Original Articles

Gaisbock's Disease: Redefinition of an Old Syndrone

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PRESENT-DAY students are usually taught that Gaisböck's syndrome is a coincidence of polycythemia vera and hypertension. However, as one follows patients with persistently elevated hematocrit values, it becomes apparent that Gaisböck may have been describing a disorder distinct from polycythemia vera. This is important since patients who have had neither an elevated total red blood cell volume, nor polycythemia vera, have been treated by phlebotomy and radioactive phosphorus. This error in diagnosis and treatment is more common than is realized.

Although he recognized increase in the erythrocyte count due to plasma loss, and forms of physiologic polycythemia, Gaisböck[1] regarded his *polycythemia hypertonica* as a true polycythemia. He regarded the presence of hypertension as the most important manifestation separating his syndrome from the Vaquez type of true polycythemia. Since hypertension is common in polycythemia vera[2] he undoubtedly included some cases in his group with polycythemia hypertonica. However, since he also considered the absence of splenomegaly as a diagnostic criterion, probably the number was small. There is undoubtedly much overlap between the syndrome described by Gaisböck and the relative polycythemia described by Lawrence and Berlin.[3] Differences in method of study and general approach make a closer comparison impossible.

The present report is an attempt to define a syndrome which appears to include the cases both of Gaisböck and of Lawrence and Berlin. Gaisböck's name is used as an eponym in recognition of his early attempt to separate an entity from the classification of polycythemia vera, where it does not belong. This problem of classification still exists 42 years later.

This study is an attempt to show that there is a distinct syndrome with many manifestations, especially vascular, which are as important as the increased hematocrit value, or more so. There may be an absolute increase in red-blood-cell volume in this syndrome which is not found in relative polycythemia from which it is distinct.

Materials and Methods

The present series consisted of 20 men from an almost exclusively male population, who were referred to a hematologist as possibly having polycythemia because of plethora or an elevated hematocrit value, or usually, both. None had either secondary polycythemia, or polycythemia vera as defined by Lawrence et al[2]:

"Polycythemia vera refers to a condition in which there is a marked and persistent elevation in the total number of red cells in the circulation, commonly with ruddy cyanosis, splenomegaly, leukocytosis and thrombocytosis, and for which no etiology can be found."

One case is presented in detail (case 20, Table 1). The patient, a 44-year-old man, was admitted to the hospital because of increasing pain in both legs on walking. For years he had noted numbness, blanching, and then pain in his hands and feet on exposure to cold. During the previous six years he experienced at least one myocardial infarction, repeated superficial or deep phlebitis, increasing claudication, and both gastric and duodenal ulcers. On physical examination he was markedly plethoric, and very tense and anxious. The blood pressure was 160/120 mm Hg. There was marked arterial insufficiency of the legs.

Received for publication Dec 8, 1964; accepted Dec 22.

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TABLE 1.—*Red Blood Cell and Plasma Volumes*

