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BONE MARROW DEPRESSION:

ITS ETIOLOGY AND TREATMENT

HOLTON C. LETSON

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BONE MARROW DEPRESSION

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 enti-
ties 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, how-
ever, 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 granulocytopenia in Berlin in 1922.
Lovett (92) first reported granulocytopenia 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 ani-
mals 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 pyocyan-
eous 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 ane-
mia 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) re-
ported a case in which the primary manifestation was
a subarachnoid hemorrhage associated with retinal hem-
orrhage and hematemesis. Laboratory studies invariably
reveal definite thrombocytopenia with resulting dis-
turbance 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 ori-
gin, 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 im-
portance 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 nu-
clein 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 circula-
tion was the source of complement which is "the single
most important factor in the destruction of bacteria
and protection of tissues." They believe that granu-
locytopenia per se causes characteristic symptoms of
mental and physical collapse and decreased resistance
to bacterial flora. Death is probably due to the over-
whelming 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 ane-
mia is macrocytic with anisocytosis, and poikylocy-
tosis, 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 can-
not be corrected. Of interest is the fact that aplas-
tic 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, ir-
respective of the cellular levels in the circulating
blood, a diagnosis of hypoplastic anemia is not justi-
fied." 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 depres-
sion 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 aplas-
tic anemia since their introduction. In 1941 Jackson
(75) wrote that of one-hundred and nine cases of granu-
locytopenia 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 com-
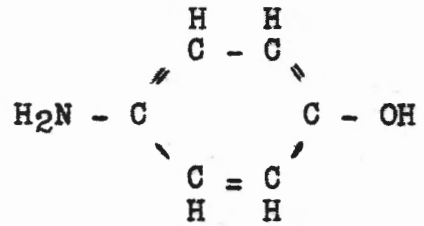plete aplastic anemia are rare with sulfonamides. Van
Dyke (156) also believes that aplastic anemia and throm-
bopenic purpura from the use of sulfas is rare, and
was one of the first to observe that granulocytopenia
rarely appears earlier than twelve days after the begin-
ning of treatment. After studying 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, sulfadia-
zine, sulfamerizine, sulfapyridine, sulfaquanidine and
succinylsulfathiazole have all been found to cause bone
marrow depression (75,106,86,50,93,60,44). Oral admin-
istration apparently is not required for the production
of bone marrow depression for a fatal case of granu-
locytopenia 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 al-
lergic hypersensitivity. The sulfonamide radical is
supposedly the etiologic agent in 50% of the cases and
the aminophenyl radical in the other 50%.

```
          H   H                               H   H
          C - C                               C - C
        //       \                          //       \
H₂N - C           C - SO₂         H₂N - C           C - OH
        \        /                          \        /
          C = C                               C = C
          H   H                               H   H
```
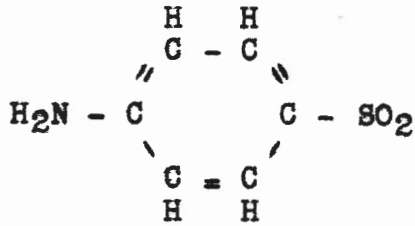
Sulfonamide Radical   Aminophenyl

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 man-
agement of the patient, (c) prolonged course of treat-
ment (over ten days) and overdosage, and (d) allergic
idiosyncrasy and sensitization." Weinberg (164) re-
ported a case of granulocytopenia due to sulfadiazine
from which the patient recovered and subsequently re-
ceived "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 granulocyto-
penia 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 syphi-
lis have been considered as a major cause of bone mar-
row 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 de-
pression and adds stovarsol to the list of arsenicals
responsible for this condition. Neoarsphenamine and
neokharsvian also should be added to the list of arsen-
icals 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 de-
pression 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 be-
cause sulfarsphenamine may be administered intra-
muscularly 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 dy-
scrasias 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 depres-
sion 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 de-
pression 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 produc-
ing 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 poly-
morphonuclear leukocytes (91). The Manchester epidemic
of arsenical poisoning from contaminated beer showed
that inorganic arsenic may first cause marrow hyper-
plasia 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 there-
by 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 be-
cause 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 granulo-
cytopenia 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 anti-
pyretic 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 phy-
sicians have prescribed a preparation which they did
not realize contained aminopyrine.   Onset of granu-
locytopenia with malaise and fever may stimulate the
patient to take more of the drug.   A few of the many
compounds containing aminopyrine to cause granulocy-
topenia 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 granu-
locytopenia. 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 anti-
thyroid 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 re-
actions 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 ob-
servation of the patient. Slight leukopenia is cause
for closer observation but not necessarily for with-
drawal of the drug, for Astwood (7) points out that a
leukopenia may be due to the thyroid disease and fre-
quently a leukopenia due to the drug itself is transi-
tory 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 hemo-
poietic tissue since 1910 when Selling (136) first des-
cribed 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 granu-
locytopenia in laboratory animals by the use of ben-
zene, 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 ben-
zene 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 de-
pression for only they are readily oxidizable. Wilson
(166) emphasized the fact that "individual susceptibil-
ity is the governing factor in the appearance of symp-
toms." It appears that "young, intelligent girls" are
the most susceptible, and negroes are far less suscep-
tible 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 per-
iod 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 result-
ing 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 neutro-
phil 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 (aurothiodex-
trose); 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 granulocytopenia 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 trin-
itrotoluene. 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 Pa-
cific 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 suppres-
sive 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 usu-
ally 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 derma-
titis. From the fact that atabrine caused aplastic
anemia is almost always preceded by a dermatitis, it
appears highly probable that the mechanism of this con-
dition is an allergic reaction as are most other causes
of bone marrow depression.

