Staff Meeting Bulletin
Hospitals of the » » »
University of Minnesota

Polycythemia

Volume X | Friday, December 2, 1938 | Number 8

STAFF MEETING BULLETIN
HOSPITALS OF THE . . . .
UNIVERSITY OF MINNESOTA

Volume X | Friday, December 2, 1938 | Number 8

INDEX

Published for the General Staff Meeting each week during the school year, October to May, inclusive.

Financed by the Citizens Aid Society.

William A. O'Brien, M.D.

I. LAST WEEK

Date: November 18, 1938

Place: Recreation Room
Powell Hall

Time: 12:15 - 1:30 p.m.

Program: Movie: "Let My People Live"

Announcements

Student Tuberculosis
J. A. Myers

Hospital Report of Tuberculosis Case Finding
Phil D. Kernan

Discussion:
Leo G. Rigler
Ruth E. Boynton
Reuben Stiehm
Horton C. Hinshaw
Harold S. Diehl

Present: 139

Date: November 25, 1938

Place: Recreation Room
Powell Hall

Time: 12:15 - 1:00 p.m.

Program: Movie of 1938 Football Season
Phil Brain, Jr.

Present: 127

Gertrude Gunn
Record Librarian

II. MOVIE

Title: "Courtship of the Newt"

By Robert Benchley

Released by: M-G-M

III. ANNOUNCEMENTS

CENTER FOR CONTINUATION STUDY

No programs during December. After January 1 the following subjects in Medicine and Hospital Administration will be offered during Winter Quarter.

1. Ophthalmology for Ophthalmologists
   Jan. 16-21, 1939
   Frank E. Burch, Chairman

2. Hospital Administration for hospital administrators and allied groups.
   Jan. 23-28, 1939
   Raymond M. Amberg, Chairman

3. Record Library Methods for hospital record librarians
   Jan. 30, 31 and Feb. 1, 1939
   Sister M. Patricia, Chairman

4. Dietetics for accredited dietitians
   Feb. 13-15, 1939
   Gertrude I. Thomas, Chairman

5. Medical Social Work for medical social workers
   Feb. 22-24, 1939
   Frances Money, Chairman

6. Neuropsychiatry for neuropsychiatrists and others
   March 13-18, 1939
   J. Charnley McKinley, Chairman

7. Diseases of the Bones and Joints for orthopedists, surgeons, and others
   March 13-18, 1939
   Wallace Cole, Chairman

8. Diagnostic Roentgenology for roentgenologists and others
   March 27-Apr. 1, 1939
   Geo G. Rigler, Chairman

Spring Program will include:

General Surgery
Obstetrics
Hematology
Gastroenterology

IV. POLYCYTHEMIA

Phillip Hallock
Wm. O. Clarke

Polycythemia exists when there is an increase in the number of red blood corpuscles per unit volume of the circulating blood. From a functional viewpoint Harrop and Wintrobe state it is more precise to apply this term to an increase in the concentration of oxygen carrying material or the red blood cell mass. Polycythemia may be broadly divided into a primary type (of unknown etiology) and secondary types resulting from known causes.

Relative polycythemia signifies that the concentration of the red blood cells are increased through a loss of blood plasma.

Transient polycythemia signifies that in response to some stimulus the red blood cells are shunted into the circulation from the spleen.

Absolute polycythemia signifies an increase which is associated with an increase in the total red mass in the circulating blood. It is divided into erythrocytosis and erythremia which is comparative in terminology to leukocytosis and leukemia.

Erythrocytosis is an absolute polycythemia which occurs in response to some known etiology.

Erythremia (Polycythemia rubra vera) is an absolute polycythemia of unknown etiology.

Polycythemia hypertonica or Gaisböck's syndrome is an erythrocytosis due to cardiovascular or renal disease. Gaisböck's description consisted of polycythemia with hypertension but no splenomegaly.

Ayerza's syndrome is an erythrocytosis of pulmonary origin with secondary cardiac involvement.

Mossa's syndrome is erythremia in which there is icterus with liver cirrhosis. Zadek proposes that the cirrhosis of the liver is a complication of erythremia.

History

In 1851, Vierordt made the first erythrocyte count and shortly after Vogel (1854) recognized a relative increase of erythrocytes during rapid dehydration. Malassez and Naunya (1872) demonstrated that relative polycythemia occurred in chronic heart disease with cyanosis. In 1890, Viault studied increased erythrocyte counts of normal people living at high altitudes.

Erythremia was first noticed by Vaquez (1892) who described a case of peculiar cyanosis, persistent increase in erythrocyte count and splenomegaly which on autopsy several years later revealed no heart lesion as he previously suspected. Other case reports followed, most important are those of Türk (1902-04), who reported 7 cases and noted the frequency of an absolute leukocytosis due to an absolute granulocytosis and a relative lymphocytosis. The accurate description by Osler, in 1903, attracted general attention to this disease as a new clinical entity.

Our knowledge today of the polycythemias is best summed up by the excellent reviews of Parkes Weber (1921, 29) Gaisböck (1922), Zadek (1927), Harrop (1928), and Harrop and Wintrobe (1938).

Classification*

I. Relative and Transient Polycythemia (Physiological)

A. Relative Polycythemia (dehydration)
1. Lowered fluid intake
2. Marked loss of body fluid
a. Persistent vomiting
b. Severe diarrhea - examples - summer diarrhea of infants, cholera, promaine poisoning,

*Modified from Harrop and Wintrobe.

arsenic, etc.
c. Copius sweating
d. Loss through insensible perspiration
(Increased metabolism) as:
(1) Hyperthyroidism
(2) Fever
(3) Acidosis

3. Shock (loss of plasma including protein through endothelial membrane of the vascular system).

B. Transient Polycythemia (Temporary release of cells from the contraction of the spleen).

1. Exercise
2. Anoxemia
a. Low oxygen tension
b. Hemorrhage
c. Suffocation
d. Carbon monoxide poisoning.
3. Drugs as adrenalin
4. Emotional disturbances as fright.

