The Use of Thorium Dioxide Sol (Thorotrast) in the Roentgenologic Demonstration of Accessory Spleens

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The removal of accessory spleens has occasionally resulted in clinical remission when manifestations of idiopathic thrombocytopenic purpura or hereditary spherocytosis have failed to be relieved or have recurred after splenectomy. It is hazardous, however, to subject all patients with clinical relapse after splenectomy to surgical exploration for accessory splenic tissue. Accessory spleens are found in only the minority of instances; they are difficult to locate even when present, and the condition of the patient is frequently so critical that the extensive exploration necessary is poorly tolerated. If it were possible to establish the presence and localization of accessory spleens prior to operation, the surgical risk would be justified. The present report emphasizes the value of thorium dioxide (Thorotrast) for the roentgenologic identification of accessory splenic tissue, and describes the remission induced by removal of an accessory spleen in a patient with idiopathic acquired hemolytic anemia in whom sustained improvement had not occurred following splenectomy.

The relationship of accessory spleens to clinical relapse following splenectomy for idiopathic thrombocytopenic purpura was postulated by Morrison, et al. in 1928; subsequent reports emphasized the theoretical importance of this factor. However, the first clinical application of this concept was not reported until 1940 when Doan referred to a patient with hereditary spherocytosis who had undergone a splenectomy in 1933 with a remission lasting four and one-half years. At this time a hemolytic relapse ensued and upon re-exploration in 1938, the removal of 5 Gm. of accessory splenic tissue was followed by a complete clinical remission. Doan subsequently described a patient who underwent a successful splenectomy for hereditary spherocytosis, only to develop acute thrombocytopenic purpura eighteen months later. Re-exploration and the removal of an accessory spleen were followed by complete recovery.

Experience with the use of thorium dioxide for the radiographic visualization of the liver and spleen was first published in 1929 by Oka and independently by Radt. In this country Yater and Otell and Ericksen and Rigler reported their experience with thorium dioxide in 1933. Clinical application of this method for demonstrating accessory spleens has been utilized in this laboratory since 1945, and other workers have emphasized its value in the management of pa-
tients with hematologic disorders. In 1951, Rosenthal, et al. reported 7 patients with idiopathic thrombocytopenic purpura who had failed to respond to splenectomy and to whom thorium dioxide had been given in an attempt to demonstrate an accessory spleen. In 2 of these cases an accessory spleen was demonstrated and its presence was confirmed by surgical exploration. Following removal of the accessory spleen, both patients experienced remissions of their disease, but in one patient the remission was only of ten days duration.

That accessory spleens are infrequently related to hematologic and clinical relapses after splenectomy is emphasized by the fact that they could be demonstrated by the thorium dioxide technic in only 2 of 9 such patients in our series: a man with hereditary spherocytosis and a woman with idiopathic acquired hemolytic anemia. In this latter patient, splenectomy resulted in a remission of only nine days duration but a sustained remission followed the removal of an accessory spleen. No accessory splenic tissue could be identified in the remaining instances, all patients with idiopathic thrombocytopenic purpura. The absence of accessory spleens was confirmed at operation in one instance and at necropsy in 2 others. This experience emphasizes the value of the technic as a method of selecting those patients for whom exploration is advisable.

