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General review of erythremia with special attention to the present day treatment

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GENERAL REVIEW OF ERYTHREMIA WITH SPECIAL ATTENTION TO THE PRESENT DAY TREATMENT

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Subject Outline

ERYTHREMIA

Synonyms

"Polycythemia Vera", "Polycythemia Ruba", "Maladie de Vaquez or Vaquez-Osler", "Erythrocythemia", "Megaloslenica", "Splenomegalic Polycythemia" (Parkes Weber), "Myelopathic Polycythemia", Polycythemia with chronic Cyanosis", "Erythrocytosis Megalospelica" (Senator), "Cryptogenic Polycythemia" (R. C. Cabot), "Vaquez's Disease", "Oslers Disease", and "Vaquez-Osler's Disease".

In this paper the term "Erythremia" and "Polycythemia Vera" are used, mainly because it is by these names that the disease is most commonly known, having come more in vogue than any of the other titles enumerated above. It seems that whenever a new disease is recognized and described, a great deal of confusion will ensue due to the multiplicity of titles that will be attached to the disease entity. It is a common occurence to attach the names of the men who first describe and give an account of the disease. Vaquez first reported a case in 1892, and Osler in 1903 reported nine cases drawing wide spread attention to the possibility of a new clinical entity. Because of this fact their names have become attached to the disease, and since that time other names have been attributed by men who have made an endeavor to so endorse the disease by a name more descriptive of the characteristics it presents. Parkes Weber (1) suggests the term "Splenomegalic Polycythemia" because of the almost constantly characteristic enlargement of the spleen

associated with an increased number of erythrocytic elements in the blood, mainly because one may have other conditions in which there is a relative polycythemia different from the disease described in this paper, and conditions not associated with splenic enlargement.

It is for the same reason that Senator (27) suggests the term "Erythrocytosis megalosplenica". The title "Polycythemia with chronic cyanosis" was introduced because an increased red blood cell count is the most outstanding and characteristic feature and associated in practically all the cases with a persistent and constant bluish discoloration of the skin. At present the name "Erythremia" as suggested by Turk of Vienna (28) and others is gaining preference over the other terminology, and it is a name well suited for the disease, as will be pointed out later when considering the etiological and pathological features of this desease.

Classification

Innumberable endeavors have been made to classify the various conditions or maladies in which a Polycythemia (an increased red blood cell count) is an outstanding feature. A simple classification and yet a suitable one is that of Pack and Craver (3) which is as follows:

"I. Functional, relative, or compensatory Polycythemia
This variety is generally physiologic and temporary. It is examplified by the Polycythemias of high altitudes, fright, dehydration, etc.

II. Erythremia, Essential or Absolute Polycythemia,

Polycythemia Vera

1. Ayerza's Desease, "Cardiacos Negros". This is a form of disease characterized by sclerosis of the pulmonary artery, enlargement of the right heart, cyanosis, Polycythemia, dyspnea, cough and hemoptysis.
2. Polycythemia Hypertonica of Gaisbock presents the clinical picture of arteriosclerosis, hypertension, nephritis, and Polycythemia.
3. Polycythemia with splenomegaly is the common sort, originally described by Vaquez (5)." It is this disorder with which this paper deals.

Definition of Erythremia

Osler (4) in his original article defines Erythremia as a "New clinical entity characterized by a chronic cyanosis, polycythemia, and moderate enlargement of the spleen. The chief symptoms being weakness, prostration, constipation, headache, vertigo."

More recently Parkes Weber (1) defines the disease in a cleaner, more detailed, and modern manner as a "morbid condition, characterized by a well-marked persistant relative and absolute polycythemia (increased number of red blood corpuscles) due to an excessive erythroblastic activity of the bone marrow, which appears to be the primary morbid factor in the condition; it is characterized likewise by a persistent increase in the viscosity and total volume of the blood, and often by a cyanotic appearance of the patient, and usually if not always, by an easily felt enlargement of the spleen."

Even this definition does not in itself seem complete in as much as it does not mention its insidiousness of onset, its characteristic and progressive course in as much as the disease is by all means a chronic one and the patients, especially in the earlier stages of the disease, are ambulator often able to go about their usual daily routine of work.

History

As before mentioned, first attention to this disease was made by Vaquez (5), a Paris physician, in 1892. Vaquez, well known for his work and researches on the pathology of the blood, described a condition of hyperglobulism with cyanosis, which he believed to be due to an overactivity of the blood-forming organs. Following this in 1895 in a supplementary note, he drew attention to the fact that the condition was associated with an enlargement of the spleen and also that there was an absence of cardiac lesions in this particular case.

In 1899 three more cases were recorded in the literature. The first to appear was the case of Rendu and Widol (6), the second by Moutard-Martin, and Lefas (7), French physicians, and the third case of that year was reported by Cabot (8) of Boston. Cabot (9) reported his second case in 1900. The fifth case was reported by Cominotti (10) in the same year. McKeen (11), a Boston physician describes the sixth case reported in the literature in an article entitled "Marked Cyanosis Difficult to Explain". In 1902 an article appeared in the Lancet by Saundby and Russell (12) entitled, "An Unexplained Condition of Chronic Cyanosis, with the Report of a Case". It was these

two men who first realized that it may be a definite clinical entity new to medical science. In the same year Turk of Vienna (28) reported a similar case and a second one in 1904. The first necropsy was reported by Weber and Watson (14), who at the time stressed the probability of a primary disease of the bone marrow.

Due credit must be given to Osler(15) for drawing wide attention to this disease. It was in 1901 when he first became interested in the disease, having at that time a case with cyanosis and a very high red cell count. Later he came in contact with two other patients presenting the same syndrome, and these two cases plus his original one founded the basis for his first paper published in the American Journal of Medical Sciences (4), entitled "Chronic Cyanosis with Polycythemia and Enlarged Spleen". It was in this paper he stated he felt he was dealing in all probability with a new disease entity. By 1904 he had summarized seventeen cases and published these in the British Medical Journal (15). It was these two papers that drew wide attention to the condition in America and England, as well as in other foreign countries, to the extent that by 1907 over seventy cases had been reported in the literature, with the realization that the condition was not nearly as rare as was first supposed, and by 1912 Lucas(16) was able to find records of 179 cases.

