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POLYCYTHEMIA, PARTICULARLY POLYCYTHEMIA VERA

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Introduction

Definitions--Polycythemia in the strict sense of the word means an increase in all of the cellular elements of the blood. However, popular usage of the term has restricted its meaning to indicate that condition in which there is an increase in the number of erythrocytes per unit volume of circulating blood. It is important to bear in mind that although five million red blood cells per cubic millimeter is the average number usually present in normal adult blood, counts even up to six million in robust active young males are by no means rare, are commonly unattended by symptoms, and to all intents and purposes appear to be quite devoid of clinical significance (64).

Polycythemia vera is a type of polycythemia which is essential or idiopathic in origin. Secondary polycythemia is a response to some exciting factor or factors, causing an increase in erythrocytes.

The purpose of this paper is to discuss polycythemia vera. Secondary polycythemia is discussed in order to obtain a proper perspective of the pathological and etiological factors involved in polycythemia vera, for it is generally agreed that secondary polycythemia has a better understood basic pathological physiology. This discussion of secondary polycythemia is included with the differential diagnosis of polycythemia vera, because the differentiation of the two is a major problem and the subject of secondary polycythemia can be handled better at that point.

Classification of Polycythemia--A classification of polycythemia is indicated in order to give an idea of the scope of the field and how the subject of polycythemia will be subdivided for presentation in this paper. Since an increase in red blood cells in analogous to an increase in white blood cells, it is only logical that some authors (65) use as a basis of their classification of polycythemia the same basis as that which is used in an increase in white cells, namely, the extent to which the cells are increased in number. The mild type of polycythemia is classified as erythrocytosis and the pronounced increment as erythremia, comparable to leukocytosis and leukemia respectively.

From the physiological viewpoint polycythemia may be classified as (a) transient or a state in which there is a loss of plasma; (b) physiological; and (c) absolute, when the total cell mass shows a marked and sustained increase.

In my opinion a combination of these two methods of classification is the best way of presenting this paper and will, therefore, be used. Erythremia will be used to indicate the idiopathic or essential type of polycythemia, polycythemia vera. Secondary polycythemia shall be termed erythrocytosis and will be subdivided as to etiology by using the physiological classification given above.

Erythremia or Polycythemia Vera

Synonyms--In the literature this affliction has been variously termed erythremia, polycythemia vera, Vaquez's disease, Osler's disease, Vaquez-Osler's disease, polycythemia with chronic cyanosis, myelopathia polycythemia, splenomegalic polycythemia, cryptogenic polycythemia, polycythemia ruba, and erythrocytosis megalosplenica. The term erythremia, suggested by Osler (107), seems to be especially appropriate, distinguishing the condition as it does from erythrocytosis or polycythemia of known origin.

Definition--Erythremia is a blood disorder of the red cell elements comparable to that of the white cell elements of bone marrow, chronic myelogenous leukemia. It is characterized by "chronic cyanosis, polycythemia, and moderate enlargement of the spleen" (105), by being slowly and intermittantly progressive, and of unknown etiology.

History--In 1892, Professor H. Vaquez (90), of the Faculte Medicin, Paris, reported a case of peculiar cyanosis with persistent polycythemia, enlargement of the spleen, vertigo, etc., and was inclined to believe that there was a functional hyperactivity of the hematopoietic organs. He regarded the condition as

being due to a congenital heart lesion, but upon death of the patient Vaquez discovered the absence of organic heart involvement.

Soon after the appearance of Vaquez's paper a series of case reports followed. Those recorded by Cabot (25 & 26), Mckeen (94), Saundby and Russell (125), Collins (32), and Hall (62) were cases of erythremia without doubt. Saundby and Russell in 1902 stated that erythremia was "evidently a definite clinical entity and one which is new to medical science" (125).

Osler's papers appearing in 1903 (105) and 1904 (106) created the most interest in this disease. In his first paper he presents three cases and in the second six additional cases which he collected from the literature. He also summarized the seventeen cases reported in literature up to the time of his second paper. In agreement with Saundby and Russell (125), he postulates that this is a new clinical entity of which chronic cyanosis, polycythemia, splenomegaly, weakness, prostration, constipation, headache and vertigo were the most characteristic features. He expressed the belief that the cyanosis probably depends upon increased difficulty of the flow of blood and the degree of fulness of cutaneous vessels. The interest stimulated by his first papers is well illus-

trated by the fact that on writting his third paper in 1908 (107) there were at least seventy cases on record.

Weber and Watson in 1904 (146) were the first to present complete postmortem and microscopic studies on a case of erythremia. They remarked on the hyperactivity of bone marrow.

Saundby in 1907 (124) discusses the theories of etiology: 1-primary over production of red cells in the bone marrow; 2-stasis; 3-diminished respiratory capacity of the blood; and, 4-diminished destructibility of the blood. He also offers a theory of his own believeing that the condition to be a cerebral-spinal neurasthenia causing vasomotor spasm. Cautley in 1908 (28) suggested that they had to deal with an inflammatory effection of blood forming organs, possibly the result of some toxin.

Our knowledge of this disease has been summarized from time to time in reviews by Lucas in 1912 (89), Weber in 1922 (145), and Harrop in 1928 (64) and 1938 (65).

Etiology of Erythremia

Factors--The etiology of erythremia is as yet only a matter of theory or rather many theories. However, in reviewing the literature certain characteristic etiological factors predominate. Race is one of these factors. Futcher (51) found that the colored race appears to experience a relative immunity. His conclusion was based on the admissions into John Hopkins Hospital where there was only one colored case out of thirty two cases of erythremia. The ratio of colored to white admissions was about one to seven. Reznikoff, Foot, and Bethea (119) noticed in the Hematology Clinic of the New York Hospital that the majority of the patients under treatment for erythremia were Jews born in eastern Europe (Russia, including Ukrania, Poland, Austria, Lithuania, Roumania, and Czechoslovakia.) They obtained records on a hundred and thirty-four cases of whom about fourty-eight per cent were Jews born in eastern Europe. The average incidence of this racial and national group in the six institutions from which the records were obtained was under ten per cent.

The age of onset of erythremia is usually in middle or late middle life, but evidences of the condition are frequently recognized at much earlier periods. The decades

during which this malady appears corresponds to those in which such changes as arteriosclerosis, emphysema, etc. occur. Futcher's series of thirty-two cases revealed a greater incidence of erythremia in males than females, there being twenty-five of the former and seven of the later (51). Other series show the same dominance of males over females. Sloan (127) describes the typical constitutional characteristics of erythremia patients as being thinness, undernourishment, and asthenia.

Theories--Hypotheses as to the etiology of erythremia seem to be divided between three theories: 1-That erythremia is a primary disease of bone marrow. 2-That there is excessive erythroblastic activity of bone marrow in this condition which is secondary to one or several different factors causing overstimulation. 3-That there is a decreased destruction or resistence against destruction on the part of the erythrocytes. It is generally agreed that the hemopoietic tissues are primarily at fault and that polycythemia and extra-ordinary increases in circulating blood volume appear to be a consequence of this hyperfunction, and the pathological alterations in the circulation which they produce seem to explain very many if not all of the clinical symptoms and physical signs.

It is the cause of this hyperfunction which is in great dispute.

Minot and Buckman (97) are the principle advocators of the theory that erythremia is a primary disease of bone marrow. They believe that erythremia should be looked upon as a neoplasm of hemopoietic tissue because of the evidence of hyperplasia and the production of immature cells. Hyperplasia of the bone marrow in erythremia is evidenced by the fact that cases upon which careful autopsies have been performed have shown a great increase in the amount of red marrow. This marrow is quite active and may be altered in character from normal. The leukogenic elements share in the process and give evidence of increased activity of the bone marrow by leukocytosis and an increase in the leukoblastic tissue as witnessed at post-mortem. Evidence of increased activity of the marrow is occasionally shown in the living subject by the presence of both abnormal and immature cells in the circulation. It is not necessary for blasts and many immature red cells to appear in the circulation as an indication of increased bone marrow activity because immature elements will appear according to the rate of growth-pressure of the marrow. From Minot and Buckman's studies it was evident that, especially in

cases of long duration and with the development of an actual anemia, a very disorderly type of blood formation with extra-medullary hemopoiesis may occur and be reflected in the peripheral blood. These points are all in favor of a neoplasm of the bone marrow. However, signs of very disorderly marrow are usually not observed because it requires a long period of time before the condition becomes sufficiently pathological to permit marked abnormality in the type of cells delivered from the marrow. Usually before such a stage is reached, the patients die from various results of erythremia per se.

Erythremia may possibly be a primary disease of bone marrow as a result of hereditary or familial tendencies. However, there is a paucity of well-authenticated reports on familial and congenital incidence of this disease. Spodaro and Forkner (129) studied a family of ten members in which polycythemia was shown to exist in seven. Herz (68) describes four families with a total of thirteen members presenting polycythemia of moderate degree without subjective symptoms. Nadler and Cohn (103) review the eleven cases reported in the literature up to 1939 but only seven of these were true familial polycythemia according to the data given. They also give data an eleven members

of a family of thirteen--two siblings were unavailable--and for the first time data on the circulating blood volume in familial polycythemia is reported. Four of the family had a marked increase in the volume of circulating cells per kilo of body weight and the total cell volume was increased in all. Since cases of familial polycythemia seem to differ from the classical cases of erythremia in that neutrophilic leukocytosis, splenomegaly, and symptoms referable to this disease are not striking features, it has been assumed that familial polycythemia is not the same as erythremia. In Nadler and Cohn's cases of polycythemia, however, the red cell mass was of the magnitude of that found in erythremia. Since Haden (59) finds an increase in cell mass to be characteristic of erythremia, it seems justifiable to include familial polycythemia in the group of cases of erythremia. Familial and hereditary tendencies definitely play a part in some case, but they are not a factor in all cases.

Some workers look on erythremia as excessive erythroblastic activity of bone marrow resulting from excessive response to agents formed in the liver, stomach, and endocrine glands. Since erythremia appears to the antithesis of pernicious anemia, Morris (100) states that it is theoretically possible that erythremia may be the result

of hypersecretion of addisin or of hypersusceptiblity of bone marrow to it. Adamson and Storey (2) found that the hemopoietic substance or addisin in the gastric juice in erythremia patients is produced in excessive amounts. Therefore, since the rate of manufacture of addisin is not augmented by administration of histamine, they suggest the possibility that histamine might be present in excessive amounts in the body of erythremic patients or that the patients might be unusually sensitive to this drug so that maximum amounts of hemopoietic substance are constantly produced.

Marshall (92) believes that the evidence she presents indicates a hormonal control by the liver which has an inhibitory action on red bone marrow. Erythremia results either when there is a decrease in the amount of inhibitive liver hormone or when the organism's need for the hormone has increased, and there has been no compensation for the increased need, so that the normal supply becomes inadequate. There is very little support for this theory and it seems very unlikely that there is such a hormone produced.

The evidence that abnormal secretions of the endocrine glands cause overstimulation of the erythremia elements of bone marrow is very scanty. Gunther (58) lists the endocrine

glands according to their ability to increase the number of erythrocytes as follows: suprarenals, sex glands, hypophysis, thyroids, adrenal organ, and spleen. Clinical conditions make it difficult to determine the part each gland plays since they are all interacting. The not too uncommon association of polycythemia with tumor of the suprarenal was recognized by Moehlig and Bates (98), but it is their contention that the polycythemia is a specific pituitary response. They believe there are secondary changes in the pituitary in response to the primary disease of the suprarenal cortex which results in the increased red cell production. Since the mesodermal bone tissue, spleen, reticuloendothelial system of the liver, etc. are known to be influenced by the state of the pituitary and since it is well known that in hyperpituitary states, such as seen in pituitary eosinophilism or acromegaly, the whole hemopoietic system becomes hyperplastic, it must be concluded that the pituitary does have an influence on erythrocyte production. However, it hardly seems probable that the pituitary could be the cause of the majority of the cases of erythremia for these cases lack other signs of pituitary disturbance. Abnormal thyroid secretion may be a factor for Tyrrell (142) reports a case of polycythemia in which the thyroid gland was hypertrophied and showed hyperthyroid

symptoms. Perhaps the polycythemia was also due to secondary changes in the pituitary.

