# PANEL DISCUSSION ON THE CLINICAL MANAGEMENT OF BLOOD DYSCRASIAS IN THE OLDER AGE GROUP*

*Moderator:* WILLIAM DAMESHEK, M.D., Professor of Medicine, Tufts University School of Medicine; Director, Blood Research Laboratory, New England Center Hospital, Boston, Massachusetts.

*Panelists:* FRANK H. BETHELL, M.D**., Professor of Internal Medicine, and Director of the Simpson Memorial Institute for Medical Research, University of Michigan, Ann Arbor, Michigan.

EDWARD H. REISNER, JR., M.D., St. Luke's Hospital, New York City; formerly Associate Clinical Professor of Medicine, New York University Post-Graduate Medical School, New York, N.Y.

STEVEN O. SCHWARTZ, M.D., Director, Hematology Department, The Hektoen Institute for Medical Research of the Cook County Hospital, Chicago, Illinois.

LEANDRO M. TOCANTINS, M.D., Professor of Clinical and Experimental Medicine, and Director, The Cardeza Foundation, Jefferson Medical College of Philadelphia, Philadelphia, Pennsylvania.

MODERATOR WILLIAM DAMESHEK: We shall begin our discussion by taking up the question of blood counts in elderly people. In younger people, blood counts vary from person to person. There is no such thing as an absolute standard for normality of blood counts. Males have more red cells and more hemoglobin than females. There have been varied speculations as to why that should be true, including the observation that the male sex hormone to some extent may be myelostimulatory.

Dr. Bethell, *do blood counts in the older age group differ from those in the younger age group?*

DR. FRANK H. BETHELL: What you have mentioned with regard to the younger age group applies to the older age group too. There is a wide range of what we might call normal.

One difficulty in obtaining data is the subject material with which one has to work. Information on blood values in older age groups has been obtained largely from studies made within institutions. Such patients are not necessarily definitely ill, but many of them have some degree of chronic disability. The result is that the frequency distribution or spread in values in the older age group is considerably wider than in normal younger adults. However, in males after the age of 55 to 60 there is a definite decline in the hemoglobin level, the red blood cell count, and the hematocrit reading toward the values in postmenopausal females. In the case of the male post-adolescent up to the age of 55 to 60 years there is an average decline in the hemoglobin from 15.6 Gm. to 14.7 Gm. per cent, and in the red blood cell count from 5,500,000 to 4,800,000 per cu. mm., with a corresponding drop in the hematocrit reading, but within quite a wide range. When some persons become old, the erythrocyte and hemoglobin values may rise almost to polycythemic levels.

* Conducted at the Third Annual Graduate Symposium on Geriatric Medicine, given by The American Geriatrics Society and The American Academy of General Practice (Rhode Island and New York Chapters), New York, N.Y.

** Deceased April 21, 1959.

MODERATOR DAMESHEK: Why should these values rise, Dr. Bethell? Is it because the patients suffer from anoxemia, cyanosis or heart failure?

DR. BETHELL: I have no idea. It may represent an effect of aging on an erythropoietic regulatory center, possibly mediated through vascular changes, local hypoxia and increased elaboration of an erythropoietin.

MODERATOR DAMESHEK: *Have you any data as to the new erythropoietic hormone in the older age group?*

DR. BETHELL: No, I have not.

MODERATOR DAMESHEK: Dr. Bethell has been working with erythropoietic hormone, which is a rather "hot" subject in hematology.

DR. BETHELL: The trouble is that our methods of measurement of the erythropoietic activity of plasma are relatively crude. We can detect differences with some degree of dependability only when the increase in activity is of the order of two to four times normal. In certain persons, there may be enhanced production of so-called erythropoietic hormone as they grow older, but we still are not able to measure such differences.

MODERATOR DAMESHEK: Dr. Reisner, *do you think that the bone marrow tends to wear out in the older age group and therefore the blood count tends to become lower?*

DR. EDWARD H. REISNER, JR.: Meaning, do I think that the marrow perhaps wears out like the myocardium or the synovial membranes?

MODERATOR DAMESHEK: Yes, or does the marrow become somewhat hypocellular?

DR. REISNER: I have puzzled over that question for a long time, Dr. Dameshek. We see a certain number of octogenarians in our hematology clinic. Most of them have pernicious anemia and have been followed for many years. During the past year, I found 2 or 3 who had received the same therapy continuously, but the blood picture had deteriorated. In these very old patients, there is usually some other cause for the anemia, such as elevation of the blood urea level or some arthritic processes. I am not at all sure that there is such a thing as primary old man's anemia representing wearing out of the bone marrow. Necropsies on old people reveal rather active marrow.

MODERATOR DAMESHEK: I had the impression that the bone marrow becomes somewhat more fatty and more hypocellular with advancing age, but I am glad to hear about your experience.

Dr. Schwartz, have you any comments to make?

DR. STEVEN O. SCHWARTZ: We carried out a series of marrow studies some years ago. We took the age of 80 as the dividing point, and considered only patients beyond that age.

MODERATOR DAMESHEK: I am glad to hear that.

DR. SCHWARTZ: Before the age of 80, one is considered young. I do not remember how many marrow examinations we made, but we found that, unless there was some obvious or occult disease, the marrow in these old people was virtually the same as in younger mature adults.

MODERATOR DAMESHEK: You agree with Dr. Reisner. What do you say, Dr. Tocantins?

DR. LEANDRO M. TOCANTINS: By the very nature of the methods some of these observations are restricted to qualitative examinations, because the total capacity of the marrow, or erythron is difficult to measure. It is just an impression that the erythron, as such, is reduced.

MODERATOR DAMESHEK: Is the total red cell mass reduced?

DR. TOCANTINS: The red cell mass, including the precursors in the bone marrow, may be reduced in volume but not necessarily in quality; and perhaps the differential counts in the sternal bone marrow would not be much below normal. Since we do not have adequate and accurate methods for measuring the erythron as such, it would be difficult to answer that question.

MODERATOR DAMESHEK: Apparently, the panelists do not know precisely whether or not the marrow wears out. Dr. Bethell gave the idea that the blood count in the older age group is usually somewhat reduced, but he then said that it may be increased. Would you want to comment further on that, Dr. Bethell?