Etiology

There has been considerable dissention between the various authors as to the etiology of Erythremia and consequently, se-

veral theories have been postulated, endeavoring to explain the pathological findings found in this particular disease. The consensus of opinion at the present time, however, is that Erythremia is a primary disease of the bone marrow. This by all means gives the most rational basis on which to found a working hypothesis and takes for its starting point the remarkable and extensive hyperplasia of the red marrow as is found in this disease. The polycythemia and the extraordinary increase in the circulating blood volume logically appear to be a consequence of this hyperfunction and the pathological alterations in the circulation which they in their turn produce seem to explain very many if not all of the symptoms and physical signs. The part played by blood destruction in the process, on the basis of the evidence which has been discovered to date must be regarded as distinctly secondary.

First observation and discussion of the possible etiology considering the hyperplasia of the red bone marrow was made by Gibson (17) at the annual meeting of the British Medical Association at Shieffield. In this paper he discussed a case in which a biopsy of bone marrow had been made from the tibia showing decidedly increased erythroblastic and leublastic activity. Again in 1912 a second biopsy was done by Alexis Thomson in the case of Watson-Wemyss (18). In this case a trephine was made through the center of the shaft of the tibia and some bone removed for examination. This was red in color owing to the presence of blood, and microscopic examination again revealed distinct, though slight, evidence both of erythroblastic and leucoblastic reaction. The reaction, since it was doubtless present in all the other long bones of the body,

was, though slight in degree, yet sufficient in his opinion to explain the increase of both red and white cells in the circulating blood.

According to Parkes Weber (1) in his most recent work the excessive formation of red corpuscles in Myelopathic Polycythemia may be regarded as analogous to the excessive formation of white blood corpuscles in cases of leukemia. It can likewise be explained as the result of a morphological and functional reversion to (or in certain cases, persistance of) a past condition (normal in fetal life and early life after birth) in which the bone marrow of the shafts of the long bones is red and still actively engaged in the formation of erythrocytes, instead of being yellow and fatty as most of it is in healthy adults. If the analogy to leukemia proves to be appropriate, the term "Erythremia" must be considered preferable to "Myelopathic Polycythemia" and various other names which have been proposed, since it implies that the disease is one which in regard to erythrocyte-formation is analogous to leukemia in regard to leucocytic formation. Weber continues farther to say that "Just as leukemia has been suggested to be a cancer like or sarcoma like neoplasm of the myeloblastic and lymphoblastic tissues, so it has been suggested that Erythremia is a neoplasm of the erythroblastic tissues of the body.

Harrop (19) is of the same opinion as Parkes Weber in that he likewise considers Erythremia to be a disease primarily of the erythroblastic tissues, but also he expounds a second hypothesis which could regard the condition of the bone marrow as secondary to one or several different factors causing over-

stimulation. It takes into account first of all the fact that the essential differences existing between polycythemia of known secondary origin and so-called true primary polycythemia are often very slight, indeed, if considered from the standpoint of clinical signs and symptoms. In view of the more recent literature, it seems quite possible that a hormonal control of the bone marrow activity will eventually be demonstrated, which governs the production or maturation of blood cells. The occurrence of hormonal imbalance as suggested by several writers will then seem very likely.

According to Parkes Weber (1), who cites Lommel, we find the latter has endeavored to show that most cases of Erythremia are really due to blood stasis (impeded circulation), as is found in polycythemia of chronic cardiac and pulmonary diseases. Due to decreased oxygenation of the blood insuch cases, the red bone marrow becomes stimulated with increased formation of red blood cells. According to this view then, the polycythemia is a conservation or compensatory mechanism in which an automatic attempt is made to make up for deficient oxygenation of the tissues by increasing the number of red cells which are the oxygen carriers of the blood. Opposing this theory, Parkes Weber states, "The signs of more or less impeded circulation do not necessarily signify that impeded circulation is the chief cause of the polycythemia."

Bence, as cited by Parkes Weber, states that "The polycythemia of Erythremia can be decreased by oxygen inhalation". Just as he claims that the polycythemia of cardiac origin and that due to high altitudes can, and consequently takes the stand as Lommel does. However, that oxygen reduces the polycythemia

cannot be confirmed by those who have endeavored to do so, by oxygen inhalation even in its most radical and modern form. Barach and McAlpin (20) treated two cases by this method and came to the conclusion that there was no significant alteration in the red blood cell count, the hemoglobin percentage or the oxygen capacity in either of the two cases of Polycythemia Vera who breathed an atmosphere containing fifty percent of oxygen for a period exceeding two weeks. This, in conjunction with others who have given the same treatment to patients with Erythremia without success, appears to make improbable the theory that Polycythemia Vera is based on an anoxemic stimulus.

Other theories concerning the probable etiology have been postulated only to receive little if any support. In view of this fact, they will be simply enumerated:

A. Increased durability of the blood cells.

B. Diminished oxygen capacity of the hemoglobin.

C. Possible toxic and infectious origin.

D. Nervous excitement and mental worry.

Symptoms

The symptom complex as is found in Erythremia is by no means constant nor uniform, and inview of this, plus the fact that the patient may often be practically symptom-free, especially in the early stages of the disease, the diagnosis is often made late in the course of the disease or may be recognized only accidentally. This is confirmed by the fact that many of the patients present themselves to their physician in the early stages, not for any disturbing symptom, but for minor changes that they have noted in their physical make-up. Patients

have been known to apply to their physician for cosmetic reasons, because of the flush of the skin, when they were otherwise symptom-free. Others may seek medical aid because of the splenic tumor, and with no other symptom to be found, even on careful questioning. Others may present themselves because of degenerative symptoms which occur at the same age as the Erythremia begins. This is especially brought out by Harrop (21), who states: "The decades during which the malady appears are just those in which the development of secondary lung changes, fibrosis or emphysema, or arteriosclerotic changes in the brain, may be the culminating event which impresses on the mind of the patient that there is some serious disroder." It seems that the nervous symptoms are among the most common for which medical advice is first sought, and, it may be noted, those symptoms which are common in mild grades of chronic anoxemia.