II. Absolute Polycythemia

A. Erythrocytosis (secondary polycythemia; compensatory; anoxic)

1. In new born (polycythemia neonatorum)
2. Heart disease and renal disease
a. Congenital heart disease
b. Acquired heart disease
c. Gaisböck's polycythemia
d. Renal disease associated with dyspnea
3. Pulmonary disease
a. Emphysema
b. Fibroid lung with or without bronchiectasis
c. Chronic bronchitis
d. Spasmodic asthma
4. High altitudes
5. Chemical and physical agents as cobalt, arsenic, phosphorous, exposure to x-ray and radium salts, etc.

B. Erythremia (polycythemia rubra vera; primary polycythemia).

Physiological polycythemia due to dehydration or loss of fluid can be readily recognized and treated by correcting the underlying cause. Erythrocytosis is a secondary or compensatory polycythemia resulting from a definite cause of anoxemia. The prognosis and treatment is entirely dependent upon the etiology.

The remaining discussion will deal with erythremia or polycythemia rubra vera including the etiological and experimental aspects of this disease.

ERYTHREMIA
(Polycythemia rubra vera)

Introduction

Polycythemia rubra vera appropriately termed erythremia by Osler and others is best defined by Harrop and Wintrobe (1938). "Erythremia is a slowly and intermittently progressive disease of unknown etiology characterized by a striking absolute increase in the number of red blood cells and in the total blood volume, and frequently by signs of generally increased bone marrow activity. Clinically these changes are indicated particularly by a peculiar reddish purple color of the skin, various vasomotor and neurologic manifestations and usually splenic enlargement."

Synonyms

Polycythemia rubra vera, splenomegalic polycythemia, Vacquez's disease, Osler's disease, cryptogenic polycythemia, myelopathic polycythemia, erythrocytosis megalosplenica, polycythemia hypervolemia, hyperglobulia.

Incidence

Occurrence. Secondary polycythemia is quite common but erythremia is a rare disease.

Races. This disease is more common in the Jewish race. Only one case has been reported in the negro race.

Sex. Males predominate in a ratio of almost 2-1 over females.

Age. It occurs chiefly in middle life and late life usually around fifty years of age. Chase and Sandesky reported a case occurring as early as seventeen years of age.

Familial Tendency. Most patients are usually isolated cases with no history of family occurrence. The first case of erythremia occurring as a hereditary anomaly was reported in 1907 by Nichmanin. The most remarkable of the families reported (Engolberg, 1920), was a grandmother who died of polycythemia and both of her daughters had it. One daughter had a child with erythremia. The other had thirteen children, seven died without knowledge of the familial tendency, and the other six children had definite erythremia.

In the familial form infantilism has been observed to be very common and in some menses has occurred very late. Familial cases occur at an earlier age.

Constitutional predisposition.

Some authors suggest there is a constitutional makeup which is stimulated by some external factor. Stout or overweight people are rarely affected and many having the disease have very narrow faces. Some say blondes are affected more than brunettes.

Pathology

At postmortem the unusual color of the skin may be observed. The capillaries are visible; they are markedly dilated. The blood grossly is characteristically dark in color, spreads slowly over glass and may be thick so it is difficult to draw up in pipette. The factor of blood viscosity is important in this condition and accounts in a great measure for slowing of the blood stream.

Due to the extreme state of plethora, the organs are engorged and hemorrhages and thrombosis occur.

The spleen is enlarged, moderately hard and dark bluish in color. On section, the follicles are not readily seen. Thrombosis, infarcts and cysts produced by hemorrhages may be found. Microscopically, there is atrophy of the follicles with both hyperplasia and hyperemia of the pulp. Occasionally myeloid metaplasia may be seen. Very rarely no splenomegaly may be encountered at autopsy.

The liver is engorged with blood and often enlarged. Cirrhosis of the liver and myeloid metaplasia may be occasionally seen. Cardiac enlargement has a slightly higher incidence in this disease.

The bone marrow is dark red in color and crowded with enormous numbers of erythrocytes as well as normoblasts. Megaloblasts are absent or very rare. All the nucleated red corpuscles are small and contain round, ripe and often pyknotic nuclei. The myelocytes, metamyelocytes and even occasionally the promyelocytes may predominate. Mature neutrophiles are reduced in number. Megakaryocytes may or may not be increased. Massive hemorrhages in the serous cavities may be found occasionally.

Diagnosis

History. In erythremia there is an insidious onset and the patient may be wholly unconscious of its presence until the attention is attracted to the unnatural redness of the face. The symptoms which are largely referable to polycythemia are usually due to the state of plethora and they may not appear until there is an engorgement of even the smallest vessels. The symptoms the physician may be consulted for are principally headache, vertigo, weakness, and erythrosis.

The nervous and psychic symptoms of the disease, together with the disturbances of the special senses are often the most striking. Of these the most prominent are headache, often resembling typical migraine, giddiness and

vertigo, lassitude and weakness, sensation of fullness in the head, numbness and tingling in the fingers, less often in the feet, burning sensations and extreme sensitiveness to cold.

Tinnitus and visual disturbances are common and transitory or even temporary, as blindness, specks and bright points in front of the field of vision. Occasionally there is diplopia, hemianopsea, and temporary paralysis of one of the extrinsic eye muscles.

Various types of paralysis, pruritis, and neuritic pains of the extremities, myoclonia, chorea and epileptiform seizures have been described.