Case and Date	Age	Height, In	Weight, Lb	Major Problem	Vascular Disease *	Peak Hematocrit, % †	Hematocrit, % ‡	Red-Blood-Cell Volume By ^{51}Cr Ml	Red-Blood-Cell Volume By ^{51}Cr Ml/Kg	Red-Blood-Cell Volume By T-1824, Ml/Kg	Plasma Volume By T-1824, Ml/Kg	Plasma Volume By ^{51}Cr Ml/Kg
1, 9/63	42	65	232	Headaches, dizziness	None	56	56	2,878	26.3	30.7	28.8	24.7
2, 7/58	31	75	220	Nervous, vomiting,	P	59	—	3,318 §	33.2			23.5
1/59				chest pain, tinnitus		—	—	3,200 §	32.0			
3/60						62	54	2,710	26.0	31.4	32.0	29.4
3, 2/62	32	68	146	Angina, migraine	H	57	52	2,296	34.6			38.4
4, 8/63	38	69	168	Myocardial infarct	H	57	57	2,659	34.8	42.0	38.1	31.6
5, 10/57	65	60	138	Shoulder pain, dyspnea, cough	H	58	52	1,972	31.4			34.9
6, 11/58	51	70	167	Cough, dyspnea	None	59	55	2,630	34.6			34.4
7, 9/60	48	69	200	Arterial occlusion	P,H,B	54	51	2,250	24.8			28.0
8, 10/63	59	68	176	Headache	None	60	60	2,953	36.8	42.6	34.6	29.9
9, 9/61	42	64	164	CVA	B,P	57	54	2,105	28.3			28.8
6/64						46	46	1,845	22.7	24.5	36.0	33.3
10, 9/61	40	62	117	Nausea, nervous, inactive tuberculosis	H	61	54	2,088	39.2	38.1	34.6	35.6
11, 1/58	44	65	160	Claudication	H,P,B	60	59	2,360	32.4			27.8
12, 11/57	44	69	240	Diabetes	None	58	56	2,907	24.9			24.6
3/60						61	54			34.8	35.3	
13, 2/64	40	66	178	Headaches, epistaxis	H	59	58	2,495	30.8	33.7	29.4	26.9
14, 3/62	68	69	175	Cataract	B	64	55	2,894	37.9	49.2	30.7	37.0
3/64						55	55	2,955	37.4			36.5
15, 11/58	31	70	192	Dysuria, chest pain	None	58	56	2,515	29.6			27.9
11/62						59	54	2,667	30.4	26.8	27.2	30.8
1/63						57	54	2,658	32.1	33.7	35.3	32.5
16, 11/62	41	66	176	Discoid lupus	None	56	52	2,409	30.8	36.0	39.4	33.6
17, 5/63	67	66	155	Myocardial infarct	H	60	61	—		38.4	30.1	
5/63							57	2,243	28.4	34.9	31.7	25.8
18, 12/62	55	66	206	Headaches, purpura	None	58	56	—		31.6	29.7	
19, 1/56	57	65	170	Arterial occlusion	H,P,B	61	—	—	—	—	—	—
20, 12/63	44	68	124	Claudication, phlebitis, myocardial farct, peptic ulcer	P,H	61	61			51.3 §	37.8	
5/64						73	73	3,201	56.8	66.6	32.5	27.7
6/64						50	50			35.4	41.5	
10/64						61	61			44.7	35.0	

* P, peripheral; B, brain; H, heart.
† Highest hematocrit value on that admission.
‡ Hematocrit value when blood volume was measured.
§ Blood volume measured in another laboratory.
Normal means and SD for males: Huff and Feller[5]
^{51}Cr Method
Red-blood-cell volume = 28.2 ± 4:1 ml/kg
Plasma volume = 38.6 ± 6.4 ml/kg
VonPorat[5]
T-1824 Method
Red-blood-cell volume = 31.6 ± 3.8 ml/kg
Plasma volume = 46.6 ± 6.3 ml/kg

The spleen was not palpable. The hemoglobin level was 20 gm/100 ml and the hematocrit value 71%. The hematocrit value was known to have been elevated in 1958 and in 1963. There had never been leukocytosis or thrombocytosis. The bone marrow was normal. The usual causes of secondary polycythemia were absent. The red-blood-cell volume was about twice normal as shown in Table 1. Fifteen hundred milliliters of blood were removed without any change in his symptoms.

Radioactive iron metabolism studies were performed in the patient in case 20 two weeks after the removal of 1,500 ml of blood. At this time 10.09 μc of iron 59 (^{59}Fe) was injected intravenously prebound to the patient's own plasma. Serial plasma samples were taken for six hours to determine plasma ^{59}Fe, and whole blood ^{59}Fe was measured repeatedly for 138 days. At the time of the procedure the plasma volume was measured by the T-1824 technique. This value and the hematocrit value were used to calculate the past phlebotomy red-blood-cell volume necessary for the calculation of percent incorporation of the ^{59}Fe.

