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Bone marrow depression : its etiology and treatment

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BONE MARROW DEPRESSION:
ITS ETIOLOGY AND TREATMENT

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PART I

ETIOLOGY

INTRODUCTION

Although aplastic anemia was described in 1888 by Erhlich (137) and granulocytopenia in 1902 by Brown (20), these conditions have existed as clinical entities for shortly more than two decades.

In 1906, Lavenson (85) wrote of seven cases and concluded that aplastic anemia was an extreme condition of pernicious anemia. In the minds of some (53) this condition was confused with pernicious anemia as late as 1932, when Fitz-hugh and Krumbhaar suggested that the disease be called pernicious leukopenia because of its similarity to pernicious anemia. In 1907, however, Crummer (29) was able to differentiate between pernicious anemia and aplastic anemia when he described a case. Carslaw and Dunn (22) are among the earliest to describe any treatment, which first consisted of an iron and arsenic preparation and later was changed to arsenic alone, orally and parenterally in the form of arsacetin--with no improvement. These authors are also among the first to list metallic poisons as having

a toxic effect on the bone marrow and causing this condition. Just as Lavenson had confused aplastic anemia with pernicious anemia in 1911, Larrabee (83) mistook this condition for lymphatic leukemia. He recommended transfusion to control the hemorrhage which frequently accompanies this disease.

Although Brown (20) described granulocytopenia in 1902 and Tuerk (151) in 1907, it remained for Schultz (135) to identify, correlate and report the essential characteristics of gramulocytopenia in Berlin in 1922. Lovett (92) first reported gramulocytopenia in this country in 1924. At that time nothing was known as to the etiology of the condition. In her studies of granulocytopenia, Lovett found that oral infections always existed and Bacillus pyocyaneous organisms were usually found in these lesions. She surmised that granulocytopenia was caused by these organisms and attempted to reproduce the disease in laboratory animals by the injection of these organisms. She was the first of many whose efforts along such lines met with failure. In the following years Kracke (80) tried to establish the oral infections and Bacillus pyocyaneous as an etiologic factor, but finally came to the

conclusion that the oral infection was the result rather than the cause of the granulocytopenia.

Although there are scattered reports of cases of idiopathic bone marrow depression resulting in granulocytopenia, hypoplastic and aplastic anemia, by and large these conditions are secondary to depressive agents--chemical, toxic, metabolic, physical agents, or nutritional. The distribution and incidence of most cases of bone marrow depression and resultant blood dyscrasias is correlated to the usage of chemical compounds (90). These etiological agents and the treatment of the conditions which they cause are to be the subject of this thesis.

Mechanical interference of bone marrow function by such processes as osteosclerosis, Hodgkins disease, and the leukemias will not be included, for these are conditions not of bone marrow depression, but of bone marrow replacement. In these conditions the picture of the peripheral blood may closely resemble that of a hypoplastic blood dyscrasia, however in these cases the remaining bone marrow is hyperplastic in a compensatory effort to maintain the peripheral circulation in a normal state (36, 169).

SYMPTOMATOLOGY OF BONE MARROW DEPRESSION

The symptomatology of aplastic anemia is the symptomatology of bone marrow depression for in aplastic anemia usually all cellular elements of the blood are affected and the symptoms due to their deficiency will be present. The different series of cellular elements of the bone marrow possess different powers of resistance to drugs and marrow depressants. The megakaryocytic series is most susceptible to depressant agents, and the granulocytic series is next with erythropoiesis the last bone marrow function to be damaged. In some cases the granulocytic series may be the only series of cells affected. The erythrocytic series as a general rule requires either a greater degree of toxicity or a different type of toxicity to cause depression, and the depression may not be manifested for as long as sixty days oftentimes, for the life of the existing red cells is from ninety to one-hundred and twenty days. Quite frequently a granulocytopenia and thrombocytopenia will accompany such an aplastic or hypoplastic anemia. Many of the same agents may cause either granulocytopenia or aplastic anemia.

Since thrombocytopenia, granulocytopenia and anemia may all occur together, the symptoms of each are of importance.

In thrombocytopenia, Sherlock and White (139) state that the "first clinical sign is always epistaxis." Bleeding from the nose and mouth and the appearance of irregular ecchymotic areas as described by Magnusson (99) are the common early signs. In female patients profuse menorrhagia may occur (134), and intracranial hemorrhage is responsible for many of the deaths due to thrombocytopenia purpura. Gitt and Weiss (57) reported a case in which the primary manifestation was a subarachnoid hemorrhage associated with retinal hemorrhage and hematemesis. Laboratory studies invariably reveal definite thrombocytopenia with resulting disturbance in the normal retraction of the blood clot, normal coagulation, and a prolongation of the bleeding time (99).

The symptoms of granulocytopenia, which may be the initial finding in aplastic anemia, are fever, malaise, pain in the gingivae, cervical lymphadenopathy, and terminal infection which is as a rule of oral origin, but may consist of such conditions as pneumonia,

and septicemia or widespread cellulitis (61, 118). On examination a relative lymphocytosis of 70% to 90% will be found and 0% to 30% granulocytes seen. The importance of the leukocyte has long been known. In 1897, Ames and Huntley (3) stated that they believed the bacteriocidal quality of blood was due to a nuclein substance in the plasma which was derived from the polymorphonuclear cell. In 1930, Roberts and Kracke (127) supported this theory by claiming that the continued disintegration of leukocytes in circulation was the source of complement which is "the single most important factor in the destruction of bacteria and protection of tissues." They believe that granulocytopenia per se causes characteristic symptoms of mental and physical collapse and decreased resistance to bacterial flora. Death is probably due to the overwhelming sepsis in the body stripped of granulocytic defenses (32). The course of the granulocytopenia is usually about two weeks, but one case following aminopyrine is recorded as three years and eight months (25).

The anemia itself, the deficiency of erythrocytes, is progressive and reaches a state in which the patient has a waxy white or "pearly" pallor, weakness, fatigue,

dyspnea. The anemia is usually normochromic, normocytic, and the reticulocyte count is low or absent. The erythrocyte count is often less than two million cells when the patient is first seen. Occasionally the anemia is macrocytic with anisocytosis, and poikylocytosis, but the presence of many such cells usually indicates an error in diagnosis. The fragility of the erythrocytes is normal (118). Death is usually caused by intercurrent infection if this anemia cannot be corrected. Of interest is the fact that aplastic anemia occurs in young adults, is more frequently seen in males than females, is acute and progressive, has hemorrhage and infection as leading symptoms and is caused by hypoplasia of the bone marrow (114,78,36). Doan (36) states that "whenever the marrow is found to be grossly and microscopically hyperplastic, irrespective of the cellular levels in the circulating blood, a diagnosis of hypoplastic anemia is not justified." A gross examination of the bone marrow is never available in life and not always after death, and it must be remembered that often in aplastic anemia a patchy involvement of the marrow is found at necropsy so that if a sternal puncture had been made through

one of the small areas of hyperplasia "even though most of the marrow tissue were aplastic and fatty, an erroneous picture of the entire bone marrow would be obtained," (76).

THE MECHANISM OF BONE MARROW DEPRESSION RESULTING IN HYPOPLASTIC OR APLASTIC ANEMIA WITH GRANULOCYTOPENIA

The etiology and mechanism of bone marrow depression resulting in such blood dyscrasias can be divided into seven groups: (1) Chemical; (2) Infectious, or Toxic; (3) Physical; (4) Metabolic; (5) Nutritional; (6) Familial; and (7) Idiopathic.