There is some evidence to indicate the possibility of a cerebral influence on the blood which may cause erythremia. Barker and Craig (10) quote Cushing as stating the belief that there is experimental and neurosurgical evidence to show that the posterior lobe and stalk of the hypophysis and hypothalamic region are concerned in water metabolism. In Barker and Craig's two cases, as well as the previously reported cases which they reviewed, there was clinical and pathological evidence of a lesion involving one or more of these parts of the brain. This makes it seem logical to suspect that the polycythemia resulted from concentrated blood with low plasma volume due to lesions of the brain centers controlling water metabolism. Another group of workers (21) have adduced the possible presence of a center for the regulation of the erythrocyte level in the diencephalon and they believe the mechanism of erythremia to be of neurogenic origin. The experimental work of Schulhof and Matthies (126) on rabbits in which lesions of the proximal part of the vegetative centers resulted in polycythemia of long duration further substantiates the possibility that the brain plays a role in the regulation of the number of circulating erythrocytes. However, in

spite of the extreme frequency of signs and sumptoms of neurological involvement in erythremia, the association of erythremia with intracranial lesions is an event of greatest rarity.

The most recent theory, that the excessive erythroblastic activity of bone marrow is due to an anoxemic response induced by subintimal and adventitial fibrosis in the arteries and arterioles of the bone marrow, is postulated by Reznikoff, Foot and Bethea (119). The findings of the frequent occurrence of erythremia in middle of late life and the resemblance of the racial and national incidence of erythremia to that of thromboangiitis obliterans naturally suggested that the blood vessels of bone marrow merited study. It is necessary to examine the bone marrow of patients whose blood counts have approached normal values by therapy in order to avoid the excessive congestion of vessels, which tends to distort the vasculature and renders it difficult to recognize. It is also necessary to use a Masson trichrome stain to bring out fibrous tissue adequately. Under these conditions of examination it was found by Reznikoff (118) that the bone marrows obtained at autopsy and by biopsy in sixteen cases of erythremia showed markedly thickened capillaries and, in most cases, adventitial and subintimal fibrosis of arteries and

arterioles. Sixty-four control bone marrows did not show these lesions. The cause of this fibrosis is not known, but it is of interest that in two early cases of erythremia inflammatory lesions were found along the course of the vessels. Fitz and his co-workers (48) believe that the vascular lesions with involvement of the bone marrow circulation make the blood behave as though the patient, to all intent and purposes were living at a high altitude. As the blood count falls to normal the blood looses its excessive viscosity thereby improving the marrow circulation with, perhaps, a new and effective capillary circulation developing to a certain extent with disappearance of the polycythemia or the patient coming back to earth so to speak. Of all the theories this one seems to be the best and most logical, for anoxemia plays a major part in the developement of erythrocytosis. However, a person can hardly keep from wondering if the vascular changes are not secondary to the increased viscosity of the blood in erythremia.

The postulation that erythremia is due to a decreased destruction of erythrocytes or to an increased resistence against destruction is mostly based on the relationship of erythremia to cholesterol metabolism. Cholesterol is strongly anti-hemolytic and the blood and serum values are

increased above normal in erythremia. Patton and his associates (108) obtained from their investigations data which makes it seem likely that there is a definite value for cholesterol in cells which must be maintained if normal protection is to be afforded. When there is an increase or a decrease in cholesterol in the blood, such occurs primarily in the plasma. The extra cholesterol in the plasma of erythremia patients gives added protection against hemolysis of the red cells. Richards and Hermann (120) states that in their group of cases they were dealing with decreased red cell destruction which was apparently dependent upon an increase cholesterol content of the blood serum. The best evidence of this theory is the comparable increase of cholesterol with associated increase in red cells during the last months of pregnancy to the increased cholesterol in erythremia (12).

Vitamin C has been considered for the last several years to play a part in the regulation of the number of red cells in the blood. Deeny's (41) investigation of the relation of vitamin C to erythremia in two cases makes it appear that there is a defect in the metabolism of vitamin C in erythremia. He gave his patients vitamin C and found that alone it had very little effect on the condition, but in conjunction with sodium bicarbonate, which raised the

threshold of excretion of vitamin C, it caused an improvement in clinical symptoms and a marked fall in the red cell count. Possibly vitamin C affects the destruction of red cells, but there is experimental evidence (11) in cobalt polycythemia to show that its effect is on the respiration of the red cells. Therefore, it seems possible that a lack of vitamin C may result in a relative anoxia with a compensatory increase in red cells. However, there should be other evidence of vitamin C deficiency present.

The etiology of erythremia is at present not known and from all indications and theories presented it seems probable that erythremia is a symptom complex which future observation will classify into different types of erythrocytosis.

Symptomatology of Erythremia

Onset--The physiological factors which are disturbed in erythremia and which cause the symptoms are chiefly: 1--Augmentation of the volume of circulating cells and total volume of circulating blood with consequent vascular accommodation; 2--increased viscosity of the blood; 3--organic disturbances of the blood vessels; 4--secondary thrombotic processes; 5--pathological changes in hemopoietic tissue; and 6--disturbances in metabolism, related to heat, water, and mineral changes.

The onset of erythremia is usually very insidious taking a matter of years to develop into a clinically recognizable case. Usually the onset is manifested by neurologic symptoms of vague nature, but any organ may be referred to. The onset is so insidious that these cases are seldom diagnosed at onset being called neurasthenia or psychoneuroses usually. As previously mentioned the onset is usually in middle or late middle life but may occur at any time.

Skin and Mucous Membranes--The color of the skin and mucous membranes is one of the most characteristic features of erythremia, but there is much variation in the color depending on the condition of the cutaneous vessels and the rate of blood flow (107). If the capillaries are

full and the flow slow, cyanosis predominates; if the current is rapid, arterial color predominates. In erythremia there is definite mingling of the two colors resulting in what might be termed a red-cyanosis but this is subject to marked variations. Redness affects largely the facial and acral regions; hands to the glove line and face and neck to the collar margin. The feet are usually less red than the hands. On the trunk and proximal portions of the extremeties the color changes are much less than on the more distal and facial areas. The skin over the trunk and back may have the mild flushed appearance of a scarlatiniform rash. The mucous membranes appear cyanotic when the skin is definitely red and the conjunctiva has a bright red, injected or inflammed appearance.

The variations in color of the skin are quite striking during the same and on different days and are strikingly evident with temperature changes or changes in position of an extremity. Redness is common during the warmer monthes and cyanosis during the colder monthes. Age and sex seem to play a part (23). Younger persons are less cyanotic than older ones, and it seems that females are less cyanotic than males. Color of the skin in cases of erythremia is largely due to one primary factor, the large increase in circulating cells and hemoglobin; and two modyfying factors,

the number of capillaries for each unit area of skin and the area of capillary blood exposed in each capillary. It is particulary important from the point of view of diagnosis to realize that patients with erythremia sometimes may show pallor due presumably to vasoconstriction or peripheral circulatory failure.

There are usually firm, red, tender nodules on the thoracic and abdominal skin in erythremic patients (113). These nodules are perivascular collections of oxidase-positive cells.

In erythremia the skin loses one of its most important functions due to the response of the capillaries to the increased blood volume (22). This impairment of the heat regulation mechanism results in intolerance to heat and cold, burning sensations of the skin, and a sense of suffocation.

Cardio-vascular System--Evaluation of cardio-vascular symptoms in erythremia is very difficult with the realization that erythremia is a disease of late adult life and, therefore, occurs at the age pericd when arteriosclerosis and hypertension are particularly frequent, so that these condition, together with cardiac hypertrophy, frequently coexist.

In erythremia the blood pressure may be normal but is usually moderately elevated (135). Occasionally hypertension arises, an association that Gaisbock tried to create as a separate disease entity, but it is now generally believed to be a mere coincidence related to age. In studing a hundred and sixty-three cases of erythremia at the Mayo Clinic, Tinney, Hall, and Giffin (135) found forty per cent had a systolic pressure more than 150mm. of mercury, twenty-nine percent more than 180 mm. of mercury, and two cases more than 200 mm. of mercury. Peacock (109) charted blood pressure against blood volume in cubic centimeters for each kilogram and could demonstrate no correlation, nor was there any demonstrable correlation between systolic blood pressure and blood viscosity. The reason the markedly increased blood volume does not affect the blood pressure is that the blood is largely stored in the venous system, liver and spleen. This increase in blood volume is brought about so slowly and the regulatory mechanism of veins and capillaries has such a wide variation that there is no reflection of this increased volume in erythremia on systolic blood pressure. Horton (74) after reviewing the literature concluded that there has not been a sufficiently large number of cases of erythremia with hypertension to permit definitely

positive statements concerning this combination as a definite clinical entity.

Vascular symptoms of erythremia may be classified in three groups: 1--Those due to vascular complications, which is one of the commonest manifestations of erythremia; 2--Those due to arteriosclerosis for it is felt in cases of erythremia that the sclerosis and calcification of the arteries of the extremities are of greater degree than is felt compatible with the age of the patient (20); and, 3--Those due to vasomotor disturbances.

Vascular complications are almost entirely due to thrombosis. Although the cerebral and peripheral vessels are most frequently involved, any vessel may be the site of thrombosis in this disease. Coronary arteries are not involved as often as cerebral or peripheral vessels, but the incidence of coronary occlusion in erythremia is higher than in the general population (135). In all phases of the disease patients with erythremia are subject to thrombosis both arterial and venous. These are largely the result of thrombocythemia so commonly present in erythremia, high blood calcium which has been reported by some observors, increase viscosity of the blood, and changes in blood vessel walls.

Arteriosclerosis causes symptoms which are typical of

arterial insufficiency. Claudication is the most frequent, being definite and disabling. There is distress on exercising, usually localized in the feet and calves of the legs, and on treatment, with reduction in total blood volume, the tolerance for exercise increases markedly. Acroparasthesia, where there is a burning distress with exercise or at night alternation of coldness of the limbs with burning distress and cramps of the muscles of the calves of the legs, may occur. However, there is absence of relief following reduction of blood volume and no form of treatment has been successful in relieving this burning paresthesia. Gangrene may occur from arterial occlusion. Disease of the peripheral arteries is relatively common in erythremia and may cause unusual symptoms and aberrant manifestations. Therefore, recognition of the association of erythremia with peripheral vascular disease makes one responsible for excluding erythremia in all cases which present evidence of peripheral vascular disease.

Vasomotor disturbances may be of the dilator type in which the symptoms suggest erythromelalgia. Brown and Giffin (20) report three cases of this type in which there was excruciating degrees of burning, usually in certain areas on the plantar surfaces of the feet. The burning was intermittant and aggravated by heat and exercise and

by dependent position of the extremity. During attacks the feet or hands become excessively red, veins engorged, and the surface temperature of the painful areas is markedly elevated. There was relief with a decrease in blood volume. A spastic type of vasomotor disturbance may occur but this is relatively rare. These attacks consist of prolonged pallor which involves single digits and is asymmetrical in distribution. Reduction in blood volume causes complete disappearance of symptoms.

Respiratory System--Respiratory symptoms may be conspicuous in erythremia although they are not stressed by most writers. Dsypnea on exertion is the most common. Hoarseness is not unusual and epitaxis may occur. Many erythremic patients acquire respiratory infections very easily and the frequency of chronic bronchitis as well as moderate emphysema is stressed by some observors (9).

It is important to determine the relationship of polycythemia to chronic pulmonary lesions because of the prognosis. Therefore, the cases of polycythemia and chronic respiratory symptoms may be divided into four groups in regards to their relative pathogenesis: 1--Cases of primary pulmonary disease with compensatory polycythemia. 2--Cases of primary pulmonary disease initiating polycythemia which progresses beyond the point of compensatory response to

produce symptoms and become a menace in itself. 3--Cases of erythremia with complicating but unassociated pulmonary disease. 4--Cases of erythremia causing or predisposing to pulmonary disease and in which it is probable that a vicious cycle might be set up, each of the conditions tending to aggravate the other. From this grouping it is evident that it is essential to determine whether or not the respiratory symptoms are a result of the polycythemia or vice versa.