Psychic disturbances as mental depression, hallucination, deteriorations, and emotional outbreaks may be encountered.

The symptoms referable to the gastrointestinal tract are very prominent in a certain group of cases. Feelings of fullness in the stomach, thirst, dyspepsia, gas pains and belching, and especially constipation are exceedingly common. Some patients have anorexia, nausea, vomiting, hematemesis, melana, pain or mass in left hypochondrium (spleen).

Cardiovascular symptoms are not the general rule or particularly prominent, but there may be dyspnea, tachycardia, palpitation, edema of lower extremities, intermittent claudication, Raynaudlike symptoms and erythromelalgia.

Sometimes respiratory symptoms of hoarseness, hemoptysis, epistaxis and bleeding from pharynx are found.

Hematuria and priapism may occur.

Physical

General Appearance

There is a characteristic brick red to dusky facies commonly called "rubor" or erythrosis rather than cyanosis. This coloration is more common on the exposed surfaces and is a mixture of red and blue depending on the state of dilatation of the peripheral vessels and the speed of circulation through these areas which is altered by the temperature and dependent position. In summer the color is red like a rose and in winter it becomes bluish. 10-15% of the patients may have a normal complexion. Lundsgaard and Van Slyke have shown that the erythrosis is due to the color the blood assumes when an abnormally large proportion of reduced hemoglobin is present in the minute skin vessels. Dryness, hemorrhages, pigmentation, acne rosacea of the skin may be present.

Eyes

The conjunctiva may be suffused and appear even bloodshot due to small superficial hemorrhage. On ophthalmoscopic examination the characteristic change in the fundus is distention and engorgement of the retinal veins which appear somewhat purplish due to the increase in blood volume and the thinness of the venous walls. Individual patients show venous engorgement, edema of discs, retinal hemorrhages, postneuritic atrophy of the optic nerve and perivascular transudation of plasma.

Ears, Nose and Throat

The ears, cheeks, and nose have a pinkish tint. The color of the mucous membranes are almost as deep as a raspberry red. Epistaxis and bleeding from the gums are common.

Lungs and Heart

Cardiac enlargement is more frequently absent than present and usually occurs only in the severe cases. Cardiac hypertrophy can not be produced experimentally by plethora. Dyspnea and tachycardia is present sometimes. Final death by cardiac failure may occur in patients who escape the fatal effects of massive hemorrhage and other vascular accidents. Vascular disease and accident are extremely common. The blood pressure is frequently normal or slightly elevated.

Abdomen

Some have described firm and tender nodules in the thoracic and abdominal skin. The liver is just palpable or larger in at least 40% of the cases. Tenderness on palpation may be present in the upper left quadrant due to splenic infarcts and a friction rub is sometimes present. Splenomegaly occurs in 75% of the cases. The edge of the spleen feels smooth and the size varies, occasionally increased to the level of the umbilicus.

Extremities

The nailbeds are usually pink. Rarely there is a club-like thickening of the terminal phalanges. The lower extremities may feel cold and clammy. Erythromelalgia and thrombo-angiitis obliterans are sometimes present. Arteriosclerosis occurs in the same proportion as in the normal for that age group. The reflexes, both superficial and deep, may vary on the two sides of the body and localized areas of anesthesia or paresthesias are found.

Laboratory Findings

Albuminuria, hyaline, and granular casts are often found in the urine while hematuria is a rare finding.

The range of hemoglobin is most commonly between 18 to 24 grams per 100 cc. or higher which is usually not as proportionally high as the erythrocyte count. The red cell count in the majority of cases is increased from 6 to 9 million per cu. mm. but may reach 16 millions. One must remember that the normal range for males is 4.6 to 6.2 millions per cu.mm. and 4.2 to 5.4 millions per cu.mm. for females (Wintrobe). On the basis of a mean corpuscular volume of 87 cubic microns, it would take about 11.5 million red cells to pack completely a volume of one cu. mm. The lowest mean corpuscular volume known in this disease is 61 cu. microns, resulting in the highest count obtained of 16 million erythrocytes per cu. mm. of blood. Both the red cell count and the hemoglobin may vary from time to time.

The hematocrit ranges from 55 to 75%. (Normally 40-46%). In the majority of cases the color index is low but may be normal. The average size of the erythrocyte and the mean corpuscular volume may be normal or somewhat smaller. The mean corpuscular hemoglobin and mean corpuscular hemoglobin concentration are normal or decreased. Reticulocytes are normal or slightly increased. Frequently, there is an increased range of resistance of the erythrocytes to hypotonic solutions.

Leukocytosis is quite common, occurring over 10,000 in more than 2/3 of the cases usually ranging from 15 to 30,000 per cu. mm. Platelets are commonly increased, ranging from 500,000 to over one million, an increase which is probably at times a factor in the increased tendency to thrombosis. The sedimentation rate is very slow. The Duke bleeding time is usually normal and the coagulation time may be slightly accelerated. The Ivy Bleeding Time is frequently increased due to the marked distention of the capillaries. The total blood volume is greatly increased and may be more than two times the normal. However, the plasma volume is only slightly increased.

Dry smear morphology may show hypochromasia, anitocytosis, poikilocytosis, polythromatophilia and nucleated red cells. There is an absolute granulocytosis with myelocytes occurring quite commonly in the older cases. The red bone marrow has previously been described.

There are no definite characteristic findings in the blood chemistry. The gastric acidity is usually normal or increased although achlorhydria has been reported. The basal metabolic rate is frequently increased to +10% and has been found as high as 52%.

Some investigators have found an increased cerebrospinal fluid in some cases showing neurological symptoms.

A diminished circulatory minute volume and an increased respiratory minute volume have been reported by a number of

investigators.