I. CHEMICAL

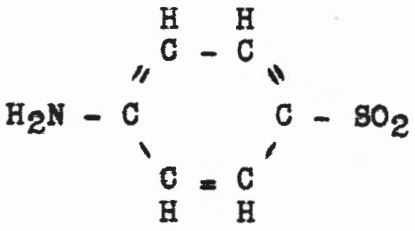
Sulfonamides:

The sulfonamide chemicals as a group have caused many cases of granulocytopenia and some cases of aplastic anemia since their introduction. In 1941 Jackson (75) wrote that of one-hundred and nine cases of granulocytopenia which he had studied, forty-two cases were due to sulfonamides--thirty four due to sulfanilamide and eight due to sulfapyridine. Also in 1941 Sutliff et al. (146) reported on sulfonamide toxicity as a cause of death in New York City during that year. Out of 74,553 pneumonia deaths, twenty-eight were the result of sulfonamide toxemias and eight were cases of granulocytopenia. Also in this group were two cases of purpura and one case of aplastic anemia. Dameshek

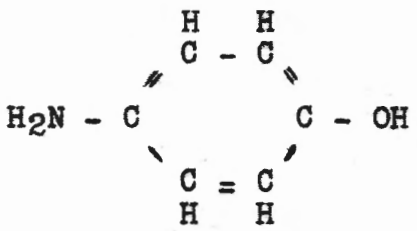
(31) believed that thrombocytopenic purpura and complete aplastic anemia are rare with sulfonamides. Van Dyke (156) also believes that aplastic anemia and thrombopenic purpura from the use of sulfas is rare, and was one of the first to observe that granulocytopenia rarely appears earlier than twelve days after the beginning of treatment. After studying two-hundred and fifty cases of granulocytopenia due to sulfonamide compounds, Long (90) stated that sulfadiazine is the sulfonamide least likely to cause granulocytopenia, followed by sulfonilamide, sulfapyridine and sulfathiazole in that order. He supports Van Dyke in the observation that granulocytopenia due to sulfonamide compounds rarely occurs before the twelfth day of treatment and adds that the most frequent time of onset is between the 17th and 25th day following administration of the sulfonamide. Sulfonilamide, sulfathiozole, sulfadiazine, sulfamerizine, sulfapyridine, sulfaquanidine and succinylsulfathiazole have all been found to cause bone marrow depression (75,106,86,50,93,60,44). Oral administration apparently is not required for the production of bone marrow depression for a fatal case of granulocytopenia has even followed the intraperitoneal

implantation of five grams of sulfonilaminde crystals (5). Sulfaquanidine in the past has been given in cases where there is lower intestine pathology because it was thought to be non-absorbable. It has been found, however, that 2/3 of the sulfaquanidine administered is absorbed before the ileocecal valve is reached. The low blood levels of the drug are due to rapid urinary excretion rather than non-absorption. For this reason, blood dyscrasias due to sulfaquanidine will be encountered just as those from any other sulfa (60). Meyer and Perlmutter (107) emphasize the danger of both marrow depression and also an accompanying hemolytic anemia in the use of sulfonamides.

Anderson et al. (3) state that sulfapyridine may cause a "maturation type" of granulocytopenia. Park (119) believes that all toxic effects of sulfonamide compounds, including bone marrow depression, are on an allergic basis. He states that such toxic reactions are acquired and are specific, thereby fulfilling the two essential requirements for a diagnosis of an allergic hypersensitivity. The sulfonamide radical is supposedly the etiologic agent in 50% of the cases and the aminophenyl radical in the other 50%.



Sulfonamide Radical



Aminophenyl

To avoid establishing such a sensitivity, Park believes that chemotherapy should not be prolonged beyond one week. Halliday (62) believes that toxic reactions due to sulfonamide compounds "result from (a) ill considered administration, (b) careless management of the patient, (c) prolonged course of treatment (over ten days) and overdosage, and (d) allergic idiosyncrasy and sensitization." Weinberg (164) reported a case of granulocytopenia due to sulfadiazine from which the patient recovered and subsequently received "two drugs which are known to be potential depressants of white blood cell formation, namely, sulfathiazole and aminopyrine. The blood count was closely followed during the administration of these two drugs and in neither instance did a neutropenia occur." From this, one may conclude that in some cases the sensitivity is confined to one sulfonamide.

Granulocytopenia due to sulfonamides is a condition which must be constantly watched for when these drugs

are given for long periods of time or when they have been given previously. The incidence of granulocytopenia is not high enough to contraindicate the use of sulfa when the need arises, but it is the general opinion of all the authorities that the sulfa drugs should not be used indiscriminately.

The arsenicals:

Organic arsenicals, used in the treatment of syphilis have been considered as a major cause of bone marrow depression. Guevara and Miranda (61) state that "Except for tryparsenamide . . . all antisyphilitic arsenicals: salvarsan, neosalvarsan, sulfarsphenamine, silver-arsphenamine, and even mapharsen and bismarsen may result in these blood changes." However Doan (36) states that tryparsenamide has caused bone marrow depression and adds stovarsol to the list of arsenicals responsible for this condition. Neoarsphenamine and neokharsvian also should be added to the list of arsenicals capable of causing bone marrow depression (69,71).

In 1930, Farley (49) stated that no one type of arsphenamine was more apt to produce bone marrow depression than any other. In 1932 however, the American

Medical Association Council on Pharmacy (27) agreed that sulfarsphenamine was far more apt to produce this condition than other organic arsenicals. The use of sulfarsphenamine is still warranted in a few cases because sulfarsphenamine may be administered intramuscularly while other arsphenamines must be given intravenously. Since that time mapharsen has come to be regarded as the least likely to cause bone marrow depression.

Imrie (71) stated that arsenicals may affect blood formation in any of three ways: (a) depression of megakaryocytes; (2) depression of the granulocytes; and (3) aplastic anemia involving all of the cellular elements of the blood which are produced in the bone marrow. He believes that the aplastic group of dyscrasias is the largest.

Boon (18) stated that in the production of bone marrow depression, the dosage of the drug is not as important as the duration of the time between the last dose and the onset of the illness. The shorter this period of time, the better is the outlook, for depression of the marrow is likely to be of a more temporary nature. Farley (49) believed that there was not an

actual aplasia, but rather a physiologic paralysis of the bone marrow. Scarf (133) stated that the double benzene ring of the organic arsenicals was probably the injurious agent and stated that bone marrow depression to inorganic arsenicals was rare. Kracke and Parker (81) believed that only drugs which contain a benzene ring with an attached amino or nitro group, being thus readily oxidizable, are capable of producing bone marrow depression. It must be borne in mind, however, that the rarity of the occurrence of bone marrow depression to inorganic arsenic preparations is quite possibly because inorganic arsenic preparations are not in common use. There are cases of inorganic arsenic poisoning showing marked diminution of polymorphonuclear leukocytes (91). The Manchester epidemic of arsenical poisoning from contaminated beer showed that inorganic arsenic may first cause marrow hyperplasia followed later by degeneration and atrophy (22). Potassium arsenite, potassium arsenate, and sodium arsenide have caused granulocytopenia, and hydrogen arsenide has been proven to be a dangerous industrial hazard (36, 61). Holley (68) now believes that the toxicity of arsenicals is due to "combination of arsenic

radical with S-H groups of the activating protein of enzyme systems to form a stable compound, which thereby interferes with tissue respiration." Loveman (91) states that a predisposed and weakened hematopoietic system is probably of great importance in every case of bone marrow depression, and most other writers agree with him (91, 36). Doan (36) states that the action of arsenicals may be either cumulative or allergic.

Statistical analyses show that one in fifty thousand to ninety thousand patients treated with antisyphilitic arsenicals developes a depression of the bone marrow (36, 51). Not all cases of bone marrow depression terminate fatally, but all cases are serious and because of the severity of these reactions, extreme care must be observed in the use of the arsenicals.

Aminopyrine:

This drug is notorious for producing a depression of the granulocytic cells of the bone marrow. In 1932 Kracke (80) attempted to reproduce granulocytopenia in laboratory animals by the injection of aminopyrine, but failed. Although aminopyrine had been suspected of causing granulocytopenia, what a great part this drug played was not realized until later. In 1934 Madison

and Squier (98) stated that the increase in granulocytopenia has paralleled the increase in the use of drugs containing aminopyrine (or amidopyrine) and especially aminopyrine compounded with a barbiturate. This drug, because of its effectiveness as an antipyretic and anodyne has insidiously invaded a great many of the patent remedies and sedatives which are so plentiful now, even though a great effort has been made to curtail the use of aminopyrine in them. Many patients take such a compound unaware that any such drug as aminopyrine is contained in it, and occasionally physicians have prescribed a preparation which they did not realize contained aminopyrine. Onset of granulocytopenia with malaise and fever may stimulate the patient to take more of the drug. A few of the many compounds containing aminopyrine to cause granulocytopenia are allonal (allylisopropylbarbituric acid with aminopyrine), causalin (amidomethylpyrazolon quinolin sulfonate), cibalgine (aminopyrine and dial), amytol compound (amytol and aminopyrine), allurate, nirvanol, novaldin. (25, 75, 110, 129).

Herz (67) believed that the pyrazolon group was the causative agent in the production of granulocytopenia.

