The Routine Hemogram

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Major blood diseases like the leukemias, the hemophilias, the hemoglobinurias and the aplasias monopolize the pages of the textbooks but they don't turn up every day in your practice; they aren't all that common. True, they are important and you need to know them, but they are only the upper crust of hematology. This article has more to say, just as you will have more to do, with another kind of hematology, minor everyday hematology which most of your lab reports will give you day by day.

Most patients who come to you and who are sick have abnormal blood pictures, but only a few of these patients could be regarded as truly hematological cases. Some may be endocrinological, some gynecological, gastroenterological, urological, some problematical; all with an abnormal hemogram. Blood cells are influenced by so many different hormones, humors and toxins, that it takes a very mild or a very stealthy disease to flourish without disturbing them. Most diseases affect at least one type of blood cell, and so change the hemogram.

Such hemogram alterations are clues which can help you make a quick painless diagnosis, or which sometimes can be pathognomic and give you the diagnosis. So why not take the trouble to look for them? Given the clinical information, all else you need is a little hematological insight, and the sense to order the hemogram before you have distorted it iatrogenically by blood transfusion, corticoids, and the like.

The clinical picture is important here because several diseases can induce the same hemogram alterations, diseases which clinically are completely unrelated. So in effect the hemogram will give you a second set of differential diagnoses, which when compared with your clinical diagnostic selection, may show only one common item, which should be the diagnosis.

You need hematological insight because the average hemogram report is so deceptive. It isn't so much a report as a compilation of accurate estimations, less accurate estimations, and rather subjective observations, which on the report are given equal billing as if they had equal validity. Ideally every abnormal hemogram should be interpreted by a practiced medical hematologist who knows the reliability of the findings and can interpret them fully in the light of the complete clinical picture. Practically speaking, in most hospitals, you, the physician, have to acquire some know-how and interpret it yourself. To help you do this, let us dissect the hemogram and see if it means what it seems to say. It should comprise estimations of hemoglobin and hematocrit, description of the blood cell morphology in the smear, and estimations of total and differential white cell counts. Let's take them one at a time.

Properly performed, the hemoglobin is a very accurate laboratory estimation, so as long as it is expressed as grams of hemoglobin per 100 ml. of blood (and not as some arbitrary percentage value), and as long as you remember that hemoconcentration can conceal an anemia and that hemodilution (hydremia) can mimic anemia, you can't go wrong. The hematocrit or packed cell volume is just as accurate. In both hemoglobin and hematocrit, the range of inherent error is no more than 5%, and, as this is largely a sampling error, it is common to both estimations; therefore the mean corpuscular hemoglobin concentration, which is computed from the other two, is just as accurate.

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This mean corpuscular hemoglobin concentration is easily obtained, reliable, and so very important. The great majority (perhaps 90%) of the anemias in this part of the world are iron deficiency anemias, and all of these can be segregated from the remainder at once by MCHC estimation. You will find some degree of iron deficiency anemia in most children and in many women of child-bearing age, and you will not be unduly alarmed. But, if you find iron deficiency anemia in a man, you should see a warning light, the red light of hemorrhage, and you should look for hemorrhoids, ulcer or cancer. There are two main types of iron deficiency anemia; the nutritional and the chronic post hemorrhagic. Usually, these two types can be distinguished by the hemogram findings alone, but we will come to that later.

The MCHC estimation also serves as a check on the apparent morphology of the red cells seen in the smear. We use it this way ourselves in the laboratory, because we know that some artefacts, like incipient rouleaux formation, or anticoagulant distortion, can make normochromic red cells look hypochromic, and conversely that a poor thick smear may make hypochromic red cells look normochromic.

Red cell size is assessed visually from the smear. Red cell counts and the mean corpuscular volume estimation derived from them are not being considered here because they are too inaccurate. A good technologist who is practicing daily with the same microscope can assess red cell size at a glance and so can give a faithful account of any anemia that has not been adulterated by transfusionally introduced foreign red cells. The occasional performer, perhaps yourself, will have more difficulty, and should therefore remember that in a good thin smear the average normal red cell is very slightly smaller than the nucleus of the average small lymphocyte.

Let there be an anemia with normocytic or microcytic red cells and the clinician will remain calm; the possible causes may be numerous but he will be patient and seek out the one responsible. Throw in some macrocytic red cells and all havoc and B^{12} may be loosed. Pernicious anemia still merits its name, because it is the most overdiagnosed disease in our modern world, and liver and vitamin B^{12} preparations are some of the most over-utilized therapeutic agents.

If the smear contains some definite macrocytes, many normocytic to slightly larger erythrocytes, and not a few dwarf microcytes and small misshapen poikilocytes, then there may really be a pernicious or other megaloblastic anemia, and you should seek the other hematological changes which will be described below. If, on the other hand, the smear reveals a biphasic population of normocytic cells and macrocytic cells (of which some are polychrome in their staining qualities), then you probably have an acute post hemorrhagic or an acute hemolytic anemia with macronormoblastic marrow response, or you may have a myelophthisic anemia and should look for the normoblasts and myelocytes which usually appear in the peripheral blood in this condition.