According to some observors (71) x-ray may be of some value in differentiating erythremia and erythrocytosis. Typical lesions may be found in cases of erythremia. These pulmonary lesions appear as circular shadows of varying size and density in any portion of the pulmonic field. By appropriate methods, it may be determined that this shadow is apparently due to a spherical lesion, sharply circumscribed, definitely outlined, and not surrounded by infiltration. These lesions rapidly reach a certain definite density and then begin to fade out until they disappear completely, leaving no trace of their existence either by fibroid or calcific changes. The entire period from the appearance of such a lesion to its disappearance may be less than three weeks. This evanescence probably explains

why this lesion is so infrequently described. These sharply circumscribed shadows must be differentiated from the focus of metastatic malignancy and conglomerate tubercle. It is difficult to state the pathological nature of the lesion but it is thought to be due to subpleural thrombus or small hemorrhage.

Gastro-intestinal System--Complaints referrable to the gastro-intestinal tract occur in the anamnesis of most patients. The symptoms may be mild and inconsequential or severe and exceedingly troublesome. Constipation is the most common manifestation referable to the alimentary tract in patients with erythremia and is variously described as being inconsistent or common (147). The next most frequent abdominal symptom usually is distention or fullness which is usually explained on the basis of pressure exerted by an enlarged spleen; it is sometimes accompanied by pain which is often localized in the epigastrium or upper left quadrant of the abdomen. Nausea, vomiting and anorexia occur quite frequently. Melana or hematemesis may occur as may bleeding into the peritoneal cavity. These symptoms seem to be the result of disturbances of the blood supply of the abdomen and especially abdominal plethora.

Patton and his co-workers (108) found that invariably

the early histories of patients with erythremia show that they were very fond of rich foods. They eat heartily and even to excess, but experience no digestive trouble. In the late or advanced stages, possibly incident to the progress of the disease, they may lose some of their digestive well being. Hyperacidity occurs in erythremia and may account for this excellant digestion and gain in weight in the early stages of the disease. Apperly and Cary (5) found that above a critical level the gastric acidity rises with the erythrocyte count to a maximum.

A number of writers have called attention to the association of peptic ulcer and erythremia. Weber and Ochsner (147) were able to demonstrate by roentgenologic or patholgic study evidence of gastric or duodenal ulcer in eight per cent of a hundred and forty two cases of erythremia. In a control group of cases of hypertension and in the general clinic population the incidence of peptic ulcer was two to three and two-tenth percent respectively. Another group of workers (139) were able to demonstrate roentgenographically peptic ulcers in seven per cent of a hundred and sixty-three cases of erythremia. Interesting speculations have been raised as to the etiologic relationship between erythremia and peptic ulcer (148). Boyd (16)

postulates thrombosis of the gastric vessels and of vessels of the first part of the duodenum which produces a destructive lesion with necrosis of the tissue. He suggests that the relationship between the two phenomena is probably a direct causal one. The great tendency for thrombosis to occur in polycythemia makes this theory seem quite logical.

Hepatic enlargement in polycythemia is common and is the result of marked distention of the vascular bed with blood. Sohval (128) found that the liver is palpable in about two-thirds of the cases of erythremia while in one-half of these there is moderate or marked hepatic enlargement. In many instances he found the degree of hepatic enlargement appeared to be related to the duration of the disease. No correlation could be established between the size of the liver and hemoglobin value, red cells, white cells or platelet counts, or volume of blood per kilogram of body weight. The presence of marked enlargement frequently signifies important liver complications. No consistent effect of treatment on the size of the liver is to be found, irrespective of the type of treatment or its effect on the blood counts and symptoms. In general the liver increases in size with the passage of time despite treatment.

Hepatic function may be impaired in erythremia by at

least five known factors; 1--distention of the portal circulation in the liver as a result of increased blood volume; 2--stasis of blood flow caused by increased blood viscosity, and in some cases by development of cardiac failure; 3--increased strain on hepatic function due to excessive hemolysis that occurs on treatment with phenylhydrazine; 4--impairment of nutrition of hepatic cells as a result of stasis of blood flow; and 5--cirrhosis of the liver for there can be no doubt that association of erythremia with cirrhosis is more than simple coincidence. Hepatic complications were found in twenty-five per cent of a hundred and sixty-three cases by one group (138).

Splenomegaly is a common finding in erythremia. Sixty-six per cent of a hundred and sixty-three cases in one series (138) showed involvement of the spleen and ten per cent of these patients mentioned symptoms referable to the spleen as their chief complaint. As in hepatomegaly, engorgement of the organ with blood is the important factor in splenomegaly. There is no general relationship between hepatic and spenic enlargement except so far as marked splenomegaly is concerned and then there is a tendency toward association of marked enlargement of the liver and spleen (128). The degree of splenomegaly and the presence

of leukemoid reaction seem to be directly correlated with the duration of erythremia (138). When the blood counts and percentage of cells as indicated by hematocrit readings are reduced by treatment the spleen may decrease in size.

Vascular complications may give rise to gastro-intestinal and abdominal symptoms, and will be discussed with the section on complications.

Neuro-muscular System--Symptoms referrable to the neuro-muscular system are the most common complaints of patients with erythremia and are mostly neurological in nature. These symptoms are often so distressing that they bring the patient to his physician, but they do not have a localizing value; they are often misleading, or they may be dismissed as functional (1). In the presence of vascular accidents, which are by no means uncommon in this disease, the diagnosis may be difficult. Sometimes the complaints mimic these found in organic syndromes.

Neurological symptoms vary from mild subjective complaints consisting of headache, vertigo, tinnitus, sensation of heat and general lassitude, to more severe symptoms including scotomata, temporary blindness, numbness of hands and feet, neuritic manifestations, and even such disturbances as paresis and paralysis. Tinney, Hall and Giffin

(136) studied a hundred and sixty-three cases of erythremia with a hundred and twenty-seven having symptoms referable to the nervous system. Fifty-five (34%) of these patients came into the clinic primarly because of neurological complaints while seventy-eight per cent of the cases had nervous system manifestations.

Headache is the most common symptom, being found in thirty-six per cent of the above cases. It varies from a sense of fullness or dull ache to throbbing pain, and is often associated with vertigo, blurred vision, and tinnitus. It is generalized in most cases, but in some instances localized to the occipital, frontal, or parietal regions.

Objective neurological signs occur as the result of thrombosis of cerebral vessels or of cerebral hemorrhages. Occasionally the neurological symptoms are such that it is very difficult to distinguish erythremia from brain tumor. It should be remembered that brain tumors can occur in cases of erythremia (two cases of cerebral neoplasm was found in the above series). In those cases in which there is difficulty in distinguishing the cerebral manifestations of erythremia and brain tumor, it is advisable to treat the patient first for his polycythemia. When the blood volume decreases to normal figures, cerebral manifestations improve except

when there is brain tissue injury. If cerebral manifestations progress despite treatment, an expanding lesion should be suspected. If the results of proper treatment are carefully observed, unnecessary surgical procedures can be avoided.

For other symptoms and complications and those discussed above with their relative incidence in two series of cases [one of a hundred and twenty-seven cases (136) and the other of fifty-nine cases (19)] see table I.

It seems evident that the neurological aspect of erythremia is quite extensive and often confusing from the point of view of the symptoms. At the same time the disease itself presents little that is primarily neurological objectively, except in respect to vascular accidents which in some cases may be so involved as to lead to mistaken diagnosis and unnecessary surgical procedures.

Mental phenomena which occur in erythremia consist for the most part of irritability, depression, and, at times, actual deterioration (149). The occurrence of psychosis is rare, for Levin (84) found only nine cases reported in the literature up to 1939. Depression states seem to be the most common. One or more of three mechanisms may be involved in causing a psychosis; 1--Increased

blood volume and increased viscosity of the blood may lead to congestion of cerebral circulation with resultant impairment of metabolism of the brain. 2--May give rise to multiple minute areas of brain softening which in turn may facilitate appearance of psychotic process that might otherwise have remained latent. 3--Serious loss of health and vitality is apt to have a demoralizing and depressing effect on erythremic patients.

TABLE I

Manifestations of Erythremia Referable to the Central Nervous System

Symptom	127 Cases	59 Cases
Headache	59	33
Vertigo	52	30
Nervousness	41	9
Weakness & Fatigue	29	
Visual disturbances	28	8
Severe neuroses with exhaustion	27	
Paresthesias	13	11
Aphasia	13	
Loss of Consciousness	10	
Tinnitus	8	4
Mental depression	7	11
Generalized pruritus		4
Complications		
Cerebral thrombosis	27	
Suspected brain tumor	8	
Choked disk	4	
Herpes	1	
Combined sclerosis	1	

Of the special sense organs, the eye is the only one which shows any significant changes or disturbances in

erythremia. As already mentioned there is the common and well known manifestation of marked and often diffuse conjunctival hyperemia in which the conjunctiva is dark-colored, injected, with dilated vessels, unassociated with inflammatory symptoms and abnormal secretion. This may antedate retinal vascular changes or be conspicuous when they are not present or not pronounced (42). The fundus sometimes appears normal, while at other times lesions exists, which may be mild or severe, depending on the severity of the disease and whether or not the patient has responded to treatment (31). The characteristic fundus picture, if such exists, consists of dilation, sometimes uneven, of retinal veins and deepening of their color, and in alterations, cyanotic it type, of the normal color of the eyegrounds usually without hemorrhages, exudate or changes in the optic nerve, and generally without marked change in the caliber and tint of the arteries. The fundus changes are a part of the general vascular disturbance. The resultant venous stasis in erythremia is the basic factor in the causation of such ocular lesions as retinal thrombosis and scattered hemorrhages, round shaped in appearance. The disc is often hyperemic and some describe a bluish cupping of the disk and when interference of

vision occurs without fundus lesions retrobulbar neuritis may be present (91). Slit lamp examination sometimes reveals the vessels of the iris to be dilated with brown areas of dust like pigment. Vision is seldom disturbed in erythremia and visual acuity is, as a rule, good even after several changes have been noted.

There are very few, if any, symptoms referable to the muscular or skeletal system in erythremia. The association of gout with erythremia is not commonly appreciated (141). Hyperuricemia is frequently associated with erythremia due to the increase in catabolism and has its origin in the nuclear material liberated by excess maturing normoblasts. In patients with gout, resultant additional increase in blood uric acid due to erythremia may be sufficient to make a mild case of gout severe and a severe case of gout difficult to control. Fortunately, treatment of gout need not be compromised for the sake of erythremia, or vice-versa. The possibility of concurrent occurrence of gout and erythremia should always be anticipated.

Genito-urinary System--Genito-urinary symptoms are the least important of all symptoms in erythremia. Occasionally symptoms of nephritis may occur. Hematuria and albuminuria may occur, the latter being quite common. Menorrhagia usually occurs in erythremia.

Laboratory Findings in Erythremia

Blood and Blood forming Organs--The blood findings are the most characteristic changes in patients with erythremia. The red cell count in untreated erythremia may vary from comparatively slight increases above normal up to thirteen or fourteen million per cubic millimeter with the average being between eight and twelve million. There is a corresponding increase in hemoglobin, ranging between eighteen and twenty-four grams per hundred cubic centimeters of blood. No characteristic qualitative differences have been found in properties of the hemoglobin of erythremic blood; iron content, gas binding properties, and spectrophotometric behavior being normal.

In erythremia, actual levels of red cells and hemoglobin may vary markedly within brief periods of time, due especially to vasomotor activity. They also may vary markedly in periods of weeks or months, due presumably to variation in equilibrium between blood formation and blood destruction. That such remissions and relapses may occur is not well recognized and it is important that it be recognized when judging the effect of therapeutic measures.

Most workers state that the blood is essentially normal in erythremia and that immature erythrocytes are seldom seen, but Minot and Buckman (97) found the red cells

changed from normal and in most instances observed evidence of immaturity. Changes from normal may, however, be slight and consist of only little variation in size with an occasional polychromatophilic erythrocyte. Greater changes are often seen featuring an unevenness in depth to which the cells take stain, probably dependent upon cells of different ages. Achromia may be marked and great variations in relation of hemoglobin to red count occur. The increase in red cell count relative to hemoglobin is practically a constant finding in erythremia so that the color index is always less than one. At times there appear many cells showing chromatophilia; some very deeply and others very slightly basophilic. Macrocytes and microcytes may occur in varying numbers and proportions. Reticulocytes average from one to two per cent and blasts not infrequently occur. The fact that immature cells and reticulocytes are usually present in comparatively small numbers in erythremia may be an indication that a balance has been reached between hyperplastic marrow and circulating blood. When there is considerable evidence of immaturity, hemorrhage or effect of hemolytic therapeutic agents must be suspected.