DR. BETHELL: One might explain the customary decline of values in the male on the basis of decreased secretion of gonadal hormone. In experimental animals this accounts for the sex difference; the castrated male rat has the same erythroid values as the intact female.

One consideration in a discussion of a possible decrease in the total erythron is whether the life span of the red blood cells is changed when people grow older. Perhaps one of my colleagues would want to comment on that. I have no information on the subject.

MODERATOR DAMESHEK: Does anyone have studies on that? I do not believe that there are many.

DR. TOCANTINS: Is there any difference with age in the rate of incorporation of iron into hemoglobin? Perhaps this would give some idea of the activity of the bone marrow. Much work has been done in the past two years on the incorporation of iron into hemoglobin in a variety of disorders. Perhaps in that way we could establish a difference in activity between old and young people.

MODERATOR DAMESHEK: We ought to get away from that subject, since we seem not to know much about it. Most studies indicate that hemoglobin and red cell values in older people are somewhat reduced, particularly in the male, so that they approach the values found in the female. As males grow older they become more like females, at least from the standpoint of male sex hormone.

Do we have to worry about deficiency states, vitamin deficiencies, and the like in the older age group? In some quarters, it is recommended that large amounts of vitamins be given to all older people. In fact, this is stressed in the promotion of some medications, perhaps known less well by the medical profession than by lay groups.

Dr. Bethell, *do you think that old people should receive large amounts of vitamins?*

DR. BETHELL: The prevalence of deficient diets in certain older age groups is much greater than among younger more active groups. The tendency toward dietary faddism in older people contributes to vitamin deficiency.

Gastric acidity is also decreased in older persons. This may have some bearing on diminished absorption of vitamin $B_{12}$, if we can establish a parallelism between decreased secretion of hydrochloric acid and of intrinsic factor. The total gastric

secretion is less in older persons, and it has been shown that serum vitamin $B_{12}$ levels tend to be lower with aging. However, it has not been demonstrated that vitamin $B_{12}$ is as well absorbed in older persons as in younger ones, or that old people can be benefited by its administration.

We are still in a position of speculation regarding the occurrence of vitamin deficiency in old age. There is no evidence that such a deficiency exists, except insofar as there may be a greater incidence of dietary inadequacy and also more disturbances in intestinal absorption in certain older persons. By no means would I agree that vitamin deficiency and a need for the administration of vitamins is a specific attribute of aging.

MODERATOR DAMESHEK: Dr. Schwartz, have you any comments on that?

DR. SCHWARTZ: When the diet is adequate, there is no more need for vitamin supplementation in the older age group than in the young.

I should like to revert briefly to a previous point. Many mistakes will be made if one accepts anemia in the aged on the basis of aging. Many underlying carcinomas and infections will be overlooked. For this reason, we are reluctant to ascribe even moderate anemia, simply to age. We often see concomitant conditions, such as hypothyroidism, chronic azotemia, subacute bacterial endocarditis, and other conditions which account for a drop in hemoglobin concentration and red blood cell count to low levels that otherwise would be considered normal because of the patient's advanced age.

MODERATOR DAMESHEK: That is a good point. The tendency years ago was to speak of old-age anemia. There is no such thing as anemia due simply to old age; one must always look for the cause of anemia in a given instance. In the older age group, one looks for conditions such as carcinoma, renal disease with uremia (a fairly common cause), or hypothyroidism.

Let us speak further about *deficiency states that may develop in older people.* Dr. Reisner, what about deficiency states? Are they likely to be of the pernicious anemia variety?

DR. REISNER: Yes. In fact, pernicious anemia is a secondary deficiency state. That is, the deficiency of vitamin $B_{12}$, which produces the anemia is itself secondary to a primary inherited disease or metabolic or cytologic abnormality in the gastro-intestinal tract.

MODERATOR DAMESHEK: You would emphasize the concept that *there is no such thing as primary anemia, but that all anemia is secondary to some well defined cause—in this instance, a constitutional gastric one.*

DR. REISNER: Yes. This constitutional gastric disorder is the most interesting aspect of pernicious anemia, at least to me. I should like to digress for a moment from the purely geriatric aspect of the subject. We have found a small number of children in whom pernicious anemia was present in early childhood: in this group, the family history of pernicious anemia was positive in more than 50 per cent. In contrast, the familial incidence in the older age group in whom the disease occurs more frequently, was only 10 to 12 per cent. This strongly suggests that children in whom the disease develops early have received a double dose of the genetic predisposing factor from both parents. *There is the hereditary*

*tendency and there is the function of time.* The stronger the hereditary tendency, the earlier in life the disease is likely to appear. For the average heterozygous patient, the disease will not develop until he has reached later life. The peak incidence of pernicious anemia is in the sixth decade.

MODERATOR DAMESHEK: The activation of the hereditary tendency, however, may be brought about by environmental factors. For example, if an older person stops eating for some reason or other—maybe because a tooth has been extracted and his mouth is swollen—pernicious anemia may develop rather acutely.

DR. REISNER: Yes, that is right. Moreover, a person who has no hereditary tendency to pernicious anemia, but whose stomach has been removed, will sooner or later show signs of macrocytic anemia. Vitamin $B_{12}$ deficiency can produce this picture, but in pernicious anemia there is a constitutional predilection.

Another interesting aspect is the *probable relationship to the tendency toward development of cancer.* The characteristic cell in gastric washings and gastric biopsy specimens from cases of pernicious anemia was first detected because of false positive findings with the Papanicolaou test on gastric washings from a group of patients at the University of Chicago. Dr. Rubin reviewed these results and found that all the patients had pernicious anemia. Extending the investigation, he noted the presence of a non-malignant cell, somewhat like the premalignant cell, apparently associated with the marked tendency towards development of cancer in these cases. The incidence of cancer of the stomach in patients with pernicious anemia is at least three times as great as in the population at large. This again points to the presence of a primary cause in the gastrointestinal tract.

MODERATOR DAMESHEK: Dr. Schwartz, have you any further comments?

DR. SCHWARTZ: The thing that interests us is the *heterogeneous nature of pernicious anemia.* I am sure that both Dr. Reisner and Dr. Bethell also have been studying this problem. We used to assume that pernicious anemia was a disease, but now we think of it as a syndrome.