There does seem to be a certain rather characteristic type of body-build in persons suffering from this disease, a fact remarked by several authors, (Harrop, Parkes Weber, and others). They are very seldom stout or overweight, but on the contrary, are usually spare, with thin, often rather narrow faces. However, exceptions to this are frequent so that it is no certain nor definite factor. From the records of Harrop's (21) cases, it was found that persons of fair complexion are more frequently affected than are brunettes, a point of similarity to Pernicious Anemia.

Due to the multiplicity of symptoms that may occur, these will be discussed separately according to systems.

Skin and Mucous Membranes

The striking color of the skin in Polycythemia Vera and

the various factors in its production have been the subject of interesting studies. Leading in this particular phase are Brown and Giffin (22-23-24). The color of the skin was first described by Vaquez, and the distinction between the color typical of Polycythemia Vera and that of ordinary cyanosis has really been well recognized by all the writers. The distribution of the abnormal skin color is of interest. It occurs especially on the exposed surfaces--the face, particularly the cheeks, the tip of the nose, and the ears are usually prominent. Sometimes it extends to the neck, but the trunk in general shows no such remarkable color change. The hands and dorsal surfaces of the forearms are colored, but less often the lower lega and feet. At times, however, expecially in patients with erythromelalgic symptoms, the coloration of the lower extremeties is very striking. It is a mixture of blue and red, the shades depending, as Osler (25) early recognized, upon the state of dilitation of the peripheral vascular network and upon the speed of the circulation through these areas. The coloration frequently has been noted from early youth, long before appearance of symptoms. Harrop (21) has especially drawn attention to the above facts. Pigmentation, usually brownish, often the result of small skin hemorrhages, is quite common in the long standing cases. These features are very striking, however, the characteristic skin color is often absent, even in cases with marked polycythemia so that the discoloration is not a constant finding and may be misleading, which is particularly stressed by Christian (26). As the red count varies from time to time, and particularly when there is a marked drop following therapy, the color changes are

apt to be abrupt and striking.

Skin lesions characteristic of the disease have been mentioned, but few have withstood the test of extensive study. Eczema and dryness of the skin are described (Harrop (21)). Brown and Giffin (24) mention the frequent occurence of paresthesias and describe these as being quite typical of the disease, noting the similarity again in this respect to Pernicious Anemia. They feel that the plethora and stasis of blood in the peripheral vessels may account for these symptoms. Cases of Erythremia with painful vasodilator disturbances are not unusual. Weber (14) has described cases of this kind as well as Brown and Giffin (24), who mention the frequent occurence of intermittent celaudication. The erythromelalgia is usually aggravated in the dependent position, when the skin deepens to a dark reddish cyanosis, often with edema, and relieved on elevation. The vascular engorgement is not limited to the skin, but may be observed likewise in the mucous membrane of the mouth, fauces, larynx, in the conjuctiva, and by opthalmoscopic examination ~~examination~~ in the retinal veins. Especially characteristic is the bluish-red appearance of the tongue.

Nervous Symptoms

Christian (26) has paid special attention to the nervous manifestations as found in Erythremia and the significance of these symptoms in view of the fact that the nervous and psychic disturbances of the disease, together with the disturbance of the special senses are often its first and most striking manifestations. Of these the most prominent are lassitude, headache (occasionally typical migrain), vertigo and giddiness, transitory

syncope, insomnia, weakness, a sensation of fullness in the head, numbness and tingling in the fingers, less often in the feet, burning sensations, and extreme sensitiveness to cold. They very often bear a marked resemblance to the symptoms of mountain sickness, a fact to which Osler (4) early drew attention. Some of the paresthesias are curious abnormalities, as in the patient described by Weber (1), who found that everything touched felt wet. Rheumatic pains are very common and are of a boring character, and maybe due in part to the pressure of the swollen hyperplastic bone marrow. Cases have been reported in the literature with an increased spinal fluid pressure, and with spinal puncture many are afforded marked relief from their distressing headaches (Harrop (21)). The cause of the increased spinal fluid pressure is attributed to the overfilling of the cerebral and spinal blood vessels.

Christian (26) has drawn attention to the interesting superficial parallel between the sensory symptoms of Polycythemia Vera and Pernicious Anemia. However there appear to be no reports in the literature noting any evidences of similar cord lesions at autopsy in polycythemia. Many writers lay stress on the role of polycythemia in many obscure neurological diagnostic problems, because a filure to keep them in mind very often has led to diagnostic mistakes andin some instances to cerebral operations, with the idea that the symptoms were the result of brain tumor. An example of this is Christian's Case IV, (26) who had had a decompressive operation because of a suspected tumor, which was, however, manifesting symptoms due to thromboses of cerebral arteries.

The incidence of symptoms referable to the nervous system in polycythemia is relatively high. Again refering to Christian (26), who has laid great stress on the nervous symptoms of Erythremia, we find that a resume of his ten cases showed mental and nervous symptoms present in all but two cases, and in most of the cases the nervous disturbances were the chief cause of the patients' discomfort. The symptoms varied in duration from a few days to many years. The most frequent symptoms in review of his cases and others were headache and dizzyness. Others frequently present were disturbances of vision, such as easily induced fatigue of the eyes, blurring of vision, scotomata often scintillating, transient blindness, hemianopsia, and diplopia. Disturbances of sensation as previously noted, particularly paresthesias, occured. In several patients motor disturbances, such as paresis and paralysis were seen.

Brockbank (30) in a review of fifty-seven cases summarized the incidence of the various nervous symptoms as follows:

Headache, 33; vertigo, 30; general weakness, 15; easy fatigability, 13; fullness in the head, paresthesias, mental impairment, 11 cases; visual disturbances, pain, nausea, and vomiting, 9 cases; nervous irritability, 8 cases; emotionalism, 5 cases; sleep disturbances, generalized pruritis, tinnitus, 4 cases; diminished hearing, heat intolerance, stumbling speech, syncope, diminished libido, uncinate fits, urinary incontenance, sensation of choking, paralysis of one side of body, one case.

The psychic disturbances are very varied and often lead

to a mistaken diagnosis of neurasthenia or of cerebral arteriosclerosis. Transient loss of memory for even the commonest events of the daily routine occur. Fits of emotional disturbance, somnolence, hallucinations, mental depression, and slurring of speech are not uncommon.

