

Pathogenesis of Secondary Anemia*

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Introduction

As a simplification, it might be said that nutritional disturbances of short duration often cause a decrease in the serum or tissue concentration of a particular nutrient. If the disturbances last longer, they may next affect the bone marrow where rapid cell growth causes a high requirement for some nutrients. Since it is the erythrocyte precursors which grow most rapidly (Reizenstein et al, 1961; Reizenstein, 1962; Cea, Skårberg and Reizenstein, 1968), anemia is often an early malnutrition symptom. If nutritional disturbances last very long, severe changes in the body composition and weight loss occur (Kjellberg and Reizenstein, 1970; Kjellberg and Reizenstein, 1970).

There are a number of disease states, however, which are characterized by a decrease in the serum concentration of some nutrients, although no deficient intake is suspected. The classic example is the low serum iron in infection (Heilmeyer et al, 1958; Heilmeyer et al, 1960) which appears to be one contributory cause of anemia; another is hemolysis caused by extracorporeal factors. In cancer, similar changes are found (Lockner, 1960); and if the inflammation or the tumor last long, severe weight loss can occur. It has been said of cancer patients that they "starve in the midst of plenty," but it is not known whether a decrease of appetite is enough to explain the nutritional disturbance or whether changes in the metabolism of nutrients occur as well.

Methods

The serum folic acid activity (SFAA) was measured with a bioassay method earlier described by Rama Rao and associates (1965). An intravenous injection was then made containing 15 μ g folic acid per kg body weight and about 3 μ c ^{59}Fe as ferrous citrate.

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Blood samples were obtained at intervals after the injection. Their radioactivities were measured in a Packard gamma spectrometer and their SFAA measured by the bioassay method. In this way the plasma elimination (PE) of folic acid and of ^{59}Fe could be determined. Later studies have been made of the PE of ^{198}Au as colloidal gold (approximately 8 μ c, 0.1—7 mg gold, particle size 15—30 m μ), which estimates the phagocytic activity of the reticulo-endothelial system.

Results and Discussion

Metabolism of Iron and Folate

In the studies to be summarized here, some of which have already been published, the metabolism of some nutrients has been studied in 445 patients (Table I). The studies began when an attempt was made to use leukemias as examples of anemias of the non-megaloblastic type in a study of the serum folate in megaloblastic anemias (Hoogstraten, Baker and Reizenstein, 1963). It turned out that many of these patients had low folates. Later, similar findings were made in other forms of malignancy, correlated in part to the histology of the tumor (Fig 1) (Rama Rao et al, 1963; Rama Rao et al, 1965). Nothing was known of the pathogenesis of the low serum folate, but an increased cellular proliferation has been suggested (Mollin and Waters, 1968). Further studies demonstrated that an increased PE of folic acid apparently explains the low serum concentration (Einhorn and Reizenstein, 1966). Similarly, the hyposideremia seems to be explained by a rapid PE of iron (Heilmeyer et al, 1958; Heilmeyer et al, 1960; Lockner, 1960; Wiklund et al, in press).

Effect of Tumor Stage

In a group of patients with cancer of the uterine cervix—a form in which the stage of the tumor can be easily determined—an attempt was made to examine the relationship between the plasma elimination and the stage of the tumor. With the aid of a computer program developed for the purpose (Reizen-

stein and Zachrisson, 1968), significant correlations could be established (Fig 2) between the stage of the tumor, the iron and folate, and the anemia (Einhorn and Reizenstein, to be published). The more advanced the cancer is, the lower are the folates, and the more anemic is the patient. Similarly, a correlation between the "severity" of leukemia, the serum folate, and the anemia could be demonstrated (Fig 3). The more advanced the leukemia is, the lower are the folates, and the more anemic is the patient. In separate studies, it has been shown that neither in leukemia, preleukemia nor early myeloma (benign monoclonal gammopathy) is it a replacement of the erythroblasts in the bone marrow which causes anemia. There are often normal erythroblast numbers in the total body. Therefore, metabolic changes such as those discussed above may be one of the causes of the secondary anemia. Finally, patients with curable cancer of the uterine cervix were studied prior to and after treatment (Einhorn and Reizenstein, to be published), and the more successful the cure was, the more normal the plasma elimination became.