The fact that this condition follows the use of drugs in which the pyrazolon group is not contained indicates that this is not so (81). Madison and Squier (98) believe that granulocytopenia due to aminopyrine is an allergic or drug reaction. Supporting this theory is a case reported by Austin (8) of granulocytopenia in a patient who recovered when the drug was withdrawn, and who later gave a very positive intradermal test to an aminopyrine preparation. Urbach and Goldburgh (155) report of granulocytopenia caused by aminopyrine suppositories in a very highly allergic individual and concluded that the mode of allergization was probably based upon a hapten mechanism, the aminopyrine probably acting as a hapten and altering tissue protein.

Thiouracil and related drugs:

Since the introduction of this group of antithyroid drugs, many cases of granulocytopenia have resulted from it. Thiourea, thiouracil, methyl thiouracil aminothiazole, and propyl thiouracil have all caused granulocytopenia (111, 88). Kahn and Stock (77) claim to have had the first case in which death occurred from granulocytopenia due to thiouracil. Morgans (111) believes that the exceedingly high incidence of toxic reactions, including

granulocytopenia, following the use of thiourea and aminothiazole, contraindicate their use. Thiouracil and methyl thiouracil depress the granulocytic cells but have a lower incidence of toxic reactions. Both Astwood (7) and Williams (165) state that approximately 10% of patients receiving thiouracil develop toxic manifestations, the most serious of which is granulocytopenia. Propyl thiouracil is supposed to have a toxicity incidence of about 2% in contrast to that of thiouracil. (88).

Most cases of granulocytopenia due to thiouracil and its related drugs occur after the drug has been given for five to six weeks. Granulocytopenia is thought to be the common blood dyscrasia resulting from the antithyroid drug because of the greater susceptibility of the myeloid series. In all probability the erythroid elements and platelets would be affected if it were possible to continue treatment and maintain the life of the patient through a period of granulocytopenia. (153). The reaction of these drugs is probably on an allergic basis. Astwood (7) reports a case of granulocytopenia due to thiouracil which recovered and subsequently suffered extreme allergic reactions (scarlatiniform

eruptions) following administration of phenobarbital and a febrile reaction following the use of sulfathiazole. Williams (165) reported two cases who had febrile reactions to thiouracil and had immediate febrile reactions when thiourea was substituted.

These antithyroid drugs show promise of becoming an important group of drugs and their use is warranted provided they are used with extreme care and close observation of the patient. Slight leukopenia is cause for closer observation but not necessarily for withdrawal of the drug, for Astwood (7) points out that a leukopenia may be due to the thyroid disease and frequently a leukopenia due to the drug itself is transitory and the leukocyte count will rise again, even though the drug is continued.

Benzene:

Benzene and benzol (a crude commercial benzene) have been known to have a depressant action upon hemopoietic tissue since 1910 when Selling (136) first described two cases of aplastic anemia, which at the time were erroneously diagnosed as purpura hemorrhagica. Larrabee (83) in 1911, wrote that benzene poisoning was one of the causes of aplastic anemia. In 1932 Kracke (80)

was able to reproduce the clinical picture of granulocytopenia in laboratory animals by the use of benzene, orthooxybenzoic acid and hydroquinone. Kracke believed that the oxidation products of the benzene were directly responsible for its leukocyte depressing properties and found that the smaller the dose of benzene used to produce the condition, the more selective became the affinity for the myelocytic tissues. In 1935 Kracke and Parker (81) claimed that only substances containing a benzene ring with an attached amino or nitro group are capable of producing bone marrow depression for only they are readily oxidizable. Wilson (166) emphasized the fact that "individual susceptibility is the governing factor in the appearance of symptoms." It appears that "young, intelligent girls" are the most susceptible, and negroes are far less susceptible to benzene poisoning than are individuals of the white race. Absorption of the benzene is usually by the respiratory tract, but may also be by way of the alimentary tract or skin. Doan (36) states that if the contact with benzene has been over a prolonged period of time without recognition of the toxic marrow effects, permanent marrow damage may result even though the result is not outright fatal--as it often is.

Tridione:

The first reports of bone marrow depression resulting from tridione (trimethyloxazolidine dione) were made in 1946 when two cases of aplastic anemia were reported (63, 95). Davis and Lennox (33) examined periodically one-hundred and twenty-seven patients taking tridione, and found that in 7% of cases a borderline neutropenia existed, and in 6.3% of the cases there was a definite neutropenia. They state however that the occurrence of the neutropenia is quite gradual and usually monthly checks of the blood are sufficient unless the neutrophil count falls to 2500 cells per cmm. Treatment with tridione should be stopped if the neutrophil count falls much below this level.

Gold salts:

Five gold preparations used in the treatment of arthritis have been found to cause granulocytopenia and aplastic anemia. These are: crisalbine (sodium gold thiosulfate); sancrosyn (another preparation of sodium gold thiosulfate); allochrysin (sodium aurothiopropanol sulfonate); solganol B (aurothiodextrose); and lopion (sodium auroallylthiourea benzoate); with no evidence that any one preparation is worse than

any other or that dosage was important. In his study, Mirik (108) found that gramulocytopenia occurred in one out of one thousand cases and approximately one-half of these were fatal. Doan (36) states that "the same type of bone marrow reactions have been described following gold therapy as have followed the use of arsenic . . .". He also believes that reactions to gold may be "anaphylactoid" or cumulative.

Trinitrotoluene:

Trinitrotoluene has been found to be a cause of aplastic anemia in the past few years. Eddy (41) McNally (104), and Sievers et al. (140) have reported cases of aplastic anemia due to this drug. It is thought that the TNT may enter the blood stream through the skin, lungs, or gastro-intestinal tract, the skin being the most important route. Supposedly only susceptible individuals are affected. Hepatic damage always is found in aplastic anemia due to TNT and some believe that the hepatic injury is the primary source of the anemia while others claim that the hemolysis is the cause of the anemia and jaundice (104). Poisoning from TNT is of particular importance during war periods when large numbers of people work for long periods of

time with explosives and chemicals containing the trinitrotoluene. At this time the incidence of aplastic anemia due to TNT is probably decreasing.

Atabrine:

In the period from July to December of 1944, the incidence of aplastic anemia of the United States Army troops located in the South Pacific, the Southwest Pacific and the China-Burma-India theaters of war was 2.8 cases per one-hundred thousand troops, while in the same period the incidence of aplastic anemia in troops in Europe was only 0.05 cases per one-hundred thousand troops. The single feature which served to differentiate these two groups was the protraced use of atabrine (quinacrine) in prophylactic and suppressive doses in the Pacific and Asiatic theaters. Custer (30) states that there were 47 cases of aplastic anemia in this period due to atabrine, twenty-five of which had been preceded by an atabrine dermatitis complex. Bone marrow in all cases was quite aplastic and all elements were affected. Any residual cells found usually were late stages in the erythropoietic series. Hemorrhage was a conspicuous feature in almost all cases and cerebral hemorrhage was the immediate cause

of death in ten cases. Drake and Moon (38) report that in their series, only two out of nine cases of aplastic anemia due to atabrine did not have an atabrine dermatitis. From the fact that atabrine caused aplastic anemia is almost always preceded by a dermatitis, it appears highly probable that the mechanism of this condition is an allergic reaction as are most other causes of bone marrow depression.

The increased rate of aplastic anemia among troops given atabrine in suppressive doses does not constitute a contraindication to the use of the drug because of the comparatively higher morbidity and mortality of the malaria against which the drug atabrine is used.

Dinitrophenol:

Dinitrophenol, a drug used in the treatment of obesity, has been accused of causing bone marrow depression. Copley (25) and Rosenthal (129) both list it as a drug causing granulocytopenia. Rosenthal states that he has seen four cases of granulocytopenia due to this drug, three of which were fatal. Pearce (118) and Wintrobe (168) both claim that aplastic anemia, depression of all elements of the bone marrow, has been caused by dinitrophenol.

D.D.T. (Dichlorodiphenyltrichloroethane):

Since its introduction late in the last war, D.D.T has been usually regarded as possessing no harmful effect upon the human body. However in 1945 Case (24) observed a granulocytopenia with a delayed absolute lymphocytosis in two "normal" individuals who had been subjected to a forty-eight hour exposure to D.D.T. three days before. Gordon (59), however, stated that D.D.T. alone is "innocuous". He believed that kerosene should not be used as a solvent for D.D.T. because of the pathological effect the kerosene might have. Wright, Doan and Haynie (173) were able to establish D.D.T. as the etiologic agent in a case of granulocytopenia in a twenty-two year old white male, with skin contamination and absorption as the mode of entrance of the chemical. They state that the toxic effects of D.D.T. are "enhanced" by mixing with certain oil solvents, and stress the importance of avoiding skin contamination when using D.D.T.