Splenomegaly

The early writers placed a great deal of stress on the enlargement of the spleen. However at the present time, it is estimated that splenomagaly is present in about three-fourths of the cases and is by no means a constant feature of the disease. The size of the spleen, in the reported cases, where splenomegaly is present, varies greatly in individual patients, and at different periods in the same patient often irrespective of treatment. Although the size is variable, it may often be palpable down to the umbilical level and hardened. When treatment produces a normal blood count or secondary anemia, or even in the absence of treatment, the spleen may diminish in size as to be no longer palpable. Considerable variation in the amount of enlargement from time to time is a common clinical observation. It is usually supposed that the polysythemia antedates the enlargement of the spleen. In Watson Wemyss' (18) cases, however, marked splenomegaly appeared before the polycythemia, and other similar instances are reported. Parkes Weber (1) considered the chief cause of the splenic enlargement to be blood engorgement, and in the light of Bancroft's (29) recent work, this seems to be a reasonable explanation. Tuberculosis of the spleen was early reported, especially in the French literature, as the primary

cause of Polycythemia Rubs, but this theory has been abandoned. The enlargement of the spleen in Polycythemia Vera is usually quite firm and smooth, as mentioned above, and in this respect feels not unlike that of myeloid leukemia. Pain in the splenic region is very common and tenderness on palpation occurs, often more marked after treatment has been instituted. Spontaneous rupture of the enlarged and engorged spleen does not seem to have occured in the reported cases.

Gastro-intestinal Symptoms

Sumptoms complained of referable to the Gastro-intestinal tract are variable both in occurance and degree. Feelings of fullness in the stomach, thirst, dyspepsia, gas pains, belching, and especially constipation, are exceedingly common. Pain, tenderness, and a feeling of tension in the left hypochondrium are complained of and of course, attributed to the splenic enlargement. Often this pain extends up into the left shoulder or down the left side and left leg. Symptoms referrable to hemorrhage may occur and be localized anywhere along the gastro-intestinal tract. Enlargement of the liver is frequently present and is usually due also to engorgement with blood. Brown and Giffin (23) reported enlargement in fifty-seven per cent of their cases at the Mayo clinic. Cirrhosis of the liver not infrequently occurs as a terminal event.

Hemorrhage and Thrombosis

We find that hemorrhage is of relatively common occurance and is one of the principle causes of death. Epi-

staxis, bleeding from the gums, hematuria, and hemorrhage after slight injuries as passing a stomach tube, bleeding from hemorrhoids, hemothorax and massive hemorrhage from the lungs must be mentioned, as well as vesicle, uterine, and vaginal bleeding, and bleeding from the bowel often precipitated by diarrhea. Hemorrhage into the peritoneal cavity and into the spleen are reported and in several instances, with fatalities. Frequently extreme degrees of anemia may thus be produced in a very short time and the change in the appearance of the patient is of course most striking. Regeneration of the blood after such an exsanguinating hemorrhage may be very rapid (Harrop(21)). Thrombosis likewise occurs and is often the cause of the nervous and mental symptoms as pointed out and stressed by Christian (26). Portal thrombosis and mesenteric thrombosis with gangrene of the gut is not so rare a finding at necropsy.

Urinary Findings

In cases of Erythremia the urine shows nothing of any practical significance. It may be either pale and abundant or highly colored and sometimes containing excess urobilin (Weber and Watson (14)) as evidenced by spectroscopic examination. It often contains a little albumin and sometimes hyalin and granular tube-casts. Occasionally much albuminuria has been recorded, as in Cautley's case, later found to be due, at necropsy, to considerable organic renal disease.

Hematological Findings

The most important signs of Erythremia are those yielded

by the examination of the blood. The red cells are increased in number, generally between seven and eleven millions to the cubic millimeter and on the average, they are usually rather increased than decreased in diameter as Vaquez (5) first pointed out. The degree of polycythemia has in some cases been observed to vary greatly from time to time. In regard to the white cells the only quite constant finding or feature is the excessive proportion of the polymorphonuclears (not rarely up to eighty to eighty-five per cent or higher). The number of white cells is, however, nearly always increased, often up to twenty to thirty thousand per cubic millimeter. The hemoglobin is practically always increased even up to one hundred seventy to one hundred eighty per cent, but the color index is most often below one. The specific gravity of the whole blood is probably always raised. The viscosity of the blood is increased, more or less proportionate to the polycythemia. The coagubility of the blood is usually increased, although occasionally it may be less than normal. The resistance to hemolysis of the individual red cells in Polycythemia Vera is variable. Minot and Buchman (13), who have gone into the hematological study a great deal in respect to findings above, also observed an increased resistance range, an increased hemolysis (fragility), with complete hemolysis at a sodium chloride concentration definately below the lower limit. These authors also discuss the response of the cells to serum dilutions, and they concluded that such behavior indicates an active hyperplastic marrow, with cells of many ages, particularly immature cells, in the circulation. Parkes Weber (1) reports

normal fragility of the red cells in Erythremia as well as other authors. The total blood volume is decidedly above normal and seems to be a consequence again of the hyperplastic erythroblastic tissues.

Pathology

The first necropsy as was mentioned before was done in 1904 by Watson and Weber (14) who give the following account of the post mortem findings: "The post mortem examination showed the presence of a certain amount of pulmonary emphysema, slight old disease of the aortic valves of the heart and an ulcer of the pyloric region of the stomach, but these changes were quite insufficient to account for the enlarged spleen, and for the polycythemia, and the other symptoms observed during the patient's life. Moreover the liver had not the typical 'nutmeg' appearance of chronic passive congestion, as it would have had if the enlargement of the spleen had been due to pulmonary emphysema and cardiac disease. On the other hand, the examination of the patient's bones showed that almost all the ordinary yellow (normal) marrow of the shafts of the long bones was in this patient replaced by red marrow from which fat cells were nearly absent, in other words, the amount of erythrocyte-forming tissue in this man's body was immensely greater than in the bodies of ordinary persons. It became therefore obvious that even if the formation of red blood corpuscles had not been particularly active in any one part of the bone marrow, the total production of red cells in the patient's body must have been greatly above the average,

to the great excess of the tissues engaged in manufacturing them. The enlargement of the spleen seemed to be due merely to increase of the splenic pulp and engorgement with blood. The organ was certainly not the site of any active erythropoitic or myeloid change. A striking feature in microscopic sections of the bone marrow was the large proportion of non-granulated mononuclear cells of the 'large lymphocyte type', probably to be regarded as 'non-granulated myelocytes' or 'myeloblasts'. In the light of later researches there can be no doubt that the bone-marrow in this case was the site of excessive leucoblastic as well as erythroblastic activity."