DR. REISNER: I call it a "family" of disorders.

DR. SCHWARTZ: We have recently restudied most of the 250 or so patients in our pernicious anemia outpatient clinic, because better methods of testing have become available with radioactive technics. About 1 in 5 of these patients either has some type of malabsorption syndrome other than pernicious anemia, or does not show the characteristic absorption of vitamin $B_{12}$ associated with typical Addisonian pernicious anemia. Yet, studying this group in retrospect, we find that clinically the disease has closely simulated classical Addisonian pernicious anemia.

Whether this group is also different prognostically or from a family standpoint, remains to be seen. Some of these patients have varying amounts of hydrochloric acid in their stomachs and yet respond in every way like patients with pernicious anemia. Incidentally, this is a fruitful area for study at the moment. I wonder if Dr. Bethell or Dr. Reisner has done any work along these lines?

DR. BETHELL: I agree with you that we are becoming more and more aware of the *disturbances in absorption* that lead to macrocytic anemia and a megaloblastic change in the bone marrow, and that may be due in some instances to a combined deficiency of vitamin $B_{12}$ and folic acid.

At times the defect in absorption appears to be limited to vitamin $B_{12}$. In any event, treatment with parenteral vitamin $B_{12}$ may correct not only the anemia but lead to improvement in the absorption of vitamin $B_{12}$ and probably also of folic acid. Clinical observations, serum vitamin $B_{12}$ determinations, and the results of Schilling vitamin $B_{12}$ excretion tests all indicate that a vicious cycle may be created whereby a poor diet may cause impaired absorption, and the resulting deficiency of vitamin $B_{12}$ may aggravate the malabsorption.

It is surprising that in many of these patients there may be no clinical evidences of malnutrition except the anemia. One would expect that the dietary inadequacy and the absorption defect would involve a number of nutrient factors.

DR. REISNER: Dr. Schwartz, your statement that some of these patients had free hydrochloric acid and yet responded in the same way as patients with pernicious anemia interests me, because we have seen that condition only in rare instances. A large number of our patients have free hydrochloric acid and fail to absorb radioactive vitamin $B_{12}$; however, this is not corrected by the addition of intrinsic factor. We do not know the exact diagnosis in these patients. They undoubtedly have a malabsorption syndrome, and they respond to parenteral vitamin $B_{12}$. The condition has been labelled sprue. Whether or not the picture is that of sprue, I do not know. However, I think that the patient with free hydrochloric acid and nonabsorption of vitamin $B_{12}$, corrected by intrinsic factor, is rare except among the younger age group. Would you like to discuss that?

DR. SCHWARTZ: Whether we call this sprue or not, is really not important. If we are going to call it sprue, we shall have to broaden our definition of sprue.

At the moment, for the lack of a better name, we are classifying all these cases as malabsorption syndromes. There is no doubt that gradually this so-called malabsorption syndrome group will have to be subdivided further into a half dozen or more subtypes. Patients with free hydrochloric acid, by definition, do not have Addisonian pernicious anemia and do not behave as though they had it, as far as the absorption of vitamin $B_{12}$ goes; but they do respond therapeutically to vitamin $B_{12}$. Most important of all, they show the clinical manifestations of pernicious anemia and respond to parenteral therapy. In the past, we have simply called them atypical or unusual cases of pernicious anemia.

MODERATOR DAMESHEK: This is a subject upon which we could spend more time. However, we should remember that pernicious anemia is only one of the deficiency syndromes that may occur in the older age group, and that these syndromes may develop for one of several reasons, *e.g.*, dietary inadequacy, a disorder of the gastric juice, of intestinal malabsorption, or liver disease. Some people have a complexity of disturbances—dietary, gastric, intestinal and hepatic—and therefore are more vulnerable to the development of a deficiency syndrome.

I think of pernicious anemia not strictly as one disease, but as a "family"

of disorders. There is the typical Addisonian variety that occurs in temperate zones and in the so-called Nordics with achlorhydria and neurologic disturbances. On the other hand, many kinds of disease much like pernicious anemia occur in the tropics; for example, tropical macrocytic anemia or sprue. Some types, such as the anemias of pregnancy, are benefited by folic acid. However, they all belong to a similar family. They all have 2 characteristics in common, namely, macrocytosis (large red cells) and megaloblastic bone marrow. Otherwise, they vary considerably.

Before proceeding, we might discuss briefly the *treatment of pernicious anemia.*

DR. REISNER: In the last two years we have seen the emergence of oral forms of therapy for pernicious anemia. I think that a word of caution is necessary.

The patient with pernicious anemia can absorb folic acid, but cannot absorb vitamin $B_{12}$ by mouth unless it is accompanied by intrinsic factor. There is definite danger in the use of "shotgun" vitamin preparations in the treatment of patients with anemia (especially if we are not sure of the nature of the anemia), because folic acid has an antagonistic effect on vitamin $B_{12}$ and aggravates the neurologic lesions of pernicious anemia.

MODERATOR DAMESHEK: Do we know for a fact that folic acid tends to have this antagonistic effect?

DR. REISNER: I do not think that it is an antagonist in the sense that it is an enemy. I think that both of these substances are mutually involved in the metabolic synthesis of nucleoproteins and that, when one is given, it speeds reactions that consume the other. Administration of folic acid to patients with pernicious anemia results in depression of their serum vitamin $B_{12}$ levels. This is probably the reason why cord disease may develop with fulminating rapidity when a patient with pernicious anemia is treated with folic acid. There are several reports of the development of combined system disease in patients who did not know that they had pernicious anemia and took multivitamin preparations containing folic acid. Conley reported a half dozen such cases in the *New England Journal of Medicine* about nine years ago. Therefore, folic acid is, to my mind, definitely contraindicated in the treatment of pernicious anemia.

DR. BETHELL: Except in combination with adequate amounts of vitamin $B_{12}$.

DR. REISNER: With adequate amounts of vitamin $B_{12}$. The use of oral therapy with a combination of intrinsic factor and vitamin $B_{12}$ will provide satisfactory control of the anemia if the intrinsic factor concentrate is potent. There is an increasing amount of evidence that many commercial intrinsic factor concentrates are not as stable as had been hoped for at first. There are several recent reports of relapses in patients treated with oral preparations.