Penicillin:

Penicillin has been hailed as the miracle drug devoid of toxic reactions. Since the use of penicillin has become so extremely widespread and almost

routine, a few toxic reactions have developed. The reaction most usually seen is a generalized erythematous, macular skin rash, similar to the Herxheimer type reaction. In 1946, Spain and Clark (142) reported the first and only case of granulocytopenia due to penicillin. This one case is not sufficient to place penicillin in the category with drugs feared as bone marrow depressants, but it would seem to signify that bone marrow depression is, in all likelihood, the result of allergic sensitization and such a sensitization may be acquired for almost any substance.

Thioglycolic Acid:

Thioglycolic acid, $HSCH_2COOH$, which is used in a "cold wave" process has been found to cause severe allergic reactions in sensitive individuals. The effect of the thioglycolic acid may also be cumulative and the patient may have remissions after contact with the acid is removed. Leukopenia and granulocytopenia are common findings along with anemia. This acid is used in concentrations of up to 5% in most of the "cold wave" preparations now on the market, and is coming to be used indiscriminately. As more of these "cold wave" preparations are used in the home, we can expect the

incidence of granulocytopenia and other toxic reactions from this chemical to increase (26).

Pyribenzamine:

Blanton and Owens (16) reported a case of granulocytopenia following pyribenzamine therapy for urticaria. Pyribenzamine (N'pyridyl-N'benzyl-N- dimethylethylenediamine hydrochloride) is a drug introduced in 1946 for the control of many allergic conditions. As the use of this drug increases it may be that the number of cases of granulocytopenia due to it will increase also. To date this is the only report of granulocytopenia due to pyribenzamine.

Acetanilid:

Acetanilid poisoning (from B.C. "Headache" powders) is reported to have caused a fatal case of granulocytopenia by Wright, Doan, and Haynie (173). Acetanilid as a rule does not cause a condition such as this although it frequently causes anemia (8).

Silver Nitrate:

Chronic silver nitrate poisoning from the use of a hair dye by the patient is reported by Alvarez and Minnhaar (1) to have caused a fatal case of granulocytopenia. Other authors (76, 118, 168) report cases

of granulocytopenia and aplastic anemia from hair dyes, probably caused by the silver nitrate contained in it.

Mustard Gas:

At the close of the last war Krumbhaar and Krumbhaar (82) stated that Yellow Cross Gas (more commonly known as Mustard Gas or bis-2-chlorethyl sulfide) caused profound leukopenia and changes in the bone marrow. Wintrobe (168) states that Mustard Gas is a potential cause of aplastic anemia. In the event of widespread use of poison gas in warfare, the incidence of bone marrow depression from this cause might increase sufficiently to be of clinical importance.

Miscellaneous:

Colloidal silver, Mercury, bismuth, phenobarbital and salicylates have been accused of causing bone marrow depression. Such cases as these are rarely seen and are recorded in literature only as isolated cases (25, 76, 118, 168).

Fitz-hugh (52) believed that substances other than drugs--food, bacterial products, and metabolites--may produce the disorder through the mechanism of acquired sensitivity. Examples of these will follow in other Sections.

II. TOXIC OR INFECTIOUS DEPRESSION OF BONE MARROW

The relationship of infection to bone marrow depression has long been questioned. The oral infections found with granulocytopenia were at first believed to be the cause of the granulocytopenia (92, 80). These were later proven to be the result rather than the cause of the granulocytopenia. Infection has, however, been proven to play a part in the production of bone marrow depression. Rosenthal (129) stated that "there is no specific infection which is responsible for the production of granulocytopenia. There is no known specific bacterial invader or virus with a selective affinity for bone marrow." Doan (36) states that "overwhelming infection, either metastatic with local marrow abscess formation and septicemia or through circulating toxins, may more or less completely inhibit or destroy the developing blood cells at their source. Any of the common pathogens may select the blood and blood forming organs for attack, but the hemolytic and green streptococci (examples are post partum sepsis and malignant endocarditis), the Freidlander's and typhoid bacilli and all of the known human disease producing viruses are the most frequent offenders."

Wintrobe (168) states that septic conditions such as diptheria, typhoid, and pnemonia may have a toxic effect upon myeloid tissues and inhibit their activity, and he is supported in this theory by Waugh, (162) who also believes that the mechanism of production of bone marrow depression is that of deficiency paralysis due to the removal of some substance necessary for the maturation of proliferating elements of the marrow. Pepper (120) believes that infection might have an allergic effect on bone marrow. Hypoplasia of bone marrow may involve erythroid elements selectively or may affect all marrow cells (170). Smith, Cohen and Nichols (141) believe that in cases of granulocytopenia due to chemicals etc., infection resulting from the loss of body resistance causes further bone marrow depression and increases the severity of the granulocytopenia. Loveman (91) believes that there may be a "syphilotoxic action " acting in conjunction with arsphenamines in the production of granulocytopenia.

Bromberg and Murphy (19) and Kracke (79) both report fatal cases of granulocytopenia resulting from prophylactic typoid vaccination. Bromberg and Murphy suggest that an overwhelming foreign protein reaction

due to the injection of this material in a sensitized individual is the cause.

Renal disease and renal abscess is blamed for bone marrow depression and aplastic anemia by many authors (83, 157, 118, 170). Vaughan (157) states that a hypoplastic hypochromic type of anemia which is refractory to treatment may occur with nephritis. Pearce lists uremia as a cause of bone marrow hyperplasis. Bethell et al. (12) state that in advanced glomerulo-nephritis with azotemia and occasionally in nephrosclerosis with absolute renal insufficiency "selective impairment of erythropoiesis occurs, the block appearing very early in the development of red cells." In this case the resulting anemia can be designated as hypoplastic.

A parasitic disease causing aplastic anemia is Hookworm Disease. Stranski and Quintos (145) describe three states of anemia of progressive severity in hookworm disease: (1) a compensated anemia in which there is an eosinophilia and increased erythropoiesis, (2) hypochromic anemia which leads into a hypoplastic tendency of bone marrow which is reversible with treatment, and (3) an aplastic anemia, "An exhaustion of the bone

marrow," for which there is no satisfactory treatment. This condition is not frequently seen in this country, but is not unusual in China.

Vaughan (157) asserts that protozoa have an inhibitory action on erythropoiesis and this is confirmed by diagnosis of aplastic anemia due to malaria by both Vaughan and Pearce (118).

Miliary tuberculosis is named as a cause of bone marrow hypoplasia by Pearce and Vaughan (118, 159).

III. PHYSICAL AGENTS

The chief physical agent causing bone marrow depression and injury is that of radio-active energy. In 1932, Kracke (180) mentioned that granulocytopenia had been caused in rabbits by a single injection of Thorium -X, radio-active Thorium. Vaughan (157) states that the anemia due to internal radiation, such as that which occurred in watch dial painters a few years ago, is associated with a hyperplasia of bone marrow and may occur years after exposure. She states that with excessive external irradiation the bone marrow becomes hypoplastic with the leukopoietic series most affected. The mechanism may be to "stimulate the cell to go prematurely through its life process rather than one of

direct toxic action on the tissue." Wintrobe (168), on the other hand, believes that the mechanism is probably that of preventing division in cells capable of either mitotic or amitotic division. He states that the Roentgen rays and especially the gamma rays of radium may cause severe and fatal bone marrow depression. The report of Spier et al. (143) of a case of fatal aplastic anemia, due to the use of Thorotrast used nine years previously, conflicts with Vaughan's description of aplastic anemia due to internal radiation, for they found marked aplasia of the bone marrow. Doan (36) states that the "blood is the most radiosensitive tissue in the body," and that this is true is reflected in the blood dyscrasias resulting from the atomic bomb explosions at Hiroshima and Nagasaki as reported by Warren (160). He stated that there were three chief groups of symptom complexes resulting from damage to hemopoietic tissue. These are:
1. Granulocytopenia differing from the usual type in the suddenness of onset. Many of the circulating granulocytes were destroyed by the radio-active energy at the same time the hemopoietic tissue was damaged and so frequently counts as low as 200 granulocytes

per c.m.m. are seen in the first few days after the blast.