The oxygen saturation value of arterial blood is in the upper limits of normal in erythremia. The venous blood is almost as rich in oxygen as is the arterial blood and the "coefficient of utilization of oxygen" is decreased. (In erythrocytosis, it is the opposite.) Lactic acid values of the blood are decreased in this disease and in erythrocytosis are increased following exercise (Hallock).

The rate of hemoglobin metabolism and wastage is essentially normal (Watson). If anything, the rate of blood destruction is somewhat reduced.

Differential Diagnosis

A great number of diseases, especially those of the cardiovascular and nervous systems may be simulated in symptomatology. By means of physical examination and laboratory findings they may be readily excluded.

Erythremia must not be confused with erythrocytosis. A complete and thorough search should be made for a cause to establish a relative polycythemia. Splenomegaly is rarely associated with erythrocytosis.

Diagnosis can be clinched by blood studies. In erythrocytosis the hemoglobin and red cell count usually do not reach such a high value as is encountered in erythremia. Polychromatophilia, normoblasts, leukocytosis with shift to the left, and thrombocytosis are rarely, if ever, found in erythrocytosis. Sternal bone marrow examination may be of value in doubtful cases. The red cell mass per kilogram is the most sensitive indicator of changes in the red cells. The red cell mass is constantly high in erythremia and not significantly changed in erythrocytosis.

The finding of increased lactic acid in erythrocytosis and decreased in erythremia following exercise offers an important means of differentiation (Hallock).

Splenomegaly and polycythemia, the two cardinal symptoms of erythremia, may be caused by syphilis, tuberculosis, hydatid disease of the spleen and obliterative thrombophlebitis of the splenic and portal veins.

Hemorrhage may be the first complaint and if massive will cause an anemia thus reducing the hemoglobin and red count but not the leukocyte count.

Myeloid leukemias must be differentiated because of the splenomegaly, leukocytosis and the presence of young forms of granulocytes in early cases. In erythremia and myeloid leukemia pathological activity of all marrow elements may occur so that rarely it may be difficult to determine which of these two conditions was primarily present. Some investigators are of the opinion that if people with erythremia do not die with any complication, they will eventually develop myeloid leukemia.

Prognosis

The clinical course of this disease is slowly progressive but may be manifested by spontaneous remissions and relapses. Patients suffering with this disease usually live eight to ten years, but seldom less than four years and quite a number of patients have lived longer than twenty years.

Death may result from:

Vascular complications
- a. Thrombosis (cerebral, portal, mesenteric)
- b. Hemorrhage (cerebral, rarely gastric varices, etc.)
- c. Cardiac failure

Intercurrent infection
Myeloid leukemia and anemia
Chronic nephritis with anemia, and also cirrhosis of the liver have been fatal sequelae.

Adequate treatment by modern methods permits a more favorable prognosis in the future.

Treatment of Erythremia

1. Prophylactic treatment

The patient must lead a life that does not cause intensification of symptoms. One should avoid the following:

a. Any mental or physical strain.
b. Alcoholic stimulants as well as tea and coffee,
c. Constipation and straining at stool.
d. Strenuous exercise. (However, it is unwise to lead a too sedentary life favoring further lagging of circulation and perhaps thrombosis formation.)
e. Overeating.

2. Venesection

About 500 cc. of blood is preferable and this follows with immediate subjective relief. In some cases remissions may occur for a considerable duration; in some, lasting for three months. At times it may be necessary to remove greater amounts of blood, up to 1500 cc. to relieve the symptoms. Spontaneous hemorrhages produce the same effect.

Systematic removal of blood over long period causes a depletion of material needed for blood formation and eventually a torpid state somewhat resembling that of a chronic post hemorrhagic anemia. Therefore, venesection should be used for immediate treatment followed by roentgen ray therapy or the more preferable one of phenylhydrazine.

3. Treatment by drugs

Benzol

This has been tried in the past but is contraindicated because of the striking effect of the drug on the leukocytes, the difficulties in regulating its dosage, and the extremely serious and distressing symptoms of benzol poisoning.

Potassium Arsenite

Forkner, Scott and Wu, in 1933 obtained distinct improvement with Fowler's solution. This drug is not advised because benefit is only temporary and symptoms of toxicity such as anorexia, nausea, slight burning sensation of toes and fingers, and even vomiting, diarrhea and slight thickening and drying of skin may occur as well as leukopenia.

N-propyl disulphide

Sharp could induce anemia by feeding of onions so N-propyl disulphide, a compound closely related to the main constituent of onion oil, was used and reduction of symptoms and improvement followed. Whether this drug possesses any value over phenylhydrazine cannot be stated as yet. The disadvantage is the disagreeable odor of onions.

Phenylhydrazine

Phenylhydrazine (C_6H_4 $HN\text{-}NH_2$) is the most effective remedy employed in the treatment of erythremia.

Phenylhydrazine is a base related to antipyrine. Liquid phenylhydrazine is itself unstable so that the crystalline hydrochloride which is less easily decomposed is used. The mode of action is not clear. Too much is dangerous and too little is ineffective. It has a cumulative action so great care should be used. In some, a tolerance to the drug has been noted. It is slowly eliminated partly in the urine which may appear dark brown.

Most workers believe that in spite of jaundice appearing under treatment no permanent liver damage occurs. Bodansky found that the liver may be damaged by this drug but it has been pointed out by others that enormous doses were used. Some investigators gave dogs the total dosage in 8 months compared to a 4-6 year therapeutic dosage and found no toxic effect. Itoh observed no demonstrable liver damage except when phenylhydrazine was given in large doses. Watson found no increase in the amount of urobilinogen in the urine following phenylhydrazine in treating cases of erythremia.

