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THE EFFECT OF GASTROINTESTINAL ADMINISTRATION OF BOVINE SPLENIC HOMOGENATE ON HEMATOPOIESIS IN MAN

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THE INFLUENCE of the spleen on the control of hematopoiesis has been studied intensively since the turn of the century, but the relationship remains uncertain.[1] Varying degrees of success in the stimulation or inhibition of myelopoiesis were encountered by the administration of spleen and splenic extracts in both man and animals.[2,3,4] In a majority of instances the splenic substances were given parenterally or in small quantities. However, the hematopoietic effect of splenic homogenate given in large amounts and intragastrically have been reported recently by us as preliminary observations[5].

Fourteen grams of bovine spleen as an homogenate were fed by gastric tube to Fischer rats weighing approximately 150 gms. Significant thrombocytosis was encountered as seen in Figure 1. The homogenate was also administered to 39 patients with a variety of hematological disorders refractory to therapy. Patients received splenic homogenates in amounts of 750 to 1,000 gms. of spleen or 15 to 25 gms./kilo., daily for 10 to 14 days. The material was pumped into the stomach as a slow drip requiring 10 to 15 hours for the feeding period, Figure 2. Bovine thymus, kidney, skeletal muscles and whole blood were administered to patients by the same method.

The majority of the initial patients receiving this method of therapy were in the terminal phase of malignant disease, Table I. Of this group, seven were considered to have received inadequate spleen therapy. They expired due to progression of their disease during or within a week after the feeding. The remainder of the patients demonstrated an effect upon the hematopoietic system. Control patients, those with normal hematologic values, responded only by transient thrombocytosis. In all individuals treated, significant elevation of serum uric acid occurred, and the maximum level achieved was 19 mg. per cent when spleen sediment of the homogenate was administered.

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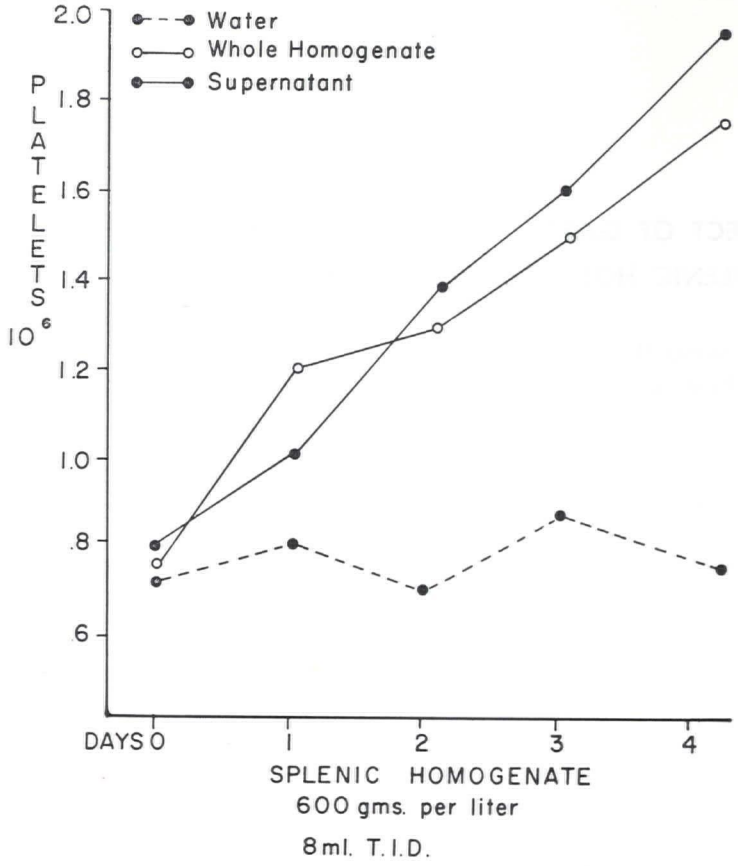

Figure 1

Thrombocytosis promoting effect of bovine splenic homogenate, 14 gms. daily, fed intragastrically to rats.

