....	2,970,000	60	1	++	1,200	Trace	1,200
20	5/29/16	Mrs. C.	Secondary anemia.....	2,850,000	60	1	++	1,000	Trace	1,000
21	5/25/16	Mr. O.	Acute catarrhal icterus†	4,800,000	90	0.9	+	1,200	0	1,200

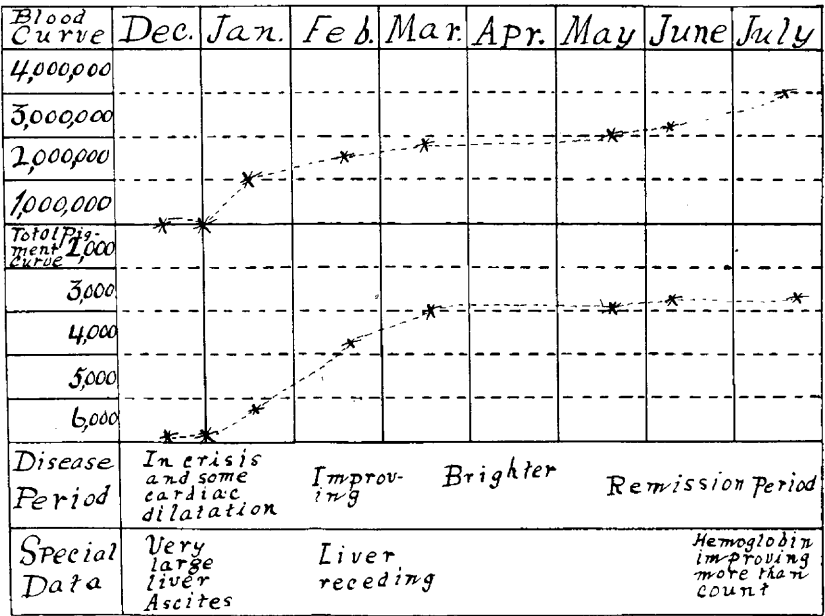
\* Confirmed at operation (guaiac positive in duodenal contents).

† Urine estimated at the same time gave urobilin 1,000, urobilinogen 600 and bilirubin ++.

under demand. The patient in Case 22 was seen at a similar period postoperative and had had the rather usual early betterment only to experience a profound recurrence, in which he was seen and studied. To our amazement the duodenal contents looked dark and yielded the extremely high values recorded. However, a quantitative urine estimation demonstrated what I anticipated, even higher values. This clarified the atmosphere. An extremely dilated heart, with fourth degree incompen-sation, and a consequent severe hepatic stasis accounted for

the findings; for it must be remarked that it is always well to guard against this possible error by noting the state of the circulation and estimating in doubtful instances the quantitative urinary pigments.

From the facts gathered together in Table 2 we can proceed with the assumption that splenectomy ablates one factor in the equation  $x-y=z$ , namely,  $y$ . However, varying with type and stage, this factor may be the lesser of the two. To estimate with some degree of accuracy this second factor,  $x$ , would mean the ability to judge in advance the probable effectiveness of splenectomy.



Curve 1.—Total red count and pigment values encountered in Case 1, portraying the remarkable parallelism between the two.

From a study of Curve 1, representing graphic parallel curves of the blood and pigment values encountered in a case under observation and study for a period of seven months, from the normal pigment level possible of designation from the data here gathered together in disease not affecting the blood, and from a study of the comparative blood and pigment values found in hemolytic icterus, in which splenectomy is so strikingly efficient, we are approaching the solution of factor  $x$ , in the above equation  $x-y=z$ , in which  $x$  represents hematopoiesis,  $y$  splenism<sup>4</sup> and  $z$  the resulting blood count. Normally the total pigments range around 1,000. This then represents physiologic splenism. The blood count stands around 5,000,000. Given the value therefor of  $y$  and  $z$ ,  $x$  can readily be determined. Reduced to simple com-

4. Spleen-liver complex.

parative figures:  $x - 1 = 5$ ; that is,  $x = 6$ . In a given unit of time 6 parts are supplied, one physiologically sacrificed, leaving a constant normal of 5. With  $x$  remaining constant, we can tabulate as follows: ( $x - y = z$ );  $6 - 1 = 5$ ;  $6 - 2 = 4$ ;  $6 - 3 = 3$ ;  $6 - 4 = 2$ ;  $6 - 5 = 1$ .