The evidence of increased erythroblastic activity in the bone marrow has been found in almost every case in which the bone marrow from the shafts of the long bones was examined after death, and in one case of erythremia, (recorded by G. A. Gibson, 1908 (17) and by Watson-Wemyss in 1911 (13), before death. G. A. Gibson (17) examined the bone marrow during life and found much the same results recorded above. In regard to that case he wrote, "Bearing in view the idea of Parkes Weber that the disease may have its origin in an increased activity of the bone marrow, it seems to be a matter of practical utility, with a view to treatment to examine the marrow of one of the long bones. The patient, who has always taken the keenest interest in his progress, welcomed the suggestion, and a small amount of bone marrow was obtained from the tibia. It showed a considerable reduction in the myelocytes and normoblasts. There was a large number of ordinary erythrocytes, with a

considerable proportion of small cells, the nature of which was difficult to determine. They may have been nucleated red corpuscles or small lymphocytes. Polymorphonuclear cells were present, and the blood channels were all widely dilated. These appearances seem to support the suggestion of Parkes Weber. While the patient was under the influence of the general anesthetic, we thought it might be of interest to obtain a few drops of arterial and venous blood to compare with that of the capillaries. A small incision into the instep allowed a drop or two to be obtained from the dorsal artery and dorsal vein of the foot, and the results of these are appended to these remarks in the form of a table;

	Artery	Capillary	Vein
Erythrocytes	11,270,000	13,490,000	10,970,000
White cells	11,800	21,800	34,000"

Much of the marrow of the shafts of the long bones which is normally of the yellow fatty kind has been found on post mortem and ante-mortem examination, as above mentioned, to have been converted into red active (blood forming) marrow, so that the total amount of erythrocyte producing marrow in the body must have been enormously increased, although the red marrow normally present may not have been altered to any great extent. Weber (1) draws attention especially to Watson's case in thich the outstanding feature was the large proportion of non-granulated mononuclear cells of the large lymphacyte type (probably to be regarded as "non-granulated myelocytes" or myeloblasts") seen in sections of the altered marrow, doubtless signifying excessive leuco-

blastic activity. In several cases the leucoblastic elements were in excess of the erythroblastic elements of the marrow. It is not clear why in Erythremia more of the bone marrow should consist of leucoblastic than of erythroblastic elements. Weber (1) is of the opinion that in the marrow of these patients (and probably also in healthy individuals) the red cells are much more rapidly produced than are the white cells by their respective "parents". Hence, even when the bone marrow consists chiefly of leucoblastic tissue, the red cells far out-number the white cells in the blood. Moreover, the average life duration of red cells exceeds that of white cells and it must be remembered, as stressed above, that the colorless, primitive stages of the erythroblasts and erythrocytes are likely to be regarded by observers among the leucoblastic, rather than the erythroblastic, elements of the bone marrow.

The enlargement of the spleen which is found to be present in most cases seems to be due partly to engorgement with blood, the organ acting as a kind of elastic reservoir and partly to the hyperplasia of the splenic pulp possibly connected with the increased hemolysis of the red cells. In this regard Brown and Giffin (22) also feel that the engorgement in Polycythemia Vera may be associated with an increased amount of blood destruction because of the accumulative evidence that the spleen normally plays such a role. The diminution in the size of the spleen which often occurs after the lowering of the erythrocyte count and hemoglobin during treatment with phenylhydrazine and radiation seem also to substantiate this view. The decrease in size following

therapy, as pointed out by Brown and Giffin (23) in a later publication, may be preceeded by a temporary increase in the size during the period of increased blood destruction. Thrombotic infarcts, past malaria, or tuberculosis may sometimes partly account for the splenomegaly and in one or two cases in which great vascular degenerative changes constituted a striking feature, t ere may have been a syphilitic element present (Weber (1)).

Increased uric acid in the blood as discussed by Isaacs (31) in absence of renal involvement, may have its origin in the liberated nuclear material formed in the increased production of red cells, from the extrusion or dissolution of the nuclear material of the normoblasts at their place of origin. The presence of the normoblasts in the circulation notonly suggests that there is an abnormal stimulus to the formation and circulation of the red cells, but also is suggestive of an endogenous source of uric acid as in health. The apparent increase in the coagulation time which may sometimes occur, as pointed out by Isaacs (31), is evidently due to the relative diminution of the febrin element and the increase in the corpuscular element in a given unit of blood clot. Occasionally the blood platelet count is increased and consequently may also be a factor in this manner.

Diagnosis of Erythremia

Erythremia is often times most difficult to recognize and diagnose, especially in the early stage of the disease, because of the absence of any marked symptom, and even in the later stages of the disease process the diagnosis may be over-

looked or confused as has already been mentioned beforehand. However, the plethoric or cyanotic appearance of the patient, the presence of splenomegaly of uncertain origin, erythromelalgia-like symptoms, or other circumstances may lead to an examination of the blood. The most important feature of the disease in making a diagnosis being the recognition of a condition of persistant absolute polycythemia and the absence of any obvious cause for any considerable "erythrocytosis" (secondary polycythemia). The obvious presence of splenic enlargement facilitates the diagnosis. Splenomegaly, as pointed out by Weber (1), due to causes other than Erythremia, such as passed malaria, syphilis, or chronic obstruction in the splenic or portal veins, if it occurs in association with some form of secondary polycythemia, may doubtless give rise to great difficulties in diagnosis.

Prognosis and Course

The prognosis of Erythremia, is dependent on a great number of factors as, general condition of the patient, such as the presence of degenerative pathological processes, the age of the patient, and the stage of the disease. Some cases seem to be almost non-progressive or seem to improve, at all events for a time, with or without special treatment. Some patients have died in a sudden exacerbation of cyanosis as reported by Herringham (32) and Weber and Watson (14). Others have died from complications due to vascular disease of the brain (Cabot (9)) or from tuberculosis and intercurrent causes. With the advent of the present day treatment, the prognosis seems to be considerably better than it was in the

past, but in any event, the fatal outcome is inevitable.

