

## UROBILIN IN THE STOOL IN PERNICIOUS ANEMIA AS INFLUENCED BY SPLENECTOMY, TRANSFUSION AND SALVARSAN \*

OSWALD H. ROBERTSON, M.D.

BOSTON

On account of the peculiar course of pernicious anemia, characterized as it is by marked remissions, there has always been great difficulty in judging fairly the effect of any method treatment. Brilliant results have been reported in certain cases from almost every therapeutic measure employed, yet it is impossible to say in many of these cases that a spontaneous remission was not beginning at the time of treatment, since the blood picture often fails to give this information. It is therefore desirable that a more reliable method be employed for determining the different stages in the course of the disease.

Since this form of anemia is accompanied by a greatly increased blood destruction, it seems not unreasonable to assume that the quantity of blood being destroyed may be regarded as an indication of the severity of the disease process. This can be determined by estimating the quantity of urobilin in the stool, since it has been shown that the amount of urobilin excreted depends directly on the degree of blood destruction present. In a previous study<sup>1</sup> of the variations in urobilin excretion in a variety of conditions, including both primary and secondary anemia, malaria, jaundice from various causes, cirrhosis, etc., it was found that only those cases which gave evidence of increased blood destruction clinically, showed an abnormal urobilin output. There were eleven cases of pernicious anemia, all of which had an increased urobilin excretion, while on the other hand six cases of secondary anemia all showed a urobilin output within normal limits.

Determinations were made on nine cases of pernicious anemia with the hope of being able to demonstrate some definite effect of treatment on the urobilin output. The estimations were begun in every case before treatment and continued during periods of time lasting from two weeks to three months. Following the different forms of treatment, averages of the estimations were made over weekly intervals

---

\* Submitted for publication May 29, 1915.

\* From the Medical Wards of the Massachusetts General Hospital.

1. Robertson, O. H.: Urobilin in the Stool—An Index to Blood Destruction, *THE ARCHIVES INT. MED.*, 1915, xv, 1072.

when possible, as this period of time seemed a fair measure of the effect produced. The method used was that described by Wilbur and Addis,<sup>2</sup> which consists in extracting the urobilin from the total twenty-four-hourly stool with acid alcohol. This extract is then diluted till the characteristic spectroscopic absorption bands of urobilin disappear and the reading made at this point. Estimations in normal persons average about 5,000 dilutions of the original volume of the stool.

In six of the cases, splenectomy was performed, three received salvarsan, and four were transfused. Of the four cases transfused, one had previously been given salvarsan. The other three were cases of splenectomy who were transfused before operation.

#### SPLENECTOMY

There are a few cases of pernicious anemia reported in the literature in which quantitative urobilin estimations were made before and after operation. Eppinger and Ranzi<sup>3</sup> report the most successful series and in their five patients there was a drop to normal in every instance following splenectomy. In one case the urobilin was still low after seven months. They do not say whether estimations were made later in the other four cases or not. All five showed marked improvement. Huber's<sup>4</sup> patient still had a high urobilin output five weeks after operation. It was quite evident, however, that blood destruction was still going on, since the red cells showed a marked decrease in number during the ten days following the estimation. Moffitt<sup>5</sup> reports one case in which the urobilin was still increased one week after operation, but estimations could not be continued as the patient died shortly afterwards from a complicating infection.

McCrudden<sup>6</sup> found in one case, three weeks after splenectomy, a urobilin output twice as great as it had been before. At the time the estimations were made, however, the red count was falling rapidly. Four months later the patient had shown considerable improvement, the red count was increasing, and the urobilin was found to be normal. A second case showed no benefit from splenectomy and although the urobilin decreased from its high figure given before operation, it did not reach normal.

---

2. Wilbur, R. L., and Addis T.: *THE ARCHIVES INT. MED.*, 1914, xiii, 235.

3. Eppinger, H., and Ranzi, E.: *Mitt. a. d. Grenzgeb. d. Med. u. Chir.*, 1914, xxvii, 796.

4. Huber, O. R. C.: *Berl. klin. Wchnschr.*, 1913, I, 2179.

5. Moffitt, H. C.: *Am. Jour. Med. Sc.*, 1914, cxlviii, 817.

6. These two unreported cases are cited with the kind permission of Dr. Francis McCrudden of the Robert Brigham Hospital, Boston.