2. Thrombocytopenia due to destruction of platelets and megakaryocytes.

3. Anemia with the bone marrow in either a hyperplastic or hypoplastic condition.

These changes may develop after heavy therapeutic radiation of large parts of the body and in poorly protected workers in radiology (43). Fortunately now, most of the workers in the field of radiology have adequate protection. The effects of radiant energy upon the bone marrow are cumulative, and after a certain point, irreversible (36).

IV METABOLIC

There are cases of bone marrow depression which appear to be caused by metabolic disorders. It is thought that "an inborn error in the metabolism of some important blood-building substance may have produced a deficiency state which has led to anemia." Some authors have "surmised the existence of an abnormality in the metabolism of the blood porphyrins, which leads to a toxic aplastic state of the bone marrow (35.)" This theory is supported by Dobriner et al.

(37) who have found that in aplastic anemia there is a pathological excretion of porphyrins which suggests that the aplastic anemia results from an intoxication. Zeltmacher et al. (174) believe that either intrinsic or extrinsic toxins are responsible both for aplastic anemia and for liver cirrhosis which frequently accompanies it. The work of Thorell (150) on cellular protein and cell formation suggests that the cause of hypoplasia is a failure of the endocellular metabolism of the cell manifested by inability for new formation of cellular protein. Rubell (130) states that the etiology of this type of anemia is unknown but mentions that it may possibly be due to a "metabolic disturbance involving some blood-building substance."

Bone marrow depression occurring with such conditions as myxedema, toxemia of pregnancy and neoplasm are also considered on a basis of metabolic disturbance.

Wilson (167) pointed out that literature concerning anemia and the thyroid gland is extremely conflicting and although he believes that marrow hypoplasia may result from cretinism and myxedema, he was forced to conclude that the thyroid gland plays a "non-specific role in hemopoiesis." Armstrong (4) reported a case

of long-standing hypoplastic anemia with myxedema, and Bomford (17) believes that myxedema is associated with hypoplasia of the bone marrow, a reduction in cellular division due to the low oxygen consumption of the hypothyroid state.

Tyslowitz and Dingemanse (152) found that injections of estrogens in dogs of both sexes produced a fall in all blood elements probably due to bone marrow depression. There have been no recorded clinical cases of bone marrow depression due to administration of estrogens. Barsby and Close (9) report a case of recurrent granulocytopenia in which the episodes occurred three to seven days after the menstrual period for four years terminating in death. No drugs known to produce granulocytopenia were taken in this period of time. The condition may have been on a hormonal basis.

Pregnancy is quite often responsible for the production of an anemia, although this is usually not of the hypoplastic type. Vaughan (159), however, states that toxemias of pregnancy were responsible for two cases of aplastic anemia. Pearce (118) states that in a case in his series, pregnancy and the delivery of twins was the etiologic factor in the production

of aplastic anemia.

Wintrobe (170) states that erythroid hypoplasia may be associated with many conditions, including malignancy. Humphreys and Southworth (70) report a case of bone marrow depression manifested by low erythrocyte count without any abnormal cells or without a decrease in leukocytes associated with a benign mediastinal tumor. There was no evidence of blood loss or destruction. That the depression was due to the tumor was evidenced when the blood picture returned to normal upon removal of the tumor.

V. NUTRITIONAL

Poor nutrition has been widely known to cause anemias, just as has pregnancy and, as in pregnancy, such an anemia is rarely the hypoplastic type. Cartwright et al. (23) believed that pyridoxine deficiency was an etiologic factor in the production of hypoplastic anemia. On experimental work on swine, they found that although pyridoxine deficiency produced the picture of hypoplastic anemia in the blood smear, the bone marrow was hyperplastic. This anemia was refractory to all forms of therapy except administration of pyridoxine. It cannot be considered as a hypoplastic anemia.

Anemia in extreme cases of scurvy has been found to be hypoplastic, possibly because of decreased oxygen consumption, due to lack of ascorbic acid which interferes with oxidative processes of the body (72). Bass (10) reported on two cases of deficiency anemias in children, one of which may have been of the hypoplastic type. Since there were no bone marrow studies done, this cannot be definitely stated to be hypoplastic. The specific deficiency was of amino acids, for the infant had been fed only goats milk due to severe allergic reactions. It was not due to iron deficiency for the anemia was refractory to all forms of treatment except amino acids derived from hydrolyzed casein.

VI. FAMILIAL AND CONGENITAL

This group of bone marrow depressions is small, but at present appears to be a growing group.

Béguez (11) has reported a familial type of malignant, chronic granulocytopenia characterized by albinism, indeterminate feverish states, nystagmus, leukopenia, granulocytopenia and lymphomonotosis. Of thirteen brothers studied, four suffered from this condition. The mechanism of this syndrome is unknown, but the author believes it to be a recessive mendelian trait.

A syndrome of a similar sort is the Franconi syndrome which consists of aplastic anemia, microcephaly, testicular hypoplasia, convergent strabismus, exaggerated deep tendon reflexes, a generalized brown melanin-like pigmentation of the skin, and frequent skeletal anomalies or defects. The cause of this is unknown, but is believed to be due to a chance aberration in one or more hereditary genes which have to do with development . . . a genetic "sport" (46).

Another group of hypoplastic anemias is that which Estren and Dameshek (45) describe as "heredofamilial hematologic conditions" . . . a familial hypoplastic anemia, differing from the Franconi syndrome in that the pathological findings are confined to the hemopoietic system. In their series they found three of seven children in one family, and five of fourteen children in another family, victims of hypoplastic bone marrow.

Other cases of chronic congenital hypoplastic anemia, though not necessarily familial, are more common. Blackfan et al. (15) emphasize the selective hypoplasia of the erythroid marrow cells and Poucher (122) states that it is manifested late in the neonatal period. Diamond and Blackfan (35) suggest two

theories: that the condition is due to an inborn error in metabolism (discussed previously); and that "there may be congenital insufficiency of red marrow tissue and inability on the part of the hemopoietic system to respond to the need for more blood as the erythrocytes wear out (35)."

VII. IDIOPATHIC

Jackson (75) states that granulocytopenia (primary) is rare and "becoming more so as the knowledge of the malady increases." This is true of all cases of bone marrow depression. Many of the cases in literature which are labeled as idiopathic are in all probability secondary to some marrow depressant which at that time was unrecognized. Kolmer (78) points out that idiopathic aplastic anemia is about 100% fatal, but Astwood (6) and Mirik (109) both cite cases in which recovery has occurred. Mackenzie (96) shows that one of the chief problems of importance in cases of idiopathic aplastic anemia is stimulation of granulocytes and the usual failure despite treatment.

THE MECHANISM OF BONE MARROW DEPRESSION RESULTING IN PURPURA

Of the cellular components of blood, three separate types are produced in the bone marrow. These are the platelets, the granulocytes, and the erythrocytes. Bone marrow depression may involve all of the cellular elements or selectively affect either of the latter two.

Platelets are formed by the megakaryocytes which are derived from the myeloblast (34). Many authors (48, 51, 101, 102) believe that extremely low platelet counts are not due to depression of the megakaryocyte, but instead to allergic destruction or removal of the circulating platelets. To support this belief Falconer and Epstein (48) claim to have returned large numbers of platelets to circulation in cases of thrombocytopenic purpura by means of injection of 1 cc. of epinephrine hydrochloride. Ferguson (51) states that in thrombocyopenia due to sulfonamides, the "rapid reappearance of platelets on recovery is not in keeping with a toxic depression of megakaryocytes. McCarthy and Wilson (101) refer to thrombocytopenic reactions as "anaphylactoid". McGovern and

Wright (102) in surveying forty-five cases of purpura hemorrhagia due to sedormid, stated that most were "an allergo-toxic" reaction and a few were the result of the patients' idiosyncrasy to the drug. Bethell et al. (13) state they believe that purpura as a toxic manifestation should not be included among conditions attributable to bone marrow depression. Goldhamer (58), when writing of thrombocytopenic purpura caused by arsenicals, emphasized the increased capillary permeability and lack of evidence of bone marrow involvement. In cases of acute thrombocytopenic purpura following rubella, Magnusson (99) noticed increased capillary fragility; and in a fatal case of purpura following administration of sulfapyridine, Sherlock and White (139) state that there was no significant change in platelet count, but a generalized vascular defect. Guevara and Miranda (61) state that "In simple thrombocytopenic purpura the initial symptoms are so acute as to suggest that the arsenicals exert a harmful effect, at least temporarily, upon the platelets in the peripheral circulation," and McCarthy and Wilson (101) have come to the same decision. Wiseman, Doan and Wilson (172) have found no evidence of a

change of megakaryocytic action in the bone marrow.