Table I

Patients Treated with Bovine Splenic Homogenate

Hodgkin's Disease	11	Myeloid Metaplasia	2
Lymphosarcoma	6	Idiopathic Thrombocytopenic Purpura	4
Chronic Lymphocytic Leukemia	1	Hypoplastic Anemia	7
Acute Leukemia		Agranulocytosis	1
Granulocytic	4	Controls	6
Erythrocytic	2	Total	45
Lymphocytic	1		

Figure 3 illustrates the hematologic response in a patient with intermittent acute thrombocytopenic purpura who was splenectomized 10 years before. She eventually became chronically thrombocytopenic and megakaryocytopenic, and failed to respond for the first time to adrenal steroids. The resultant thrombocytosis was accompanied

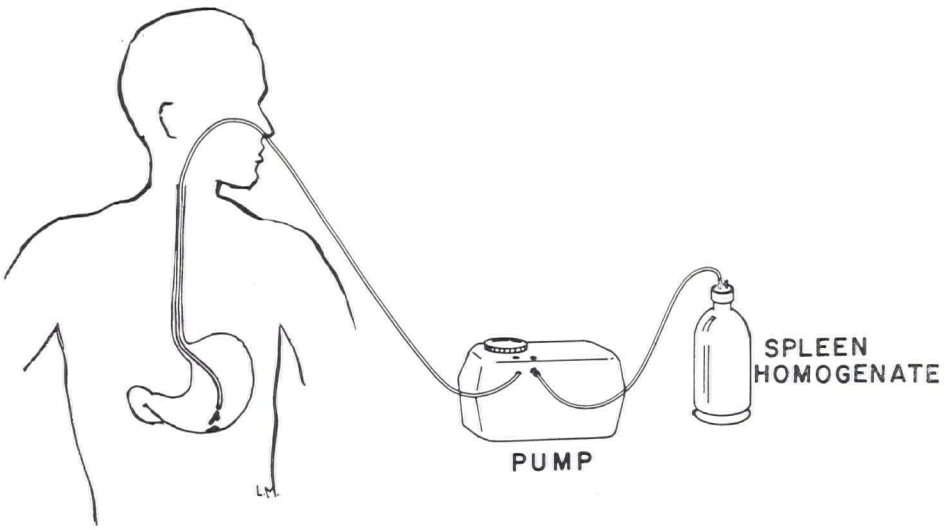

Figure 2

Schema of administration of splenic homogenates to patient.

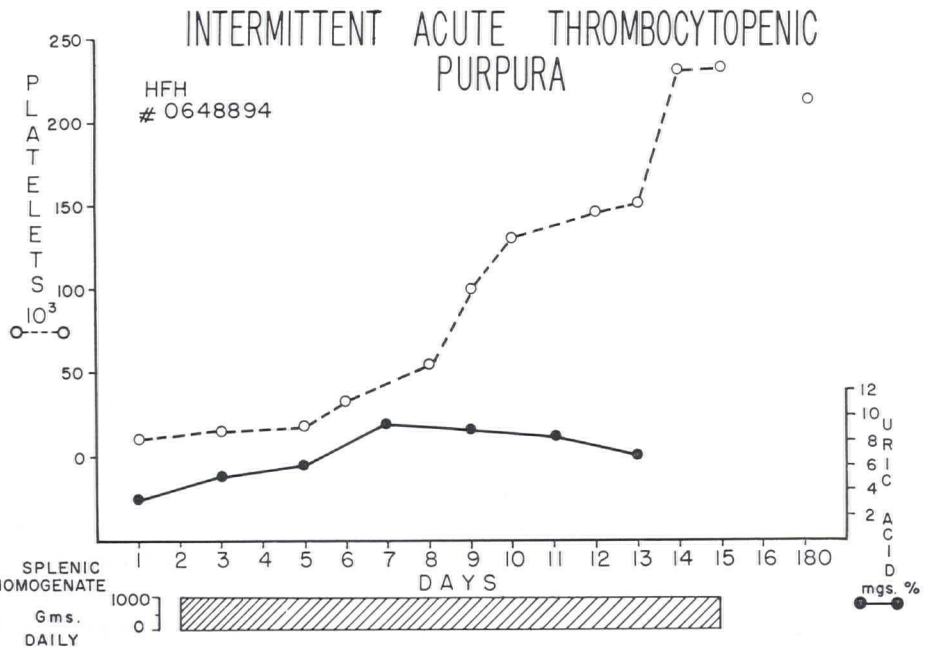

Figure 3

Platelet response of a patient with intermittent acute thrombocytopenic purpura in which the disease became chronic.