Treatment of Erythremia

Osler (4) in his original article recommended for the treatment of Erythremia, venesection, oxygen inhalation, and X-ray to the spleen. McLester (33) was the first to use benzol in this country and make a clinical record of the same. However, it was suggested for this use to him by Selling, who studied its influence in the anemia of certain factory girls whose occupation led to the inhalation of benzol gas. His subsequent experimental work on animals showed that benzol caused, first of all, a marked reduction in the white blood cells, and later a diminution in the red blood cells. Examination of the tissues of animals thus poisoned indicated a selective action on the bone marrow. McLester's (33) case treated with benzol responded with a marked reduction of red cells and amelioration of symptoms. McLester (33) also cites cases reported in foreign literature, mainly German, in which the results with the use of benzol gave gratifying results. Arsenicals, splenectomy, venesection, and saline infusions, also preparations of spleen were tried and used mainly in Germany with much less or no results.

Of the drugs tried in treating this disease, phenylhydrazine hydrochloride has by all means received the most extensive use, especially so in recent years, and it appears to be the drug of choice in our modern day treatment. Citing Giffin and Conner (35), who make a brief historical resume of its use, we find that it was first employed experimentally in animals by Hoppe-Seyler in 1885; later Morawitz and Pratt

in 1908 used it for the purpose of producing anemia in animals, and Eppinger and Kloss, in 1918, were the first to apply it clinically in cases of Polycythemia Vera. Trevor Owen (36 and 37) was the first to make clinical records of its use in this country, and subsequently other investigators have reported their results of the administration of this drug. The reports appearing in the literature since Trevor Owen's first paper concerning the treatment of Erythremia with phenylhydrazine, have in the main been very favorable. Good results are reported especially by Owen (37), Brown and Giffin (39), Allen and Giffin (2), Hurwitz Levitin (43), Stealy (38), Cabot (40), and others, who have had considerable experience and leading the field as far as treatment is concerned in this country.

Attention to possible serious unfavorable effect of phenylhydrazine has been stressed in many instances. In the early cases, before the dose and course of administration were definitely established, an unnecessarily severe anemia was produced and occurrence of thrombosis was noted. The anemia, however, disappeared rapidly, and the patients as a rule were in much better general condition, with marked symptomatic improvement following an initial course of phenylhydrazine hydrochloride. Untoward effects of treatment by phenylhydrazine hydrochloride in Erythremia are stressed by Giffin and Conner (35) and by Bryan McNamara (41) and Sansum (42). In Bryan's (41) case, which was a woman sixty-five years of age, with advanced arteriosclerosis, loss of weight, and enlargement of the liver and spleen, a total dosage of 2.9 grams of phenylhydrazine hydrochloride was followed by rapid

reduction of erythrocytes from 6,550,000 to 2,540,000. The patient became comatose and died sixteen days following the beginning of treatment. Giffin and Connor (35) in 1929 reported two cases demonstrating the disastrous effect that may result following administration of phenylhydrazine. In their first case, which is similar to that reported by Bryan, again stresses the fact that small doses may cause an extreme degree of hemolysis in a debilitated patient with advanced degenerative changes. The patient sixty-eight years of age was admitted to the hospital in very poor health. The patient was given one gram of phenylhydrazine twice daily over a period of eight days. On the fifth day the red blood cells numbered 4,440,000, and on the eighth day they had fallen rapidly to 2,370,000. Death occurred on the ninth day following the beginning of treatment. In their second case, one is led to infer that exacerbation of pre-existing thromboses of recent origin, in a case of Erythremia, may be initiated by a very small dose of this drug. McNamara and Sansum (42) again in their case stressed the point that a very marked decrease of red cells may occur with very small doses of the drug which demonstrated the great importance of using good judgement and great care in treating patients with this drug and also the necessity of keeping careful watch over the patient during the administration of the drug. McNamara also demonstrated in their case the cummulative action of the drug and how the red blood cell count continues to fall even after cessation of administration.

Brown and Giffin (39) in an early series of seven cases demonstrated:

1. A hemolytic effect of the drug;
2. Stimulation to the production of leukocytes, in which it differs from benzol, the latter decreasing the white blood cells before that of the red, and consequently one of the bad features of the use of benzol in treatment of Polycythemia Vera;
3. It showed marked reduction in the volume of the blood, proportionate to the decrease of erythrocytes;
4. Elevation of the blood urea.

The elevation of the blood urea followed the changes in the blood and although renal injury due to the drug could not be excluded, it evidently was due to destruction of red cells rather than renal retention. In three of the seven cases peripheral thrombosis occurred during excessive destruction of blood and following treatment, the clinical improvement was satisfactory in all but one case, which was complicated by marked arteriosclerosis and hypertension. The dosage given in this series of cases was one-tenth gram three times daily to total dosage of from 3.4 to 7.6 grams which is considerably higher than the dosage used at the present time.

Experimental work has failed to demonstrate definite serious toxicity. It has been suspected that injury to the liver and kidneys might result either from the drug itself of from excessive hemolysis, but clear cut proof of thishas not been obtained from dosages sufficient to decrease markedly the red blood cell count. Hurwitz (43) however, stresses the fact that large doses of phenylhydrazine is a powerful protoplasmic poison, causing extensive fatty degeneration of the liver and has a marked reducing effect on the hemoglobin,

forming with it a green compound known as hemoverdin. Large doses such as would cause marked hepatic damage, are not required in successful treatment of this desease. Allen and Giffin (2) in 1928 gave phenylhydrazine to dogs on 146 days over a period of eight months, with a total dosage comparable to that of four to six years of treatment of Polycythemia Vera in man, and the dogs were well at the end of the experiments. Final studies of renal and hepatic function made one month after the drug had been discontinued gave readings within normal limits. Thrombosis did not occur in the dogs under observation, and the data indicated that renal function was at least adequate after prolonged treatment, although it did not prove that the function of the kidneys was not somewhat impaired by the drug.