The blood volume was measured in all cases but one (case 19) in which a sharp drop in the hematocrit value following a 500-ml phlebotomy was strong evidence against significantly increased total red-blood-cell volume. The red-blood-cell volume was measured directly in 18 cases by the radioactive chromium (^{51}Cr) technique.[4] The plasma volume was measured, usually at the same time as the red-blood-cell volume, by the Evans blue dye technique in 12 of 18 cases. Normal values were taken from the study of VonPorat.[5] The ^{51}Cr measurements were technically un-

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TABLE 2.—*Clinical Summary: 20 Patients*

Clinical and Laboratory Findings	No.
Plethora	17
Blood pressure >140/90 mm Hg at some time	14
Headaches	9
Obese (so described by examiner)	8
Nervous or tense	9
Dizziness	7
Sustained hypertension	4
Vascular disease *	13
Heart only	6
Brain only	1
Peripheral only	1
Multiple systems	5
Heart alone and combined	10

* Of four patients who have died, three are known to have died of vascular disease and the fourth died suddenly at home.

satisfactory in an additional case and only the dye plasma volume was measured. Whenever the total body hematocrit was used in a calculation it was assumed to equal 0.92 venous hematocrit. Trapped plasma was ignored.

Results

The clinical and laboratory findings are given in Tables 1 and 2. The red-blood-cell volume was within two standard deviations of normal in 15 cases but in the upper range of normal in several of these. It was slightly elevated in three (cases 8, 10, and 14), and markedly elevated in the patient in case 20. The plasma volume was low by direct measurement in nine patients and normal in ten (by direct measurement in three of these). When normal, it was usually in the lower range of normal. The blood volumes were related to body weight. Some of the patients were obese. Keith et al [6] observed that obese people have relatively less blood per pound of body weight than normal subjects, and since then there has been controversy in relating blood volume to body size. Kaung and Peterson [7] found that some of their patients with relative polycythemia had a normal red-blood-cell volume when it was related to weight but slightly increased when it was related to surface area. A change in the method of expression of blood volume would probably move some cases of the present series out of the normal range. Our normal values were based on weight. The series of subjects used for the normal value for red-blood-cell volume included a large range of body sizes,[8] and a change in method of reporting data would not make a fundamental change in results. Therefore, blood volume was expressed on a weight basis only. Blood volume was only one factor in the exclusion of polycythemia vera in the present series; the absence of panmyelosis and the long-term clinical picture were considered equally important.

Twelve patients were followed from one to ten years (average, 4.8 years), and there was never any real change in their basic disorder or any persistent change in hematocrit value. Vascular disease in some cases became evident with time. Repeated blood volume measurements were made in the patients in cases 2, 9, 12, 14, and 15 over a period of two to five years, and no significant changes were observed. However, there were several instances of a lowering of hematocrit values during a particular hospitalization. One patient (case 17) showed a steady lowering in his hematocrit value from 60% to 46% and in his hemoglobin level from 21.6 to 15.4 gm/100 ml during a 30-day recovery from a myocardial infarction. The patient in case 10 (Fig 1) showed several similar periods of lowering of hematocrit values during a 10-year period. There was no consistent clinical change following a lowering of the hematocrit value. Phlebotomy was performed on the patients in cases 2, 8, 9, 10, 12, 15, 19, and 20. Blood was removed repeatedly from some patients. Good responses were few and minor. The patients in cases 9, 14, and 19 received radioactive phosphorus (^{32}P) at least twice each, but there was little effect on the blood count or on clinical manifestations.

Previously,[9] I demonstrated that the measurement of the disappearance of intravenous cyano-

TABLE 3.—*Family 1—Five Siblings* *

	Case 9	Case 10	Brother	Sister
Present age, years	46	51 ‡	56	50
Hematocrit value	57% †	61% †	44%	46%
Plasma volume, T-1824 method	—	34.6 ml/kg	—	—
Red-blood-cell volume, ^{51}Cr	28.3 ml/kg	39.2 ml/kg	—	—
Vascular disease	Present	Present	Absent	Absent
Hypertension	Present	Present	Absent	Absent
Nervous or tense	Present	Present	Absent	Present
Obesity	Mild	Absent	Mild	Absent

* One sister who was not examined was said to be well.
† Had been higher previously.
‡ Died.