Studies (97) on the fragility of red cells in salt solutions revealed the following abnormalities for eryth-

remic blood; 1--A greater than normal difference between concentration in which hemolysis begins and concentration in which it is complete (lengthening of the resistance span). 2--Beginning hemolysis in concentration of salt definitely greater than 0.42 per cent, with complete hemolysis at the normal point or in weaker salt solution than normal. 3--Complete hemolysis occurring in concentrations of salt definitely lower than 0.28 per cent with increased or decreased initial hemolysis. 4--"Trickling effect" in which there was a slow onset of hemolysis; slight, but definite, occurring of hemolysis in high concentration of salt, with marked hemolysis occurring in not far from the same concentration as seen in the case of normal cells which normally is close and not far from the very beginning of hemolysis. These abnormalites are not characteristic of erythremia, but are probably related to alterations in blood production and perhaps blood destruction. It is suggested that the lengthened resistance span is due to cells of greater age variety than normal; that an increase of resistance, especially maximal resistance, is dependent upon an increase of some form of immature cells; and that decrease of minimal resistance is indicative of some hemocidal influence on cells, or perhaps due to relatively

large numbers of old or pathological cells. Their (Minot and Buckman's) data (95) brings out another point: That humoral factors may play an important part in blood destruction in erythremia. Normal red cells begin to hemolyze at higher concentrations when mixed with serum of some patients suffering from erythremia, than they do when mixed with serum of normal persons. The serum appears to exert a hemolytic influence on red cells.

In erythremia there is usually a leukocytosis, polynucleosis, increase of immature polymorphonuclear cells and thrombocytosis present. The white cells in the peripheral blood reflect the leukoblastic activity of bone marrow by an increase in the white count. Many cases have white counts between fifteen and twenty-five thousand, and not a few on record in which a leukocytosis of from twenty-five to forty thousand is reported (64). An increase percentage of bone marrow is present for differential counts often show seventy-five to eighty-five per cent or even higher percentage of polymorphonuclears. It is not uncommon to find a few, and occasionally many, immature white cells in the circulation. Detailed appearance of polymorphonuclear cells as well as immature cells may deviate from normal, as shown by variation in their size and by the character

of their cytoplasmic granulations and nucleus (97). These features are of the type one may associate with hasty or abnormal formation.

Platelet elements of marrow may also become involved in the disease process, so that there may be an increased number in the blood stream and even megacarycocyte nuclei may enter the circulation.

The volume of blood in erythremia as measured by both the dye and the carbon monoxide method appears to be greatly augmented, a fact which is in close agreement with clinical observations and findings at autopsy. The blood volume may be increased two or even three times the normal value. This characteristic increase in blood volume is due almost entirely to an increase in the cell mass, for there is remarkedly little variation in the plasma volume from normal (59). Determination of total blood volume by the dye method and determination of velocity of blood flow are entirely too difficult and cumbersome for routine clinical application. Therefore, one group of workers (52) found that the relationship of plasma, circulating red cells and total blood volume in terms of per cent of normal to the red count revealed that the red cell count is a very fair indication of the degree of elevation above normal of both circulating red

cells and total blood volume. The hematocrit determination of relative proportion of cells to plasma, involves no technical difficulties and may, therefore, be of practical value as an aid to diagnosis when it is elevated (83). Total blood volume is important in differentiating between erythrocytosis and erythremia.

Of the physical properties of blood, the increased viscosity probably stands first in physiological importance. The viscosity of the blood in erythremia may be increased above normal five to eight times (64). This is due primarily to a great excess of erythrocytes over plasma. The specific gravity of erythremic blood varies between 1.075 and 1.080, as compared with the normal of 1.055 to 1.065 (118). The sedimentation rate, as might be expected from the increase in cell mass, is greatly retarded. Cook and Somogyi (34) found that the blood in patients with erythremia show a greatly increased rate of glycolysis, but Harrop (64) found no difference in the glycolytic behavior of erthtremic blood as compared with normal human blood. The evidence concerning the clotting time in erythremia is somewhat conflicting, but the majority of writers state that the blood of erythremic patients clots with abnormal rapidity. This abnormal tendency to clot is probably the result of thrombo-

cythemia and an increased calcium content in the blood. This together with slowing of blood flow and stasis in many areas furnishes an explanation for the frequency of thrombus formation. Against this assumption of decreased clotting time is the frequent occurrence of hemorrhages. This tendency to bleed may be due in part to poor clot retraction because of increased cellular mass and decreased plasma and to distention of vessels. It seems probable that there may be a variability in blood clotting time occurring in the same patient. Bleeding time is variously stated to be normal or somewhat delayed. The carbon dioxide combining power in erythremia is rather low as is the carbon dioxide content of venous blood. This is due at least in part to the fact that blood cells contain only about sixty per cent as much available serum as base as normally.

The extensive hyperplasia and proliferation of red bone marrow in erythremia seems to be of primary etiological importance. Bone marrow punctures reveal enormous numbers of mature erythrocytes as well as normoblasts. Occasionally megaloblasts are to be seen but they are rare. The white cells are also enormously increased in numbers, with many myelocytes. Eosinophils are prominent and

neutrophilic leukocytes are proportionately diminished. Megakaryocytes are often increased. No essential differences are reported between this picture and the picture in autopsy material. There is widespread conversion of fatty marrow into red marrow in all of the bones and the blood spaces are crowded with red cells. All varities of white cells are present in the bone marrow and it was concluded by Hirshfeld as quoted by Harrop (64) that so far as the proportion of this type of cell was concerned, the hyperplastic marrow did not differ much from normal red marrow. Extramedullary hyperplasia of myeloid tissue may occur in spleen, liver, and lymph nodes. Hirsch (70) believes that marked sclerosis of bones occurs in the advanced stages of the disease with enroachment on the bone marrow compartments causing a compensatory increase in extramedullary foci. The enormous increase in concentration of red cells per unit volume, as well as tremenduous increase in total blood volume, through out all of the tissues of the body seems to be a direct consequence of bone marrow hyperplasia.

Other Studies Concerned with Pathologic Physiology and Chemistry--It is believed by most writers that the basal metabolic rate in erythremia is increased because

of the relationship between leukemia and erythremia and the increased, active blood formation. Issacs (78) suggests that the increase of metabolism is dependent upon the liberation of an excess of nuclear material formed in the increased production of red cells. Bliss (15) on the other hand found no evidence that the basal metabolic rate was dependent on, or related to, increase in blood and cell volume for each unit of body weight or surface area. Moreover, the basal metabolic rate in the twenty-three cases he studied bore no relationship to hemoglobin concentration or red cells; in fact, there did not seem to be any correlation between metabolic rate and severity of the disease as evidenced by general symptoms. Due to the conflicting evidence there seems to be no relationship between the metabolic rate and the syndrome erythremia.

The cardiac output in erythremia as most of the other laboratory findings is not a definite feature. It has been variously reported as normal or either increased or decreased from normal. The majority of the workers in this field believe that the cardiac output at rest in erythremic patients is normal (4). If the cardiac output and blood pressure are normal in uncomplicated erythremia the work of the heart,

at least in the resting subject, must be normal. Grollman (57) states that since there is a normal cardiac output in erythremia it is usually accompanied by normal metabolism, meaning that the amount of oxygen carried to the tissues by each unit of blood (the arteriovenous oxygen difference) is also normal. The oxygen capacity of blood, on the other hand, being markedly increased, loses a smaller fraction of its total oxygen than normally and hence oxygen utilization is only about two-thirds of normal. Since the arterial and venous blood oxygen contents are increased to the same degree, the arteriovenous oxygen difference must be normal.

Goldsmith (56) is the principle advocator of the theory that cardiac output is increased in erythremia. He showed that when the blood volume and hematocrit reading were elevated the cardiac output increased and when these values returned to normal the cardiac output was lowered and the arteriovenous oxygen difference was more nearly normal.

Other groups of workers (132 & 85) measured the cardiac output and their data demonstrated that an increase in erythrocytes and in hemoglobin in erythremia is associated with a decrease in the volume output of the heart. It

appears that an increase in the arteriovenous oxygen difference and decrease in cardiac output is proportional to the increase in the amount of hemoglobin and augmented number of red cells. For, with a decrease in hemoglobin and in red cell count under treatment, the arteriovenous oxygen difference decreased to normal and cardiac output increased. They conclude that since each unit volume of polycythemic blood contains an unusually large quanitity of hemoglobin, the oxygen requirement of tissues can be satisfied by a cardiac output which is smaller than normal, the maintenance of normal cardiac output under these circumstances would impose needless work on the heart. It appears likely that the decrease in cardiac output observed represents an adaptation of the circulatory mechanism to avoid needless work.

In erythremia the nail fold capillaries show a definite engorgement of either one or both the venous and arterial segments, although this is not uniformly present in all loops (21). Engorgement is more evident on the venous side. The total length of the loops are greater than in normals of a like age. The caliber of the venous limb is distinctly widened and occasionally huge dilated limbs are seen. The arterial limbs of the loops are not enlarged to the same

extent as the venous. The velocity of the capillary flow is distinctly and uniformly decreased (4). The movement of the red cells is en masse rather than in the rapid single-file manner usually observed in normals. The cells form densly packed masses with twisting onward motions. The velocity of flow in the capillaries reflects the rate of flow in the entire vascular system in erythremia. The rate of circulation, as tested by the histamine method, when measured from leg to face or from arm to face reveals a decrease in the circulatory rate it being from five to ten times slower than in the normal subject (20).

Regarding a number of the constituents of blood, the reported analyses are so conflicting as to give one the impression that no characteristic or markedly abnormal findings occur. These include the concentration of cholesterol, total serum proteins, serum albumin-globulin ratio, blood fats, serum bilirubin, concentrations of various inorganic anions and cations in serum, and various non-protein-nitrogen constiutents.

Increased output of urobilin has been observed at times during the course of this disease (97). This is, however, by no means a constant finding. The increased output of urobilin brings up the question of blood destruction in

erythremia and all of the present day evidence goes to show that alteration in blood destruction can have but slight direct influence upon erythremia.

Relation of Erythremia to Leukemia, Anemia, and Thrombocythemia

The fact that all elements of bone marrow are involved in erythremia has already been brought out. Therefore, one begins to wonder what the relationship is between erythremia, leukemia, thrombocythemia, and even anemia. This relationship has been aptly diagramed by Moschowitz (101) and is reproduced below:

Biology of Polycythemia Vera

Polycythemia vera
- Leucemoid phase--chronic myeloid leukemia
- Thrombocythemia (thrombosis)
- Anemia
  - aplastic
    - exhaustion
    - osteosclerosis
  - leukemic
  - macrocytic
  - hemolytic
  - secondary (e.g. hypertensive disease)
- Excessive nuclear destruction----gout

By studying a composite picture of erythremia one notices a definite trend for erythremia to transform into leukemia and in rare instances vice versa (81 & 110). This transition varies from leukocytosis through erythro-leukemia to chronic myelogenous leukemia usually. As already mentioned leukocytosis is not an uncommon occurrence in erythremia and is usually progressive. Also in most instances of long duration there is usually some relatively slight degree of myelocytosis corresponding to an increase in leukoblastic

elements in bone marrow. It is believed that criterion for assuming the presence of myelocytes as a leukemic manifestation is the prolonged presence of myelocytes over a period of two or three years (110). The leukocytosis or myelosis in erythremia is referred to as the leukemoid reaction (97) or subleukemic myelosis (110). One group (137) studied a hundred and sixty-three cases of erythremia and found the incidence of leukemoid reaction to be ten per cent and they also found that the degree of splenomegaly, presence of leukemoid reaction and duration of erythremia appeared to be directly correlated in their series.