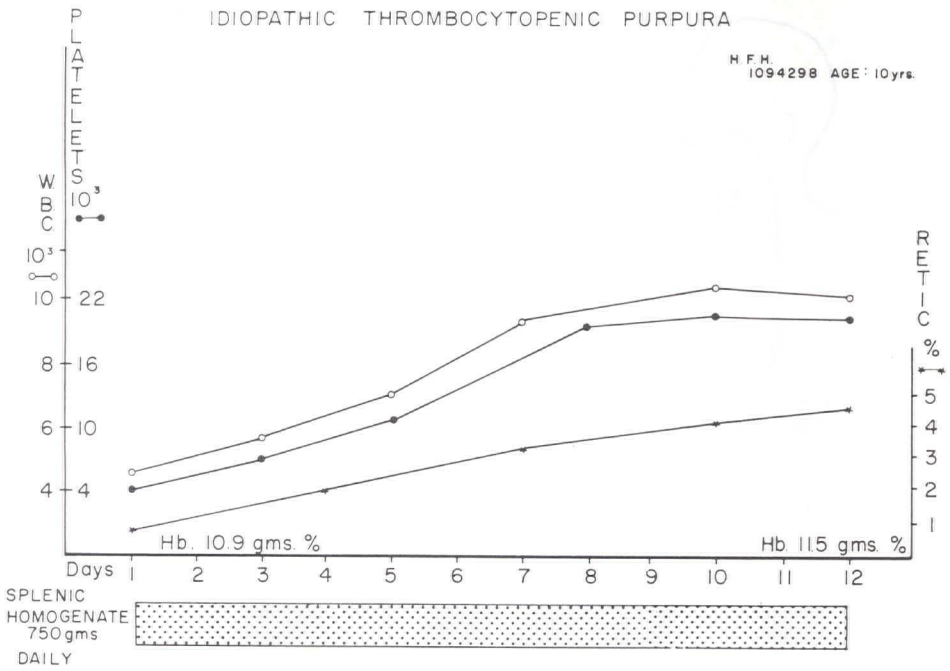

Figure 4

Hematological response of a patient with acute idiopathic thrombocytopenic purpura.

by an increase in the numbers of megakaryocytes in the bone marrow, both of which persisted for many months. Three patients with acute idiopathic thrombocytopenic purpura, who failed to respond to steroid therapy and/or splenectomy, were administered the splenic homogenate. One of the three is shown in Figure 4. Associated with the thrombocytopenic state was a mild leukopenia and anemia. After the bovine splenic feeding, the leukocyte count reached normal levels with a marked shift to the left in the leukocytic differential. A minimal platelet and reticulocyte response was observed. A progress bone marrow examination after therapy demonstrated intense hematopoiesis with a marked increase in numbers of megakaryocytes with normal levels, permitting therapy with nitrogen mustard. An excellent clinical remission was obtained, and adequate platelet counts were maintained for over 60 days, Figure 5. In six other patients given simultaneous splenic homogenate and nitrogen mustard, myelotoxicity appeared to be reduced.

A patient with congenital familial erythroblastopenia (congenital hypoplastic anemia), previously splenectomized, showed a reticulocytosis of 6 per cent with an elevation of blood hemoglobin, after having been fed the bovine splenic homogenate intragastrically. This individual was treated at home for 150 days with approximately 500 ml. of bovine splenic supernate daily. Figure 6 illustrates the hematological response. The hemoglobin rose from 6 gms. to 12 gms. over a four month period, the highest level obtained during his life. Figure 7 illustrates the clinical hematological