Dosage and Administration

Capsules of phenylhydrazine hydrochloride usually containing .1 gm. are given orally. It is best not to give more than 1.0 gm. divided in equal portions for 5 to 10 days. This should be followed by a period of observation (without the medicine for about a week) to see whether or not there is any cumulative action. Subsequent dosage may be resumed as required by the patient which is guided

by frequent blood examination, .1 to .2 gm., two or three times per week may be satisfactory, but in many cases .1 gm. daily may be necessary until the hemoglobin falls to the proper level (below 100% Hemoglobin). The interval between doses becomes gradually longer with hope of finally maintaining the blood count within normal limits on .1 gm. once a week. After two to four years it should be discontinued temporarily for months to years. In some cases a tolerance develops, which is usually temporary, so larger doses should be used very cautiously by checking frequently with blood studies. Treatment should be discontinued when there is jaundice, marked leukocytosis, or persistent elevation in the percentage of reticulocytes.

In administration of this drug:

1. The patient should be kept ambulatory.
2. Advanced cases confined to bed should not receive phenylhydrazine.
3. It should not be given to patients with marked arteriosclerosis and to those who manifest evidence of thrombosis or advanced visceral injury.
4. Those that show rapid hemolysis should discontinue treatment.

The earliest effect is on the leukocytes which decrease when the drug is stopped. Leukocytosis cannot always be used as a reliable index since the increase may be due to the breaking down of the red cells and at other times to stimulation of the hemopoietic system. Evidence of blood destruction appears early, an increase in the serum bilirubin often being noted after the second dose. Methemaglobin may appear. A drop of erythrocyte count follows shortly after the appearance of leukocytosis and the magnitude of decrease is related to the amount given. Effects continue 7 to 10 days after the drug has been stopped.

Erythrocyte size continues to be normal unless the anemia is severe. Increase in recitulocyte counts may appear and rarely does the response exceed 6%. The blood volume characteristic of erythremia diminishes coincidentally with the erythrocytic destruction.

With moderate doses slight jaundice, anorexia, pruritis, vertigo, and lumbar pain are noticed occasionally. Weakness may be noticeable during blood destruction. The urine may be dark brown and from larger doses it may be almost black. Reducing substances may appear in the urine giving a false assumption of glycosuria. Many other findings have been reported but most have been coincidental.

The symptoms of erythremia are reduced and disappear in most patients. Reduction of blood volume is not always followed by pre-existent hypertension or cardiac hypertrophy. In resistant cases it will be necessary to use both phenylhydrazine and irradiation.

Acetyl phenylhydrazine

Stone, et al, 1933, claim that this drug is less toxic and easier to regulate than phenylhydrazine. Since its action is quite similar to that of phenylhydrazine it is given the same way, and it also has a cumulative action. He advocates dosages of .1 gm. daily by mouth in gelatin capsules. The consensus of opinion is that phenylhydrazine is preferable.

Irradiation

Both Vaques and Osler noticed improvement of erythremia from irradiation but Stengel, in 1907, was the first to advocate its use. Next to phenylhydrazine, radiation therapy is recommended as the method of choice in erythremia. Methods vary from roentgen ray treatment of the long bones, the spleen, stomach, and radiation of the entire body.

Radiation of Spleen

The early radiations were first directed to the spleen; however, today the opinion is that it does more harm than good.

Radiation of Stomach

Some workers have used x-ray therapy to the stomach in hope that the intrinsic

factor is decreased but this method is of no proved value.

Radiation of Long Bones

The hyperplastic marrow of long bones is particularly sensitive to these rays. Radiation of long bones follows with considerable improvement if done correctly. Some therapeutists systematically map out and treat the entire skeleton with the exception of the head, and in young males the pelvic bones. Little effect if any is derived from treatment of the flat bones.

Irradiation of whole body

A few recommend irradiation of the whole body protecting the eyes and genitalia in daily doses for six days. Courses of treatment are repeated as necessary.

In summing up radiation therapy, the method of choice is the systematic radiation of the long bones. All forms of x-ray therapy should always be regulated and controlled by frequent blood examinations and the indices should be the leukocyte and erythrocyte counts. In cases that do not respond to phenylhydrazine, roentgen therapy may be tried alone or in conjunction with the drug.

The danger is that once the damage is done it is irreparable. If too extensive the possibility of aplastic anemia, acute leukemia, and grave hemorrhages may occur.

The beneficial effects are the production of long remissions lasting as long as a year. It is less likely to be followed by thrombosis so it is the best method of therapy to use for bedridden patients.

Miscellaneous Methods of Therapy

Gastric lavage

Many attempts have been made to treat erythremia by attempting to wash out the intrinsic factor and a few reports of beneficial results have appeared. On the whole the results with this method have not been encouraging.

Ascorbic acid

Barron had success in treating animals with ascorbic acid who were made polycythemic with cobolt. Therapeutically this has been of no value.

Spleen therapy

There is no convincing clinical evidence whatever that the feeding of spleen or splenic extracts are beneficial

Splenectomy

This is theoretically contraindicated and has been shown to be valueless and even harmful. The spleen is a storehouse or reservoir for excessive amounts of blood and the enlargement is simply due to engorgement. In addition, there is a high incidence of fatalities after splenectomy in this disease.

Diets

Iron free, high fat or low purine diets are of no value and have only made patients unhappy with ill considered dieting restrictions. Since constipation is so frequent, anticonstipation diets are advisable.

In treating erythremia, especially by venesection, an iron deficiency often develops which may be corrected by the administration of iron salts.

Gastrectomy

Singer reported a case of a male with erythremia who underwent a gastric resection for a peptic ulcer. This resulted in a permanent return of the red cell count to normal.