Polychrome red cells are non-nucleated erythrocytes which take up a little of the blue stain in ordinary blood smear preparations, and they are essentially reticulocytes. So their frequency should be assessed when the smear is examined. Any significant degree of reticulocytosis is readily appreciated in ordinary Wright-stained smears as an obvious increase of polychrome red cells; and it is patently very important to know in any case of anemia whether the marrow is responding or not. In pernicious anemia (untreated), polychrome red cells are only slightly more numerous than normal but they are abnormal in color, blue-purple instead of the usual dirty grey.

Platelets also can be seen in the smear and can easily be distinguished from dust and dye particles and from cell debris, whereas in direct platelet count preparations these distinctions cannot be made with certainty. So don't despise an experienced technologist's assessment of platelet population in a blood smear. It's the next best thing to a pluperfect direct platelet count.

Neither the total white cell count nor the differential white cell count are anywhere as accurate as hemoglobin or hematocrit estimations. Around a 20% range of error is the best you can expect from them, and it requires rigorous technique to produce even this kind of accuracy. Flawed as these results may be, one still accepts and uses them because they are so valuable and informative; or rather because they become valuable and informative when they are expressed or examined in an appropriate manner.

Having counted total leucocytes per cu. mm. of blood, and then estimated the proportionate frequency of the various leucocyte types in a stained blood smear, the laboratory may feel bound (by some kind of scientific morality) to express its results in just this way, as a total white cell count and a separate percentage differential count. But there is no compulsion on you to examine the results in this form. In fact it is blind percentage-wise foolishness to do so, because this presentation will only mislead you, and because you will obtain much more orientated information if you convert the figures to give absolute counts, (per cu. mm.) of each different leucocyte type. There are powerful theoretical and practical reasons for examining only absolute differential leucocyte counts.

Theoretically there is no evidence of an omnipotent homeostatic mechanism which can regulate the proportionate frequency of the various leucocytes in the peripheral blood. Instead, each leucocyte type appears to be regulated by separate gov-

erning mechanisms almost completely independent of the others. Hence, one disease can induce an absolute increase or decrease only of neutrophils and another only of lymphocytes or only of eosinophils. Generalized leucocytosis is extremely rare, and only unusually severe toxic states can produce generalized leucopenia.

Why these vague terms, leucocytosis and leucopenia, survive, even in allegedly up-to-date hematology textbooks, is beyond comprehension. They should be replaced by the categorical terms, neutrophilia, neutropenia, eosinophilia, lymphopenia, etc. The normal range (for adults) of absolute leucocyte counts derive from the routine hemogram is as follows:

Neutrophils	2,000—7,000	per cu. mm.
Eosinophilis	0— 400	per cu. mm.
Basophils	0— 100	per cu. mm.
Lymphocytes	1,000—3,500	per cu. mm.
Monocytes	50— 600	per cu. mm.

As a practical illustration of just how deceptive a percentage differential can be, let us consider this hypothetical case. Imagine a man who normally has high normal absolute counts of the various leucocytes as illustrated below, who then (because of a headache) takes some analgesic tablets containing amidopyrine, and who develops therefrom a neutropenia (together with a mild physiological variation in his absolute lymphocyte count) as illustrated. Dissatisfied by the results of this self-medication he then visits a doctor and omits to mention his therapeutic adventure. Along with other investigations the doctor orders a hemogram and receives a report on the white cells as illustrated in the last column below.

Before Amidopyrine		After Amidopyrine		Reported Thus: W.B.C. 5,000	
Neutrophilis	6,000 per cu. mm.	1,500	per cu.mm.	Neutrophils	30%
Eosinophils	400 per cu. mm.	400	per cu.mm.	Eosinophils	8%
Lymphocytes	3,000 per cu. mm.	2,500	per cu.mm.	Lymphocytes	50%
Monocytes	600 per cu. mm.	600	per cu.mm.	Monocytes	12%

Confronted with such a report the doctor will almost certainly preoccupy himself with the apparent eosinophilia and monocytosis, perhaps muttering as an aside something about "relative lymphocytosis". In other words he would worry about what actually are normalities and he would miss the abnormality.

It is quite true that these absolute leucocyte figures are not very accurate and therefore that the information they give is only suggestive (unless the pathological change is gross), but at least it is factual information which they provide and not just a mathematical illusion. With the leucocytes one must accentuate the absolute and eliminate the relative.