As Hurwitz (43) points out, patients appear to show marked differences in their response to phenylhydrazine. A dose of phenylhydrazine which in one patient will produce marked destruction of red blood cells, will in another patient produce little effect. This fact is demonstrated by citing two of Owen's (36 and 37) cases, one required 2.6 grams to reduce the blood count to normal, whereas the other patient required almost twice the dose (4.3 grams). The total amount of phenylhydrazine required in the initial course as studied by Brown and Giffin (39) varied from 3.4 grams to 7.6 grams. In a case belonging to Hurwitz (43), nine-tenths gram of the drug produced a marked destruction of red blood cells and a hemolytic crisis, a dose much below that given above. Consequently it is quite obvious that no hard-and-fast rule as to dosage can be given.

There has been a great deal of discussion in the literature concerning the toxic effect of phenylhydrazine hydrochloride on the liver and the kidneys. Stealy (38) reports a case of Polycythemia Vera in which treatment with phenylhydrazine had been given for three years, during this time there was no clinical or laboratory evidence of deranged hepatic or renal function. In review of Giffin and Allen's (2) article it seems to be conclusive that the relatively small dosage necessary for the control of this disease is not harmful to renal or hepatic function in the absence of advanced visceral or vascular disease.

In the great majority of instances the treatment of Erythremia with phenylhydrazine hydrochloride has given most gratifying and encouraging results. In a high percentage of patients the blood count will easily be brought down to normal with complete remission of a good many of the symptoms.

Giffin and Allen (44), who have made a study of more cases than any other men in this country, have found from their experience that patients aged less than sixty years with Polycythemia Vera, and who are not in the advanced stage of the disease, can safely be given an initial course of phenylhydrazine in one-tenth gram doses two or three times daily until a total dosage of three to four grams of the drug has been administered, or if less than this dose is required, until definite clinical evidence of active hemolysis presents itself. The drug in such dosage is cumulative in its action, and hemolysis almost always continues for a week or ten days following its withdrawal. During this initial treatment the 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. On the other hand, phenylhydrazine should be given cautiously, if at all, in cases with advanced arteriosclerosis and visceral lesions, in cases in which the patient is bed-ridden, in cases in which the history is suggestive of extensive pre-existing thrombosis, and in cases in which patients are aged more than sixty years. In certain such cases rapid hemolysis and fatal ou come have occurred with small dosage.

In some of the earlier cases the treatment was omitted completely after the initial course and resumed only when the polycythemic state became marked and symptoms again became aggravated. This type of treatment had distinct disadvantages, especially because of the fact that the daily administration of phenylhydrazine requires close observation by the physician, and the patient must look forward to recurring periods of disability. It was recognized and stressed by Giffen and Allen (44) that an ideal method of treatment would be one which would maintain the patient in a more nearly normal condition so far as symptoms, erythrocyte count, and blood volume were concerned. Consequently by the method of trial and error, they finally found that the administration of from one to three one-tenth gram doses of phenylhydrazine one day of each week, the dosage being varied chiefly according to the symptoms, was usually fo lowed by very satisfactory results. They also discovered that long-continued administration of the drug in this manner was followed in some cases by apparent complete inactivity of the disease, so far as the polycythemic state is concerned, with maintainance of normal

blood count and blood volume for many months without the drug.

In a survey of forty-one cases in the experience of Giffin and Conner (35) since 1924, twenty-five patients have maintained a very satisfactory condition. As a result of their experience with phenylhydrazine therapy, they found it wise to declare the following principles of treatment:

1. Patients with advanced Polycythemia Vera of a grade necessitating confinement to bed should not receive phenylhydrazine.
2. Extreme caution should be observed in administering phenylhydrazine to patients more than sixty years of age, to patients who have marked arterio-sclerosis, and to patients who manifest evidence of advanced visceral injury. It is wise to give a very small dose to such patients, possibly only one-tenth or two-tenths grams and to observe the effect over succeeding days. This, however, should not be done if the patients are bed-ridden.
3. Patients who have probably had thrombosis should be treated cautiously.
4. Every effort should be made to keep the already sluggish circulation as free as possible. Treatment is best carried out with the patient ambulatory. If a patient is under observation in a hospital, he should be kept on his feet as much as possible. Massage and exercise indeed have been proved to be satisfactory measures.
5. Excessive dosage in the initial course of treatment is not necessary; a total initial dosage of from

1.3 grams to 3.5 grams seems to be sufficient. The subsequent dosage can be determined by the patient himself in view of his symptoms, and patients with less advanced disease have done exceedingly well on from one-tenth to three-tenths grams of the drug each week. Experience may indicate that the daily administration of the drug over a period of a week or ten days is not necessary, and that a small dose each week will be safer and will be sufficient to control the symptoms and to maintain the efficiency of the individual.

X-ray Therapy

Roentgen therapy in Erythremia dates back to the time the disease itself was described and reported. The therapy at that time was irradiation of the spleen. It was used most routinely by the earlier writers with little or practically no results, and has today been practically discarded. Guido Milani (45) summarizes the roentgen therapy to the spleen in Erythremia by saying that it has proven to be a complete failure. Today, however, roentgen therapy of the long bones has been gaining considerable importance in the treatment of Erythremia and is considered by some the treatment of choice. However, it does not receive nearly the consideration in the literature as compared to phenylhydrazine nor has it been used in nearly as many instances.

Milani (45) reports two cases treated by x-radiation with excellent and lasting results. In the first case the patient was treated with five irradiations, applied to the sternum divided into three sections and on the vertebral column di-

vided into five sections. The blood count in this case was reduced from 12,000,000 to 6,000,000, and the patient, at first unable to work, was later able to resume her usual duties. In the second case irradiation therapy was applied to the bones of the upper and lower limbs. At the beginning of the course of the treatment the red blood cell count was 11,200,000, and this in the course of thirty-eight irradiations was reduced to 4,200,000 cells.

In commenting on these two cases plus those quoted to date mainly in the foreign literature, Milani concludes that, "Roentgen therapy represents the most efficacious and the most certain means for the cure of Vaquez's disease, and, when it is well applied and regulated and accurately supervised, gives brilliant and lasting results, arresting the fetal evolution of the disease".