For the present, the most satisfactory method of therapy for the patient with pernicious anemia is regularly spaced injections of vitamin $B_{12}$.

MODERATOR DAMESHEK: Dr. Bethell, you are a therapist in this field. What do you say to that?

DR. BETHELL: I would certainly agree that the place of the combination of intrinsic factor and vitamin $B_{12}$—the official U.S.P. preparation known as Vitamin $B_{12}$ with Intrinsic Factor Concentrate—is now somewhat in question. In

fact, it is likely that such preparations will be eliminated from the U. S. Pharmacopeia.

Recently in Chicago a report was made to the effect that patients become refractory to intrinsic factor concentrate, but this claim has not yet been completely documented. It was not shown in the Chicago study whether the preparation used had retained its activity. One of the difficulties has been to establish a reference standard for assay of Vitamin $B_{12}$ with Intrinsic Factor Concentrate by any technic of absorption or excretion of radioactivity. Standard reference materials which possess established activity at the outset apparently lose some activity while standing on the shelf. There is always doubt about the potency of intrinsic factor preparations after the lapse of considerable time, and doubt as to whether or not they will be as active as the original material from which they were made.

Consequently, I agree that parenteral vitamin $B_{12}$ therapy is the treatment of choice for all patients with pernicious anemia. That does not mean that oral preparations may not be used as supplements, if desired. Whether there is any real merit in so doing is open to question, except possibly as a means of decreasing the parenteral dosage or prolonging the intervals between injections.

MODERATOR DAMESHEK: Thank you Dr. Bethell. We shall have to leave the interesting subject of pernicious anemia and go on to another. *Neoplastic states have some bearing on the blood picture in the older age group.*

A neoplastic condition that occurs in the older age group more than in any other is *multiple myeloma.* It is a proliferating disease involving plasma cells throughout the entire body, particularly in the bone marrow. However, it is a generalized disorder that seems to be a rather chronic leukemic proliferation of the plasma cell series. Dr. Tocantins, have you any comments on multiple myeloma?

DR. TOCANTINS: Speaking for myself, the extent of our ignorance with regard to the nature of multiple myeloma can be classed as phenomenal. It is really disappointing because it is the general impression that we see more cases of multiple myeloma than we ever saw before.

MODERATOR DAMESHEK: Do you think that is because the incidence is increased, or because the diagnosis is more readily made?

DR. TOCANTINS: That is difficult to tell. I know of no statistics that have dealt adequately with that point. The incidence seems to be increasing. That is just an impression, however, based upon the fact that we are seeing about 1 case every three or four weeks in our 1000-bed hospital—sent to us either by an orthopedic surgeon or by a nose-and-throat man, or sometimes seen in our own medical wards. That is a large number of cases compared with our former experience.

It is true that sternal punctures are being performed more commonly and that roentgenographic examinations are being made more frequently. All these things have contributed to making the diagnosis.

MODERATOR DAMESHEK: If you were in general practice, what would make you think of the possibility that a given person had multiple myeloma?

DR. TOCANTINS: We usually tell our residents that when a man past age 50 has anemia, pain in the back and urinary disturbances, think of multiple myeloma. That is a rough way to make a diagnosis. The presence of anemia, pain in the back and urinary disturbances, particularly nocturia, frequency and proteinuria, strongly favor the likelihood of multiple myeloma.

MODERATOR DAMESHEK: Do you mean pain in the back and kidney disturbances?

DR. TOCANTINS: I mean anemia, pain in the back, and some manifestation of renal insufficiency. Other diseases may produce the same combination of symptoms, but in the absence of other obvious causes, we would think seriously of multiple myeloma.

Approximately one-fourth of patients with multiple myeloma have hemorrhagic manifestations. Some of these manifestations are due to thrombocytopenia, to changes in the proteins or in prothrombin, to deficiency of accelerator factors, or to excessive amounts of anticoagulants. In a few cases there may be a combination of all these factors. These manifestations can be most disturbing because they nearly always interfere with therapy, which is usually suppressive.

The use of urethane may not be strictly suppressive therapy; it is palliative because it is directed mainly against pain, but possibly it is suppressive. $P^{32}$ is another form of treatment, but we have had more trouble with it than good luck. Local roentgen therapy has been successful in our hands in a few instances, especially in patients who have a great deal of bone pain. General body irradiation, whether internal or external, is contraindicated.

The main points to be stressed are the need to be aware of the disease and the possibility that it may be masked by chronic renal disease, chronic anemia or lumbago, and the fact that we can do very little for these patients except in a palliative manner.

MODERATOR DAMESHEK: What are the diagnostic features of multiple myeloma that enable us to recognize it more readily from the beginning? Dr. Schwartz, would you care to comment further?

DR. SCHWARTZ: I should like to underline what Dr. Tocantins has said. We go even further. We teach that any patient who has an unexplained anemia should be suspected of having multiple myeloma until proved otherwise.

MODERATOR DAMESHEK: Above what age?

DR. SCHWARTZ: The age of 45 or 50 years, as Dr. Tocantins has said. I think that this disease is definitely in the ascendancy. We have been examining bone marrows long enough not to have been missing multiple myeloma for the last twenty years. In the last ten years, we have been seeing a tremendous increase in the number of cases. There is never a time when we do not have from 1 to 3 cases in the hospital.

The interesting thing is that it may manifest itself in so many ways. The classic triad consists of back pain, anemia and renal insufficiency. Occasionally a patient will come in with nosebleed, and only the fact that the anemia is disproportionate to the amount of bleeding calls attention to the possibility that there is some underlying disease. Patients come in with tumors of the jaw, with

pathologic fractures, with unexplained "refractory" anemias, and innumerable other manifestations. Unless one is constantly on the alert for the diagnosis of multiple myeloma, most of the cases will be missed for a long time. It is not just because we are making more roentgenographic examinations and performing more electrophoretic studies that we are picking up these cases. The increasing awareness undoubtedly is contributing to early detection, but I am sure the total incidence is much higher than in the past.