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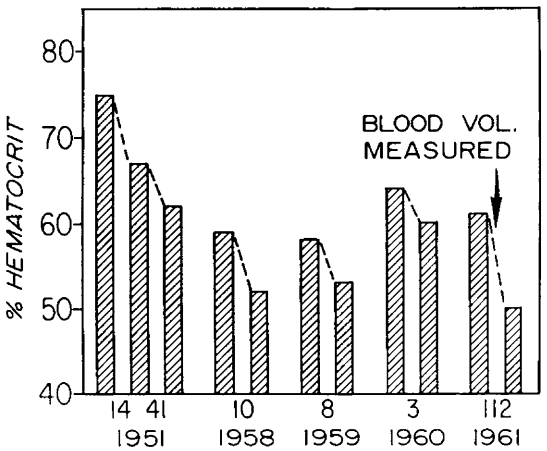

Fig 1.—Fall in hematocrit value during five hospitalizations of the patient in case 10 over a ten-year period. The numbers between the vertical bars refer to the days between measurements of hematocrit.

cobalamin (vitamin B_{12}) from the plasma was useful in separating polycythemia vera (where disappearance was delayed) from other types of polycythemia. The procedure was performed on the patients in cases 2, 9, 10, 12, and 15 and gave normal results.

The fraction of the injected ^{59}Fe removed per hour in the patient in case 20 was 0.26. The plasma iron turnover was 6.4 μg/kg/hr. Both were subnormal.[10] The incorporation of iron into the erythrocytes reached a normal figure of 81.5% on day 32 but the rate of incorporation was abnormally slow and irregular (Fig 2). According to the studies of iron dynamics, erythropoiesis was subnormal, in sharp contrast to the increased erythropoiesis of polycythemia vera.[10]

The disorder described here as Gaisböck's disease was found twice in more than one member of a family. The patients in cases 9 and 10 were brothers. A sister (Table 3) had none of their problems with the exception of nervousness, and a brother was found to be well. Two siblings were similarly affected in family 2 (Table 4). One had died before becoming known to us and was not studied in detail. There was a high incidence of myocardial infarction and hypertension in this family, which occurred in the absence of increased hematocrit values.

Comment

The most important aspect of the present study was the demonstration that a group of patients who were suspected of having polycythemia vera, sometimes to the point of treatment, in fact had something else. Many of these patients showed a normal total red-blood-cell volume coupled with chronically low or low-normal plasma volumes. This state could change toward normal over a period of days but eventually the original pathologic state would return. Lawrence and Berlin [3] termed this situation *relative polycythemia* and considered it to be a syndrome with certain specific manifestations, in addition to altered blood volumes. Their terminology failed to distinguish the chronic type from the acute relative polycythemia which is usually due to dehydration. The term *polycythemia* does not seem applicable to a situation in which there is too little blood. They also used the term *polycythemia of stress*. They,[11] like Harrop [12] previously, observed rapid hemoconcentration with a change from low to high altitudes. They likened this stress to that of the psychoneurosis of many of their patients with chronically lowered plasma volumes. Ultimately it may be proven that they were on sound physiologic grounds, but there is still too little knowledge about the subject to permit the use of the word *stress* in an etiologic sense. Kaung and Peterson [7] applied the term *pseudopolycythemia* to the syndrome described by Lawrence and Berlin. This is the best of the present terminologies but it should be applied only to the state of increased hematocrit due to a chronically low plasma volume.

Some of the patients in the present series present a syndrome which is referred to as

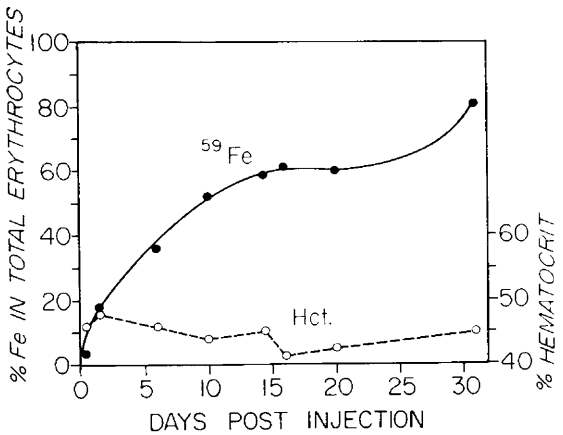

Fig 2.—Percent of tracer dose of radioactive iron incorporated into the total red-blood-cell mass. Study started two weeks postphlebotomy.