Case Reports

1. L. N., (B.H. #193409)

A white female, 69 years of age had always enjoyed excellent health until the latter part of 1948, at which time she noted the onset of vague gastro-intestinal distress related to the ingestion of certain foods. She was hospitalized in June, 1949, in Springfield, Mo. for evaluation, at which time physical examination was found to be within normal limits except for the presence of a palpable liver and pallor of the skin. The significant laboratory data were as follows: WBC 2,000 per cu. mm.; hemoglobin 11.9 Gm. per 100 cc.; platelets “normal”; reticulocytes 25 per cent. One bone marrow examination was interpreted as normal and a second showed defective maturation of granulocytes. Gastric analysis revealed a histamine-refractory achlorhydria. The patient’s blood type was Group A Rh positive and she was given one transfusion. Following her discharge from the hospital, the white blood count slowly returned to normal. In October, 1949, she spontaneously developed purpura which subsided without therapy. She continued to feel well during the early part of 1950. In June the hemoglobin value was 13 Gm. per cent. However, in August, 1950, the red blood count fell precipitously to 1,830,000 with 6.6 Gm. per cent hemoglobin; the white blood count and differential were normal. There was no history of bleeding and the patient was again hospitalized in Springfield, Mo. for re-evaluation. At this time both the liver and the spleen were palpable. Laboratory data revealed a normocytic, normochromic anemia; white blood count 13,000, with nucleated red cells observed in the circulating blood. Bone marrow examination showed erythroid hyperplasia. The osmotic fragility of the erythrocytes was increased and the Coombs test was positive. A gastro-intestinal x-ray series was negative. A diagnosis of idiopathic acquired hemolytic anemia was made and three blood transfusions were given without effect on the blood values. On September 20, 1950, a splenectomy was carried out (fig. 1). No accessory spleens were noted. One week after the operation the red blood count was 3,160,000 with 10.5 Gm. per cent hemoglobin. Two days later, the hemoglobin suddenly fell to 8 Gm. per cent without signs of bleeding. Because of evidence of recurrent hemolysis, the patient was started on ACTH, receiving intramuscular injections of 20 mg. every 6 hours. This was continued for a period of three weeks, during which time the evidence of hemolysis subsided and the hemoglobin rose to 12.2 Gm. per cent. She continued to feel well until December, 1950, when a hemolytic relapse occurred and the hemoglobin value dropped spontaneously from 13 Gm. per cent to 10 Gm. per cent. Corti-
sone was given in an unknown quantity for a short time without obvious effect. By January 18, 1951, the hemoglobin had fallen to 9.3 Gm. per cent and ACTH was again started. One week later the hemoglobin value had risen to 10.2 Gm. per cent, the ACTH was discontinued and the patient was referred to Barnes Hospital for further evaluation.*

Laboratory data at the time of admission on January 30, 1951 were as follows: RBC: 3,260,000 per cu. mm.; hemoglobin 10.2 Gm. per 100 cc.; WBC 12,400 per cu. mm.; reticulocytes 6.2 per cent. The Coombs test was positive to a dilution of 1:2560. Osmotic fragility of the erythrocytes was increased. Sternal bone marrow aspiration revealed erythroid hyperplasia. A gastrointestinal x-ray series and cholecystogram were normal. Fecal urobilinogen excretion was 216 mg. per day with a hemolytic index of 42. Hepatic function studies included a two plus cephalin-cholesterol flocculation; icterus index 5 units; no BSP retention after 40 minutes.

The patient was given thorium dioxide in an attempt to demonstrate the presence of an accessory spleen. Twenty-five cc. of a 25 per cent colloidal suspension of thorium dioxide (Thorotrast), diluted with 75 cc. of saline, were injected intravenously. This was repeated on the following two days so that a total of 75 cc. was injected. Roentgenograms taken 24 hours after the last thorium dioxide injection disclosed a small round area of increased density in the left upper quadrant measuring 3 cm. in diameter; this radio-opacity had not been present on the roentgenogram of the abdomen taken prior to the injection of thorium dioxide. It was felt that the position, size and shape of this area of density were compatible with the presence of an accessory spleen (figs. 2a and 2b).

On February 4, 1951, ACTH† was started. Twenty-five mg. were given intravenously over an 8 hour period on each of the first 4 days; then an average of 80 mg. were injected daily in intermittent intramuscular doses for the next 11 days. During this period of therapy the patient felt quite well. There was a persistent rise in the erythrocyte and hemoglobin levels and a fall in the titer of the Coombs test. On the day of discharge from the hospital and the last day of ACTH therapy, the red blood count was 4,160,000 per cu. mm.; hemoglobin 12.8 Gm. per 100 cc.; reticulocytes 8.8 per cent; white blood cells 8,650 per cu. mm.; and the Coombs titer was positive to a dilution of 1:80. On the day following discharge from the hospital she started taking cortisone, 25 mg. by mouth, four times daily. She continued to

* We are indebted to Dr. L. Richard Webb, Jr., Springfield, Mo. and Dr. Albert Mendeloff, St. Louis, Mo. for permission to follow this patient.
† Kindly furnished by the Armour Laboratories, Chicago, Ill.
feel well and blood values were sustained at a normal level, but in March, 1951, she was observed to have developed a moderate hypertension and persistent ankle edema. Because of these signs, cortisone was discontinued on March 23, at which time the erythrocyte count was 4,000,000 with 12.9 Gm. per cent hemoglobin. Shortly thereafter she again developed evidence of hemolysis and on April 6, the red blood count had fallen to 3,900,000 with 9.8 Gm. per cent hemoglobin. ACTH was started on this day and continued until May 8, by which time the red blood cell count had risen to 4,440,000 with 12.0 Gm. per cent hemoglobin.