The combination of erythremia and leukemia is thought by some authorities (118 & 102) to be a definite clinical entity and is referred to as erythro-leukemia. In rare cases the leukemic component of the erythro-leukemic syndrome becomes malignant, and granulocytes are enormously increased in number including a considerable number of unripe forms, as in ordinary cases of myeloid leukemia (144). The leukemic component of erythro-leukemic syndrome is usually of non-malignant type; in fact, it is no more malignant than the erythremic component. When the leukemic component does become malignant it usually transforms into chronic myelogenous leukemia, but there are two cases

reported in which acute leukemia developed as a terminal phase (63). However, in both of these individuals the leukemic manifestations appeared while they were receiving x-ray therapy. The blood picture is not the only indicator of leukemic change, for postmortem studies reveal true myeloid leukemic infiltration (97 & 122).

How frequent the transformation of erythremia into leukemia occurs cannot be affirmed with any assurance because observations upon this disease are limited to only a small part of its life cycle, but that it is fairly common is indicated by the observations of Minot and Buckman (97) who report this transition in three out of fifteen cases. The cause of this transformation is as obscure as the cause of erythremia and of leukemia. Klumpp and Hertig (81) after a survey of the cases in the literature which present combinations of elements of both diseases suggest that there is an initial polycythemia in the early stages of all cases of myelogenous leukemia and in cases of erythremia appearance of marked leukocytosis with immature myeloid cells in the blood stream is generally a late manifestation and is evidence of more profound disorganization of bone marrow activity.

Most authorities (81 & 116) believe that when a case

presents a composite picture of myelogenous leukemia and polycythemia, or phases of each, it is more likely to be leukemia than erythremia.

It has been observed that a number of untreated cases of erythremia eventually develop an anemia. This transition has resulted in several different types of anemia as presented in the diagram given on page 50.

Aplastic anemia results principally from the exhaustion of the bone marrow by its abnormal, excessive, prolonged activity (118). The blood formation becomes very disorderly and extramedullary hematopoiesis has been observed (116), all of which is reflected in the peripheral blood picture. This type of anemia has been noticed to occur as the result of osteosclerosis in cases of erythremia as reported by Minot and Buckman (97) and Hirsch (70).

Anemia accompanies most of the reported cases of transition from erythremia to leukemia. In all of Minot and Buckman's cases (95) (three out of fifteen) there was observed a striking pathological change coincident with the developement of the anemia. During the period of anemia the red cells showed marked variation in size and considerable variation in shape. Microcytes were evident, but never in profusion. Macrocytes of abnormal shapes occurred and true

megalocytes were found. Uneveness in the depth of staining of the cells was unusually striking. Frequently observed was a considerable increase in the polychromatophilic cells and reticulocytes. Blasts were a feature; all types being present. The developement of the marked anemia in these three cases was dependent upon the disorderly proliferation of the myeloid tissues.

The relationship of erythremia to macrocytic anemia, particularly pernicious anemia, is of very great interest. This is especially true since two blood conditions so diametrically opposit cause very similar symptoms (30). This relationship has already been discussed with etiology of erythremia, for it is possible that erythremia is due to an excess of hemopoietic factor which is present in deficient amounts in pernicious anemia. An anemia resembling hematologically macrocytic anemia has been reported (13) but whether these are nostogically transitions into pernicious anemia is very much open to question.

That the anemia may be of a hemolytic type is indicated by an increased output of urobilin, an increased fragility of red cells, icteric tint of these patients, positive indirect van den Bergh reaction of the blood, and deposits of hemosiderin in the liver (97 & 7). This type of anemia

may be an over compensation of a compensatory mechanism on the part of the individual to remove the excess of red cells by increased activity of blood destruction; the hemocidal process becoming so excessive that anemia ensues. Avery (7) states that the increase in size of the spleen noted in some of his cases certainly suggests increased hemolytic activity and cannot be due entirely to myeloid and erythroblastic metaplasia which takes place.

The anemia in which erythremia may terminate may be secondary. This happens particularly when associated cardio-vascular-renal hypertension reaches its terminal nephritic phase (101). Secondary anemia may result from treatment by radiation, benzol or phenylhydrazine, or repeated venesections.

The third morphological component of blood, namely the blood platelets, occasionally partake in the general rise accompanying the erythroblastic and leukoblastic activity in erythremic bone marrow. Numerous observors have reported an increase in megacaryocytes in erythremic bone marrow (97, 77, 122, & 143). Occasionally megacaryocytes may be found in the peripheral blood and their presence is indicative of the bone marrow being under intense strain (96). Accompanying this increase in megacaryocytes

is a thrombocythemia. This transition must be fairly common because Rosenthal and Bassen (122) found thrombocythemia in thirty per cent of their cases. The relationship between thrombocythemia and thrombosis has already been commented upon. The opposite phenomena of thrombocythemia, thrombocyotpenia with purpura, may develop in some cases of erythremia (118). This phenomena has been attributed to the final exhaustion of bone marrow.

In evaluating the hemopoietic changes in erythremia it is important to be sure that the final picture may not be due in part to prolonged depression therapy. As is evident from the foregoing discussion the evolution of erythremia is various, depending on incidental transitions and opportunity to observe this malady over a prolonged period. Evaluating a case of erythremia at any particular time does not necessarily imply that it is the end result, for any or all combinations are possible in erythremia and it should be realized that exhaustion of one element may occur while another begins or continues to hyperfunction. Seeing the disease in one of its terminal phases often makes it difficult to diagnose erythremia for cases may appear to be primary chronic myeloid leukemia or anemia and sometimes it is difficult to reconstruct the previous clinical history.

Clinical Course, Complications, and Duration of Erythremia

Since erythremia is a disease of many years duration and of insidious onset, the opportunity to observe the entire life cycle of this syndrome is very rare indeed. The clinical changes in erythremia may develop so insidiously as to make it impossible to determine transition from one stage to another and the later phases of the disease may appear to be entirely unrelated to the original polycythemic stage. The earlier phases of the disease are practically unknown for there is no method of recognition before the hematologic features are fully developed and then, even after symptoms have become apparent, it is frequently a matter of years before they become severe enough to cause the patient to consult a physician.

The earliest phase of erythremia might be referred to as the developmental phase. The duration of this phase can only be conjectured for no adequate hematological tests have as yet been devised for diagnosis in this phase and no symptoms are as yet present. Apparently it requires several years for this stage to reach its peak (122).

Since erythremia may be asymptomatic, an asymptomatic phase is very likely. Early in this stage the blood volume is greatly increased but the erythrocyte count and hemoglobin may lie within a normal range (108). The presence of this

phase is usually accidentally discovered when the patient appears for a routine blood examination or for some unrelated condition. Harrop (64) stated that in the course of routine blood examination in students it is not uncommon to find one or more students with a high erythrocyte count. In two of such instances studied by Harrop the spleen was definitely palpable.

The symptomatic or polycythemic phase is the stage best known to clinicians because both the clinical and hematologic findings present a clear clinical entity. Symptomatic and hematologic changes may continue until death, for as already pointed out the entire bone marrow is involved and not merely the erythroblastic elements . The original polycythemic picture may be accompanied by change into either leukemia or thrombocytopenia or both. Any or all combinations are possible during this phase. The duration of this phase is long, possibly ten to twenty years or even longer (122).

The symptomatic phase may be altered by any therapy given and the response to therapy varies markedly in different patients. A so called normal state in which hemoglobin and red cells return to normal may be induced by treatment, the duration of which varies greatly. After this normal state there is a tendency for the hemoglobin

and red cell count to return to their previous high levels. Rosenthal and Bassen (122) have observed that after prolonged treatment, particulary with phlebotomies and phenylhydrazine, the hemoglobin values tend to remain normal or subnormal while the erythrocyte count returns to its former high mark. They refer to this phenomena as the chlorotic stage.

The anemic phase is the final phase of this disease for unless the disease terminates early in its course by complications or later by leukemia, the tendency is ultimately toward a marked anemia. Patients who reach this stage may be regarded as having survived the entire course of erythremia (122). This anemic phase varies in different patients for all the bone marrow elements may be depressed or one or the other or both may persist to be hyperactive. Therefore, the anemia may have an associated leukopenia, thrombocytopenia, leukemia or thrombocythemia or any combination of these.

Erythremia should be considered as an ever changing condition; its various transitions being so gradual as to be almost imperceptible. It should be remembered that the terminal stages of this disease may become leukemic, thrombocythemic, or anemic or may reveal various combinations of

any or all of these.

Complications of erythremia are nearly all vascular in nature and result largely from an increased tendency toward thrombus formation as a result of slowed circulation in a vascular bed which is distended by a greatly increased blood volume. Another important factor may be the increase in the number of platelets, and an increase in serum calcium may be a contributory factor. It is also possible that the intima is injured by a distended blood supply to it or from excess wear and tear by fluid of increased viscosity which will predispose to the formation of thrombi. Thrombi account for about one-third to one-half of all the deaths ascribed to erythremia (133). Norman and Allen (104) observed ninety-eight cases of erythremia at the Mayo clinic over a period of seven years and found the incidence of vascular complications to be thirty-four percent. In studying patients of similar sex and age but without erythremia the incidence of vascular complication was much smaller. Thrombi occur principally in the cardiac, cerebral, hepatic, portal, and mesenteric vessels but may occur in any vessels of the body.

Coronary thrombosis, when it occurs in erythremia, results in the typical clinical picture of coronary occlusion. However, it does not appear to occur with as great a frequency

as does thrombosis in other organs (104). This may be due to the fact that stagnation is not as marked in the vessels of a muscular organ in active contraction as it is in vessels of less active organs, even though the other factors that increase the liability to clotting are operative.

Cerebral thromboses may occur in any of the cerebral vessels and are quite common occurrences. They give rise to definite neurological signs and symptoms which frequently confuse the diagnosis, especially when the patient is seen for the first time. The incidence and main features of cerebral thrombosis have already been discussed. Multiple cerebral thrombi are thought to cause chorea and Kotner and Tritt (82) report such a case of erythremia complicated by chorea and they also review four similar cases found in the literature.

Intra abdominal vessels are frequently the sites of thrombosis. The usual sites being the portal vein, hepatic veins, and mesenteric vessels. Thrombosis of the portal vein occurs not too infrequently (6) while the hepatic veins are one of the rarest and most important sites of venous thrombosis in erythremia (128). It is important to differentiate between portal thrombosis and hepatic thrombosis for the former has a fairly good prognosis lasting several

years and producing few if any clinical manifestations, while in the later the course rarely exceeds six months and the outcome is always fatal (128).

One of the points of diagnostic usefulness in differentiating hepatic and portal thrombosis is ascites. Ascites is a constant finding (and likely to be of rapid development) in thrombosis of the hepatic veins and uncommon in thrombosis of the portal vein. Mercurial diuretics seem to be ineffective in ascites due to thrombosis of the hepatic veins, while they seem to be successful when thrombosis of the portal vein is present. However, cirrhosis of the liver, which is not a too infrequent occurrence in erythremia, may also cause ascites and on the basis of statistical frequency it is the more likely diagnosis, especially if the ascites has accumulated slowly and has responded to mercurial diuretics and if the liver is observed to decrease gradually in size. Edema and anasarca are late manifestations of hepatic vein thrombosis.

Enlargement of the liver is practically constant (and typically rapid) in thrombosis of the hepatic veins and uncommon in thrombosis of the portal vein. Here also cirrhosis of the liver complicates the picture, for the enlargement may be due to cirrhosis. When thrombosis of hepatic veins

supervenes during the course of an established cirrhosis, there may be little or no enlargement of the liver, depending on the previous size of this fibrotic, non-expansile organ.

Jaundice is common (and usually terminal) in thrombosis of the hepatic veins and is rare in thrombosis of the portal vein except in the presence of ascites. Here, too, cirrhosis complicates things for it frequently has associated jaundice.

In summarizing the points of differential diagnostic usefulness there is a sudden enlargement of the liver, rapid accumulation of ascites, resistance of ascites to mercurial diuretics, and a markedly abnormal cholesterol partition in thrombosis of the hepatic veins; occasional decrease in size of an enlarged liver and effectiveness of diuretic measures in ascites of cirrhosis; and infrequency of ascites, hepatic enlargement, and jaundice in thrombosis of the portal vein.