MODERATOR DAMESHEK: This plasmocytic proliferation produces a striking protein disturbance. The globulins in the serum become greatly increased. As a result, rouleaux formation in the blood increases so that a smart technician and the physician frequently can detect the disease by looking at a blood smear. An alert technician can detect aggregates of red cells when using Hayem's solution, which contains bichloride of mercury, a protein precipitant; the red cells tend to form clumps in the pipette and in the counting chamber. There are numerous protein changes that account for many of the features of the disease. The electrophoretic pattern is one of them. Proteins may block the renal tubules and cause a nephrotic condition. Amyloidosis may develop. Therefore, one should always be looking for multiple myeloma. Unfortunately, we cannot do much by way of treatment. We give large amounts of urethane, and we sometimes try one of the alkylating agents such as Leukeran (CB-1348). At times, we use corticosteroids. Unfortunately, we do not have much success with the therapy of multiple myeloma.

We shall now take up another subject bearing on neoplasia. *Does chronic lymphocytic leukemia in the older age group differ from that in the younger?* Dr. Bethell, would you care to comment?

DR. BETHELL: Chronic lymphocytic leukemia is the most common of the leukemias in the older age group; the median age is about 62 or 63 years. Paticularly in older persons, the question often arises as to whether treatment should be instituted when the diagnosis is first made. Frequently, the diagnosis is made on the basis of a blood count performed for some other condition, or on the basis of a general physical examination. An elevated leukocyte count is found, with a predominance of lymphocytes that are well differentiated. There may be little or no associated anemia or thrombocytopenia. At the same time, surprisingly, examination of the bone marrow may often show a heavy infiltration of lymphocytes.

In the absence of definite symptomatology, anemia, thrombocytopenia, or marked tumefaction, it is our practice to withhold therapy and observe the patient at intervals of three months. If the condition remains stationary, it may be possible to prolong the intervals between examinations for as long as six months. It is not uncommon to keep such patients under observation over a period of years. We have one patient who has come to us for fourteen years; his white blood cell count has remained stable at a level of about 40,000 to 50,000 leukocytes and 70 to 80 per cent lymphocytes. He has not had any treatment. Nothing can be gained by instituting therapy in such a case.

When, however, the leukocyte count is rising, or when there are other evidences of activity, treatment should be started. One has a choice between

radiation and a chemotherapeutic agent. The agents that have proved most satisfactory have been the alkylating drugs, triethylene melamine or TEM, and more recently chlorambucil, which is now sold in this country under the trade name of Leukeran. Dr. Dameshek has already referred to it. Chlorambucil has advantages in terms of adjustability of dosage and relative lack of cumulative action in comparison with TEM. Therefore, chlorambucil is now used by us in the treatment of most patients with active chronic lymphocytic leukemia, unless there is a clear indication for the use of local irradiation. We no longer employ total body irradiation or radioactive phosphorus in the treatment of chronic lymphocytic leukemia. We occasionally use topical irradiation for enlarged nodes or an enlarged spleen.

In chronic lymphocytic leukemia there is frequently a concomitant or secondary form of so-called hypersplenism, usually manifested by hemolytic anemia and sometimes by thrombocytopenic purpura. Patients who have remained in a stationary state for some time, may show the development of hemolytic anemia or thrombocytopenia as the first manifestation of activity of disease. These conditions may demand other types of therapy, although treatment of leukemia itself should always be considered as the primary objective.

For the treatment of hypersplenism, corticosteroids are indicated. A relatively small dosage—as little as 10 mg. of prednisone daily—may serve to keep the condition under control. On the other hand, splenectomy is definitely of value in some of these patients whose hemolytic anemia or thrombocytopenia cannot be controlled with moderate-sized doses of adrenal steroids.

MODERATOR DAMESHEK: That was a fine summary of the problem of chronic lymphocytic leukemia in the older age group. I should like to emphasize your recommendation that if an older person (say, past the age of 60 years) has a count of 25,000 to 50,000 white blood cells with lymphocytosis, no symptoms and no large lymph nodes, he should be left strictly alone. Much trouble can be caused by giving him irradiation or a chemotherapeutic agent, as anemia may develop following such therapy. Then, the anemia must be treated, and this is often a worse problem than the leukemia. If one leaves the leukemic situation alone when the leukocyte count ranges between 25,000 and 75,000, and follows the case at intervals of three to six months (not too often, else the patient become nervous) the result will be just as good as if treatment were given, and frequently much better. With respect to therapy, Dr. Schwartz, do you have any other comments?

DR. SCHWARTZ: No, but I have a question. In older persons we often find leukocyte counts of, say, 10,000 to 15,000, with perhaps 40 to 50 per cent lymphocytes and a moderate lymphoid hyperplasia of the bone marrow. I should like to know what the members of the panel think about these patients. Do they have chronic leukemia? We follow them for years. Their counts do not change, and the clinical status does not change. The spleen does not become palpable, and the nodes do not enlarge. Should this condition be called leukemia, or should it be called benign lymphocytosis of the aged? Is this a normal variation that occurs in elderly persons?

MODERATOR DAMESHEK: I discussed that point yesterday with a physician

from Washington (Public Health Service) who was in my office. He is a man aged 67 with a leukocyte count of 20,000, and he has been worried about it during the past ten years. Ten years ago, he found that he had a leukocyte count of 10,000 with 50 per cent lymphocytes. Now, he has a count of 20,000 with 65 per cent lymphocytes.

I told him that the question of whether or not this represents leukemia is a matter of semantics. We do not know what leukemia is anyway. He simply has lymphocytosis. About twenty years from now his leukocyte count may rise to 80,000, but by that time neither he nor I need worry about it.

For him, and for these other people, the best procedure is to regard the condition as a relatively benign lymphocytosis. If you want to dignify it by the term leukemia, you can. We must realize that there are relatively benign types of leukemia that continue for many years, though there are also acute types.

We should discuss the acute type of leukemia. *Do the panelists think that the incidence of acute leukemia is increasing in the old age group?* Dr. Reisner?

DR. REISNER: I think that the incidence of leukemia is increasing at every age. In general, however, acute leukemia is a disease of younger persons. The younger the age group, the more acute the leukemia, but we do encounter it in older people. I have been struck by the fact that most of the patients that I have seen with acute monocytic leukemia—and there are not many because it is a rare type of leukemia—have been in the older age group. I do not know whether that has been the experience of others.