Apparently, however, there are cases in which a thrombocytopenia is found accompanying a granulocytopenia or a reduction in all blood cellular elements produced in bone marrow (93, 115). Limarzi and Schleicher (87) reported on a study of seven patients with essential thrombocytopenic purpura and a group of normal subjects. They found that in cases of essential purpura the megakaryocytes are almost all young and platelets reduced equally in bone marrow and peripheral circulation because of an inhibitory action the spleen exerts against the maturation of the megakaryocytes.

From this diverse and conflicting material it would seen that only when there is generalized bone marrow depression is depression of the megakaryocyte found.

BONE MARROW DEPRESSION

PART II

TREATMENT

There are four essential features in the treatment of bone marrow depression. These are: (1) removal of the etiologic factor; (2) combating granulocytopenia; (3) combating erythrocytopenia; and (4) prevention of hemorrhage due to low platelet count. It is generally believed that removal of the etiologic factor is the most important. Any or all of the other features of treatment may be necessary, varying with the individual case. Many features of the treatment overlap each other, an example of which is the supposed stimulation of all marrow elements by many of the same chemicals.

REMOVAL OF THE ETIOLOGIC FACTOR

Forkner (54) believes that all forms of therapy which have been acclaimed in the literature are disappointing and that their apparent success is due to the fact that most of the series of cases have been more or less "picked". He believes that the most important factor is to remove the offending agent which allows the marrow to undergo regeneration. Several authors (7, 54) report cases of bone marrow depression in which the patient recovered upon withdrawal of the offending agent.

Although mere cessation of administration of the offending drug may be sufficient in a few cases, in many cases the offending drug remains in the body for quite some time due either to poor excretion or to the fact that it is in combination with the tissues and systems within the body. In such cases it may continue to exert its harmful effect upon the bone marrow. Some authorities (49, 91) advocate the administration of sodium thiosulfate intravenously to attempt to neutralize the remaining arsenic in blood and tissues in cases of arsenical poisoning.

Early in the last war the British government developed a drug to be used to combat the poison gas, Lewisite, which they feared would be used against them in the war. Toward the end of the war when the danger of poison gasses faded, the Allied governments released this product for civilian investigation and use, and only within the last year have many reports of its action and effectiveness been written. BAL (British Anti-Lewisite), which has the formula $CH_2SHCH_2SHCH_2OH$ or 2,3 Dimercaptopropanol (131), has a selective affinity for the arsenic radical and may prevent the combination of the arsenic radical with the SH groups of the activating protein of the enzyme systems which interferes with tissue respiration. The compound resulting from the combination of BAL and arsenic is stable, non-toxic, and rapidly excreted by the kidneys (1, 68). Welfare (163) believes that the special affinity BAL holds for arsenic is that it supplies more readily available sulfhydryl groups. Stoken et al. (144) showed that BAL can bring about a significant degree of reactivation of the already poisoned enzyme systems. Waters and Stock (161) and McManus (103) both state that BAL is of value in bone marrow depression

due to arsenicals. Rundle (131) believed that BAL was effective not only in removing arsenicals, but also gold salts in cases of toxic reactions, and Telfer (148) adds lead to the list. Antimony, bismuth, mercury, chromium and nickel are effectively removed from laboratory animals by the use of BAL. At a future date it will be more possible to evaluate correctly the use of BAL in cases of bone marrow depression. At this time it appears to have a very favorable effect.

Removal of infection is essential in cases in which the bone marrow depression is due in part or totally to infection. The treatment of such infection is the same as the treatment of infection resulting from granulocytopenia and will be discussed under the section on treatment of granulocytopenia.

TREATMENT PERTAINING TO RELIEF OF GRANULOCYTOPENIA AND ITS EFFECTS

Such treatment can be divided, for the sake of discussion, into three sections: Efforts toward stimulation of granulocytopoiesis; Efforts toward maintenance of peripheral granulocytes; and The battle against infection. Clinically, of course, these must each be brought into effect simultaneously.

EFFORTS TOWARD THE STIMULATION OF GRANULOCYTOPOIESIS

The literature presents a very confused picture as far as therapy and stimulation of bone marrow function is concerned. The list of preparations reported to have caused recovery from granulocytopenia is a long one, and is by no means static, for investigators are constantly adding to this list and at the same time removing preparations which were acclaimed hopefully a few years ago and now have been found to be useless or even harmful.

Pentose Nucleotides:

At the present time pentose nucleotide and associated substances such as nucleinic acid and adenine

sulfate occupy a front line, but debatable, position in the therapy of granulocytopenia. Ames and Huntley (2) in 1897 reported that an "apparent production of leukocytosis" is a result that appears to be quite constant following the use of nucleinic acid, regardless of the route of administration. Drury (40) stated that nucleic acid and its derivatives, even down to simple products such as adenine and guanine are capable of producing leukopenia followed by polymorphonuclear leukocytosis. He believes that they act as chemotactic substances. Reznikoff (123, 124, 125) reported in 1931 and 1933 that adenine and adenine sulfate and guanine were effective in stimulating production of granulocytic cells, but in 1940 he stated that he used pentnucleotides without being convinced of their value. Jackson and his associates (73, 74) however, remained convinced of the merits of nucleotides over a similar period of time. In 1931 they stated that inactive bone marrow was frequently stimulated by nucleotides and that the first sign of improvement always occured between the fourth and seventh (usually on the fifth) day after nucleotides were administered. In 1939 they analyzed a series of cases

of granulocytopenia and found the mortality of seventy-five untreated cases to be 78%, while the mortality of eighty-five cases treated with pentose nucleotides was 35%. Pentose nucleotides should be given in 10cc. doses intra-muscularly four times daily (62, 74, 125). Reznikoff (125) warns that a 1 cc. test dose should be given first to determine if the patient has any sensitivity to it. Halliday (62) has described a case where the patient has been maintained on pent-nucleotide and fresh whole blood for six months in a rather decompensated condition. Dreverman (39) and many others recommend that pentnucleotide used along with yellow bone marrow is the most satisfactory treatment and states that "each plays a part in the maturation of polymorphonuclear cells."

Yellow Bone Marrow:

Administration of bone marrow is another form of treatment which is accepted at the present time. Marberg and Wiles (100) announced in 1938 that they had succeeded in concentrating the granulocytopoietic fraction of yellow bone marrow which could be given orally. From a series of clinical cases they concluded that their concentrate of yellow bone marrow

contained "a substance or substances which act to stimulate the maturation or liberation of leukocytes of the granulocytic seres." In 1939 Osgood et al. (117) advocated transfusion of unconcentrated marrow to provide cellular elements and also in the hope that some cells would be carried to the marrow in the blood stream and set up areas of regeneration by metastasis. A variation of this is the method advocated by Wilson (166) in which 2 - 5 cc. of bone marrow are taken from a compatible donor and are introduced directly into the sternum of the patient in an effort to set up areas of regeneration. There have been no further reports giving information as to the success of this treatment. Morrison and Samwick (112) state that injection of normal marrow "may stimulate maturation of hematopoietic constituents already present in the diseased marrow, thus supplying a factor to overcome a deficiency disease." Dreverman (39) supports this and believes that yellow bone marrow and pentnucleotide should be given together. Although yellow bone marrow may have been successful in stimulating hemopoiesis in some cases, there are also many cases in which it has failed (62, 35, 117).

Liver, and Liver Products:

The treatment of bone marrow depression with liver has been rather disappointing. This condition is sometimes designated as anemia and granulocytopenia which is refractory to liver and liver extracts. Rosenthal (129) lists liver extract as one of the products stimulating leukopoiesis. The literature, however, is full of cases which did not respond to liver extract (42, 62, 112) and rather devoid of cases responding to liver extract. Favorite et al. (50) report a case of acute granulocytopenia with recovery in which liver extract had been used. Unfortunately for statistics, possibly fortunately for the patient, other drugs had been used with the liver extract and results were inconclusive. Faber (47) reports a case of granulocytopenia due to sulfapyridine which showed improvement after treatment with fresh liver and penicillin.
In 1930 Upham and Nelson (154) reported a case of rapidly failing bone marrow depression which had shown no response to transfusions, liver extract, or cooked liver. A dose of 250 grams per day of fetal calves liver was given with no effect. Then doses of 600-800 grams of cooked fetal calves liver were started

and were followed by a definite improvement in all phases of the bone marrow depression. Granulocytes and erythrocytes increased and the purpuric manifestation decreased although there was no discernible change in the platelet count. Complete recovery did not occur, however. The following year Noland (116) obtained about the same results by feeding raw fetal calves liver.

