

A Speculative Approach to the Myeloproliferative Syndromes

By JEROME I. BRODY AND FERNANDO RODRIGUEZ

THE PURPOSE of this report is to describe two well-known clinical conditions which have not been associated specifically with the myeloproliferative syndromes. A recent clinical and patient-record review in this hospital discovered an apparent increase in diabetes mellitus and one example of scleroderma associated with this group of blood abnormalities. Although the patient number admittedly is not very large and only a single instance of scleroderma was recognized, these combinations are of special interest because they suggest certain humoral and metabolic factors which may be related to and correlated with the pathogenesis of these blood dyscrasias. The observations which follow are presented not as experimental or statistical data but rather in the form of suppositions perhaps relevant to the varied features of the myeloproliferative disorders. A total of 66 cases were classified under the category of myeloproliferative syndromes and a summary of the individual diagnoses is given in table 1.

Diabetes Mellitus and the Myeloproliferative Syndromes

There were 11 patients out of a total of 66, 16.7 per cent, who had some evidence of abnormal carbohydrate metabolism. Although this may represent an actual increase in clinically manifest or latent diabetes, the values do not have statistical significance mainly because the incidence of diabetes mellitus, in this particular hospital population, is not known at the present time. It may only be suggested, therefore, that the incidence appears to be greater than that for the general population.^{1,2} Six patients with chronic granulocytic leukemia, two with polycythemia vera and one with agnogenic myeloid metaplasia had overt diabetes mellitus with fasting hyperglycemia and glycosuria. Two other patients with myeloid metaplasia had only intermittent, occasional glycosuria but showed marked postprandial hyperglycemia after a high carbohydrate meal.

The observed abnormal carbohydrate metabolism may be a fortuitous occurrence in this relatively small number of patients or merely may be an expression of the increased metabolic activity which is present in leukemia and related disorders.^{3,4} On the other hand, there are several reasons why it may reflect yet another coexistent systemic metabolic or specific cellular enzyme disturbance in addition to those already described in these blood dyscrasias. Hyperuricemia commonly accompanies such hematologic abnormalities⁵ and mirrors increased nucleoprotein and nucleic acid turnover. In addition, on a

From the Department of Medicine, Veterans Administration Hospital, and the University of Miami School of Medicine, Coral Gables, Fla.

Submitted Oct. 17, 1961; accepted for publication Dec. 15, 1961.

Table 1.—*Myeloproliferative Syndromes Observed from 1955–1961*^a

Diagnosis	Age range (years)	Number
Acute granulocytic leukemia	20–78	21
Chronic granulocytic leukemia	30–79	18
Polycythemia vera	34–73	12
Agnogenic myeloid metaplasia with myelofibrosis	59–70	12
Essential hemorrhagic thrombocythemia	64, 68	2
Erythremic myelosis	79	1
	Total	66

^aAll patients were male except one female with polycythemia vera and the patient with erythremic myelosis.

cellular level, the alkaline phosphatase content of peripheral blood polymorphonuclear leukocytes is abnormal⁶ so that in chronic granulocytic leukemia it is generally decreased or absent, and in polycythemia vera and myeloid metaplasia it is usually elevated. It should be mentioned in this regard that elevations of another enzyme, erythrocyte glucose-6-phosphate dehydrogenase, has been observed in patients with thyrotoxicosis,⁷ a nonhematologic hypermetabolic disorder, which may be associated with hyperglycemia and abnormal glucose tolerance curves. This further suggests a relationship between general body and hematopoietic tissue metabolism.

In four instances of chronic granulocytic leukemia, the initial symptom which brought the patient to the physician was failing vision. Because leukemic infiltration of the optic fundus commonly occurs in this type of leukemia, another basis for this abnormality often is not considered in spite of the fact that these lesions may not be distinguished from those of diabetic retinopathy solely by observation. It is quite possible that greater attention to both the fasting and postprandial blood sugar levels may discover an increasing number of patients in this category with deranged carbohydrate metabolism as an integral part of their primary hematologic disease. In this regard it is pertinent that a study of the periodic acid-Schiff (PAS) reaction of granulocytes in patients with diabetes mellitus and blood disorders showed that 6 of 10 patients with polycythemia vera had a PAS pattern found in diabetes mellitus. Overt diabetes mellitus was present in one patient and in the remaining five diabetes eventually was discovered.⁸

It is perhaps also relevant that the metabolic irregularity was noted only in polycythemia vera, myeloid metaplasia, and chronic granulocytic leukemia and not in the other diseases comprising the group. This observation may reflect a closer relationship between these members which have a longer clinical duration and which are less rapidly progressive. Finally, it is of singular interest that an increased incidence of diabetes mellitus has been detected in patients with endometrial carcinoma,⁹ suggesting that apparent clinical diabetes mellitus, in certain patients, may mirror the diffuse histochemical changes which develop in potentially malignant and malignant disease states.