I have seen several cases of acute leukemia develop in elderly men who had been under treatment for a long time with Gantrisin or some other sulfonamide, for chronic urinary-tract infection complicating prostatic obstruction.

MODERATOR DAMESHEK: Dr. Bethell, have you any comments on this leukemia problem in the older age group?

DR. BETHELL: I agree that the incidence of acute leukemia in this group is increasing, particularly the variant of granulocytic leukemia that has monocytic characteristics. It is not usually the true monocytic or histimonocytic type but is more likely to be the myelomonocytic variety. I am impressed by the number of patients past the age of 50 who have this condition. Often it is subleukemic, with actual leukopenia, and rapidly developing thrombocytopenia.

MODERATOR DAMESHEK: Do you think that these cases used to be called anemia in the past; or do you really think that the incidence is increasing?

DR. BETHELL: I do not think that many of these cases would have been called anemia, at least not if any reasonably adequate blood examination had been made, because even the peripheral blood film usually contains markedly abnormal cells.

MODERATOR DAMESHEK: Then, why do you think that the incidence is increasing in the older age group? I have some ideas about that, but perhaps you could say something about it.

DR. BETHELL: I think that the increasing incidence of acute and subacute leukemia is related to environment. The environmental factors are probably cumulative, and that is why we are seeing a higher incidence in older persons.

One such possible factor has already been mentioned, namely, the use of sulfonamide drugs. There may be many other factors that have a cumulative effect in causing the increased incidence of leukemia.

MODERATOR DAMESHEK: *Is ionizing radiation perhaps the most important single mechanism in the development of leukemia?*

DR. BETHELL: Only in certain population groups. It has been shown beyond doubt that under circumstances of chronic exposure to radiation, as in the case of radiologists or of persons who have been treated for spondylitis by radiation therapy, there a higher incidence of leukemia. As for the population at large, I do not believe that we can incriminate radiation, because the majority of our patients have not had any unusual number of diagnostic roentgenograms. Many have had none. Even if natural or background radioactivity is of etiologic importance in leukemia, it would seem that its role is merely contributory. However, one must recognize the hazard of irradiation and admit that any added exposure, no matter how small, may enhance the risk of developing leukemia.

MODERATOR DAMESHEK: Dr. Schwartz, do you want to comment on that with regard to acute leukemia? You had some other ideas about this.

DR. SCHWARTZ: I should like to digress for a moment. We know the dangerous potential of ionizing radiation. Yet, I am sure that at least 2 members of this panel treat a fairly benign condition known as polycythemia, in the older age group, with ionizing radiation. This is done in spite of the fact that there is a definite increase in the incidence of conversion of polycythemia to acute leukemia, and in spite of the fact that we know that this is probably largely if not entirely due to ionizing radiation. I should like to know the justification for this.

Another point concerns the evolution of acute leukemia. We follow these patients for a number of months, and occasionally for a number of years. The disease starts as a typical hypoplastic or aplastic anemia. We examine the marrow again and again and, even in retrospect, find no evidence of leukemia. Then, after months or even years, there evolves a classic fulminant acute myeloblastic leukemia. This is a challenging problem. What is the cause-and-effect relationship between the long aplastic phase and the development of leukemia in these patients?

MODERATOR DAMESHEK: Dr. Tocantins, do you have any comments?

DR. TOCANTINS: I can add little to what has already been said. I want to endorse emphatically the comments made by Dr. Bethell and Dr. Dameshek about the benign character of lymphocytic leukemia in the aged. This condition can hardly be called leukemia when a person can live fifteen or twenty years with it and die at the age of 85. I know of such a case in a woman who was never treated. Her white blood cell count was 100,000 or so, with 90 per cent lymphocytes. It is difficult to put this disease in the same category as other leukemias. The term has thrown a great deal of anxiety and terror into peoples' minds. It is about time that we give the disease a different label. Much of the treatment is actually reassurance and explaining to the patients the nature of the disorder. They should be kept from becoming white-cell conscious. This is difficult to

achieve if we continue to stress the leukemic aspect and they read about in it the press. There is a great deal to be done along these lines, because the form of leukemia that is most common in the aged is chronic lymphocytic leukemia. We all have seen examples of overtreatment and unnecessary treatment for this condition, and a great deal of anxiety produced in the family and in the patient by overzealousness in management.

MODERATOR DAMESHEK: To revert to acute leukemia, Dr. Schwartz has made some interesting and challenging observations. I doubt that we should attempt to answer at this point, but should perhaps leave it for some other panel.

*What are we going to do for persons in the older age group with acute leukemia?* Are we going to treat them vigorously by chemotherapeutic methods, or are we going to treat them by more gentle procedures? In view of the known end-results at present in this older age group with acute leukemia, so how should we treat them? Dr. Reisner, have you any comments?

DR. REISNER: This is really more of a moral social problem than a medical one. I recently had to treat a woman aged 85. I did not subject her to a course of marrow-depressing agents, which might add to her misery. My primary object was to keep her comfortable. There was no point in prolonging her life a couple of months. On the other hand, we know that a child will respond better to treatment; in this case one has every reason to try all known methods to keep the child alive and comfortable as long as possible, in the hope that some better treatment will become available.

Older patients do not as a rule respond well to the agents that we have at our disposal. When one uses massive steroid therapy, there are the complications of water retention and electrolyte disturbance. The aged do not respond as well as the young to the antimetabolites. One really has a problem.

MODERATOR DAMESHEK: That is true, with one exception. Dr. Schwartz mentioned hypoplastic leukemias, if you want to use that term. There are older people with pancytopenia—a reduction of red cells, white cells and platelets—in whom the diagnosis varies from aplastic leukemia to leukemia; it is difficult to say which. Once in a while, abnormal cells are found in the blood and in the marrow.

Lately, I have been referring to some of these cases which show a few myeloblasts in the blood as "5 per cent leukemia"; in other words, leukemia not involving the entire bone marrow or the entire body. The host may live in peaceful coexistence with the leukemic proliferation for a number of years. Such persons may be benefited by the use of small doses of corticosteroids and by other gentle methods of therapy.

I would agree that to push chemotherapy in the older age group is unjustified. Dr. Schwartz, have you any further comments?

DR. SCHWARTZ: No.

DR. REISNER: Would you call those cases that you have just described acute leukemia?