Folic acid:

Folic acid also occupies a debatable position regarding its therapeutic value in bone marrow depression. In 1945 Endicott et al. (44) reported that folic acid (Lactobacillus Casei Factor) prevented or corrected granulocytopenia and to a lesser extent aplastic anemia in rats being fed succinylsulfathazole. Black and Stanbury (14) gave enthusiastic reports of the value of folic acid in granulocytopenia, but admitted that their studies were inconclusive and that further work must be done. Gendel (56) states that he has found that in the use of folic acid in cases of aplastic anemia, the erythrocytes slowly improved, but that folic acid had no effect upon the granulocytic series, which is in direct contradiction

to the other reports. It must be remembered, however, that most of the other studies were done on experimental animals and not humans.

Pyridoxine:

In 1944 Cantor and Scott (21) proposed the use of pyridoxine (vitamin B_6) for the treatment of granulocytopenia of toxic origin and described three cases in which pyridoxine had been used. In these cases pyriodoxine hydrochloride was administered intravenously in doses of 125 mg.-200 mg. per day. In each case the temperature fell to normal and symptoms disappeared within 48 hours. The authors concluded that "pyridoxine acts by direct stimulation of the myelocytic elements of the bone marrow." Menten and Graff (105) in studying the effects of folic acid upon granulocytopenia felt that a second factor or enzyme might be involved, and so they administered folic acid and pyridoxine together. They finally came to the conclusion, however, that pyridoxine, "the adjuvant selected . . . for use with L. casei factor, might advantageously be replaced by some other member of the vitamin B group." Sievers et al. (140) treated two patients suffering from aplastic anemia with pyridoxine

with equivocal results, and recommended further clinical trial of the drug.

Fever and Protein Shock:

Cross (28) described a case of granulocytopenia treated by transfusions, during the last of which the patient experienced a severe rigor lasting fifteen minutes and a sustained fever. A blood smear taken immediately showed a slight increase in the neutrophilic cells. Four hours later the temperature reached 105.6 degrees and a blood count at that time revealed a leukocytosis of 40,000 cells per cmm., 85% of which were immature polymorphonuclear cells. By the next morning the temperature had returned to normal and the patient had recovered. From this, Cross concluded that induced and controlled hyperpyrexia, i.e. protein shock, might be useful in aborting attacks of the disease. However, Kracke (79) reported a case of granulocytopenia due to typhoid vaccine in which the patient experienced daily fevers and Bomberg and Murphy (19) reported a case of granulocytopenia which they attributed to protein shock. Both of these cases would tend to discount the therapeutic value of hyperpyrexia or protein shock in treatment of granulocytopenia.

Adrenalin:

Astwood (6) and Loveman (91) both advocate the use of adrenalin in the treatment of granulocytopenia. Astwood uses three-eights of a grain per six hours because he believes that it causes mechanical expulsion of cells from the spleen, lymph nodes, and bone marrow, and may possibly stimulate production of new cells. January et al. (76) state that "the effects have been transient and without permanent effect." Rosenthal states that turpentine hyperdermatically may have a similar effect (129).

X-Ray:

X-Ray treatment of granulocytopenia has not met with widespread approval. Rosenthal (128, 129) stated in 1930 that it failed to benefit granulocytopenia, but in 1938 he recommended mild X-Ray to the long bones. Tausig and Schnoebelen (147) advocate one-twentieth of an erythema dose of X-Ray through a copper filter, believing that it causes a leukocytosis. Guevara and Miranda (61) state that X-Ray has not proven satisfactory in their series of cases and Reznikoff (125) states that X-Ray treatment is actually dangerous for although it may temporarily cause

a remission due to transient hyperemia, greater depression will become apparent after the treatment than before. Herrman (66) also believes radiation to be harmful in bone marrow depression.

Vitamins and Yeast:

It is natural that vitamins might play a part in the symptomatic treatment and many authors recommend high vitamin intake on such a basis (36, 41, 106, 110, 166). Guevara and Miranda (61) state that neither vitamins A, D or B have a specific effect toward stimulating granulocytosis. Pettit (121) advocated one pint of orange juice daily in the diet, presumably for the vitamin C content. Rhoads and his coworkers (126) state, however, that "vitamin C has failed not only to alter the course of the disease, but also to control the hemorrhagic phenomena," and are supported in this by Diamond and Blackfan (35).

Mirik (109) suggests the administration of 3 gm. daily of brewers yeast during convalescence from aplastic anemia, and Menten and Graff (105) pointed out that yeast can effect a conversion of pyridoxine into the more active compounds, pyridoxal and pyridoxamine.

EFFORTS TOWARD MAINTENANCE OF PERIPHERAL GRANULOCYTES DURING THE PERIOD OF HYPOPLASIA OF THE BONE MARROW

Transfusions:

Farley (49) recommended transfusions in case of bone marrow depression to provide (1) erythrocytes and hemoglobin, (2) Polymorphonuclear leukocytes, (3) to combat infection, and (4) to supply soluble ferments probably decreased or absent from the patient's serum. Eddy (41) suggests the use of concentrated cells from fresh blood so that the granulocytes will be good. Wilson (166) advocates multiple small transfusions in granulocytopenia. Reznikoff (123) believes that blood transfusions, especially large transfusions, decrease the polymorphnuclear cells in the peripheral blood; and, because of this depressing effect, transfusions larger than 250 cc. should not be given. Forkner (54) confirms this and states that transfusions are actually harmful in cases of granulocytopenia.

Splenectomy:

Rhoads and his associates (126) believe that "for carefully selected cases with ample functioning

bone marrow, and evidence of definitely increased hemolysis, splenectomy may be a useful procedure." Unfortunately, in bone marrow depressions the bone marrow is not "amply functioning" and there is usually no increased hemolysis. Wilson (166) believes that the spleen may inhibit the bone marrow and advocates splenectomy in cases of bone marrow depression. Shaw and Oliver (138) report a case of aplastic anemia, in which all cellular elements were affected, which was definitely benefited by splenectomy, and Estren and Dameshek (45) state that in familial hypoplastic conditions, splenectomy might be of value, except in cases of complete or almost complete aplasia of bone. Diamond and Blackfan (35) describe a case in which splenectomy was of benefit in a case of chronic hypoplastic anemia of children. Hench and his associates (65) believe that splenectomy is contraindicated in cases of "Felty's Syndrome" because it is possible that the syndrome may be a defense mechanism on the part of the reticuloendothelial system to infection in which the lymph nodes are the first line of defense and the liver and spleen the second line of defense.

TREATMENT DIRECTED TOWARD COMBATING INFECTION RESULTING FROM GRANULOCYTOPENIA

Penicillin:

The main cause of death in patients with granulocytopenia is not due to the granulocytopenia per se, but rather from the infection resulting from it (133). Bethell and his associates (13) state that "use of penicillin seems to be logical, because it is the most effective agent available for the control of the sepsis which is the cause of death." Also, penicillin is the drug least likely to cause any bone marrow depression itself. In 1942 Dameshek and Wolfson (32) suggested the use of sulfonamides for the control of sepsis. However, since the introduction of penicillin, it has been the drug of choice due to the fact that the sulfonamides are one of the leading causes of granulocytopenia. Penicillin is particularly valuable in granulocytopenia following antisyphilitic therapy because of its effectiveness against the spirochete as well as its effect upon the sepsis due to the granulocytopenia. (103). Smith, Cohen and Nichols (141) believe that in drug induced granulocytopenia the resultant infection may cause further bone

marrow depression and advocate the use of penicillin. MacKenzie (98), the Livingstons (88), and many others have reported cases of granulocytopenia with recovery which they feel was made possible by the use of penicillin. In a case of granulocytopenia due to propyl thiouracil reported by the Livingstons, both penicillin and streptomycin were used successfully.