Myeloid Metaplasia, Myelofibrosis and Scleroderma

Scleroderma is a generalized disease of various body organs resulting in diffuse proliferation of connective tissue and sclerosis of the collagenous

bundles composing this tissue.¹⁰ It is more common in females and generally has its onset before the age of 50.¹¹ The unusual development of scleroderma in a patient with myeloid metaplasia and myelofibrosis suggested that perhaps fibroplastic proliferation, considered to be an integral part of the myeloproliferative syndromes,¹² may be limited not only to the reticuloendothelial, blood forming, and parenchymal organs, but may occur in other areas where connective tissue is present. A recent review of 63 cases of idiopathic myelofibrosis confirmed that diffuse fibrosis of varying degrees was present in all organs and body structures.¹³

This concept is illustrated, in part, by the present 66 year old white male patient with myelofibrosis and myeloid metaplasia of three years' duration. He developed tightness of the skin around the mouth and small joints of the hand unaccompanied, however, by signs of cardiovascular, gastrointestinal or renal disease. There was, on palpation, decreased resiliency of the skin but no evidence of arthropathy and no complaints of arthralgia were elicited. A skin biopsy revealed changes compatible with the diagnosis of scleroderma. A major, almost incapacitating, symptom during this period of observation had been prolonged and persistent generalized pruritus. The striking features of this particular case are that the sclerodermatous change was apparently limited solely to the integument, occurred in a 66 year old male, was unassociated with the other signs present in the ordinary type of scleroderma, and occurred several years following the onset of myelofibrosis, suggesting that the fibrosis of the bone marrow and skin may have a common basis and may be interrelated.

In trying to develop an integrated hypothesis it became apparent that two other clinical entities, the carcinoid syndrome and urticaria pigmentosa, have symptoms such as flushing of the skin, vasomotor instability, episodes of tachycardia, and therapy resistant generalized pruritus, which also may be present in patients with the myeloproliferative disorders. Furthermore, both conditions have as an integral part of their problem extensive systemic fibrous tissue proliferation.¹⁴⁻¹⁹ The specific feature of the carcinoid syndrome is a marked increase in serotonin and its metabolites, and in urticaria pigmentosa the most significant observation is the prominent tissue mast cell infiltration of the skin.

As an extension of this thesis it may be appropriate to suggest that the tissue mast cell, whose primary function remains unknown, may account for some of the microscopic and clinical manifestations of the myeloproliferative disorders for the following reasons. The mast cell is a connective tissue cell^{20,21} found in 70 per cent of normal bone marrows²² and which, under neoplastic conditions, may contain excess serotonin.^{23,24} In addition, recent observations suggest that the mast cell may be intimately involved in the connective tissue changes which occur in certain of the collagen diseases.²⁵ Also, urticaria pigmentosa and polycythemia vera have occurred simultaneously²⁶ and marked mast cell proliferation has been recognized in a patient with erythremic myelosis.²⁷ In addition, the mast cells of urticaria pigmentosa may proliferate into the peripheral blood, at which time the disease simulates a leukemic process.²⁸ Finally, the experimental injection of serotonin creatine sulfate into the dermis of rats resulted in collagenous and fibrous tissue proliferation.

Table 2.—*Excretion of 5-Hydroxyindoleacetic Acid Per 24 Hours*

Diagnosis	Value (mg.)
Polycythemia vera	8.0
Polycythemia vera	3.3
Polycythemia vera	8.5
Polycythemia vera	26.2
Myelofibrosis	2.0
Myelofibrosis*	6.0
Myelofibrosis	2.5
Myelofibrosis	11.0
Essential hemorrhagic thrombocythemia	6.0
Acute granulocytic leukemia	5.4
Acute granulocytic leukemia	10.0

*Patient with scleroderma-like skin changes.

However, skin away from the area of injection was normal and fibrosis of the visceral organs was not noted,²⁹ suggesting that this material was fixed *in situ*.