Because of the persistent evidence of hemolysis whenever adenocortical hormone therapy was discontinued, it was felt justified to remove the accessory spleen which had been demonstrated on her previous admission to Barnes Hospital. On May 21, 1951, she underwent a laparotomy. After a difficult exploration, a 2 x 3 cm. nodule having the gross characteristics of splenic tissue was exposed and removed from the retroperitoneal region of the left upper quadrant near the pancreas. Pathologic examination of the tissue identified it as an accessory spleen with an intact capsule. A radiograph of the specimen (figs. 3a and 3b) proved that it contained a radio-opaque material and that it undoubtedly produced the shadow noted on the roentgenogram of the abdomen. Recovery was uneventful and she was discharged from the hospital on May 31, with 4,330,000 red cells per cu. mm., 13.4 Gm. per cent hemoglobin and 2.8 per cent reticulocytes. Following the operation, the patient remained perfectly well for eight months. During this time the red cell and hemoglobin values were normal without evidence of hemolysis. On November 10, 1951, the red cell count was 5,000,000 with 14.0 Gm. per cent hemoglobin.

On December 31, the patient suddenly developed a generalized petechial rash and had a massive gastro-intestinal hemorrhage. A platelet count revealed 30,000 platelets per cu. mm. and she was immediately transfused with whole blood (fig. 4). A total of 8500 cc. of blood was given in 7 days in order to combat shock and replace blood loss. ACTH was started intravenously on January 6, 1952 at which time the platelet count was 15,000. Two days later there was no further evidence of bleeding and on January 10, the platelets had risen to 280,000. The following day ACTH was discontinued; the platelet count was 650,000 per cu. mm.
Fig. 3(a).—Photograph of accessory spleen removed from Case 1 (L. N.)
(b).—Roentgenogram of accessory spleen removed from Case 1 (L. N.) demonstrating a central opacity corresponding to the shadow observed on clinical roentgenogram (fig. 2b).

Fig. 4.—Clinical course of Case 1 (L. N.) from January, 1952 to March, 1952.
On January 14 a few petechiae appeared on the lower extremities and the platelets fell to 38,000 per cu. mm. Thrombocytopenia persisted without further evidence of purpura for the following 4 days and ACTH was again started on January 17. By January 21, the platelet count had risen to 216,000 and the dosage of ACTH was decreased. Cortisone was started at this time; 100 mg. were given daily until January 26 at which time she was placed on a maintenance dose of 75 mg. ACTH was discontinued on January 24. The patient has continued to feel perfectly well without evidence of purpura and the platelet count has remained normal to the present time.

2. C. W. (B.H. # 24083)

A white male 41 years of age had mild episodes of jaundice throughout childhood. An anemia was first discovered in 1930 at age 21. At this time, laboratory examination revealed an elevated icterus index, spherocytosis, and increased osmotic fragility of the red blood cells; a diagnosis of hereditary spherocytosis was made. There was a history of "chronic jaundice and anemia" in his maternal grandfather. On October 30, 1930, he underwent a splenectomy, at which time considerable difficulty was encountered, due to adhesions. Because of this, a small remnant of splenic tissue was "shaved off" and left in situ. Postoperatively the patient did well and the evidence of hemolysis disappeared. However, in 1937 and again in 1938, the patient had recurrent episodes of jaundice and anemia. In 1942, he developed primary atypical pneumonia and a third hemolytic crisis occurred. Hematologic evaluation again revealed anemia with spherocytosis and a reticulocytosis of 14.4%. Following therapy for the pneumonia, the patient felt well but again developed a hemolytic crisis in 1945. At this time he was given thorium dioxide in an attempt to visualize splenic tissue. A 24 cm. round radio-opaque shadow was seen lying posteriorly in the left upper quadrant (fig. 5a). The patient refused exploratory laparotomy and was followed as an outpatient. Hematologic evaluation in 1946 and 1947 revealed spherocytosis with evidence of chronic hemolysis. No further hemolytic crises occurred until November, 1951, at which time the patient complained of weakness and increasing jaundice. This subsided within a few days. In December, 1951, repeat x-ray films of the abdomen again revealed a radio-opaque shadow in the left upper quadrant which was similar to that noted in 1945 (fig. 5b). Hematologic data obtained on December 18 revealed RBC 4,100,000 per cu. mm., Hgb. 13.6 Gm. per 100 cc., spherocytosis, reticulocytes 12.4 per cent, increased osmotic fragility of the red cells, icterus index 50, and a negative Coombs test. The patient felt well at this time and was not willing to undergo further surgical exploration.