There are some indications that other nutrients are involved. The decrease in atheromatosis that can be demonstrated in cancer patients may suggest a disturbance in lipid metabolism (Table II).

Poor Appetite?

Is a decrease in appetite enough in those patients with malignancy to explain the pathological metabolism of some nutrients? This is conceivable, for an increase in PE of nutrients follows some deficiency states secondary to reduced intake (Mollin and Waters, 1968). To examine this question, the PE of folate was studied before and after the correction of a possible nutritional deficiency. Large quantities of folic acid were given, but the PE of folic acid was not normalized. These results suggest that the increased PE of iron and folic acid in patients with malignant disease is not secondary to a reduction in appetite alone, but that a disturbance in the PE of nutrients is a direct effect of the primary disease. The question now is how this effect is produced. Is it produced by tumors only?

Non-Malignant Tissue Damage

We know from the studies of Heilmeyer (Heilmeyer et al, 1958; Heilmeyer et al, 1960) and of many others that an accelerated PE of iron also occurs in infection. Here it results in a maldistribution of iron, which is deposited in the reticulo-endothelial cells and is thus unavailable for erythropoiesis. It could be shown (Elman and Reizenstein, 1963; Elman et al, 1964; Mollin and Hoffbrand, 1965; Elman et al, 1970) that the PE of folic acid was also increased in non-infectious inflammatory disease such as rheu-

Diagnosis	Number of Patients
Leukemia	46
Malignant lymphoma	14
Cancer of the uterine cervix	57
Other forms of cancer	64
Inflammatory disease, ischemic necrosis, thyrotoxicosis	103
Operative trauma	21
Controls	140

* Many studies performed only in some of the patients. December, 1968.

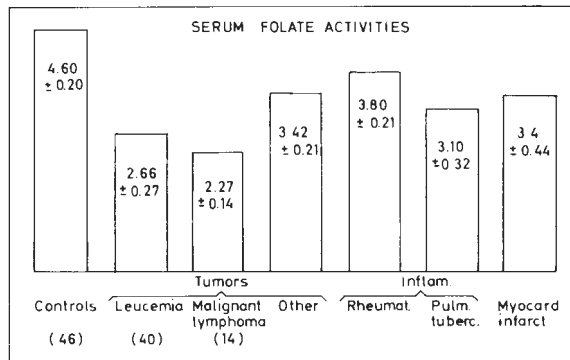


Fig 1—Serum folates in patients with different tumors and inflammations.

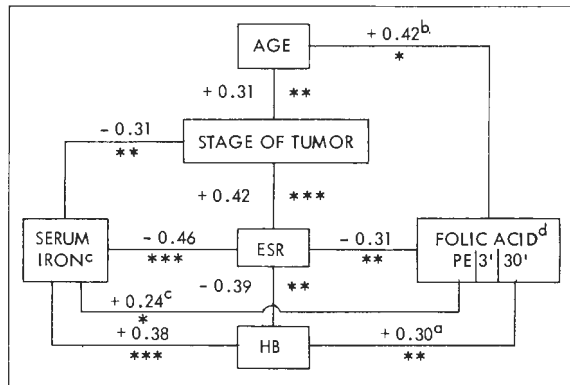


Fig 2—Secondary nutritional anemia in 78 patients with cancer, prior to treatment. Lines indicate correlations between the clinical observations (*—significant at the 95% level, ** at the 99.0 and *** at the 99.9); figures and signs indicate correlation coefficients. The more advanced the tumor, the lower the serum iron and folates, and the more severe the anemia. PE is folate plasma elimination rate. Concentrations are also indicated, 3 and 30 minutes after injection. a. Hemoglobin had the correlation +0.25 to folates at 15'. b. Same correlation coefficient found between age and folates at 3' and 30'. c. Serum iron was also correlated ($\gamma = +0.24$) to pre-load folates. d. Pre-load folates were correlated ($\gamma = 0.61$) to folates 15' after injection.

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TABLE II

Atheromatosis at post mortem* in patients with malignant tumor. Means \pm SE of mean.