In the six cases of this series treated by splenectomy,<sup>7</sup> the urobilin estimation before operation varied from 10,300 to 46,000; the highest was given by Patient 3, who showed the most rapid drop in red count and hemoglobin. Immediately following splenectomy there was a marked diminution in urobilin output which reached normal in all but two cases.

In Case 1 it is seen that the urobilin output three and one-half months after splenectomy was not only normal, but exactly the same as it was immediately afterwards. During this time the number of red cells had increased from 2,500,000 to 5,000,000.

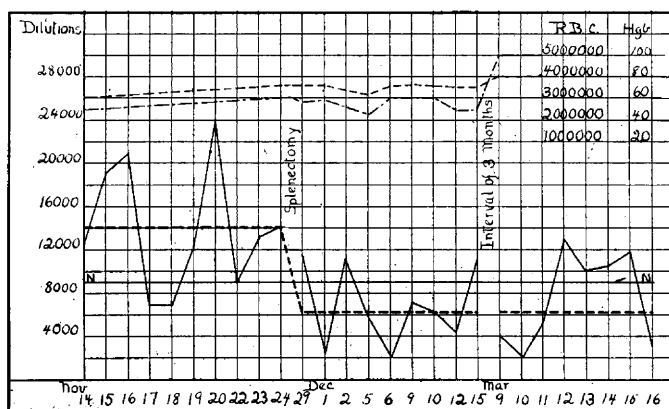


Chart 1 (Case 1).—The curves in this and Charts 2 and 3 have the following significance: ———, daily urobilin excretion; ———, average daily excretion; ———, upper limit of normal average daily excretion; ———, hemoglobin; ———, red blood cells. N. B.—The normal average daily excretion is about 5,000 dilutions.

The urobilin in Case 2 immediately before splenectomy was not as much above normal as in the other cases, yet the drop afterwards was quite as definite. At the end of three months, however, the patient showed an output of 14,000. While there was definite improvement both in his general condition and blood, yet the blood picture still showed the characteristic appearance of pernicious anemia and the red cells were slightly under 4,000,000.

Case 3 just before operation gave the exceedingly high estimation of 46,000. There was an immediate drop to 14,600 afterwards, with a subsequent rise to 20,000 at the time of discharge from the hospital. During this time he had shown a striking improvement generally and

7. A complete clinical report of Cases 1 to 5 appears in *The Journal of the American Medical Association*, 1915, lxxv, 216.

his red cells had reached 4,000,000, but the appearance of the cells was unmistakably that given by pernicious anemia.

The chart of Case 4 was almost identical with that of Case 1, except that before operation the urobilin was 13,000 and the red count 1,500,000. Immediately following splenectomy the urobilin dropped to 3,500 and two and a half months later was 7,400. The qualitative and quantitative improvement in the blood was equally as marked as in Case 1.

Case 5 had a red count of about 2,000,000 and a urobilin output of 14,000. Following operation the urobilin dropped at once to 7,900. After two months and a half it had increased to 16,000 which was higher than before operation. He had shown the least improvement of any of the patients and at the time the last estimations were made his red cells numbered only 2,900,000.

Case 6 before splenectomy had a urobilin output of 21,900 and a red count of 1,632,000. This patient showed the same evidence of marked bone marrow stimulation following splenectomy as seen in the other five cases, i. e., the appearance of blasts and Howell-Jolly bodies in the blood. The urobilin dropped to 16,900 but did not go any lower while under observation. The number of red cells at the time of discharge was practically the same as before operation, but there was definite improvement in the general condition. No further estimations have been made, since this patient was the last one of the series operated on and has only just left the hospital.

The marked drop of urobilin in these cases is of considerable significance, since it completes the picture of a beginning remission. The appearance in the blood of blasts and Howell-Jolly bodies indicated bone marrow stimulation, while the decrease in urobilin output indicated an accompanying diminished blood destruction. The return to an increased output in Cases 2 and 5 is in accord with the persistent markedly abnormal appearance of the blood picture. The same may be said of Cases 3 and 6, which showed a definite drop but did not return to normal.

#### TRANSFUSION

The influence of transfusion on urobilin excretion seems to depend chiefly on the reaction of the patient to the newly introduced blood. Three of the four cases showed a definite stimulation of the bone marrow and in all three the urobilin output was temporarily increased. The fourth showed no such change.