It is evident that thrombosis of the portal vein is a relatively benign complication of erythremia, but it carries with it the threat of ultimate mesenteric thrombosis and intestinal gangrene. Thrombosis of either the superior or inferior vena cavae or both may occur but this is rare (114).

That hemorrhage should be a complication of erythremia

seems parodoxical after the above discussion, yet one group of observors (137) in studying a hundred and sixty-three cases of erythremia found hemorrhagic manifestations in thirty-two per cent. Hemorrhage is most commonly seen postoperatively, but purpuric manifestations and cerebral hemorrhages have been reported. The great distention that occurs in the vascular system is undoubtably the most important factor in the causation of hemorrhage.

The transition of erythremia into leukemia, thrombocythemia, or anemia might also be considered complications. There is one case reported in which a stem cell sarcoma of the primitive red cell type resulted as a phase of overcompensation following exhaustion of erythropoiesis (111). Other complications which have been described are erythromelalgia, myocardial infarction, angina pectoris, occlusive disease of peripheral arteries, phlebitis, and vasomotor neurosis.

It is very difficult in a disease of this character, in which the history of onset is so indefinite, to determine the exact duration of erythremia. The course of the disease is exceedingly slow and chronic (and barring the occurrence of one of the serious complications) usually end fatally within ten or fifteen years from the time of onset of symptoms

(53); the average duration being six to eight years. During this time the patient may expect several years of comfortable existence.

Diagnosis and Differential Diagnosis of Erythremia--Discussion of Erythrocytosis

The data leading to the correct diagnosis of erythremia can usually be obtained from the history and physical examination. Careful consideration of the laboratory findings gives further criteria for the establishment of a definite diagnosis of the condition and for differentiating doubtful from true cases of polycythemia.

Suspicious point in the history are: 1--multiplicity of symptoms, especially those relating to the central nervous system, 2--complaint of severe headache, including migraine, 3--complaints referable to vascular disease of the extremeties, and 4--history of severe bleeding following even slight operative procedures. In some cases, the great multiplicity of symptoms is present with the result that neurasthenia may be diagnosed; in most cases, however, emphasis is placed by the patient on one bodily system or the other. Symptoms referable to the central nervous system are present in almost every case. It is quite unusual to find these patients complaining of only two or three symptoms. The main symptoms are listed in table II.

In the physical examination one looks particularly for high facial coloring, appearance of reddish cyanosis in erythremia as compared to the blue color in erythrocytosis,

highly colored mucous membranes and conjunctivae, dilated retinal vessels, large spleen and liver, thick red hands and feet, and a thickly coated and fissured tongue. In regards to the plethoric appearance of erythremic patients Christian (29) makes the following statement: "If one has in mind the very striking appearance of some patients of this group with their marked cyanosis, or probably better, reddish cyanosis it would seem as if this disease would be recognized promptly; but, alas, how often do we fail to see what is just in front of our eyes because with vision is not combined thinking and the application of experience acquired by previous observation and reading."

Salient features on which diagnosis is based are the hematologic findings, consisting of elevated erythrocyte count, hematocrit and hemoglobin level; leukocytosis with nuclear shift to the left is usually present and platelets are increased in number in most instances. As evidence of hyperplasia and overactivity of the bone marrow there are polychromatophilic and an occasional nucleated red cell in the peripheral blood stream. The total blood volume is increased in erythremia and this is due predominately to an increase in the red cell mass. There is little or no increase in the volume of plasma. The increase in red cell

mass produces marked increase in the viscosity of the blood, commonly to four or five times normal values, and an increase in the specific gravity of the blood to 1.075 to 1.080 as compared to normal values between 1.055 to 1.065.

TABLE II

Diagnosis of Erythremia (35)

Symptoms:	Headache, vertigo, visual disturbances, colored scotomata, paresthesia
	Symptoms referable to vascular disturbances of the extremeties
	History of profuse hemorrhage after minor trauma
	History of venous and arterial thrombosis
	Multiplicity of symptoms
Signs:	Plethoric appearance of face and conjunctivae
	Dilated retinal veins
	Thickly coated and fissured tongue
	Splenomegaly and hepatomegaly
	Red hands and feet
Laboratory:	Elevated red cell count (above 6 million per c. mm.)
	Elevated hemoglobin
	Elevated leukocyte count
	Elevated polymorphonuclear percentage
	Elevated platelet count
	Elevated hematocrit
	Elevated blood volume
	Distended capillaries
	Sternal bone marrow biopsy: red cell hyperplasia, megakaryocytic hyperplasia.

Allen (3) states that unfortunately one cannot put too much reliance on laboratory reports of the number of red cells in each cubic millimeter of blood when erythremia exists. This is in part because many technicians have not been trained to recognize the condition in which there is

an abnormally large number of red cells in each unit of blood and partly because the number of cells is so great that it is difficult to count them accurately.

Sternal bone marrow biopsy may occasionally be of diagnostic value and is always of great interest from the pathological standpoint. It is intensely hyperplastic in all elements. There is an extremely large number of megakaryocytes present which crowd certain sections and are important in some cases.

It should be emphasized that not every symptom, sign or available bit of laboratory evidence is present in every example of this disease. Dameshek and Henstell (35) believe the following minimal data should be present before a definite diagnosis of erythremia is made: plethoric appearance, splenomegaly or hepatomegaly, definitely elevated erythrocyte count, elevated platelet count, and elevated hematocrit. In a doubtful case procedures of blood volume estimation and capillary microscopy may be helpful.

Differential diagnosis of erythremia is almost entirely limited to erythrocytosis which will be discussed later. The difference in plethoric appearance of these two conditions has already been brought out. However, symptoms and signs are of little value in differentiating; therefore, laboratory

data is the most valuable differentiating criteria. The erythocytes per unit of blood are always increased in erythremia and also in erythrocytosis, so the diagnosis of erythremia cannot be made on the increased number of cells per cubic millimeter alone. The blood volume is a valuable aid in differentiation for in erythrocytosis the blood volume is seldom increased while in erythremia it is always increased. Haden (59) states that the diagnosis of erythremia is not justified without demonstrating such an increase, but Moschowitz (101) believes that this distinction is not valid and that in the final analysis the essential diagnostic differential between uncomplicated erythremia and erythrocytosis is the normal oxygen saturation of the blood in the former. X-ray may occasionally be of value in the differentiation. Erythremic patients reveal increased prominence of truncal shadows of the lungs when cyanosis and vascular engorgement are present and also transient lesions, spherical, sharply circumscribed and not surrounded by evidences of pulmonary infiltration (72).

At times polycythemia may have to be differentiated from other diseases. It may be confused with chronic nephritis for a plethoric condition may be present in both conditions and most cases of polycythemia show slight

degrees of albuminuria, at times a few casts and hypertention, and at times definite, although slight, elevation in blood non-protein nitrogen. Differentiation between congestive heart failure and erythremia may be necessary. In congestive heart failure the plasma volume is greatly increased, whereas in erythremia the plasma volume is essentially normal. In individual cases the total blood volume may be as high in congestive heart failure as in erythremia. For this reason a hematocrit becomes a useful diagnostic procedure, and at a hematocrit level of over fifty-five the diagnosis of erythremia is justifiable in the absence of physical signs of congestive heart failure (52). The clinical distinction of erythremia becomes difficult when seeing an occasional patient who presents himself in the late stages with an anemia rather than polycythemia. The correct interpretation can usually be made from the past history (14). Complications also confuse the diagnosis and here the past history is also valuable.

In concluding diagnosis it might be said that the diagnosis of a condition seen only rarely in every day practice usually rests first upon thinking of the possibility of its presence and second upon attempting to

prove or disprove this by appropriate tests. No one test, except possibly a constantly and greatly elevated erythrocyte count, is of pathognomonic diagnostic significance in erythremia.

Erythrocytosis--Erythrocytosis is the response of the individual to some known stimulus with a resulting increase in erythrocytes per unit volume of blood. The etiology furnishes a basis for classifying erythrocytosis.

The first type of erythrocytosis is temporary or relative and is due to the loss of plasma from any cause with consequent alteration in the proportion to plasma and cells of the blood or hemoconcentration. It results from dehydration, severe diarrhea or vomiting, loss of plasma from the surface of the body as in burns, shock, excessive sweating, and any other condition in which body fluids are lost. The hemoconcentration returns to normal with administration of the necessary fluids to bring about normal relationship between plasma and cells.

Erythrocytosis may be a physiological occurrence at the extremes of life, following vigorous exercise, premenstrual, prenatal, after a heavy meal, etc. At birth the red cell count is rather high due to the relative anoxemia of intrauterine life. Four or five days after birth the

red count begins to decrease and gradually gets down to a level which is somewhat lower than the adult count. There is also an increase in erythrocytes per unit of blood in the senium (64). The number of red cells is higher in thin muscular individuals and is higher in the winter than at other seasons of the year in all people (115). After vigorous exercise, over heating, and as a premenstrual episode an increase in erythrocytes in the peripheral blood occurs and is due to the spleen suddenly being called upon and responding by throwing an excessive number of red cells into the circulation possibly thru the intermediaion of the sympathetic nervous system and consequent stimulation of the adrenals (83). An increase in erythrocytes occurs in the last few months of pregnancy and is probably due to the increase in blood cholesterol which inhibits hemolysis of the red cells (12). A local increase in red cells may be found where ever there is stasis such as occurs when an arm is at a lower level than the body or if a tourniquet is applied. Application of heat and cold also cause local increases in red cells due to vasodilatation.

Absolute erytocytosis, which is not due solely to the redistribution or concentration of circulating blood volume,

may occur. The usual causes are high altitudes, obstructed gas exchange, Ayerza's syndrome, and congenital heart disease. There appears to be two stages in the production of erythrocytosis resulting from exposure to high altitudes. One appears quite rapidly, unattended by evidence of new blood formation, as after a balloon ascension or among aviators or after suddenly lessened air pressure. It seems to all likelihood that this stage is due primarily to a rapid extrusion of red cells into the circulation, especially from the spleen. The other stage, which appears only after a sojurn of some days at low barometric pressures, is accompanied by evidence of erythroblastic activity in the circulating blood. This second stage is an acclimitization for high altitude and diminished oxygen saturation of arterial blood. Acclimitization to high altitude may be congenital or acquired (99). The second type requires readjustment of the biologic mechanism for fitness to life at high altitude. Bodily disturbances are produced by prolonged effects of high altitude on unadapted subjects resulting in mountain sickness. Among the most common symptoms of mountain sickness are headache, dizziness, ringing in the ears, vaque pain in the extremities, cough, shortness of breath on exertion, palpitation, moderate hemoptysis,

epitaxis and gastric distress with a feeling of indigestion; cyanosis, dilated superficial vessels, and moderate to conspicuous clubbing of fingers and toes are the prominent features (76). The erythrocytosis and symptoms subside immediately when a patient with mountain sickness descends to sea level.

Erythrocytosis may be due to a lowered oxygen tension in the blood as a result of obstructed gas exchange either in the lungs or their passageways. Emphysema with its fibrosis of lung radicles and increased residual air in the lungs, which hypothecates lessened total absorption area, causes a polycythemia. As long as the emphysema is uncomplicated the red cell count will not reach any striking figure, but soon a vicious circle is established by beginning failure of the right side of the heart, for when the right side of the heart is severly impaired, polycythemia becomes an outstanding feature (87). Other conditions causing a polycythemia are stenosis of the trachea or larynx, compression of the thorax, masses producing mediastinal obstruction, gas poisoning by pulmonary irritants, clinical or experimental pneumothorax, chronic cirrhotic pulmonary phthisis, and lung tumors or tumors pressing on the lungs. That the removal of the cause results in cessation

of the polycythemia is definitely proven. Cases of cavernous hemangioma of the lungs illustrates this. In cavernous hemangioma of the lung polycythemia is constant with the degree depending on the size of the arterio-venous fistula (55). Removal of the growth is followed by an immediate cessation of all signs and symptoms and by a rapid decrease in the polycythemia (67).

Ayerza's syndrome is not generally accepted as a definite clinical entity and there is very little written on it in English. The syndrome comprises chronic cyanosis, pulmonary emphysema, hypertrophy of the right heart and sclerosis of the pulmonary artery plus polycythemia (83).

Congenital heart disease, in particular pulmonary stenosis, may cause polycythemia. The polycythemia occurs as a result of obstruction or abnormality in the pulmonary circulation.