Seven patients with idiopathic thrombocytopenic purpura were given thorium dioxide after splenectomy had failed to induce a permanent remission (table 1). In no case was an accessory spleen demonstrated.

DISCUSSION

The possible physiologic mechanisms involved in the relationship of accessory splenic tissue to acquired hemolytic anemia or thrombocytopenic purpura will not be discussed. It is admittedly surprising that small amounts of splenic tissue seem to be related to some of the relapses which occur after splenectomy. The emphasis in this presentation, however, pertains principally to the roentgenographic technic of demonstrating accessory spleens after the injection of thorium dioxide.

Evans, et al.15 have commented upon the "spectrum-like" relationship between acquired hemolytic anemia and idiopathic thrombocytopenic purpura. It is of interest that L. N. has manifested at various times, thrombocytopenia without evidence of anemia, acquired hemolytic anemia without thrombocytopenia, and thrombocytopenia with sensitization of the red cells but without anemia.
Several aspects of Case 1 (L. X.) deserve emphasis. The patient responded satisfactorily to the administration of ACTH and cortisone, after relapse had occurred following the original splenectomy. Our experience agrees with the reported clinical evidence\textsuperscript{16–19} that remissions may be induced in cases of acquired hemolytic anemia by administration of ACTH or cortisone; in some instances, such remissions may persist following cessation of therapy. However, as is ex-

**Fig. 5(a).** Roentgenogram of upper abdomen of Case 2 (C. W.) after injection of thorium dioxide, demonstrating a spherical opacity in the left upper quadrant suggesting the presence of an accessory spleen (1945).

**Fig. 5(b).** Roentgenogram of upper abdomen of Case 2 (C. W.) six years later (1951) showing persistence of opacity in left upper quadrant. The subhepatic densities probably represent migration of thorium dioxide into regional lymph nodes.
emphasized by L. N., relapse may follow withdrawal of the hormones, and for various reasons, both medical and economic, protracted therapy may not be feasible or desired.

The use of thorium dioxide in Case 1 established the presence of an accessory spleen. At the time of the exploratory laparotomy for its removal, the surgeon

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Sex</th>
<th>Age at Onset</th>
<th>Duration Before Splenectomy</th>
<th>Remission Following Splenectomy</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>3. M. L. (B. H. #190302)</td>
<td>F.</td>
<td>41</td>
<td>2 mos.</td>
<td>none</td>
<td>No response to ACTH before or after splenectomy. Pt. died of cerebral hemorrhage two months after splenectomy. No accessory spleen found at necropsy.</td>
</tr>
<tr>
<td>4. E. B. (B. H. #27649)</td>
<td>F.</td>
<td>33</td>
<td>12 yrs.</td>
<td>1 yr.</td>
<td>Pt. died of cerebral hemorrhage four years after splenectomy. No accessory spleen found at necropsy.</td>
</tr>
<tr>
<td>5. R. L. (B. H. #75073)</td>
<td>F.</td>
<td>15</td>
<td>1 mo.</td>
<td>9 yrs.</td>
<td>No accessory spleen found at exploratory laparotomy at the time of relapse. Periodic thrombocytopenia and granulocytopenia have continued for four years since relapse following splenectomy.</td>
</tr>
<tr>
<td>6. H. S. (B. H. #19137)</td>
<td>M.</td>
<td>23</td>
<td>8 yrs.</td>
<td>none</td>
<td>Transient elevation of platelets during cortisone administration. Chronic thrombocytopenia has persisted for fourteen months since splenectomy.</td>
</tr>
<tr>
<td>7. F. C. (B. H. #198188)</td>
<td>F.</td>
<td>45</td>
<td>4 wks.</td>
<td>none</td>
<td>No response to cortisone. Chronic thrombocytopenia has persisted for nineteen months since splenectomy.</td>
</tr>
<tr>
<td>8. M. H. (C. H. #40204)</td>
<td>F.</td>
<td>17</td>
<td>3 mos.</td>
<td>3 yrs.</td>
<td>Chronic thrombocytopenia has persisted for eleven years since relapse following splenectomy.</td>
</tr>
<tr>
<td>9. A. J.</td>
<td>F.</td>
<td>27</td>
<td>2 yrs.</td>
<td>none</td>
<td>No response to ACTH or cortisone. Chronic thrombocytopenia has persisted for eight months since splenectomy.</td>
</tr>
</tbody>
</table>

stated that if the accessory spleen had not been demonstrated preoperatively it might not have been isolated because of the extensive peritoneal adhesions.