The increased rate of aplastic anemía 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 de-
pression. 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 im-
portance 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 penicil-
lin has become so extremely widespread and almost

routine, a few toxic reactions have developed. The
reaction most usually seen is a generalized erythema-
tous, 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 re-
sult 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 suf-
ficiently to be of clinical importance.

Miscellaneous:

Colloidal silver, Mercury, bismuth, phenobarbital
and salicylates have been accused of causing bone mar-
row 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 de-
pression 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 cir-
culating 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 pro-
ducing 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 mar-
row depression is that of deficiency paralysis due to
the removal of some substance necessary for the matur-
ation 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 resis-
tance causes further bone marrow depression and in-
creases the severity of the granulocytopenia. Love-
man (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 re-
port 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 hyper-
plasis. 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 hook-
worm disease: (1) a compensated anemia in which there
is an eosinophilia and increased erythropoiesis, (2)
hypochromic anemia which leads into a hypoplastic tend-
ency 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 in-
hibitory 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 pre-
maturely 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 prob-
ably 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 depres-
sion. 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 radio-
sensitive 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 result-
ing 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.   Thrombpcytopenia due to destruction of platelets
and megakaryocytes.

3.   Anemia with the bone marrow in either a hyperplas-
tic or hypoplastic condition.

These changes may develop after heavy therapeutic
radiation of large parts of the body and in poorly pro-
tected 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 cer-
tain 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 pro-
duced a deficiency state which has led to anemia."
Some authors have "surmised the existence of an ab-
normality in the metabolism of the blood porphyrins,
which leads to a toxic aplastic state of the bone mar-
row (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 accom-
panies it.   The work of Thorell (150) on cellular pro-
tein 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 con-
ditions 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 injec-
tions 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 oc-
curred 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 pro-
duction 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 oxy-
gen 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 hypo-
plastic 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 al-
lergic 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 mal-
ignant, 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 (pri-
mary) 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 lit-
erature 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 granu-
locytes 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 per-
meability and lack of evidence of bone marrow involve-
ment. 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 sim-
ple thrombocytopenic purpura the initial symptoms are
so acute as to suggest that the arsenicals exert a
harmful effect, at least temporarily, upon the plate-
lets 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 dis-
appointing 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 with-
drawal 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 ad-
ministration 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 re-
sulting from the combination of BAL and arsenic is
stable, non-toxic, and rapidly excreted by the kid-
neys (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, regard-
less 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 cap-
able of producing leukopenia followed by polymorpho-
nuclear 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 pro-
duction 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 nucleo-
tides over a similar period of time. In 1931 they
stated that inactive bone marrow was frequently stimu-
lated by nucleotides and that the first sign of im-
provement always occured between the fourth and seventh
(usually on the fifth) day after nucleotides were ad-
ministered. 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 con-
cluded 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 in-
jection 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 pentnucleo-
tide should be given together. Although yellow bone
marrow may have been successful in stimulating hemo-
poiesis 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 some-
times designated as anemia and granulocytopenia which
is refractory to liver and liver extracts. Rosenthal
(129) lists liver extract as one of the products stim-
ulating 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 in-
conclusive. Faber (47) reports a case of granulocy-
topenia 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 manifes-
tation 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 depres-
sion. 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 succinylsulfatha-
zole. Black and Stanbury (14) gave enthusiastic re-
ports 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 im-
proved, but that folic acid had no effect upon the
granulocytic series, which is in direct contradiction

to the other reports. It must be remembered, how-
ever, that most of the other studies were done on ex-
perimental animals and not humans.

Pyridoxine:

In 1944 Cantor and Scott (21) proposed the use of
pyridoxine (vitamin B_6) for the treatment of granu-
locytopenia of toxic origin and described three cases
in which pyridoxine had been used. In these cases
pyriodoxine hydrochloride was administered intraven-
ously in doses of 125 mg.-200 mg. per day. In each
case the temperature fell to normal and symptoms dis-
appeared within 48 hours. The authors concluded that
"pyridoxine acts by direct stimulation of the mye-
locytic 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 clin-
ical 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 gran-
ulocytopenia due to typhoid vaccine in which the patient
experienced daily fevers and Bomberg and Murphy (19)
reported a case of granulocytopenia which they attri-
buted 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 expul-
sion 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 cop-
per 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 ac-
tually 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 co-workers (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 PERI-
PHERAL GRANULOCYTES DURING THE PER-
IOD 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 trans-
fusions 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, trans-
fusions 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 hypop-
lastic 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 IN-
FECTION RESULTING FROM GRANULOCYTOPENIA

Penicillin:

The main cause of death in patients with granu-
locytopenia 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 pen-
icillin 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 penicil-
lin, 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 val-
uable 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 granulocy-
topenia 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 pen-
icillin. In a case of granulocytopenia due to propyl
thiouracil reported by the Livingstons, both penicil-
lin 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 treat-
ment 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 ar-
sphenamine 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 prepar-
ations; 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 ery-
throid 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 hyper-
plastic. 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 de-
pression following the use of arsphenamines, advo-
cated the use of "ventriculin", a proprietary pre-
paration of descicated hog stomach which is adminis-
tered 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 hypoplas-
tic 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 re-
ported 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 trans-
fusions as the main method of treatment. Only three
of these recovered. Loveman (91) believes that fre-
quent 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 trans-
fusions and red blood cell infusions with eventual
recovery. The patient died one year later, however,
of liver insufficiency, secondary to advanced and wide-
spread hemochromotosis which in turn had developed
from the repeated transfusions necessary to prolong
the patient's life.

In chronic hypoplastic anemia of the late neo-
natal 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 erythro-
cytes 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 radio-active 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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