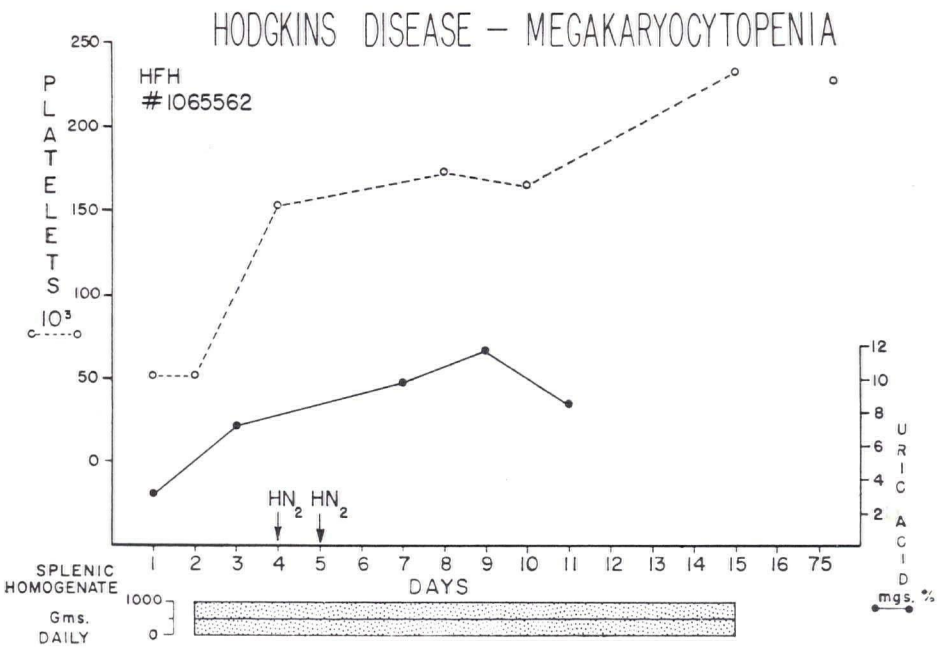

Figure 5

Platelt effect in a patient with Hodgkin's disease and chronic thrombocytopenia treated with splenic homogenate and nitrogen mustard.

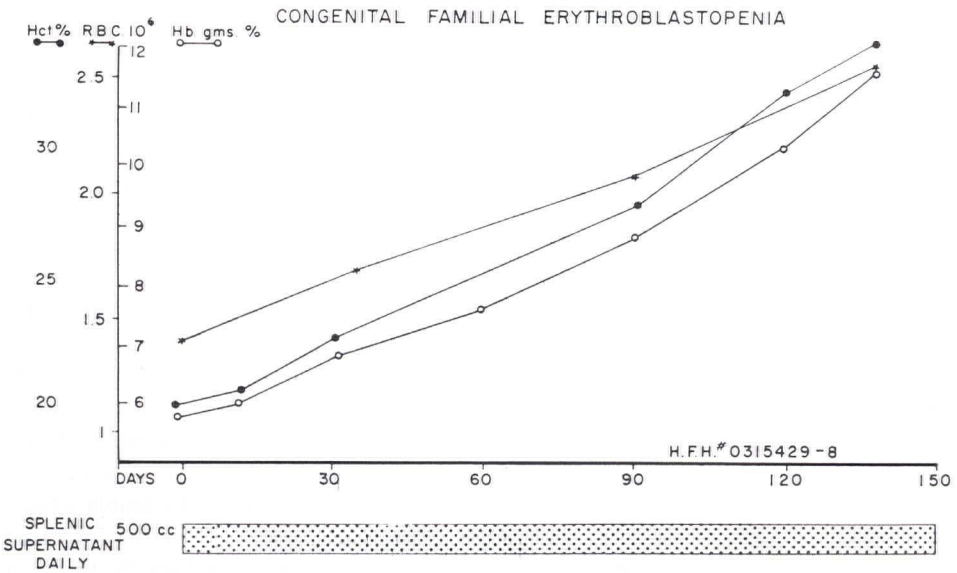

Figure 6

Hematologic response of a patient with congenital familial erythroblastopenia.

response of a patient with refractory anemia of 10 months duration. She had been previously treated with transfusions, steroids, hematinics, and androgens without benefit. This patient was also leukopenic. After therapy with splenic homogenate, reticulocytosis of 8 per cent was encountered as well as an elevation of the leukocyte count to near normal levels. The hemoglobin rose from 8 to 11½ gms. per cent. Three months after discontinuance of therapy, mild anemia and leukopenia again recurred.

Figure 8 represents a patient with agranulocytosis produced by chlorpromazine. When therapy was initiated the patient was critically ill, suffering from severe ulcerative stomatitis and pharyngitis, pneumonia and septicemia. On the fourth day of therapy there was evidence of beginning hematologic and clinical remission. The white blood cell count returned to normal levels and was associated with a moderate thrombocytosis.