	Cancer [§]	Other Patients [†]
No. of patients	50	50
Mean age, years	61, 26 \pm 1, 36	65, 54 \pm 0, 49
Degree of atheromatosis [†] (1-6)	3, 28 \pm 0, 25	4, 34 \pm 0, 22

* Karlöf I, Reizenstein P: (1951) unpublished.

[†] A subjective classification of atheromatosis was used by several observers, who did not know the purpose of the study: 1) absent, 2) negligible, 3) moderate, 4) rather pronounced, 5) pronounced and 6) calcified, extensive with necrotic plaques. The statistical difference between the groups is significant ($0.01 > p > 0.001$).

[‡] Dying from non-malignant causes.

[§] Different forms.

TABLE III

¹³¹I-Albumin distribution
Relation extravascular/intravascular albumin*

	M	M	Range	S.E.
Controls	5	1, 3	1, 1-1, 6	0, 07
Burns (7 days after burn)	9	3, 9	2, 4-12, 5	0, 31

* Intravascular albumin was studied by measuring blood ¹³¹I; the extravascular albumin was obtained by subtracting the intravascular radioactivity from the total radioactivity found in the whole body counter. The difference is statistically significant ($p < 0.001$).

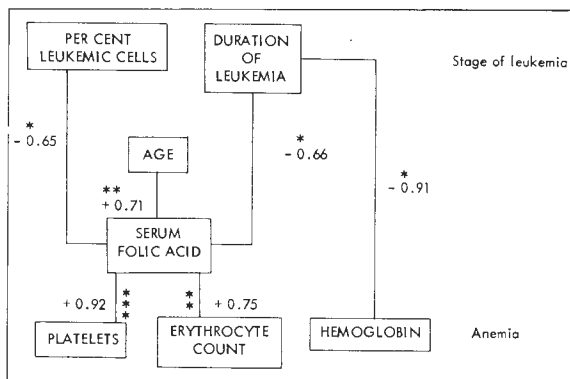


Fig 3—Secondary anemia in patients with chronic myelocytic leukemia. See legend for Fig 2. The longer the duration of the leukemia and the higher the proportion of leukemic cells, the lower the serum folic acid and the blood counts.

matoid arthritis (Fig 4), and that acceptable and significant correlations were found between the iron and folate turnovers. The longer the duration of the disease and the higher the erythrocyte sedimentation rate, ie, the worse the disease, the lower were the serum iron and cholesterol and the folate, and the more anemic the patients became. Similar findings could be demonstrated in inflammatory diseases of an infectious nature, such as pulmonary tuberculosis (Mollin and Waters, 1968; Elman et al, 1970). A similar decrease in the serum precipitable iodine, which was correlated to the decrease in albumin, has been demonstrated earlier in chronic inflammation and malignancy (Engström and Markardt, 1955), and of magnesium in burns (Broughton, Andersson and Boroden, 1968).

The finding of an increased PE of iron and folate in inflammatory as well as in neoplastic tissue damage did not suggest that the factors causing it could originate exclusively in tumors. For this reason we studied the effect of the damage of normal tissues of a nature other than inflammatory or neoplastic. We examined the effects of ischemia and of mechanical and thermal trauma.

The serum folate was shown to be low in patients with myocardial infarction (Elman et al, 1969) where we also observed low concentrations of serum iron. However, this has not yet been systematically studied. As for mechanical trauma, patients subjected to operations with minimal bleeding (inguinal hernia) were studied prior to and the day after operation. In every single patient the PE of iron was more rapid after operation. However, these patients were subjected to trauma and to at least some unavoidable bleeding, and it was uncertain which of these two factors caused the increased PE of iron. For this reason, the effect