THE NATURE OF POLYCYTHEMIA

Considering the numerous etiological factors held responsible for the cause of erythremia one can only conclude after a critical examination of the literature that the true nature of the disease still remains unsolved. However, in the consideration of the etiologic factors certain features of the disease should be mentioned. As a general rule polycythemia vera appears in the middle decades of life. (In our series 75% of the cases fell in the middle decade of life). These patients are usually isolated ones with negative family history. In addition to these cases a smaller number (about 25% in our series) are reported of the occurrence of the disease in more than one member of the family (heredofamilial type). The striking feature of this latter group is the fact that the age incidence is much lower than in the isolated group. Yet the clinical picture is almost indistinguishable except that leucocytosis and immature cells are not found in the circulating blood in the type that occurs in young adults. The question arises whether erythremia represents a constitutional defect brought on by some unknown external factor and which may at times be transmitted so that the descendents manifest the disease when younger or whether the isolated and familial cases are entirely different conditions. Our studies strongly suggest that both types have a common etiological background inasmuch as they both give a characteristic lactic acid response.

Three possible factors may operate singly or in combination to produce the pathologic physiology of erythremia. These are as follows:

1. Increased activity of blood forming apparatus.
2. Increased length of life of red corpuscles.
3. Diminished destruction of erythrocytes.

The last hypothesis may be readily rejected. Repeated investigations concerning this point by Minot and Buckman, Zadek and Watson have demonstrated that there is no decrease in blood destruction in this disease. As a matter of fact the opposite condition is more often encountered.

Regarding the second hypothesis satisfactory evidence is lacking. In regard to the first hypothesis supporting evidence is available. Vaquez, Türk and others have shown that there is a functional hyperactivity of the blood producing organs. Blood marrow studies carried out by Zadek further substantiate the idea. Thus the increased activity is manifest not only in the erythroblastic elements, but also in the leucocyte and platelet forming tissues. The general tendency is to produce adult forms of red blood cells although not infrequently immature red cells such as normoblasts, polychromatophilic cells, and some premature leucocytes (myelocytes) are found. These facts strongly suggest that erythremia is analogous to leucemia. Minot and Buckman have reported cases of erythremia which had eventually changed over to myeloid leucemia. Two cases in our series eventually developed the picture of myeloid leucemia. Weber, Minot and Buckman are of the belief that erythremia is much similar to leucemia, a form of malignant hyperplasia. The principal objection to this belief as pointed out by Weber is that in erythremia the tissues are not invaded, unlike what is characteristic of neoplastic growths.

Many investigations have advanced the theory that erythremia is a consequence of an oxygen deficit (anoxemia) and have sought to disclose possible etiological factors. Thus Bence was of the opinion that the disease resulted in a diminished power of the red cells to absorb oxygen. On the other hand Rover and Koranyi showed there was no decreased combining power of hemoglobin in erythremia. Recently attempts have been made (Reznikoff, Fant and Bethea) to relate erythremia to recognized physiological processes. They concluded that anoxemia of the bone marrow produced not by a general arterial oxygen unsaturation but by a local stasis as result of vascular changes was the fundamental cause of erythremia. These conclusions were based on study of the blood vessels of the bone marrow. They

observed distinct capillary thickening in seven bone marrow specimens for polycythemia vera patients and in six of these marked subintimal and adventitial fibrosis of subarteriolar capillaries, arterioles, and arteries. These changes were not found in control specimens.

Freifeld suggested as an etiological factor an increased number of megacarocytes stuffing the capillaries of the lung. According to her theory some unknown agent causes stimulation of myeloid tissue in the bone marrow with formation of large number of megacarocytes. These cells plug the lung capillaries, interfere with oxygen exchange and give rise to polycythemia.

Naegili's conception is that there is a disturbance in the physiological regulation of erythropoiesis. This view is accepted by Zadek. Some writers implicate the negative nervous system. Hattinger believes that polycythemia vera is related to disorders of the endocrine gland.

Several writers, Hitzenberger, Tuchfeld and Morris, have suggested that erythremia is the antithesis of pernicious anemia. They believe that polycythemia vera may be referable to excessive and continuous activity of the anti-pernicious anemia principles in erythropoiesis. In support of this hypothesis of gastrogenic polycythemia may be mentioned the case reported by Karl Singer of Vienna in which a man who had polycythemia vera associated with a duodenal ulcer underwent gastric resection with a resultant return of cell count to normal. Morris, Oerting and Briggs and Hitzenberger all of whom observed marked decrease in the erythrocyte count of erythremic patients treated by gastric lavage. Baroth and Fülop made similar observations. The benefit following gastric lavage was only temporary, lasting only during period of treatment. Hitzenberger radiated the stomach of one of his patients with the intent of decreasing gastric secretion. In this case only temporary relief was reported. Unfavorable reports following gastric lavage were made by other investigators.

However, too serious consideration need not be given to the possibility that excessive and continuous activity of Castle's intrinsic factor can lead to the reverse of anemia, namely polycythemia. If this were true, polycythemia could be induced in any normal individual by a continual administration of liver preparations. On the contrary it has been shown time and time again that liver preparations are not effective in the normal person nor do they produce polycythemia in patients with pernicious anemia. Furthermore, one does not find in the blood of cases of pernicious anemia when the erythrocyte count is normal, nucleated red cells, polychromaphilia, and other evidences of bone marrow hyperactivity that characterize erythremia.

In summing up the data concerning the etiology of erythremia, one is confronted with many different and divergent opinions, none of which seem to be in substantial agreement and furthermore none of which appear after critical inspection to provide a satisfactory basis upon which the nature of the disease can be clearly and rationally elucidated.