Now from Curve 1 we gather the information that as the blood count rises the pigment values fall. This makes it self-evident that the other possible table of variations cannot obtain in pernicious anemia; to wit: ( $x - y = z$ );  $6 - 1 = 5$ ;  $5 - 1 = 4$ ;  $4 - 1 = 3$ ;  $3 - 1 = 2$ ;  $2 - 1 = 1$ .

For in this relationship the value of  $y$  is constant and low.

To determine, hence, in a given case what may be styled the hematopoietic-hemolytic index resort may be had to the formula, H.-H. Index =  $\frac{z+y}{x}$ , in which  $y$  represents the first figure of the blood count,  $z$  the same of the pigment values in round numbers, and the value of  $x$  is 6. In Case 11, Table 1, for instance, the blood count standing at 2,000,000, the pigment values at 3,200, the hematopoietic-hemolytic index is  $\frac{2+3.2}{6} = \frac{5.2}{6}$  or 0.87. With the index less than normal by a slight margin only, a marrow possible of recovery to a normal output might be hoped for. While, on the contrary, in a case of the type of Case 12, with the blood at 1,500,000 and the pigment at 2,200, the index =  $\frac{1.5+2.2}{6} = \frac{3.7}{6} = 0.6$ —a severely negative index, —hypohematopoiesis—and a restitution ad integrum would seem improbable. Contrasting these indexes in the slowly recovering pernicious anemias after splenectomy with the index in hemolytic icterus, as illustrated in Case 7, in which the blood picture approaches the normal in a short space of time, we find that with the blood count at 2,500,000 and the pigment total at 5,600 the index is heavily plus, namely, 1.4.

Judged by the hemolytic index, Cases 1, 2, 3, 4, 9, 10, 11, 15 and 16 appear favorable for splenectomy. Case 11 bears this out in two clinical features, the persisting icterus, pointed out as a favorable indication in our former paper, and a definitely enlarged, hardened spleen. Early in the disease, not necessarily in the mere point of time, this organ is definitely enlarged in favorable types.

In the face of the fact that urobilinogen is peculiarly and intimately associated with structural changes in the total liver parenchyma, it will be reserved for future confirmation whether for the index the total of both urobilinogen and urobilin be the proper value of  $y$  or urobilin only.

Incidentally, this study of duodenal pigment values has served to provide a most simple and reliable method of differentiating severe anemias due to enteric bleeding from parenteral types. Cases 7, 13,

14 and 18 in Table 3 were regarded as parenteral in type. In Case 7 with the absence roentgenographically of a persistent filling defect and of motor disturbances, of lactic acid and the related organism, and of occult blood in the stomach contents, with a blood picture so typical of the pernicious type as to be tentatively so regarded for months, it remained for the duodenal pigment analysis to definitely decide the case to be one of enteric bleeding. In Case 13 the imitation was complete, even to the point of typical remission periods. Here, after repeated trials, a positive guaiac in the stools was of help.

The more pronounced the degree of anemia, and hence the closer the blood picture imitation of the parenteral type, the more strikingly are the pigment values at the opposite pole of oligochromemia in enteric bleeding.

#### SUMMARY

1. Splenectomy apparently immediately and permanently reduces the excessive blood-derived pigments of pathologic hemolysis to a normal level. There is no proof that a recurrence of a pernicious blood and clinical picture after splenectomy is due to a reestablishment of excessive blood destruction.

2. Bearing in mind that fully developed pernicious anemia is a late bone-marrow exhaustion of a primary hemolytic process, we know our endeavor to gain a preoperative knowledge of the competency of the marrow is necessary to a proper selection of favorable operative cases. A plus hematopoietic-hemolytic index in a given case should be regarded as one factor favorable to permanent postoperative recovery.

3. The classic blood picture of pernicious anemia may be successfully imitated by chronic enteric bleeding anemia. For a reliable means of differentiating these fundamentally dissimilar conditions, a quantitative estimation of the duodenal pigments is decisive.

Our thanks are extended to the Rochester Clinic and Dr. Tuohy of Duluth for the opportunity graciously accorded us of making the above studies on private patients.

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