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TABLE 4.—*Family 2*

	Age, Yr	Hematocrit, %	Arteriosclerotic Heart Disease	Hypertension	Excessively Tense	Comment
Parents						
Father	—	—	—	—	—	Death due to cancer of the rectum
Mother	68 *	38	Present	—	Present	Death due to MI †
Siblings						
13 (case 13)	40	59	Present	Present	Present	MI
21	41 *	60	Present	—	Present	Death due to MI
22	44	50	Present	Present	Absent	MI
23	31 *					Death due to cancer of the cervix
24	50	Hemoglobin, 11.5 gm/100 cc	Absent	Present	Present	
25	59 *	—	Probable	—	Absent	Death due to heart disease
26	39	42	Absent	Absent	Present	
27	40	—	—	—	—	Not examined

* Died.
† Myocardial infarction.

Gaisböck's syndrome. Common manifestations were plethora, vascular disease (most commonly of the coronary arteries), labile hypertension, headaches, excessive nervousness or tension, and obesity. The hematrocrit levels, hemoglobin values, and erythrocyte counts were elevated. Splenomegaly and panmyelosis were absent. There was usually pseudopolycythemia, a slight increase in total red-blood-cell volume or, in one case, a marked increase. There were two families each with two cases in siblings. This group of patients is similar to that described by Lawrence and Berlin,[3] with the probability that the present series represents cases of longer duration and with more advanced vascular disease. The present cases are also much like those of the original series of Gaisböck who described polycythemia, hypertension, arteriosclerosis, psychoneurosis, and stress in his group. He did not measure blood volume.

Case 20 is presented in detail because the patient had an extreme form of Gaisböck's disease, clearly defining the manifestation while sharply separating it from other types of polycythemia. The patient's appearance was that seen in severe polycythemia vera. The salient manifestations were severe arteriosclerosis and recurrent phlebitis, excessive nervousness, and hypertension. There was no relative polycythemia since the red-blood-cell volume was almost twice normal. It was not polycythemia vera because panmyelosis and splenomegaly were absent, and radioactive iron studies did not show increased erythropoiesis.

There is still another syndrome which may be closely related to that of the present series. This is the syndrome of primary erythrocytosis of childhood, which has been known for 25 years, and was recently discussed by Abildgaard et al.[13] The disorder is familial and has been demonstrated in children as young as 6 years of age with the probability that it is present even earlier in life. There is an increase in total red-blood-cell mass. Headaches, lethargy, and dizziness are common. Parents of some of these children have been shown to have the disorder; hence it is known to persist into adult life.

A great deal of study is necessary before the syndrome commented on here can be accurately identified and understood. Cases of childhood primary erythrocytosis should be followed throughout life to learn the natural history of this disease. Family studies and long-term follow-up studies should be made in cases both of pseudopolycythemia and of Gaisböck's syndrome. The use of such fundamental studies as those of iron metabolism may be helpful in separating the several syndromes. There is much to be learned regarding the effect of increased concentration of erythrocytes on tissues, and on vascular occlusion. The cause of the symptoms is not well understood. Most important of all would be an understanding of the mechanism by which the patients develop and maintain this peculiar pattern of blood volumes. Conley et al [14] believed that the multiple abnormalities in Gaisböck's syndrome were a consequence of a genetically determined constitution and that there was no cause-and-effect relationship between the increased hematocrit level and the vascular disease. Probably they are correct, but more concrete evidence is needed. The syndrome

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commented on here should not continue to be overlooked because, in agreement with the cited authors, we have found it to be more common than polycythemia vera.

Summary

The present study was concerned with a group of 20 patients who were thought to have polycythemia vera or secondary polycythemia but actually had something clearly different. Some patients had an elevated hematocrit value due solely to the combination of a normal total red-blood-cell volume with a low total plasma volume. This state was referred to as pseudopolycythemia. Many had a syndrome referred to as Gaisböck's syndrome. There was either a pseudopolycythemia or increased red-blood-cell volume. Vascular disease and hypertension were common. Splenomegaly and panmyelosis were absent. The syndrome was familial in two cases.

The data and conclusions of Russell and Conley (in addition to their other data [14]) are presented in a more detailed form in an article which was published after the submission of this manuscript for publication.[15] The cases presented by Russell and Conley and those presented here are so similar that it is obvious that we are both describing the same syndrome.

Generic and Trade Names of Drugs

Cyanocobalamin—Berubigen, Bevatine, Bexii, Crystwel, Dodecabee, Dodex, Hemomin, Rametin, Redisol, Rubramin, Sytobex.

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