Bibliography

Gaisböck, F.
Diagnosis and Treatment of Primary Polycythemia.
Klin. Webnsch 2:699, 1923.

Hallock, Phillip.
Blood Lactic Acid after Exercise with Particular Reference to Polycythemia Rubra Vera.
Proc. Soc. for Exp. Biol. and Med. 38: 587, 1938.

Harrop, G. A., Jr.
Polycythemia Med. 7:291, 1928.

Harrop, G. A., Jr. and Wintrobe, M. M.
Polycythemia, Handbook of Hematology (First Edition)
Downey, Hal. Vol. 4: 2365, 1938

Hayden, R. L.
The Red Cell in Polycythemia in Relation to Diagnosis and Treatment.
Am.J.Med.Sci. 196:493, 1938.

Minot, G.R., and Buckman, T.E.
Polycythemia Rubra Vera, the Development of Anemia; the Relation of Leukemia; Consideration of the Basal Metabolism; Blood Formation and Destruction and Fragility of the Red Cells.
Am.J.of Med.Sci., 166: 469, 1923.

Norman, I.L., and Allen, E.V.
Vascular Complications of Polycythemia.
Am.Heart J., 13: 257, 1937.

Osler, W.
Chronic Cyanosis with Polycythemia and Enlarged Spleen; a New Clinical Entity.
Am.J. M. Sci., 126: 187, 1903.

Reznikoff, P., Foot, N.C., & Bethea, J.M.
Etiological and Pathological Factors in Polycythemia Vera.
Am.J.M.Sci., 189: 753, 1935.

Watson, C. J.
The pyrrol Pigments, with Particular Reference to Normal and Pathological Hemoglobin Metabolism.
Handbook of Hematology (First Edition), Downey, Hal., Vol. 4: 2447, 1938.

Case Reports

1. 55-year old male admitted 7-25-38, complaining of diarrhea past 3 years, vague epigastric distress past two years, unnatural flush of face, headaches, progressive hoarseness, firm tender mass on right side of neck and 40# weight loss past 1½ years.

Slightly emaciated, temperature, pulse and respiration normal. Purplish-red flush of face with suffusion of conjunctiva. A group of firm, tender nodes were present at the angle of right jaw and cervical region. Adenoma, firm and size of walnut in right lobe of thyroid. B.P. 110/60.

Urinalysis showed trace of albumin. Hemoglobin 105%, red blood count 6,400,000, white blood count 7,500 with 68% neutrophils. Hematocrit 52%. Mean corpuscular volume was 97 cu. microns. Total blood volume 5.8 liters with 2.9 liters being plasma. Sedimentation rate was 2 mm. at end of 2 hours. BMR + 24%. Blood Wassermann negative. BUN and blood sugar was normal. Gastric analysis showed free HCl. Trace of occult blood in stools.

X-ray showed metastasis to pelvic bones. Left ventricular enlargement of heart. Mass in superior mediastinum interpreted as moderately enlarged thyroid. Intravenous pyelogram negative

Negative lactic acid response to exercise. Sternal biopsy showed hyperplastic normoblastic marrow. Biopsy of cervical node showed adeno-carcinoma of thyroid cells.

The patient developed a deep black cyanosis of the face, base of neck and arms and died suddenly. No autopsy.

Diagnosis:
Carcinoma of thyroid with metastasis.
Erythrocytosis (secondary polycythemia).

---

2. Forty-five year old Jewish female, admitted to hospital 10-12-38, complaining of epigastric distress since 1931. Anorexia, nervousness, headaches, and weakness past two months. Brick red facies with suffused conjunctiva and deep red colored mucous membranes. Eyegrounds showed markedly dilated veins. Heart and lungs showed no abnormalities. Blood pressure 140/100. Liver and spleen palpable. X-ray and fluoroscopic examination showed a left ventricular heart. Electrocardiogram showed left axis deviation. Vital capacity 2.2 liters.

Urinalysis showed moderate amount of albumin. Hemoglobin 118%, red blood cells 8,070,000, low color index, white blood count 16,400, with 86% neutrophils Blood volume 18.23 liters (plasma 4.81 l Average RBC diameter 7.1 u. Hematocrit 72%. M.C.V. = 94 cubic microns. Sedimentation rate showed no fall of erythrocytes at end of 2 hours. Fragility test normal. Circulation time from arm to tongue 18 seconds. Platelets 160,000 cu. mm.; coagulation time 6½ min,, Ivy bleeding time, 17 minutes. NPN = 52 mg. %. Positive lactic acid response to exercise

Diagnosis
Erythremia (polycythemia rubra vera).