Case 2 (C. W.) illustrates several important points. Although the patient feels well at the present time, there is definite evidence of a chronic hemolytic anemia due to hereditary spherocytosis. The remission induced by splenectomy lasted for approximately seven years, but since then he has had at least five hemolytic crises. Radiographic visualization of splenic tissue was carried out fifteen years...
after the splenectomy and was still demonstrable six years later. The spherical configuration of this radio-opaque shadow and its location are compatible with the presence of an accessory spleen, but this may be a hypertrophied remnant of splenic tissue that was not removed at the time of splenectomy in 1930. An irregular dense shadow was also noted in the subhepatic area in the roentgenograms taken in 1951 which was not present in 1945, and probably represents migration of thorium dioxide to subhepatic nodes. With the use of the thorium dioxide technic, a probable explanation for the relapse in a disease in which permanent remission can be induced by complete removal of splenic tissue has been elicited.

Comprehensive reviews on the late effects of thorium dioxide in man have emphasized that its use is not without hazard. The diagnostic dose of 75 cc. of thorium dioxide is equivalent to 3 micrograms of radium salt. Serious late sequelae have been reported with as little as 1 microgram of radium deposited in the body. The development of malignant tumors, aplastic anemia and disabling fibrosis and scar formation following the administration of thorium dioxide have been reported in the literature. A recent survey was conducted by Thomas, Henry and Kaplan who sent a questionnaire to 132 radiologists; they received data regarding 4,325 patients in whom thorium dioxide had been used. The number of malignancies discovered was so small that it was considered that the possible induction of a malignancy was only a potential rather than an important clinical danger. In fact, these authors felt that in view of the long standing and widespread use of thorium dioxide, the low incidence of malignant tumors did not lend any support to the hypothesis that this material is carcinogenic in man. Despite the paucity of authentic thorium dioxide-induced tumors in man, the results of animal experiments appear to justify the conclusion that the potential hazard of carcinogenicity must be considered. Although Spier, et al. reported a patient who died of aplastic anemia nine years after the administration of thorium dioxide, other studies have not revealed evidence of hematologic abnormalities or bone marrow depression.

The more significant complication is the late fibrosis and scar formation which may occur either in the liver or spleen or at sites of accidental extravasation at the time of injection. Thomas et al. felt that this complication occurred with sufficient frequency to militate against the employment of thorium dioxide for diagnostic purposes except in extreme urgency. These considerations might represent a contraindication to the use of thorium dioxide in an asymptomatic patient; but when a hematologic relapse occurs, the hazards of the disease may far exceed those which might result from the use of the material. The development of safer materials which can be used to opacify the spleen is already in progress.

The few patients whom we have had the opportunity to re-examine after an interval of several years have exhibited no untoward effects which might be attributable to thorium dioxide. The liver shadow has usually changed from a homogeneous to a reticulated opacity, resulting from the accumulation of thorium dioxide in the portal areas. Another feature has been the appearance of discrete dense shadows in the subhepatic area due to accumulation of thorium dioxide in the lymph nodes draining the liver. In the search for an accessory
spleen, its occasional location in such sites as pancreas and scrotum should not be overlooked.

**Summary**

Experience with the use of thorium dioxide sol (Thorotrast) in the roentgen demonstration of accessory spleens is described. The importance of the application of this technic to the clinical management of patients with hematologic relapse following splenectomy is emphasized and illustrative case reports are presented.

Nine patients were given thorium dioxide in an attempt to demonstrate an accessory spleen. A remission was induced in 1 patient with acquired hemolytic anemia, who had failed to respond to splenectomy, by removal of an accessory spleen demonstrated with thorium dioxide. A second patient with hereditary spherocytosis who relapsed seven years after splenectomy was shown to have an accessory spleen. Seven patients with idiopathic thrombocytopenic purpura who had relapsed following splenectomy were given thorium dioxide and in no case was an accessory spleen found.

**REFERENCES**

THOROTRASY DEMONSTRATION OF ACCESSORY SPLEENS

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