In view of the association of the mast cell with connective and bone marrow tissues, both histogenetically and morphologically, and the association of serotonin with the mast cell and tissue fibrosis, the amount of 5-hydroxyindoleacetic acid (5-HIAA) excreted in the urine over a 24 hour period was determined in 11 patients of the present series. In three patients with polycythemia vera, three with myelofibrosis (including the patient with scleroderma-like skin changes), one with essential hemorrhagic thrombocythemia, and one with acute granulocytic leukemia, the amounts were within the normal range of 2–9 mg. in a 24 hour period.³⁰ However, one patient with polycythemia vera excreted 26.5 mg. in 24 hours, one with myelofibrosis excreted 11 mg. in 24 hours and one patient with acute granulocytic leukemia excreted 10 mg. in 24 hours. These results are summarized in table 2. None of the patients with the minimal or mild elevated excretory levels had diarrhea, hypertension or bronchospastic phenomena and no evidence of a carcinoid tumor was found in the latter two cases at postmortem examination. In addition, fruits such as bananas, and drugs such as chlorpromazine, were not knowingly ingested during the urine collections.

As is often the situation, a hiatus exists between theory and fact so that these results are, in essence, indeterminate and neither prove nor disprove the hypothesis. However, failure to demonstrate increased levels of 5-HIAA in all patients may be due, as was suggested by the experimental observations, to the intramedullary and intradermal fixation of the serotonin without detectable release of this material into the peripheral blood. In addition, a serotonin metabolite other than 5-HIAA or a related compound may have been present and remained undetected by the analytic methods employed. It is also possible that concentrations of other substances contained by the mast cell such as heparin and histamine,³¹ which have been implicated in the growth of connective tissue when determined in similar patients, may be abnormal. Finally, it is suggested that greater attention both clinically and by microscopic examination to the skin of these patients may disclose a greater incidence of unusual alterations than formerly was supposed.

COMMENT

The myeloproliferative syndromes probably are a group of histogenetically related blood dyscrasias whose manifestations may be protean.³² Their interconnection is emphasized by the fact that many times it is difficult to make a differential diagnosis between myeloid metaplasia, granulocytic leukemia and polycythemia vera. Leukocytosis with peripheral blood leukocyte immaturity, active bone marrow leukocyte proliferation, and bone marrow fibrosis interspersed with foci of active erythropoiesis and myelopoiesis may be found in all three diseases. However, the fundamental and primary stimuli which produce the variability of clinical and morphologic expressions remain undisclosed. It is possible that the origin and particular development of each individual entity depend on subtle modifications of tissue growth determinants. The unusual associations described suggest that such alterations may not be limited to hematopoietic tissues but are actually widespread systemic abnormalities. It may be feasible, at a later date, to define the evolution of these blood dyscrasias on the basis of specific biochemical and metabolic errors.

SUMMARY

1. A survey of 66 cases of the myeloproliferative syndromes revealed two clinical conditions not associated specifically with this group of blood dyscrasias.

2. Of particular interest were an apparent increased incidence of diabetes mellitus, and myelofibrosis associated with scleroderma.

3. These combinations may reflect a biochemical or metabolic error which may be present in some of these patients (such as increased 5-HIAA) and which may be related to the course, progression, and symptomatology of these disorders.

SUMMARIO IN INTERLINGUA

1. Un revista de 66 casos del syndromes myeloproliferative revelava duo conditiones clinic que non habeva essite associate specificamente con iste gruppo de dyscrasis del sanguine.

2. De interesse particular esseva le constatacion de un apparente elevation in le incidentia de diabete mellite e de myelofibrosis associate con scleroderma.

3. Iste combinationes possiblementemente reflecte un error biochimic o metabolic que pote esser presente in certes de iste patientes (p. e. augmento de acido 5-hydroxyindoloacetic) e que es possiblementemente relationate con le curso, le progression, e le symptomatologia de iste disordines.

REFERENCES

1. Wilkerson, H. L. C., and Krall, L. P.: Diabetes in a New England town: A study of 3,516 persons in Oxford, Massachusetts. *J.A.M.A.* 135:209, 1947.
2. Spiegelman, M., and Marks, H. H.: Age and sex variations in the prevalence and onset of diabetes mellitus. *Am. J. Pub. Health* 36:26, 1946.
3. Riddle, M. C., and Sturgis, C. C.: Basal metabolism in chronic myelogenous leukemia. *Arch. Int. Med.* 39:255, 1927.
4. Lennox, W., and Means, J. H.: Study of basal and nitrogenous metabolism in a case of acute leukemia during