There is only one aspect of the differential white cell count in which the proportionate frequency of one cell type relative to another has any significance. This exception is an important one and it refers to the young neutrophil granocyte known as the "stab" cell. This stab cell bears the same relationship to the mature segmented neutrophil granulocyte that the reticulocyte bears to the mature erythrocyte. Therefore the stab cell is in the same homeostatically controlled system as the segmented neutrophil granulocyte and the proportion of stab cells to segmented cells is just as significant as the proportion of reticulocytes to mature erythrocytes, (i.e. the reticulocyte count). This analogy between the neutrophil and the red cell can be stretched further, because some severe inflammatory states have an effect on the

neutrophil leucocytes analogous to the effect of hemolytic anemia on the red cells. In these infections, the absolute neutrophil count becomes subnormal (due to some toxic effect) but the proportion of stab cells increases because there is increased production of granulocytic cells by the marrow. The normal range of the mature granulocyte-stab cell ratio is from 6-1 to 10-1. If the ratio is lower than this, there is almost certainly neutrophil granulocytic hyperplasia of the marrow, and if it is higher than this, then there is probably some granulocytic hypoplasia.

Neutrophilia (also known as neutrophil leucocytosis) has many causes which are well known and will not be enumerated here. The proportion of stab cells is increased in all states of neutrophilia except abating ones, and even mild inflammatory conditions insufficient to produce overt neutrophilia are often betrayed by an increase in the proportion of stab cells.

Neutropenia (less than 2,000 neutrophils per cu. mm.) may occur in a severe form as in agranulocytic angina or acute myeloblastic leukemia (and even a percentage differential will pick these out), or it may exist to a mild degree (which would be missed by the percentage method but is nevertheless very important diagnostically) as in pernicious anemia, hypopituitarism, toxic infections, toxicity produced by drugs, and chronic irradiation disease.

Eosinophilia is almost pathognomonic of an allergic reaction and is especially marked in reactions to parasitic infestations. It occurs frequently but not invariably in Hodgkin's disease. Many adult anemic patients receive some treatment with liver or incompletely purified Vitamin B_{12} before being examined hematologically, and these patients usually show some degree of eosinophilia; indeed this is probably the commonest cause of eosinophilia in this part of the world. As already has been demonstrated in the hypothetical case, percentage figures are very misleading with reference to eosinophilia and it is essential to determine the absolute eosinophil count which normally is less than 400 per cu. mm.

Eosinopenia is usually part of an acute reaction to stress or corticoid therapy and is not detectable by the relatively crude methods under discussion.

Basophilia (that is basophil leucoytosis) is uncommon and when it does occur it is usually of slight degree. Its significance is obscure, but when it is found one should always take steps to exclude chronic myeloid leukemia and related myeloproliferative disorders. The upper limit of normal is around 100 per cu. mm.

Lymphocytosis occurs to a striking degree in cases of pertussis, and to a less marked degree in many viral infections including acute infectious lymphocytosis, mumps, chicken pox, rubella, and infectious hepatitis. Secondary syphilis and brucellosis may also induce lymphocytosis, and a mild degree may be found in both hyperthyroidism and hypothyroidism, probably in those cases having an appreciable lymphocytic infiltration of their thyroid glands. In some viral infections the lymphocytes may be atypical and may more or less closely resemble the Downey cells of infectious mononucleosis.

Lymphopenia (less than 1,000 lymphocytes per cu. mm.), unless it is extreme, is only detectable by the absolute method of evaluation, and it is a highly suggestive finding. The causes of lymphopenia very well exemplify the differential diagnostic value of the hemogram, because these causes are clinically completely unrelated and readily separable. They are radiation sickness, corticoid therapy, cytotoxic drug therapy, cirrhosis of the liver and Hodgkin's disease.

Monocytosis (more than 600 per cu. mm.) is popularly associated with infectious mononucleosis which is in fact rather an atypical lymphocytosis. True monocytosis is of frequent occurrence though usually of mild degree. Monocytosis occurs in any resolving acute infection, any subacute or chronic infection (including tuberculosis), and in Hodgkin's disease (in which it is the earliest, the most consistent, and the most persistant hematological change).

Monocytopenia is probably uncommon but in any case it is not detectable in a routine hemogram.

All these many changes are possible in the hemogram, and the combination or permutation of these various changes in one individual hemogram yields what might be called "hemogram syndromes", syndromes constructed entirely of particular combinations of hemogram alterations. Some of these laboratory syndromes are completely diagnostic, while the remainder yield a laboratory differential diagnosis which can be matched with a clinical differential diagnosis. A few examples are listed below, but many others exist or remain to be discovered by those who will look for them.

SOME HEMOGRAM SYNDROMES

	R B C size	M C H C	Polychromasia	Platelets	Neutrophils	Stabs	Eosinophils	Lymphocytes	Monocytes
Hodgkin's disease	—	×	×	×	+*	+	+*	—	+
Pernicious anemia	+	×	+	—*	—	—*	×	×	×
Simmond's disease	×	×	—	—*	—	—	×	×	×
Post-hemorrhagic anemia	—	—	+	+	+*	+	×	×	+*
Nutritional iron-deficiency anemia	—	—	×	×	×	×	×	×	×
Viral diseases	×	×	×	×	—*	+	×	+	+*
Polycythemia vera	—*	×	+	+	+	+	+*	×	×

× —No change
\+ —Increased
\+*—Sometimes increased
— —Decreased
—*—Sometimes decreased