Erythrocytosis may result from the action of various chemical agents and pharmacologically active substances. The various inorganic salts of arsenic, phosphorous, cobalt, and manganese produce a polycythemia with chronic administration. Cobalt has a true hemopoietic effect and is used extensively in producing experiments polycythemia (36). Manganese makes the effect of cobalt more marked (80).

Various organic compounds such as anilin dyes, toluylendiamine, nitrobenzol, and atoxyl, may cause

erythrocytosis. Adrenaline and related substances (ephedrine and amphetamine) are the pharmacologically active substances which produce an erythrocytosis. Davis (39 &40) believes that the polycythemia in response to chronic administration of these drugs is due to the drugs increasing hempoiesis by causing local hypoxia of the bone marrow thru decreased blood supply to this tissue as a result of vasoconstriction. The polycythemic response to acute administration of these drugs is due to splenic contracture (134).

Polycythemia is believed to be a regular sign of carbon monoxide asphyxia (17). The polycythemia is supposed to compensate for the hemoglobin fixed to the carbon monoxide and thus to contribute in the defense of the organism. As a rule a gradual disappearance of the polycythemia follows the disappearance of the carbon monoxide hemoglobin, however, the polycythemia may persist for several months (43).

Prognosis and Treatment of Erythremia

Since erythremia is a disease characterized mainly by its complications, the prognosis depends on the type and severity of these complications. In the early stages of the disease, the greatest danger to patients with erythremia is the occurrence of thrombi or emboli. Because of the decreased resistence to infection among patients who have erythremia, another danger is the developement of intercurrent infection. If the patient is fortunate enough to escape these complications and treatment is instituted, the prognosis is good. The course of erythremia in cases in which treatment is not given in usually slowly progressive, although it may be interrupted by spontaneous remissions, sometimes of long duration. When anemia is severe and leukemoid reaction becomes so marked that the peripheral blood picture resembles that of myelogenous leukemia, the prognosis is poor and treatment is of little avail. In general the prognosis of erythremia is favorable (140).

The aim of treatment in erythremia is either to inhibit the production of or increase the destruction of red cells so that the number per unit volume of blood tends to approach normal. It is believed advisable to treat erythremia if for no other reason than to prevent

vascular complications (104). There are many methods of therapy, but today there are only four accepted methods of treatment, which methods have been tried and found effective and which can be used over long periods of time (33). These methods are the use of phenylhydrazine, Fowler's solution, irradiation, and venesection. Different patients respond differently to the various methods and what is good for one patient may not be good for the other.

Phenylhydrazine and Other Hemolytic Agents--Phenylhydrazine is the principle hemolytic drug used in the treatment of erythremia. The drug is cumulative in its action and, therefore, it should be remembered that hemolysis almost always continues for a week or ten days following its withdrawal. During the initial treatment, patients should be treated as though they were ambulatory, under hospital observation if possible, and every effort should be made to keep the circulation free and active. Phenylhydrazine should be given cautiously, if at all, in cases with advanced arteriosclerosis and visceral lesions, in cases in which the patient is bedridden, in cases in which the history is suggestive of extensive preexisting thrombosis, and in cases in which the patients are aged more than sixty years. In certain such cases rapid hemolysis and fatal outcome have occurred with small dosage.

It is recognized that the ideal method of treatment is one which would maintain the patient in more nearly normal conditions so far as symptoms, erythrocyte count, and blood volume are concerned. Giffin and Allen (53) found that the initial course of phenylhydrazine hydrochloride therapy should be one-tenth gram doses two or three times daily until a total dosage of from three to four grams of the drug has been administered, or, if less than this dosage is required, until definite clinical evidence of active hemolysis presents itself. After the initial course of treatment, and within a few weeks at the most, phenylhydrazine should be given in tenth-gram doses three or four times a week or in sufficient dosage to maintain the erythrocyte level between five and six million per cubic millimeter. Experience has indicated a small dose each week is safer than daily doses, for thrombosis is more likely to occur following daily administration of phenylhydrazine than following other forms of treatment (54). Long continued administration of the drug in this manner is followed by apparently complete inactivity of the disease, so far as the polycythemic state is concerned, with maintence of normal blood count and blood volume. An active preparation of phenylhydrazine hydro-

chloride must be obtained and it should be freshly placed in capsules each week as needed. Patients should be warned against increasing or decreasing the dosage too much or withdrawing the drug without careful consideration; these instructions prevent extreme swings in the erythrocyte count and blood volume. Patients should have a complete blood count done at least once a month.

The relatively small dosage of phenylhydrazine necessary for the control of erythremia in man is not harmful to renal and hepatic function in absence of advanced visceral or vascular disease. Examination of blood films morphologically during treatment has not revealed marked toxic abnormalities of the leukocytes (53). However, it is important to recognize that clinical experience has shown that phenylhydrazine in small dosage may cause rapid hemolysis and fatal outcome among older patients with advanced visceral disease. That phenylhydrazine is a safe drug if handled properly is well illustrated by Stealy's case (130 & 131) which was treated for eleven years with phenylhydrazine. Phenylhydrazine should not be given if the diagnosis of erythremia, with increased blood volume, cannot be well established.

Acetylphenylhydrazine is believed to be better than phenylhydrazine because it is less toxic (93). As with

phenylhydrazine, patients given acetylphenylhydrazine vary greatly in sensitivity to the drug, both from the standpoint of toxic effect and hemolytic action, and with such a great variation in effect, the use of the drug is very unsatisfactory in most cases.

Haden's routine (60) of administration of acetylphenylhydrazine is a one-tenth gram given daily for ten days unless contraindications arise. Hemolysis may continue after the drug has been withdrawn so if daily counts show evidence of rapid cell destruction, the drug should be discontinued at once. It is desirable to work out a regular dosage after the initial course. One dose of one-tenth gram weekly may be sufficient. The same precautions are to be observed as when administering phenylhydrazine. Jaundice, gastrointestinal disturbances, and sudden drop in red cells are among the danger signals in using either phenylhydrazine or acetylphenylhydrazine.

Benzol is another hemolytic agent which has been used but it is more toxic than either phenylhydrazine or acetylphenylhydrazine. Regardless of the hemolytic agent used the routine treatment should be an individual problem and the maintenance amount is arrived at by the trial and error method.

Fowler's Solution--Fowler's solution, a solution of potassium arsenite, induces remissions in erythremia characterized by reduction of red cells per unit volume of blood, hemoglobin and hematocrit values to normal or nearly normal, increase in body weight, increase in strength, and subsidence or d sappearance of symptoms. The action of Fowler's solution is disputed as to whether it is hemolytic or has a depressing effect on the bone marrow. The latter view is generally accepted.

The method of administration of Fowler's solution as established by Forkner and Scott (50) begins with doses of three to four minims (0.18 or 0.24cc.) three times a day. The initial dose is continued for two days, and then the total daily dose is increased by three minims. This amount is given for two days. Thereafter the dose is increased at the same rate until the first sign of intoxication, anorexia, is noted. This sign, as a rule, is first noticed when the dose reaches about twenty-four minims (1.48cc.) daily. When this dose of eight or ten minims three times a day is reached, or earlier if indicated, subsequent increments in amounts of the drug must be added more slowly at a rate of increase of not more than one minim to the

total daily dose. By such a method, the medication may be carried out up to twelve, fifteen, or even twenty minims (0.74, 0.92 or 1.25 cc.) three times a day. Continued increase until the desired effects are obtained or until the limit of tolerance has been reached is essential for frequently the best therapeutic results are to be obtained with a dose which is near the upper limit of tolerance. With a solution of potassium arsenite the tendency is to give too little rather than too much. Mild toxic symptoms are to be disregarded, or the best results often will not be obtained. When the blood has improved considerably or when the limit of tolerance has been reached, Fowler's solution should be gradually withdrawn. The daily dose may be decreased by one minim daily until the patient is taking about five minims three times a day, which amount may be continued without harm. Remissions may be prolonged at least for several months by continuation of medication in reduced amounts.

If, with the larger doses of Fowler's solution, rather severe toxic symptoms develop, the drug may be entirely omitted for forty-eight or seventy-two hours and then resumed in doses equivalent to about three-fourths of the amount the patient was taking at the time of the development

of symptoms. From this point the drug may again be increased or may be decreased as indicated by the effects on the patient. The medicine is best given after meals well diluted in orange or tomatoe juice or some other flavored drink.

The character of the signs and symptoms of toxicity of Fowler's solution depends on several factors, chief of which seems to be the susceptibility of different persons to arsenic. Other factors are: quantity of arsenic ingested with each dose, amount of dilution of the medicine and relation of the time of meals to time of taking the medicine. The loss of appetite and later mild nausea are perhaps the most common early symptoms, indicating that the limit of tolerance for the solution is being approached. Vomiting usually indicates that the medicine has been increased too quickly, or that the patient's gastro-intestinal tract is in an unusually irritable state. Diarrhea consisting of from four to six rather loose movements daily is a common symptom when larger doses of the drug are taken. Chemosis of the conjunctivae, lasting a few days, is a troublesome but not a serious complication. A slight burning sensation in the toes and fingers occurs occasionally, but no permanent changes occur. In rare instances peripheral neuritis may follow the administration of arsenic. Pigmentation of the

skin and hyperkeratosis occasionally occur following in the wake of long continued treatment with Fowler's solution.

Irradiation--As with its sister blood dyscrasia, chronic myelogenous leukemia, irradiation has established itself as one of the best and most lasting methods for the treatment of erythremia. The methods of giving x-ray therapy in erythremia varies among three types: irradiation of the long bones and sternum, irradiation of the spleen, and "spray x-ray therapy." At the present time most observors are in favor of the last method.

Kaplan (79) is the principle advocator of treating erythremia through small ports, particularly the bone marrow sites of erythropoiesis of which he believes the ribs and sternum show superior sensitivity. He recommends individual doses of a hundred and fifty to two hundred roentgens every three days. It is advisable to curtail treatment when the count begins to show a constant decline; furthermore, the level of the erythrocytes must be judged in relation to the symptomatology. In the absence of uncomfortable symptoms, treatment need not be administered in the presence of a red cell count of six million or therabouts. Irradiation of the spleen has no lasting effect on the symptoms or red cell count of erythremia (121).

Irradiation of the body as a whole with high voltage roentgen rays is diversely termed total irradiation, tele-

roentgenotherapy, roentgen baths, or spray therapy. Hunter (75) gave the first account in English of this type of therapy in 1936. Spray therapy, when administered in small doses over long periods of time, has astonishingly prolonged depressant effect on the blood forming organs, produces no disturbing clinical symptoms, and may be given without interruption of the patients daily work.

In spray therapy the patient is placed two to two and a half meters from the anode of the therapy tube, either in a chair or on a stretcher. The patient faces the tube with no lead protection of any kind. Thirty to fifty roentgens are given at a treatment, and the treatments are administered every day or every second day. This dosage is measured at the patients distance and also calculated from the intensity at fifty centimeters by the inverse square law. The amount of filtration seems to make no difference in the results (112). The total dose varies from two hundred to twelve hundred roentgens per series, with the average between five hundred to six hundred roentgens in one group of patients (121).

The white cell level is the most accurate measure for determining the amount of spray therapy to give in any one case. Daily white count should be made and when the number

per cubic millimeter drops below four thousand, the treatment should be stopped. If this rule is followed, an overdose can be avoided. The white count continues to drop for a short time after the cessation of treatment, but then gradually returns to normal. Hemoglobin determinations and red cell counts are unnecessary during therapy, because no change is evident in these elements until one or two months after the patient has been treated.

Repetition of roentgen therapy of the entire body from the standpoint of dosage is not contraindicated. However, if at the end of three months after a series of treatment the red cell count has not fallen satisfactorily the course of treatment should be repeated cautiously. When the red cell count raises above six and a half to seven million the series should be repeated. Remission of symptoms is variable in length of time, but longer on the average than with other methods of treatment.

The dangers of spray therapy are leukopenia and late irradiation anemia. However, the anemia need not necessarily be due to treatment. When leukopenia results the patient is unable to combat intercurrent infection.