- Roentgen-ray treatment. Arch. Int. Med. 32:705, 1923.
5. Talbot, J. H.: Gout and blood dyscrasias. Medicine 38:173, 1959.
 6. Wiltshaw, E., and Moloney, W. C.: Histochemical and biochemical studies on leucocyte alkaline phosphatase activity. Blood 10:1120, 1955.
 7. Pearson, H. A., and Druyan, R.: Erythrocyte glucose-6-phosphate dehydrogenase activity related to thyroid activity. J. Lab. & Clin. Med. 57:343, 1961.
 8. Gärtner, I., and Nordèn, A.: Studies on periodic acid-Schiff reactive material in white blood cells from the peripheral blood of patients with diabetes, polycythemia and chronic lymphocytic leukemia. Acta med. scandinav. 169:289, 1961.
 9. Editorial: Diabetes and endometrial cancer. Lancet 1:496, 1961.
 10. Piser, W. H., and Helwig, E. B.: Progressive systemic sclerosis-visceral manifestations in generalized scleroderma. Arch. Dermat. u. Syph. 72:535, 1955.
 11. Leinwand, I., Duryee, A. W., and Richter, M. N.: Scleroderma (based on a study of over 150 cases). Ann. Int. Med. 41:1003, 1954.
 12. Vaughn, J. M., and Harrison, C. V.: Leukoerythroblastic anemia and myeloscrosis. J. Path. & Bact. 48:339, 1939.
 13. Pitcock, J., and Reinhard, E. H.: *Quoted in Clinicopathologic Conference.* Am. J. Med. 31:124, 1961.
 14. Thorson, A., Bjork, G., and Waldenstrom, J.: Malignant carcinoid of small intestine with metastases to liver, valvular disease of the right side of the heart (pulmonary stenosis and tricuspid regurgitation with septal defects), peripheral vasomotor constriction and unusual type of cyanosis: A clinical and pathologic syndrome. Am. Heart J. 47:795, 1954.
 15. Asboe-Hansen, G., and Wegelius, O.: Serotonin and connective tissue. Nature, London 178:262, 1956.
 16. Sutton, R. L.: Diseases of the Skin. St. Louis, C. V. Mosby Co., 1956.
 17. Ellis, J. M.: Urticaria pigmentosa, a report of a case with autopsy. Arch. Path. 48:426, 1949.
 18. Stutzman, L., Zsoldos, S., Ambrus, J. L., and Asboe-Hansen, G.: Systemic mast cell disease. Am. J. Med. 29:894, 1960.
 19. Ende, N., and Cherniss, E. I.: Splenic mastocytosis. Blood 13:631, 1958.
 20. Nickel, W. R.: Urticaria pigmentosa. Mastocytosis: Staining. A consideration of various manifestations. Arch. Dermat. 76:476, 1957.
 21. Fawcett, D. W.: An experimental study of mast cell degranulation and regeneration. Anat. Rec. 121:29, 1955.
 22. Johnstone, J. M.: The appearance and significance of tissue mast cells in human bone marrow. J. Clin. Path. 7:275, 1954.
 23. Sjoerdsma, A., Waalkes, T. P., and Weissbach, H.: Serotonin and histamine in mast cells. Science 125:1202, 1957.
 24. Ono, S., Zompetti, L., Hagen, P., and Furth, J.: Relation of mastocytoma to mast cell leukemia and of heparin, histamine and serotonin to mast cells. Blood 14:770, 1959.
 25. Smyth, C. J., and Gum, O. B.: Vasculitis, mast cells and collagen diseases. Arth. & Rheumat. 4:1, 1961.
 26. Bowdler, A. J., and Tullett, G. L.: Urticaria pigmentosa and polycythemia vera. Brit. M. J. 1:396, 1960.
 27. Zlotnick, A.: Acute erythremic myelosis. A case report. Israel Med. J. 19:188, 1960.
 28. Friedman, B. I., Will, J. J., Freiman, D. G., and Braunstein, H.: Tissue mast cell leukemia. Blood 13:70, 1958.
 29. MacDonald, R. A., Robbins, S. L., and Mallory, G. K.: Dermal fibrosis following subcutaneous injections of serotonin creatine sulfate. Proc. Soc. Exper. Biol. & Med. 97:334, 1958.
 30. Sjoerdsma, A.: Medical progress. Serotonin. New England J. Med. 261:181, 1959.
 31. Morriowe, T. G.: Formation of collagen fibers by the action of heparin on soluble collagen. J. Exper. Med. 96:107, 1952.
 32. Dameshek, W.: Some speculations on the myeloproliferative syndromes. Blood 6:372, 1951.

Jerome I. Brody, M.D., Assistant Professor of Medicine, University of Miami School of Medicine, and Chief, Hematology Section, Veterans Administration Hospital, Coral Gables, Fla.

Fernando Rodriguez, M.D., Formerly Resident in Medicine, Veterans Administration Hospital, Coral Gables, Fla.