Case 2 showed the most marked stimulating effect of transfusion. The red cells increased from 1,600,000 immediately afterwards to 3,200,000 within six days and there was an accompanying shower of blasts. At the same time the urobilin increased from 17,000 to 22,000

This case shows quite strikingly how the urobilin output follows the changes in the course of the disease, the beginning remission being accompanied by a drop to normal.

Cases 3 and 6 were also transfused. In Case 3 the resulting numerical increase was not marked, but the appearance of blasts made it seem certain that bone marrow stimulation had occurred. The urobilin before transfusion was 30,000; during the week following it was 46,000. At this point splenectomy was done, so it was not possible to observe the effect further. Case 6 showed during the week preceding transfusion, a urobilin excretion of 20,900. During the week

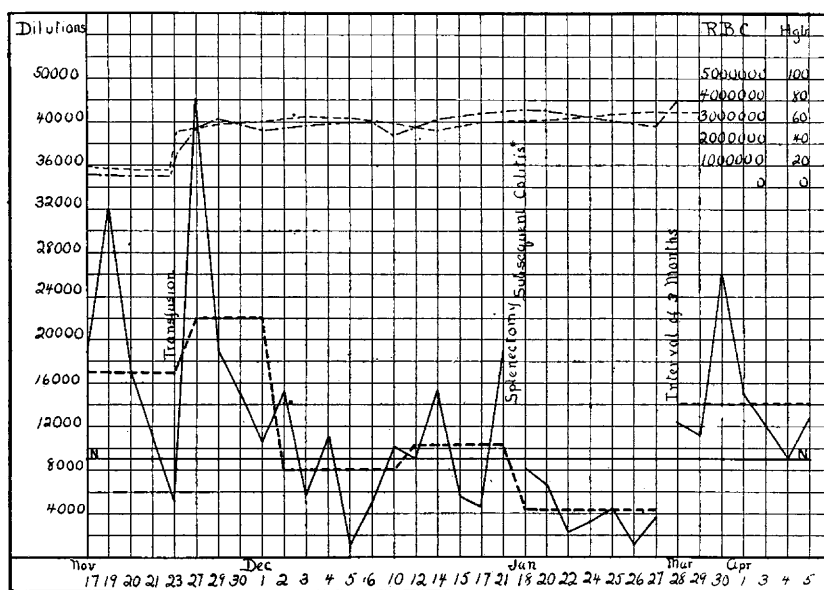


Chart 2 (Case 2).—No tests were made during period of colitis as estimations on diarrhea stools are inaccurate. This is due to the fact that with an increased rate of passage of the bile through the intestinal tract, a smaller proportion of bile than normal is transformed into urobilin.

following, it had increased to 30,000 and at the same time the red cells increased from 1,400,000 immediately after transfusion, to 2,300,000. The patient then had a severe attack of tonsillitis which seemed to check the beginning remission as the blood count ceased to rise and even showed a downward tendency. The urobilin returned to its former level.

Case 7 had received previously several doses of salvarsan. Following transfusion there was no change in the blood other than the temporary increase in the number of red cells due to the newly introduced blood. From the chart one might infer that instead of increasing,

as in the other two cases, the urobilin output was diminished after transfusion. However, on account of the fact that two weeks had elapsed since the last estimation, one cannot say whether the drop occurred before or after transfusion. At any rate it seems quite apparent that there was no increase in urobilin.

#### SALVARSAN

The administration of salvarsan seems to have no constant effect on urobilin secretion. Case 7, as indicated in the chart, received five injections of salvarsan at weekly intervals. Three of the doses were followed (Chart 3, Case 7) by a drop in urobilin and two by a decided