These results must be interpreted in the light of the natural course of disease, unexplained spontaneous remissions together with pre- and current adjunctive therapy when designated. The possibility of bone marrow stimulation resulting from the endotoxin of coliform organism contamination of the homogenate must be considered.

The patients tolerated gastrointestinal feeding of splenic homogenate well. An occasional individual developed gastrointestinal irritation with diarrhea. This was usually associated with high doses of the homogenate given at rapid speeds. Extreme care is necessary in the preparation of the homogenate to avoid excessive bacterial contamination. Aseptic and sterile techniques and constant refrigeration during the preparation and storage of the homogenate are required.

In two patients with known chronic renal disease, the splenic feedings were discontinued because of the appearance of clinical uremia which occurred within five days. The uremia cleared promptly after the discontinuance of the feeding and the administration of fluids. The thirteenth patient administered bovine splenic homogenate was an elderly man with an initial uric acid of 7.1 mg. per cent. Four days after the discontinuance of therapy, he developed his first clinical attack of gout.

The administration of bovine thymus to a patient with agammaglobulinemia for a period of but four days produced no noticeable response other than an elevation of the blood uric acid. A patient with thymoma and erythroblastopenia similarly failed to respond to thymic homogenate administered over a period of twelve days. Two patients given kidney, one given skeletal muscle, and one given whole blood failed to show significant alteration of their hematological values. Four patients with acute leukemia were given intragastric splenic homogenate without favorable effect. Indeed, the malignant process appeared to be enhanced as evidenced by the increased number of circulating and bone marrow blast forms. In two instances in which a diagnosis of early leukemia was in doubt, the diagnosis was apparent immediately after a course of splenic feeding.

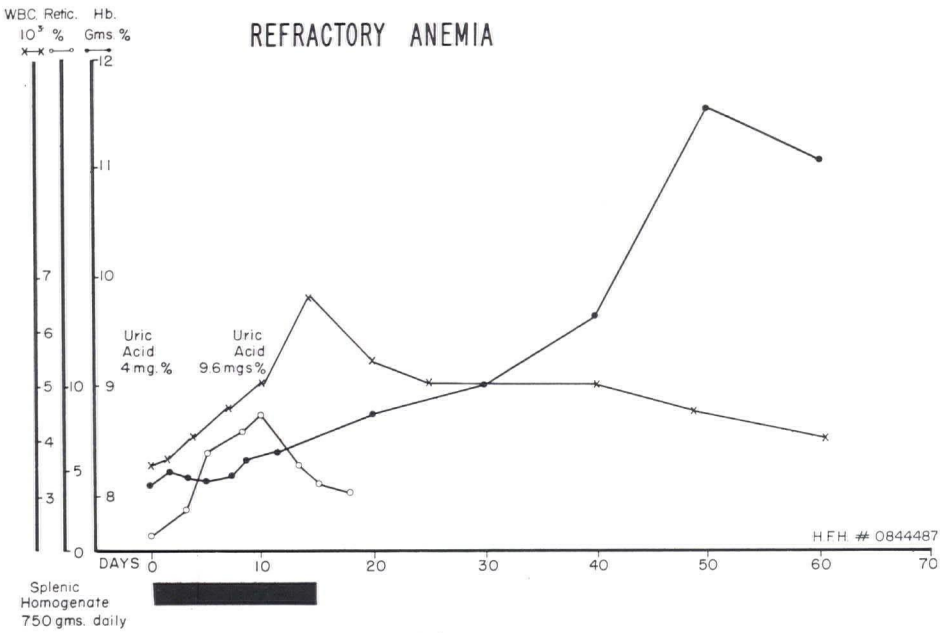

Figure 7

Partial clinical remission in a patient with chronic hypoplastic anemia which persisted for 5 months.