MODERATOR DAMESHEK: That is a matter of semantics. There are myeloblasts in the blood, and therefore some people would call these cases acute; on

the other hand, they frequently run a chronic course. Acute and chronic are clinical terms. Dr. Bethell, have you any comments?

DR. BETHELL: With regard to the treatment of acute leukemia—there is no arbitrary age after which one ceases to obtain beneficial results. Therefore, we cannot discard specific therapeutic measures in the treatment of older persons with acute leukemia or with the type of leukemia to which reference was made. As long as a patient fares reasonably well with blood transfusions and perhaps small doses of corticosteroids, I would be averse to using chemotherapy. When the patient is not doing well, 6-mercaptopurine may prove beneficial even in persons past 70 years of age.

MODERATOR DAMESHEK: Lately, we have been administering large doses of corticosteroid in the form of prednisone (Meticorten). Remissions can be obtained with 1000 mg. of prednisone daily, but this dosage causes psychotic reactions and other difficulties. We can obtain the same results with a dosage of 250 mg. daily, and to a lesser extent with 100 mg. daily. Therefore, I favor prednisone therapy rather than the use of the more myelotoxic chemotherapeutic agents. However, Dr. Bethell's comment that age should not be the determining factor is probably warranted.

We have not had much chance to discuss hemorrhagic manifestations. We might spend a few minutes on that, because Dr. Tocantins is an authority on that subject. *Is so-called idiopathic thrombocytopenic purpura common in the older age group, or is its incidence related to something else?*

DR. TOCANTINS: Generally, idiopathic thrombocytopenic purpura is a disease of young people, primarily children. The greatest frequency is before the age of 10. The frequency curve drops rapidly; less than 5 per cent of the cases are observed in patients past the age of 50 years.

"Idiopathic" means that we do not know the cause. In thrombocytopenic purpura in the aged, we should think of 2 causes: 1) drug sensitization or intoxication, and 2) neoplastic disease. We put drugs ahead of neoplastic disease, because synthetic agents are being used more than ever. It is a natural consequence that we see more and more drug-induced disorders, particularly in persons who have used drugs for a long time or have had an opportunity to become sensitized to them by repeated use. Quinidine thrombocytopenia occurs much more often than previously, or at least it seems to be recognized more frequently.

MODERATOR DAMESHEK: If you see a patient in the older age group with acute fulminating thrombocytopenic purpura, you have to think of quinidine, do you not?

DR. TOCANTINS: I would think of drugs. Quinidine would be one of them, particularly if there was a history of arrhythmia, or if the patient had been treated for cardiac symptoms. Then, I would think of quinidine right away.

MODERATOR DAMESHEK: Are there any other such drugs?

DR. TOCANTINS: Sedormid and the sulfonamide drugs. Many people are still taking amidopyrine, barbiturates and antihistamines.

MODERATOR DAMESHEK: Barbiturates? I did not think that they caused any trouble.

DR. TOCANTINS: Yes, Dr. Harrington has reported a few cases.

MODERATOR DAMESHEK: I always thought that phenobarbital and aspirin were about the only drugs that did not cause hematologic disorders. They may, of course, cause other troubles.

DR. TOCANTINS: Aspirin has been reported to cause hematemesis and hypoprothrombinemia.

MODERATOR DAMESHEK: Dr. Reisner, you reported a case of thrombocytopenic purpura due to Diamox. Is that right?

DR. REISNER: Yes. It is the only one I know of; but as the drug is a sulfonamide, one would expect sooner or later to encounter such a case. Diamox is used a great deal in the older age group as a diuretic, but I do not think that this rare occurrence of purpura is any contraindication to its use. If purpura should develop, Diamox should be discontinued immediately.

MODERATOR DAMESHEK: I suppose we ought to know what we are giving in these drugs. Dr. Schwartz, do you have any comments on these cases?

DR. SCHWARTZ: We should not forget gin and tonic as a cause of thrombocytopenic purpura. Apparently, the quinine in the tonic may occasionally cause thrombocytopenia.

MODERATOR DAMESHEK: You are not pulling our legs on that, are you?

DR. SCHWARTZ: No. This is one of the most interesting causes of thrombocytopenic purpura.

MODERATOR DAMESHEK: Dr. Bethell, have you any further comments?

DR. BETHELL: I want to emphasize the periodicity of the action of quinidine in thrombocytopenic purpura. Almost always there is a history of repeated administration, and finally a fulminating attack precipitated perhaps by a single dose of quinidine which is frequently overlooked. A patient may come in with generalized bleeding, and the fact that one pill was taken preceding this dramatic event is often not noticed.

MODERATOR DAMESHEK: If we do have a patient with idiopathic thrombocytopenic purpura, we should not rush to perform a splenectomy but should treat the patient with such medical measures as plastic-bag fresh blood transfusions. One of the corticosteroids, notable prednisone (Meticorten), has been very effective in our hands.

I shall now call for questions from the floor.

DR. REISFELTER (Roslyn, N. Y.): *In view of the general use of aspirin and its compounds* by the laity for practically all complaints, plus the publication of reports advocating the drug in the treatment of arthritis, I should like to know *what work has been done to determine whether there is a tendency for the drug to produce blood dyscrasias in the aged.* In our own experience in private practice and at the New York Medical College, Flower-Fifth Avenue-Metropolitan Hospital group over a period of approximately ten years, the incidence of gastrointestinal disturbances and accompanying anemia has been greater than 10 per cent following the use of this drug alone or in combination. I cannot reconcile this with Dr. Dameshek's remark that aspirin is more or less innocuous.

MODERATOR DAMESHEK: Innocuous hematologically.

DR. REISFELTER: I cannot agree, because I have had 2 outstanding cases, one in a male and one in a female, following only three weeks' use of Bufferin and Anacin. The patients were told that these were allergies. Do we consider those just allergies?

MODERATOR DAMESHEK: What kind of cases were they?

DR. REISFELTER: In both of these cases, we were unable to do anything.

MODERATOR DAMESHEK: What kind of cases were they?

DR. REISFELTER: They were perforations of the stomach that required gastrectomy.