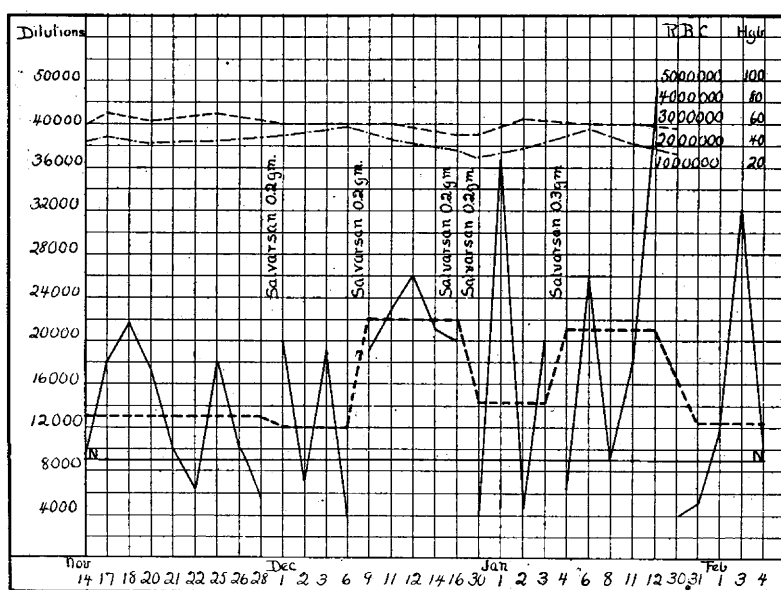


Chart 3 (Case 7).—Urobilin curves during the administration of salvarsan.

rise. But it will be noted that accompanying these fluctuations in the urobilin, there were corresponding variations in the red count. When the number of red cells was diminishing there was an increase in the amount of urobilin excreted, denoting a greater blood destruction; while on the other hand, when the red cells began to increase there was an immediate decrease in urobilin, indicating a lessened degree of blood destruction. Since the blood count showed no constant change following salvarsan, we seem justified in concluding that this drug had very little, if any, effect on the urobilin excretion in this case.

Case 8 had an output of 30,000 before salvarsan. During the two weeks following a single dose—0.3 gm.—the urobilin dropped to

12,500. This showed undoubtedly a marked decrease in blood destruction. However, a complicating factor entered here in the form of a severe throat infection which began about this time, and produced marked prostration. The patient died at the end of two weeks. A plausible explanation of the decreased urobilin output in this case was a diminished blood production, due to bone marrow injury resulting from extreme toxemia, rather than to any effect of salvarsan.

Case 9 received two doses of salvarsan. Following the first dose there was no change in the urobilin excretion. Estimations could not be made after the second as the patient became incontinent of feces.

This absence of any real effect of salvarsan on the urobilin output coincides with the absence of symptomatic improvement in these patients.

#### DISCUSSION

From a study of these nine cases it is seen that the effect of treatment on the urobilin is most marked in the cases of splenectomy. Here the drop in urobilin output, occurring long before there was any change in the number of red cells, gave us early information as to the benefit resulting from this procedure. Again, the finding of a high urobilin excretion in several of the cases months after splenectomy, together with the abnormal appearance of the red cells, makes it seem doubly certain that the improvement in these cases is only temporary, in spite of the fact that the number of red cells is well up toward normal.

Judging by the variety of both clinical and blood pictures seen in grave anemia, it seems reasonable to assume that the bone marrow may show varying degrees of functional activity. This may range on the one hand from a markedly hyperactive bone marrow, associated with a great increase in blood destruction, to a very much depressed bone marrow activity on the other, presumably resulting from extensive injury, and unaccompanied by abnormal blood destruction. Splenectomy has been advocated in pernicious anemia on the theory that by taking out the spleen, the chief hemolytic agent is removed. Therefore this operation should have its most marked beneficial effect in those cases in which the anemia is accompanied by a greatly increased blood destruction. Thus, in deciding the advisability of splenectomy it seems fair to regard the urobilin output as one of the important indications of how much benefit may be expected from this procedure. But when the anemia results chiefly from a depressed marrow functioning, we would expect much less benefit from splenectomy, or none at all, depending on the degree of bone marrow injury. This latter type in its most marked form—aplastic anemia—is a rare condition.

## SUMMARY AND CONCLUSIONS

1. Splenectomy: In six cases of pernicious anemia with splenectomy, the urobilin output which had previously been high, showed a marked decrease immediately after operation. The two cases in which the urobilin later returned to a high figure, as well as one case with a persistently increased output, showed definitely less improvement than the two cases in which the urobilin remained normal.

2. Transfusion: Three of the four patients transfused gave evidence of a resulting bone marrow stimulation and at the same time showed a temporary increase in urobilin excretion. The one case in which transfusion was without effect showed no such increase.

3. Salvarsan: In three patients treated with salvarsan, there was practically no effect, either on the course of the disease or on the urobilin excretion.

4. It seems fair to conclude that:

1. Variations in the urobilin output may be taken as an index of corresponding changes in the course of the disease.

2. Such variations in the urobilin may occur before there is any change in the number of red cells.

3. The determination of the urobilin output as an index of blood destruction is the most accurate means we have of estimating the effect of treatment.

Massachusetts General Hospital.