V. GOSSIP

Charlie Rea is back from Bermuda with a rapidly fading tan. He reports that it is an ideal place to spend a honeymoon, but his family suspect that they will have to look at the pictures for some time to come. Charlie is more interested in seeing Sperling's pictures of "the" wedding which he frankly confesses is rather a hazy memory.....And speaking of Bermuda, did you notice that the St. Paul Junior League's announcement of its free tickets at the drawing in the recent ice follies show stated that the destination would be "Bermuda."..... ..Thanksgiving day is said to be the most disabling of all of our national holidays as the day after finds the greatest number of people absent from work. This is probably the reason that the administration entertains us with the annual showing of the highlights of the football season. This year's pictures are unusually good. Careful editing by Phil Brain and his associates is responsible for a compact resume of more highlights than one usually finds. The audience probably enjoyed the deliberate steal of the ball by Nebraska's Dodd from Minnesota's Buhler more than Larry did. Looking over the crowd at the showing one observed Minnesota's line coach, Health Service physician, George Hauser, Canada's pride and joy; head obstetrician, Red McKelvey, whose prowess on the Canadian football gridiron is only equalled by Red Grange in this country; head of the Mayo Foundation, Donald Balfour, the descendant of the discoverer of oxygen; Surgeon James Priestley of the Mayo Clinic; and many other greats and near greats. Thanksgiving Day also brought other problems, notably a rush of people to give skin to one of our young patients. Although the burn was not recent, staff surgeons decided to try skin grafts from donors to cover the area temporarily, a method which has been tried with success elsewhere. When the father was told to bring donors, he decided to go to a radio station for help. Before long the papers had it, and, as it was Thanksgiving, the people were full of the spirit of giving. When the news broke, they either called to volunteer their skin or came in person. The desk people stopped counting when the number passed 500. Incidents like this illustrate power of our modern methods of communication, and the charity of people..... ..Father Virgil Michel, Dean of St. John's College died November 26 and was buried from the Abbey Church Tuesday, November 29. His fatal illness was due to a skin infection originating on his chin. Dean Virgil Michel was widely known for his work as an educator and for his interest in the liturgical movement. His funeral service carried out all the fine traditions which he had sponsored. The crowd at the funeral represented the old and the new as the ancient customs of his community were carried out in modern settings. Representatives from most of the midwestern universities were present. The Benedictians are buried in plain black cloth covered boxes. Prior to the funeral service, a blanket of roses which completely covered the casket was removed. It was the gift of a good friend in the Department of Philosophy at the University of Chicago. After the funeral mass the body was carried to the community cemetery near the college in a hearse of ancient vintage drawn by two farm horses. The funeral procession followed with nearly 200 of his brother monks chanting his beloved liturgy for the dead. At the grave the ancient reminder of our earthly origin was reenacted when shovels of dirt were dropped on the casket which rested in the bottom of the grave. The day was unusually bright and sunny, so that no curtailment of the outdoor ceremony was necessary. Benedictine funerals in their final rites seem unusually appropriate, for these men live in communities in rural areas and never locate in cities.....Plans are being completed to memorialize the 50th anniversary of the first class to enter the Medical School of the University of Minnesota. An appropriate program will be carried out in the early spring.....The Hospital Auxiliary card party at Powell Hall on Tuesday of this week was a great success. More than $125 was raised to support the activities of this most helpful group... ...At a parent-teacher association meeting the other evening a Health Panel was the main feature of the program. When questions were solicited from the audience, a lady arose to find out why

the school didn't supply soap for the children. The principal told her that the children misused the cakes in a variety of ingenious ways. The lady stood up to inquire why they didn't have soap dispensers. The principal replied that the children broke them by knocking them off the wall. The lady arose to find out why the Board of Education didn't supply soap for the children. The principal replied that it was an economy measure. The lady arose to find out why soap was selected in the economy move. The principal replied that he didn't know. A mere man timidly suggested that if parents wanted their children to have soap they could bring it to school for their own use. The lady arose to say that she doubted that the schools had ever had soap. The principal replied that she was wrong, that at one time they did have soap. The lady arose to say that she had been around schools for 17 years and she had never seen soap. The principal replied that she must have been in the wrong schools because they had had soap in the last 17 years. The organization finally passed a resolution asking the Board of Education to supply the schools with soap, after which coffee and cake were served.....When it was learned that we were going to have a Thanksgiving Day without a wedding, Ophthalmology fellow, Carl Benkwitz, saved the day by marrying Janet Sanders at 4:00 p.m. The wedding took place somewhere in St. Paul and was duly witnessed and filmed by his department associates. Congratulations and best wishes. I have been waiting a long time for the opportunity to record my impression of Dr. Benkwitz' smile. It is without a doubt the most natural effervescent wholehearted spontaneous smile that I have witnessed. If he smiles that way every morning of his married life, his wife will have little excuse for not starting the day right. And speaking of smiles, Pediatric interne, Becker, is no slouch at this smiling business. I have often wondered what the effect would be when Dr. Benkwitz and Dr. Becker met in the hall. I suppose just a case of "smilin' through." .....Drs. Peyton and Hall have been hunting in the north woods. In other years Dr. Peyton freely volunteered details of his expeditions. This year he has little to say, although they did bring home two deer. According to Dr. Peyton much of their time was spent in getting lost and having someone find them, which isn't much news.....Obstetrician, Leonard Lang, will soon open his downtown office. There is some question as to whether or not his euphoria is entirely explained by this event.....The boys from the deep south seemed to be the only ones who were bored at the showing of the football pictures. In addition to our weather which they cordially dislike, their next peeve is our willingness to tell how good we are in football. Apparently they feel that we underrate their section, and give ours too much credit. In spite of it all, they become good Minnesotans during their stay here..... ..The training school office will not be the same without Dorothy Brick, the genial secretary, who is now Mrs. Cliffdrd Hanson of Owatonna. Believe it or not, the Bricks are Irish, being descendents of one O'Bric, who has many descendents in this country.....Health Service dentist Pierre ("Pete") Regnier was buried this morning. He died after an illness of several months. Pete has been with the Health Service for 9 years and was very well liked. Well known to the public as one of the football greats of Doc Williams' days, he had a host of friends who regret his passing.....Herman the cop was given a party at the brewery the other night to celebrate his 30th anniversary on the force. He has been stationed at the University of Minnesota most of this time. When Herman arrived without his uniform it was a big surprise as few people had ever seen him in civilian clothes. Although the supper was a buffet affair, the tables groaned under the weight of ham, sausage, rye bread, cheese, and other good things to eat. Herman has an unusual record of keeping down trouble and staying out of it. Unlike other campus cops he has few thrilling escapades to relate, preferring to spend the time telling of his new grandchild. P.S. He has never tried it on Charlie Hayden.

.....