Grenz rays, electro-magnetic oscillations of about two Angtrom units which produce characteristic biological and clinical manifestations, have been used by Bucky and

Uttal (24) in the treatment of erythremia. Absorption of Grenz-ray is almost complete in the skin--eighty-eight per cent is absorbed in three millimeters of skin and only twelve per cent reaches the subcutaneous tissue in this instance; while more than ninety per cent of roentgen rays pass thru such a layer of skin, indicating that its action is different than that of x-ray in erythremia. It was the experience of these writers that decisive results were not to be expected from but one series of treatment and the physician should not be discouraged, therefore, if improvement does not set in even after a lapse of several weeks. The first evidence of improvement is generally symptomatic, and not until later does a diminution in red cells and hemoglobin began to be demonstrated.

In administration of Grenz-ray in erythremia the surface of the trunk is divided into eight to twelve fields--from four to six on the anterior and from four to six on the posterior aspect--so as to give a right and left abdominal and a right and a left thoracic area, with corresponding fields on the dorsal surface. Assuming that the stimulus would have to be repeated and treatment, therefore, extended to cover a certain period of time, they (Bucky and Uttal) treated an area daily, so that after a lapse of eight days each area had one radiation. In

order to prolong the stimlus, the whole procedure was then repeated, except that now an interval of one day was interpolated between each two exposures. This procedure requires twenty-four days and one complete treatment of this sort is called a series. There is not the slightest danger in repetition, for doses employed cause no demonstrable change in the skin. Simple though the procedure may be in itself it must be based upon scrupulously exact dosage, and must, therefore, be supervised by an experienced operator. The single dose which the writers employed amounted at fifteen centimeters focal distance and with a field about fifteen centimeters in diameter to some hundred and fifty roentgens. It is usual to find patients more resistent to Grenz-ray therapy if they were previously given x-ray.

The latest therapy used in erythremia is the use of radio-active substances, especially radiophosphorous (88). Radiophosphorous is selectively taken up by bone, bone marrow, leukemic tissue, and any rapidly growing tissues. These tissues, therefore, will be selectively radiated. However, it is impossible to maintain a continuously uniform exposure.

Radioactive phosphorous may be administered either orally or intravenously; intravenous is preferable.

Single oral doses varied from one to twenty millicuries in one series of cases (49). The radioactive phosphorous is given in the form of sodium phosphate. When the drug is given orally the phosphate may cause a diarrhea resulting in a loss of some of the drug. The first intravenous dose should be small, one-tenth to three-tenth millicures, and if this is well tolerated, larger doses (one to three millicuries) may be given. The frequency of administration depends on the patient. Usually repeated small doses are preferable to a single large dose. The total number of doses varies according to the hematologic and clinical status and response of the patient.

Fitz-Hugh and Hodes (49) claim that radiophosphorous has no danger of cumulative radiation effect since it has a half life of fourteen and three-tenth days. Nearly fifty per cent of any given dose is normally excreted during the first six days and excretion is continued thereafter. Thus after six weeks no significant amount of radiation can be found in any tissue following a single administration of radioactive phosphorous. Radiophosphorous is quickly concentrated in the bone marrow, liver, spleen, bones and so forth of erythremic patients, for various amounts are absorbed and excreted by circulating red cells, reaching a peak of exchange between twelve and twenty-four

hours after consumption (45). The radiophosphorous which is concentrated in the bone marrow continues to bombard the erythropoietic tissue for days. Both radiophosphorous and roentgen radiation probably decrease the red cells by retarding the mitosis of normoblasts in the early prophase (62). Therefore, improvement is rarely obtained until treatment with radioactive phosphorous has been carried out for two or three months.

Complications to radiophosphorous in the forms of anemia, leukemia, and thrombocytopenia are frequent occurrences (44). In most instances there is excellant evidence to show that these complications are induced by the therapy and are not manifestation of the disease per se. They frequently occur weeks or several months after the last injection of radiophosphorous has been given, because the drug continues to radiate energy for weeks. Usually these complications are of short duration and not serious. Aplasia of the bone marrow has also occurred as a result of radiophosphorous therapy (66) and one group of writers (61) report a case which developed acute leukopenic myelogenous leukemia.

The blood of patients treated with radioactive phosphorous should be studied at frequent intervals so that

hematologic changes can be recognized early and further administration stopped before irreversable toxic effects on the bone marrow are produced.

Treatment with radioactive phosphorous is in no way curative; but the disease can be more readily controlled with internal radiation. Results obtained, ease of administration, absence of radiation sickness and toxic symptoms, concentrated effect of irradiation on the cells of the bone marrow, together with the fact that radioactivity disappears gradually and the dosage can be adequately controlled indicate that this method of treatment of erythremia is superior to other methods employed in the past. However, radioactive phosphorous is, at the present time, difficult to secure and very expensive.

Venesection--Venesection is the oldest and the least used method of treating erythremia at the present time, for it is usually considered to be a measure of expediency rather than one of real value. However, venesection is a safe, reasonably efficient form of therapy, all patients respond to this treatment, and all toxic reactions are avoided. Since the blood of patients with erythremia is not as free flowing as normal blood and clotting in the needle and tubes is more prone to occur, it is desireable to use a needle

no smaller than a number fifteen bore and no longer than one inch. The rubber tubing should be as short as conveniently possible. An adapter between the needle and the tube nearly always impedes the flow of blood and is, therefore, undesirable.

The amount of blood to remove at each venesection and the frequency of removal are greatly disputed. Haden (60) believes that the most satisfactory method of treatment of erythremia is the removal of a sufficient quantity of blood to produce an iron deficiency, thus preventing formation of red cells. The excess red cells are completely removed if no contraindications arise. He has devised a formula making it easy to calculate the amount of blood to be removed. This calculation is based on the red cell mass which is determined from the total blood volume and hematocrit reading and the normal red cell mass of the patient. After the red cell mass is reduced to normal by venesection, the regeneration of the blood is slow. Patients vary in the rate of regeneration but usually venesections are required only at intervals of six to twelve months. Haden also states that if the spleen is very large and the leukocyte count high, especially if myelocytes appear, irradiation of bone marrow and spleen should be utilized also.

Removal of four to five hundred cubic centimeters of blood from an erythremia patient may be expected to give prompt relief of such symptoms as headaches, nervousness, palpitation, and unpleasant heat sensations and to reduce the red cell count, hemoglobin content and viscosity at least temporarily (73). As a rule the reduction occurs within a few days, but occasionally the full effect is not realized until the fifth or seventh week. Remissions last for a varying length of time, the extremes being a few days and a year. Usually the blood-lettings of four or five hundred cubic centimeters affords subjective benefits for about two months and, paradoxically, lesser quantities (350 to 450 cc.) seem more effective in this respect than larger (700 to 750 cc.).

The removal of small quantities of blood is thought to be more effective than the removal of large quantities. (69). Large removals result in partial symptomatic relief of certain symptoms, but undesireable symptoms are also produced. No symptoms are produced by small venesections. When small venesections are employed there is a gradual reduction of hematocrit, blood viscosity, and hemoglobin. This effect is in sharp contrast to that produced by large venesections in which a sharp fall is followed by an equally

sharp rise.

The estimation of the red cell volume is the best guide for the therapeutic use of venesections in the treatment of erythremia. However, the hematocrit reading alone with hemoglobin estimation and red cell counts serve as an adequate substitute (69). The blood viscosity and specific gravity determinations offer no advantages, either of accuracy or simplicity.

The present common objection to the use of venesection in the treatment of erythremia is based on the premise that repeated bleeding stimulates the bone marrow excessively, tending to premature exhaustion. However, Falconer (46) found that venesections, used as a means of reducing red cells and hemoglobin in erythremia, does not increase the reticulocyte per centage above normal limits.

Venesections may be a useful adjunct to phenylhydrazine therapy by permitting smaller doses of this drug to be efficient in maintaining an approximately normal blood level (46).

Miscellaneous--The remaining methods of treatment to be discussed have all been tried in erythremia but none of them have proven too successful or have been studied very thoroughly. Diet with a low iron content used with the

hope of inhibiting red cell production by producing an iron deficiency anemia has not been successful (85). Splenectomy has been tried but is contraindicated in erythremia for the red count rapidly increases after the operation with resulting death. Saurer (121) reports such a case.

Falconer (47) treated eleven patients with lead compounds both orally and intravenously over periods of time varying approximately from one to five years. Nine cases were relatively free of symptoms during the treatment and were able to continue their work. The dangers of lead are real and should be emphasized. Administration of lead acetate by mouth is rather unsatisfactory because one does not know how much lead a patient is absorbing and because cummulative effects may not be evident until toxic episodes occur. Intravenous use of lead may damage the liver, central nervous system, or peripheral nerves. Colloidal lead phosphate given intravenously was found to be efficient in controlling symptoms and reducing the blood level in erythremia. Colloidal lead phosphate begins to destroy red cells immediately after it has been administered.

Davis (37 & 38) found that choline hydrochloride and liver depresses hemopoiesis in experimental polycythemic

dogs, and that it tends to return the red cell number to normal. Follow up work on Davis' experiments was done by another group of workers (95). Their work was done on five cases of erythremia in man, and, although there results were not absolutely conclusive, it was their interpretation that administration of raw calf liver or choline hydrochloride is probably without value in the treatment of erythremia.

On the theory that erythremia is due to an excess hemopoietic factors, some observors (18) have used gastric lavage in the treatment of erythremia. Lavage of the stomach in their case of erythremia resulted in an improvement of the clinical picture with a decrease of the individual cell constituents of the blood.

One group of observers (86) going on the rational that myxedema produces anemia and a decreased blood volume subjected their patient to a total thyroidectomy. After the operation all the alteration in the blood of the patient were in the direction of normal. The patient was relieved of her erythremic symptoms, but her post-operative complaints were those of myxedema.

The results of oxygen therapy have been observed in erythremia (8). There was no significant alterations in the erythrocyte count or hemoglobin percentage noted.

Symptomatic and Prophylactic Treatment--Symptomatic and prophylactic treatment are important in erythremia, for in addition to treating the blood in erythremia, the patients must be treated. Erythremic patients, if properly treated, may have a long life, if not a merry one (117). It is important for the physician to pay attention to the emotional factors for these patients are high strung, nervous and irritable. These emotional factors may cause much unhappiness to the patient and they make treatment difficult.

As far as possible a physician should avoid putting patients with erythremia to bed, because they are prone to develop thrombosis and it is better to keep them fairly active. These patients also have a marked congestion of the mucous membranes, so a diet must be selected which will minimize the possibility of irritating the membranes. The diet should exclude condiments, too much roughage, alcohol, and foods and liquids which are very hot, as all of these may irritate the congested gastro-intestinal mucosa. Above all, it is important to keep the patients blood count at a level which gives the greatest comfort and least complaints rather than reach some arbitrary base line on the chart. To reiterate the physician must not treat a blood count but the entire patient.

Pathological Anatomy of Erythremia

The most striking feature on post mortem examination in erythremia is the extreme engorgement of all the organs with blood. Thrombi and hemorrhages are frequently to be noted.

The spleen is nearly always enlarged and is smooth, moderately hard and dark bluish in color. Thrombi, anemic infarcts, and cysts produced by hemorrhages are to be found (65). The follicies are not readily seen.

The liver is enlarged in most cases and is markedly hyperemic. When thrombosis of the hepatic veins occurs, it is markedly enlarged with acute passive congestion, and central hemorrhages, atrophy and necrosis are to be found (128). Cirrhosis of the liver may be present and subsequently the liver may be shrunken and nodular, owing to connective tissue replacement and parenchymal hyperplasia. Thrombosis of the portal vein is usually revealed to be an old thrombotic process with some canalization.

The kidneys usually show no characteristic abnormalities in addition to the general hyperemia. Occasionally changes of chronic nephritis or arteriosclerosis may be encountered but these are not always associated with erythremia and may be an unrelated condition.

The brain shows tremenduous dilatation of the blood vessels, including both arteries and veins. Rupture or thrombosis of these vessels may occur. A more or less complete anoxemia of the central nervous system has been noted (143).

The bone marrow has already been discussed. To briefly summarize--the marrow of the long bones is engorged and the short bone contain marrow which is characterized by erythroblastosis and leucoblastosis. Increase in megakaryocytes is common.

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