MODERATOR DAMESHEK: When I said that aspirin was innocuous, I meant hematologically. You have before you, in myself, a living example of a person sensitive to aspirin from the gastro-intestinal standpoint. I did not say that aspirin was innocuous. It may upset the stomach and cause gastritis and hemorrhagic gastritis, but hematologically I know of no difficulties. Dr. Tocantins has said this also, and he knows something of the literature. I do not doubt the validity of your statements; but hematologically, as far as I know, aspirin has no effects.

DR. REISFELTER: What about depression of prothrombin?

MODERATOR DAMESHEK: Possibly, yes. What about that, Dr. Tocantins?

DR. TOCANTINS: Yes, but large amounts are necessary. In a normal person, it would take perhaps 1–2 grams of aspirin a day to cause a depression of prothrombin, and even then it would take perhaps four or five days to produce a depression to around 30 per cent of normal. I do not think that depression of prothrombin is an important cause of hemorrhages.

MODERATOR DAMESHEK: Aspirin upsets the stomach. We know that. Dr. Bethell, have you any further comment as to whether or not aspirin causes hematologic disturbances?

DR. BETHELL: No. My experience over the past quarter-century indicates that aspirin and phenobarbital do not cause hematologic reactions. That is not saying that they do not cause any other trouble.

MODERATOR DAMESHEK: Are there any other questions?

DR. FRIE: I should like to ask Dr. Schwartz *whether the ingestion of hydrochloric acid in therapeutic doses would enhance the absorption of vitamin* $B_{12}$.

DR. SCHWARTZ: No. Hydrochloric acid itself does not enhance the absorption of vitamin $B_{12}$. It is the intrinsic factor, which is also absent in the patient with pernicious anemia, that enhances the absorption of vitamin $B_{12}$.

DR. FRIE: Thank you. My second question concerns *the finding, in rare instances, of an elevated blood count in the older patient with carcinoma.* Usually carcinoma provokes secondary anemia of the hyperchromic type with a decreased number of red cells. The reverse may happen in some cases, that is, an increased number of red blood cells in advanced carcinoma. We have found this in Scandinavia. It would be interesting to know the point of view of the panelists with regard to this finding. Perhaps metastases in the marrow of the long bones stimulate hematopoietic activity. If so, this would be significant from a prognostic standpoint. What do you think about it?

MODERATOR DAMESHEK: Dr. Bethell, will you take that?

DR. BETHELL: Polycythemia has been reported in association with certain benign and malignant tumors. I know of no explanation. I am not aware of any evidence that carcinomatous metastases to long bones have a myelostimulatory action.

MODERATOR DAMESHEK: In a few cases of hypernephroma associated with erythrocytosis, in an occasional case of fibroid of the uterus, and in a few cases of neoplasm of the brain or the pituitary, there may be a high red blood cell count. However, it is quite unusual.

Are there any other questions?

DR. MURRAY JACKSON (New Rochelle, N. Y.): I recently saw a case of *polycythemia that developed rapidly after an extensive series of diagnostic roentgenograms.* I wonder if any members of the panel have seen a similar occurrence?

MODERATOR DAMESHEK: By diagnostic roentgenograms, do you mean that the patient went from pillar to post and underwent a gastro-intestinal x-ray series done in each place?

DR. JACKSON: That is right—over a short period of time—only they were roentgenograms of bone.

DR. TOCANTINS: I was going to ask, what were the indications for the roentgenograms?

DR. JACKSON: I saw the patient afterwards. I do not know.

DR. TOCANTINS: It is conceivable that the patient might have had polycythemia before the x-ray exposures were made.

MODERATOR DAMESHEK: I would think so. I have never heard of anything like that, but it is possible. Are there other questions?

SPEAKER FROM THE FLOOR: *The question was raised about the use of thyroid in elderly persons* because true thyroid deficiency can cause a decrease in the blood count in old age. Can it be given empirically, or should serum protein-bound iodine determinations be made? If the PBI level is normal, should one give thyroid to elderly persons? What would be the recommended dose?

MODERATOR DAMESHEK: Dr. Bethell? This is really an endocrinologic question.

DR. BETHELL: It takes a fairly profound degree of hypothyroidism to decrease erythroid values materially. I do not see any justification for treating mild anemia empirically with thyroid. One has to make a more searching inquiry as to the nature and cause of the anemia and not assume that it is on the basis of deficient thyroid function.

DR. REISNER: I see no objection to the use of so-called "shotgun" preparations *after* you have thoroughly investigated the cause of the anemia in an older patient who may have deficient absorption of iron, deficient absorption of vitamin $B_{12}$, or a slight underfunction of the thyroid. It is feasible to employ a multiple preparation such as Hemosules, Hematinic, or Feosol Plus.

DR. BETHELL: Do you also use thyroid?

DR. REISNER: The inclusion of ½ to 1 grain of thyroid is not enough to cause the patient any trouble. Occasionally, a patient will feel better when a little thyroid is added.

SPEAKER FROM THE FLOOR: Do you think that is the art of medicine rather than the science?

DR. REISNER: Yes, but just because we are scientists we must not forget the art.

SPEAKER FROM THE FLOOR: Would you say a few words about *the hazards of some of the newer tranquilizers?*

MODERATOR DAMESHEK: Dr. Bethell, you are a member of the Pharmacopoeia Committee. What do you say about that?

DR. BETHELL: We know that such drugs as chlorpromazine (Thorazine) and promazine (Sparine) may cause depression of the bone marrow, and that the continued use of drugs of this type is likely to lead to some degree of leukopenia and occasionally to frank agranulocytosis or aplastic anemia.

As for meprobamate (Equanil, Miltown), I am not aware of any such reports, except 1 in which the drug might have been the cause of severe leukopenia.

MODERATOR DAMESHEK: A few cases of leukopenia have been recorded, chiefly with the initial use of the drugs in Europe. In this country, maybe 1 or 2 have been reported.

DR. SCHWARTZ: I am aware of at least 1 case of fatal aplastic anemia.

MODERATOR DAMESHEK: It points to the fact that if we as physicians use drugs, we should know all there is to know about them. We should know their formulae, and should realize their potentially dangerous effects. If they are benzene-ring derivatives they may damage the bone marrow, either totally with aplastic anemia, or selectively with agranulocytosis, thrombocytopenic purpura or anemia.

I want to thank the audience for its attention, and the panelists for their excellent discussions.