Oral Hygiene:

Pettit (121) was one of the first to concentrate on preventing the oral infections which are invariably present with this condition. He believes that treatment from an oral standpoint has two objectives: "(1) to attempt to prevent continuous loss of blood from the gingivae, and (2) to eliminate the foci of infection which might form toxins depressing cellular elements in the bone marrow." He advocated scaling and polishing the teeth and a mouth wash of sodium dichromate (5 grams) and boric acid (4 grams) and, in the event of Vincent's angina, he believed that arsphenamine in glucose should be applied locally. Osgood et al. (177) favor sodium perborate mouth washes.

Diphteria Antitoxin:

Loveman suggests that should the granulocytopenia

make possible the establishment of a diphtheria-like growth in the throat, diphtheria anti-toxin should be given at once (91).

TREATMENT CONCERNED WITH THE ERYTHROCYTOPENIC PHASE OF BONE MARROW DEPRESSION

STIMULATION OF ERYTHROPOIESIS

Many of the substances which are used in the hope of stimulating erythropoiesis have been discussed under the section devoted to granulocytopoiesis. Such substances include liver, and related preparations such as extracts and fetal liver; bone marrow preparations; pentnucleotides; folic acid; vitamins and diet; adrenalin; light X-Ray and brewers yeast. In general these substances have been of less value in promoting erythropoiesis than granulocytopoiesis, but many of them are used for this purpose, none the less.

There are other preparations, many of doubtful value, which are advocated in stimulation of the erythroid series of bone marrow cells.

Cobalt:

Wintrobe and his associates (171) have found that in laboratory animals the administration of cobalt causes polycythemia and is capable of overcoming the anemia produced in rabbits by benzol. The bone marrow is reported to change from fatty and aplastic to hyperplastic. It is their hypothesis that cobalt favorably

influences the utilization of iron for synthesis of hemoglobin. The mode of action is unknown. Liver, liver extract and vitamin C are reported to nullify the effect of the cobalt. Previously Diamond and Blackfan (35) reported the use of cobalt with iron without effect in the treatment of chronic hypoplastic anemia in children. These authors were also administering vitamin C, which may explain the failure of the cobalt to cause erythropoiesis.

Iron:

Although iron in the form of ferrous sulfate is frequently given in cases of anemia due to bone marrow depression, there is little evidence that it is of any value. Mirik (109) reported a case of idiopathic aplastic anemia with recovery in which iron was one of the many features of treatment. There is no reason to suppose that it played any significant part in the recovery of this one case, and Harrison (64) and Herrman (66) both believe iron to be of no value.

Intramuscular injections of umbilical blood:

Freudenberg (55) in treating a case of congenital aplastic anemia administered ten injections of 30 to 40 cc. each, of umbilical blood with a resultant

reticulocytosis of 16,000. In the bone marrow the cells typical of erythropoiesis increased from 12% to 31%. To my knowledge no further clinical trials of this unusual form of treatment are recorded.

Arsenicals:

Treatment of aplastic anemia with arsenic, and with arsenic and iron, has been used for quite some time. Thomas (149) and Carslaw and Dunn (22) reported the use of arsenic preparations--and subsequent failure--in the treatment of aplastic anemia in 1910. Inorganic arsenicals continued to be recommended as late as 1936 when Astwood (6) advocated the use of arsenic and iron preparation. In 1937 Sharp (137) stated that "Arsenicals, as bone marrow stimulants, are definitely contraindicated." Arsenicals, in either organic or inorganic form may cause bone marrow depression and should be avoided if such pathology already exists.

Radiant energy (ultra-violet light):

Laurens and Mayerson (84) in studying the effects of radiant energy upon anemia found that it causes a marked increase in the reticulocyte count and later an increase in the erythrocyte count in dogs. It was

also found, however, that hemoglobin formation was inhibited during the radiation and for two to four weeks afterward. This work was not significant, for it was not done upon cases of bone marrow aplasia. Guevara and Miranda (61) state that the use of such radiant energy is of no value.

Ventriculin:

Loveman, (91) in the treatment of bone marrow depression following the use of arsphenamines, advocated the use of "ventriculin", a proprietary preparation of descicated hog stomach which is administered by mouth to produce a reticulocytosis. Rhoads and Barker (126) state that stomach preparations in maximum dosage by both oral and parenteral routes have uniformly failed. Since that time very little work has been done with such preparations.

Aminoacids:

Bass (10) found that in one case of hypoplastic anemia due to nutritional allergy, the administration of amino acids derived from hydrolyzed casein resulted in improvement.

TREATMENT DIRECTED TOWARD MAINTENANCE OF ERYTHROCYTES IN PERIPHERAL CIRCULATION

Transfusion:

Transfusion is the main method of maintaining elements in the peripheral circulation during hypoplastic periods of the bone marrow. Some authors (126) state that transfusion has only a transient effect. That this fact is recognized, is shown in a case reported by Osgood and his associates (117) in which as many as forty-three transfusions were given over a fifty-two day period. Harrison (64) has reported a case of aplastic anemia which had received over one-hundred transfusions, of a full pint of blood each, over a period of five and one-half years, which is an incredibly long course for aplastic anemia in an adult. McCarthy and Wilson (101) reported thirty-four cases of aplastic anemia, seventeen of which received transfusions as the main method of treatment. Only three of these recovered. Loveman (91) believes that frequent small transfusions of 200-300 cc. are best and advocates administering them as often as three or four times a week if necessary. Humphreys and Southwork (70) point out one of the dangers of continued massive

transfusions. They recorded a case of aplastic anemia which was maintained for twenty-two months by transfusions and red blood cell infusions with eventual recovery. The patient died one year later, however, of liver insufficiency, secondary to advanced and widespread hemochromotosis which in turn had developed from the repeated transfusions necessary to prolong the patient's life.

In chronic hypoplastic anemia of the late neonatal period, Diamond and Blackfan (35) state that "Transfusions have been the only form of treatment effective in raising the levels of the erythrocytes, although all known methods of hemopoiesis have failed. In such cases as these, transfusions are necessitated approximately every one or two months as the erythrocytes wear out. Pearce (118) states that "Enough blood should be given to keep the patient comfortable. It is unnecessary and perhaps inadvisable to give enough blood to bring the red cell count up to normal." Fresh blood, instead of bank blood, should be used. Rubell (130) states that the "difficulties of giving repeated transfusions to small infants are obvious, and intramedullary infusions may have to be resorted to."

Splenectomy:

Splenectomy apparently is of value in some cases of bone marrow depression. This has been discussed more fully under treatment directed toward maintenance of the leukocyte count.

Oral Hygiene:

Oral hygiene as presented by Pettit (121) on the section devoted to antisepsis is important in preventing chronic oozing of blood from the gingivae.

MEASURES TO CONTROL PURPURIC MANIFESTATIONS

Transfusion is the most widely used method of controlling the hemorrhagic manifestations of bone marrow depression through the provision of platelets and other constituents of normal blood (126, 38).

Hemostatic preparations such as calcium chloride and calcium lactate have been advocated by several authors (101, 91). Schneider (134) used ergot and calcium in an attempt to control profuse menorrhagia. Musser (113), in addition to using calcium in an attempt to control hemorrhage, used 20 cc. of horse serum. All of these preparations have been used without success.

Splenectomy is apparently of no value in treating purpura of this origin, for it is not advocated.

SUMMARY AND CONCLUSION

1. The symptomatology of bone marrow depression was discussed.

2. Etiology of bone marrow depression was discussed and was classified into seven different types: (1) Chemical. The main constituents of this group are the sulfonamides, arsenicals, aminopyrine, thiouracil, and benzene. (2) Infectious. This group includes abscess, renal disease, malaria, and tuberculosis. (3) Physical. This consists of X-Ray and radioactive substance. (4) Metabolic. (5) Nutritional. (6) Familial. and (7) Idiopathic.

3. Treatment of bone marrow depression was found to consist of several factors: withdrawal of the causative agent; stimulation of hemopoiesis by such agents as pentnucleotides, yellow bone marrow, and cobalt; maintenance of cellular elements of blood in the peripheral circulation by means of transfusion and splenectomy; and the battle against infection through the use of anitibiotics such as penicillin; and transfusions to control purpuric manifestations.

Bone marrow depression is a serious occurrence, and at best has a grave prognosis. In the event of bone marrow depression of either the granulocytes or the erythrocytes, or both, all forms of treatment thought to have any favorable effect upon the condition should be tried immediately to prolong the life of the patient and to stimulate the bone marrow to production of the cellular elements of blood.

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