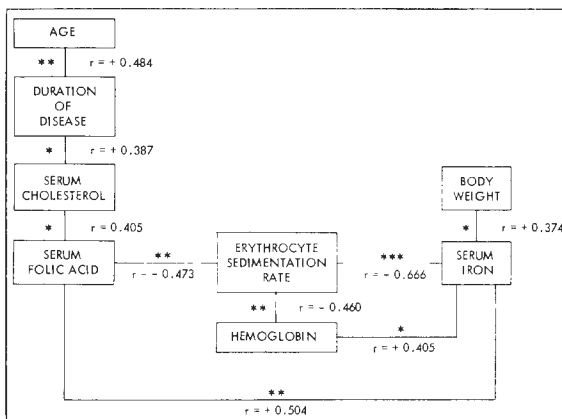


Fig 4—Secondary anemia in rheumatoid arthritis. See legend for Fig 2. The longer the duration of the disease, and the more severe the disease as indicated by the erythrocyte sedimentation, the lower the folates, iron, and cholesterol, and the more severe the anemia.

of trauma without bleeding (operations of the lateral meniscus in a bloodless field) and that of bleeding without trauma (phlebotomy 100–150 ml) were studied. The result suggested that it is the trauma which is responsible for the increased PE of iron (Åsén et al, 1969) and not the bleeding.

In the group with thermal injury, only the PE of albumin has been studied so far (Birke et al, 1968). An increased PE with a maldistribution of albumin was found even after small burns (Table III).

Role of Factors Released

A similarly increased PE of albumin can be demonstrated after other forms of trauma; and it has also been shown that the serum concentration of albumin is reduced in tumor patients (Reizenstein, 1970).

The findings described have been summarized in Table IV. If an increased PE and a decreased serum concentration of every nutrient had been found in all the patients with tissue damage of a malignant inflammatory, ischemic or traumatic nature, then it would be quite likely that the effect of tissue damage was to cause a rapid plasma elimination and a decreased serum concentration, ie, a maldistribution of some erythropoietic factors. Some substances like albumin and cholesterol not involved in erythropoiesis, but in the general nutritional condition of the patient, appear to be similarly affected. In fact, the metabolism of proteins with a molecular weight around 70,000 like albumin and transferrin might even be intimately related to that of folate, cholesterol, iodine, iron and magnesium.

Almost nothing is known about what causes the accelerated plasma elimination. Cortisone, thyroxine

and serotonin apparently do not cause an increased PE (Åsén et al, 1969; Birke et al, 1968). The effect appears to be related to increased capillary permeability and to the reticulo-endothelial activity. In post-operative patients, the latter is significantly increased. Both the synthesis and breakdown of fibrinogen—possibly in reticuloendothelial cells—are increased after operation (Davies, Liljedahl and Reizenstein, 1970) and this could explain the correlations found between the PE rates and the erythrocyte sedimentation rates.

The reticulo-endothelial system could also be responsible for the immediate post-traumatic hemolysis even of red cells formed before the trauma. Whether it is stimulated by antigenically active factors, liberated by tumors or damaged tissue, we do not know. The immuno-depressant cytoxan “normalizes” the PE of iron, but not of radio-gold.

Summary

In patients with tissue damage of a malignant, infectious, inflammatory, ischemic or surgical nature, the plasma elimination (PE) of folates, iron, albumin and cholesterol appears to be increased. Not all substances have been studied in all diagnostic groups.

The secondary anemia in myeloma and leukemia appears to be caused by factors other than a reduction in the number of erythroblasts. There is generally a correlation between the PE rates, the stage of the tumor or inflammation, and the anemia. It is suggested that the mechanism demonstrated contributes to the development of the anemia and possibly to the weight loss.

Increased capillary permeability and reticulo-endothelial activity could possibly explain PE and break-

TABLE IV

Rapid PE or low concentration (both marked +) of nutrients in serum in patients with ischemic, inflammatory, malignant or traumatic tissue damage. Brackets indicate results from literature.

	Fe*, conc.	Fe, PE	PGA, conc.	PGA, PE	CHOL conc.	ALB., PE	E.S.R.
Cardiac infarction	+		+		+		
Inflam.: Rheum. arthrit.	+	+	+	+	+	+	+
Pulm. TBC	+	+	+	(+)		(+)	+
Tumor: Leuk.			+	(+)	(+)		
Lymphoma			+	(+)	(+)		
Cancer		+	+	+	+		(+)
Trauma	+	+				+	(+)

* Abbreviations indicate iron, folate, cholesterol and albumin.

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down of small proteins and substances carried by them, as well as phagocytosis and lysis of some red cells.

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