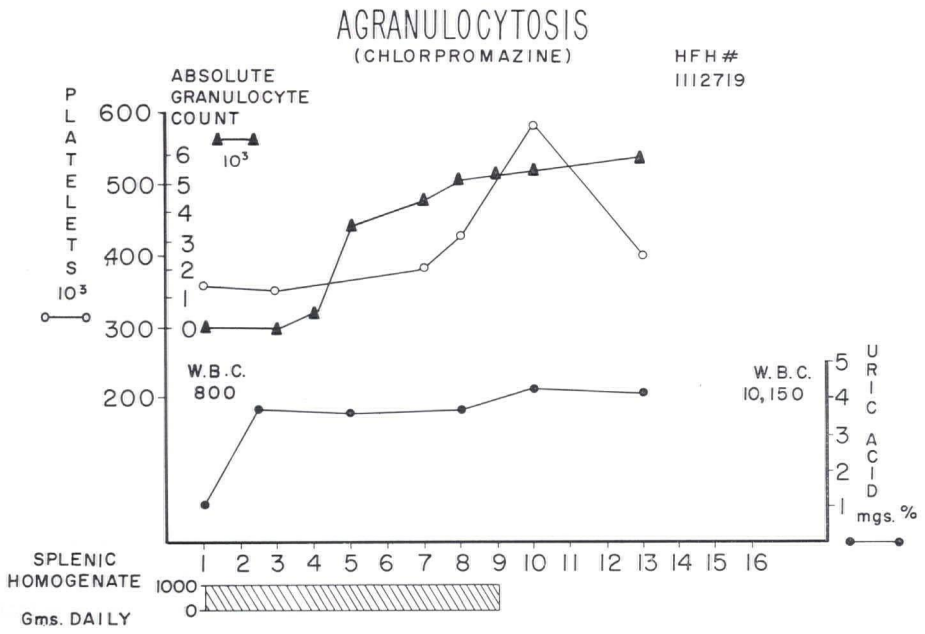

Figure 8

Complete hematological remission obtained in a patient with severe drug induced agranulocytosis.

Discussion

Stimulated by the observations of Whipple, Leake, in 1924, studied the effect of extracts of spleen and red bone marrow individually and in combination on hematopoiesis, both in animals and in man.[6,7] He was able to demonstrate an increase in the number of circulating erythrocytes, hemoglobin, and granulocytes in his subjects. Sandler, in 1949, reported observations on experimental studies of the erythropoietic effect of yellow bone marrow extracts and batyl alcohol.[8] Bone marrow treated with alcohol, frozen, and then extracted with petroleum ether produced a white crystal precipitate shown to be batyl alcohol. Experiments in albino rats demonstrated that yellow bone marrow increased erythrocytic numbers and that batyl alcohol gave the same type of reaction. Oral batyl alcohol was given to normal males, resulting in reticulocytosis but with no conclusive evidence of increased red cell count or hemoglobin.

In 1951, Schleicher reported that thrombocytosis and megakaryocytosis increased in man when fed orally dessicated beef spleen and abdominal lymph nodes.[2] Recently, Berliner described a patient with hemorrhagic thrombocythemia treated successfully with the ingestion of raw spleen.[3] In 1962, Crosby presented evidence of a myeloinhibitory factor in spleen fed to rats.[4]

Splenic bovine spleen, both as a homogenate and as an extract given parenterally, has been reported to afford protection from acute radiation sickness in animals and in man.[9] Spleen cells and extracts have also been recorded to favorably influence the clinical course of patients with wire-spread malignancy.[10]

The effect of nucleic acid and its degradation products in deficiency states are known to have favorable results upon the hematological response in red and white blood cell production. Pisciotta has shown that chlorpromazine partially inhibits nucleic acid synthesis in persons sensitive to the drug and that in tissue cultures an excess of ribonucleic acid and desoxyribonucleic acid are capable of overcoming the depressant action of drug in vivo in tissue culture.[11] Erythropoiesis was studied in bone marrow cultures by Hammarsten in patients with rheumatoid arthritis[12]. He found splenic extracts or amino acid solutions significantly increased erythropoiesis in rheumatoid arthritis but not in a variety of other chronic disease states.

Because of extreme technical difficulties in the preparation and administration of splenic homogenates, extract concentrates have been prepared. This material produces thromobocytosis in rats and is awaiting clinical trials. Contemplated extension of this method of therapy includes treatment of patients with anemia of chronic renal disease and thalassemia. Investigation is underway to evaluate the protective action of splenic homogenates and extracts on the bone marrow in subjects receiving radiation and myelotoxic chemicals.

Summary and Conclusions

The gastrointestinal administration of bovine splenic homogenate appears to have a myelostimulatory effect. This response is most noticeable in the presence of cytopenia. Observations thus far suggest the principle activity to be in the supernatant. Apparent responses may be non-specific due to the absorption of nuclear protein degradation products or of a myelostimulatory factor(s). There is obvious need for confirmation of these results in man.

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