Pack and Craver (3) feel that the rationale of radiation therapy for this disease is based on the character of the pathology. The principal mechanism in the maintenance of the blood picture seems to be a chronic over-production of red blood cells rather than a delayed destruction or prolonged life of these cells. Insomuch as the red blood cells are probably destroyed as rapidly as in a normal individual, the continued high erythrocyte count is due to an abnormal and increased activity of the blood-forming organs. The mode of the normal physiologic regulation of the number of blood cells per unit volume of blood is even less well known than the mechanisms of the normal regulation of body temperature at a constancy of 98.6 F. When this balance between production and destruction of erythrocytes is disturbed in polycythemia it is assumed

that the normal rate of destruction is insufficient to counteract the increased rate of production of these cells. The stimulus or cause of this condition is unknown, but the chief seat of action is in the bone marrow, where there is definite anatomic evidence of increased erythroblastic activity. Although it remains impossible to irradicate the cause of this disease, the logical procedure in treatment would be an attempt to inhibit this excessive erythropoiesis. Pack and Craver (3) continue to point out the clinical analogy of erythremia to leukemia: "Their relationship is apparent because they occur during the same age periods; they pursue the same chronic progressive and fatal evolution and certain transitional forms of the disease exist. Consequently, since experience indicates that irradiation is the most satisfactory treatment treating myelogenous leukemia, therefore it seems reasonable to apply the same theropeutic measure in cases of Polycythemia Vera.

In the opinion of Pack and Craver (3) radium and roentgen rays are superior to chemical agents such as benzol and phenylhydrazine. The results, although temporary, are of a longer duration than occur with benzol or phenylhydrazine. If the locus of this disease is primarily in the bone marrow as indicated by the hyperplasia of this tissue, then it is logical to suppose that the proper treatment must be directed to the bone marrow.

The amount of irradiation given in cases of Erythremia is variable and depends on the severity of the disease. These men continue to say: "Radiation therapy improves the general health and prolongs life, but is incapable of preventing the

ultimate fatal ~~outcome~~ termination of the disease. The intensity, dosage, and interval between treatments should be carefully controlled in order to avoid the possible danger of radiation osteitis". Connery (46) reports a case history demonstrating the beneficial effect of phenylhydrazine hydrochloride and deep X-ray radiation, also the cumulative action of the drug, the low level to which the red cells had to be reduced before symptomatic relief was obtained and the apparent lack of renal and hepaticfunctional damage following drug therapy.

The patient first of all was observed for a period of two weeks after which time phenylhydrazine hydrochloride was administered in three-tenth gram doses, given every other day until ten doses had been administered. During the period of administration of the first seven doses, there occurred no significant change in the red blood cell count and hemoglobin. Following the eighth and ninth doses, there occurred a sharp drop in the count from 7,500,000 to 4,000,000 in a period of six days. Treatment was discontinued after the four million mark was reached. With the red cell count at four million, where it remained for one week, the patient was not relieved of his symptoms, and consequently treatment was again resumed with a decrease in the red blood cell count to three million, which continued to decrease following withdrawal of the drug until the low level of 1.9 million was reached and the patient became symptom-free. This marked reduction from four million took place following a single does of the drug.

The patient was kept under close observation following discharge from the hospital and remained symptom-free for ten months in spite of a constant slow rise of the red cell count

and hemoglobin values. After the ten-month period with with return of the symptoms, the patient was subjected to deep X-ray radiation to his long bones. Deep (high voltage) X-ray were used with copper and aluminum filters. At each visit 25% of the erythrema dose was given over the part being radiated. Four radiations, i.e. a full erythema dose constituted a course of treatment for a particular region. At first the treatments were given at weekly intervals, later tri-weekly. The red cell count was reduced to 4,700,000 with a corresponding reduction in hemoglobin and the patient remained symptom-free.

In conclusion of this case Connery feels that where the patient can be seen at regular and short intervals and frequent red cell and hemoglobin determinations made, phenylhydrazine hydrochloride may be given preference, and its action is much quicker. Otherwise deep X-ray therapy over the long bones would seem to be the treatment of choice, but the response is much less rapid in the latter. However, the red cell count and hemoglobin values will remain at their normal levels for a longer period of time.

* * *

In making a brief recapitulation of the subject matter at hand, it seems essential to bear in mind and to mention a few of the more important features of this disease process. First of all regarding the incidence, we find that with the advent of our present day knowledge of pathology and diagnosis, Erythremia occurs not infrequently and is not nearly as rare a condition as was thought by the men who first described the disease. The etiology of Erythremia is still unknown

and, consequently as a result of this fact, many theories have been expounded in making an endeavor to explain the cause of the characteristic features that this pathological condition presents. Of these theories, however, it seems logical to accept that one which regards the pathological processes to be primarily within the bone marrow and due to hyperplasia of the same, and that this hyperplasia is neoplastic in nature or due to some endogenous stimulus (that is within the body), probably hormonal in origin.

The essential points to bear in mind in making a diagnosis, aside from the physical findings, is an examination of the blood demonstrating an absolute polycythemia. Only on examination of the blood can a positive diagnosis be made, and then only with the exclusion of all possibilities of a secondary polycythemia.

Although a final fatal outcome is inevitable the disease responds markedly to treatment with a resulting marked alleviation of the distressing symptoms which may be present. However before instituting therapy several precautions must be taken and an estimation made of the general physical condition of the patient. This is extremely essential because of the hazardous and fatal results which may occur if these precautions are not taken.

There are two procedures of choice in selecting the treatment for the patient. The first, and the one which has had extensive use in the past few years is the use of phenylhydrazine hydrochloride. This however is to be used in carefully cases, i.e. those patients under sixty years of age, who are ambulatory, and who show no marked vascular degenerative

changes. In these patients administration of the drug should be made under close hospital observation with the patient ambulatory at the time of treatment. Also frequent determinations should be made of the red blood cell count and hemoglobin. Patients who show degenerative vascular changes and patients who are bed-ridden are to be treated most cautiously with this drug if treated at all. After the initial course of treatment in which the blood has been brought down to normal limits, the red blood cell count can be kept down with the administration of a small dose of this drug each week.

The second procedure of choice is the use of x-ray radiation to the long bones of the body. This likewise brings about a reduction in the number of red blood cells in the circulation, but the response to treatment is much slower than with the use of phenylhydrazine hydrochloride, however the results are by far much more lasting. The use of x-ray radiation must be handled by a competent radiologist and the treatment does not necessitate hospitalization, nor the close observation as in the use of phenylhydrazine. The use of both procedures, that is a combination of phenylhydrazine hydrochloride and deep x-ray radiation, has been tried with gratibying results.

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