Technical Papers

The Anemia Associated With Chronic Infection[1]

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A study of the anemia accompanying such chronic conditions as empyema, osteomyelitis, endocarditis, and various other chronic infections in humans has revealed a rather characteristic chemical pattern. There is a pronounced hypoferremia which is accompanied by hypercupremia, an increase in the erythrocyte protoporphyrin and coproporphyrinuria. These results are briefly summarized in Table 1. Only male

TABLE 1

Summary of the Chemical Characteristics of the Anemia Associated With Chronic Infection

	Plasma Iron γ %	Serum Copper γ %	Erythrocyte protoporphyrin γ/100 cc. RBC	Urinary coproporphyrin γ/24 hr.
Normal				
No. of cases .	20	25	10	22
Average value	120	116	30	106
Chronic infections				
No. of cases .	19	11	19	14
Average value	29	220	175	278

patients were used in the study. Morphologically the anemia was found to be normocytic, or slightly microcytic and slightly hypochromic.

The administration of iron by mouth to these patients was associated with no significant increase in the content of iron in the plasma, in sharp contrast to the finding in normal persons. Intravenous administration of iron was associated with a rise in the plasma iron level of somewhat smaller degree than occurs normally and a return to preinjection levels which took place much more rapidly than is normal. In these respects the anemia associated with chronic infections is similar to the anemia of iron deficiency. Hypoferremia, hypercupremia, and an increase in erythrocyte protoporphyrin are also common to both conditions. Unlike iron deficiency anemia, however, the anemia of infection does not respond to either oral or intravenous iron therapy. We have been unable to obtain evidence that the anemia associated with infection is hemolytic in nature or that there is a defective synthesis of either globin or protoporphyrin.

This evidence may be interpreted as indicating that there is a failure to form heme because of lack of sufficient iron to incorporate into the protoporphyrin molecule. As a result, protoporphyrin and copper are not utilized, and their quantity increases, awaiting the time when iron will be made available so that the formation of heme may proceed at its normal rate.

To investigate more completely the pathogenesis of this anemia, intramuscular staphylococcal abscesses were produced in 3 adult dogs. The plasma iron level dropped precipitously from levels of 150 to 275 micrograms per cent to levels of 15 to 30 micrograms per cent in 48 hours. This was followed in approximately 15 days by the development of moderate anemia. By this time the plasma iron level had returned to normal. This stage was followed shortly by clinical improvement and disappearance of the anemia. The intramuscular injection of staphylococcal toxin or typhoid vaccine produced less definite changes. The intramuscular injection of sterile turpentine into 16 dogs produced a sharp fall in plasma iron within 48 hours in all of the animals. A second injection of turpentine was followed by the development of a moderate degree of anemia. This indicates that neither bacteria nor their toxins are essential for the production of hypoferremia and suggests that an inflammatory reaction *per se* is capable of producing this change. We are unable to state with certainty whether a specific substance is elaborated by an inflammatory reaction. The intravenous injection into each of 7 dogs of 50 ml. of sterile pleural fluid, obtained following the intrapleural injection of turpentine, resulted in a suggestive, but not a profound, lowering of the plasma iron.

Menkin (*1, 2*) has shown that there is an accumulation and fixation of iron in inflammatory tissue. Schäfer (*3, 4, 5*) has demonstrated that there is an increased iron retention in febrile conditions in children and that during mild infections in mice iron accumulates in the reticulo-endothelial system. On the basis of these observations, together with the data we have presented in humans and in dogs, it now seems possible to outline a working hypothesis for the pathogenesis of this anemia.

According to this hypothesis, as a result of an inflammatory reaction, iron is diverted to the tissues and is not made available for hemoglobin synthesis. As a consequence of this increased demand of the tissues for iron, the removal of this element from the

[1] The work described in this paper was carried out under a contract recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the University of Utah.

blood stream is hastened and possibly its absorption from the bowel is even increased. Because iron is not made available for use by the bone marrow, the reaction

$$\text{Protoporphyrin} + \text{Iron} \xrightarrow{Cu^{++}} \text{Heme}$$

cannot proceed and anemia develops.

The fault in iron metabolism cannot be corrected by the administration of iron. This is probably because of the persistent and urgent demand for iron to fulfill some function in relation to infection, which has a greater priority for iron than hemoglobin formation.

These experiments are to be reported in detail in the near future.

References

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An Observation on the Red Cell Content of the Blood of the Thoroughbred Horse[1]

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While making observations of the blood of the horse, we noticed consistent differences between the thoroughbred and the cold-blooded horse with regard to the red cell count per cubic millimeter and the hemoglobin content in grams per 100 ml. of blood. The average values obtained in the thoroughbred animal have also a relation to age, as is shown in Table 1, which includes standard errors and average values for the mean corpuscular hemoglobin.

TABLE 1

Group	Number in group	Red cells millions/mm.^{3}	Hemoglobin grams/100 ml.	Mean corpuscular hemoglobin, $\gamma\gamma$
Thoroughbreds				
Foals	8	12.91 ± 0.73	13.86 ± 0.31	10.7
Yearlings ..	12	12.50 ± 0.74	14.13 ± 0.46	11.3
2–3 years ..	12	10.80 ± 0.25	14.10 ± 0.46	13.1
Older horses.	8	11.55 ± 0.74	15.37 ± 0.78	13.3
Cold-blooded horses	10	7.94 ± 0.28	12.63 ± 0.33	16.0

The differences between the means of the red cell counts of the two- to three-year-old horses and those of the foals and of the yearlings are significant, as also is the larger difference between the means of the counts of the two- to three-year-olds and those of the counts of the cold-blooded horses.

Table 1 shows that the red cell count and hemoglobin content in the thoroughbred are higher than the count and hemoglobin content in the cold-blooded horse, the red cell count for which is usually given as between 6 and 8.5 million.[2] At the same time the quantity of hemoglobin per cell is smaller. Table 2, which gives the average hemoglobin content, mean cell volume, and mean corpuscular hemoglobin concentration in 5 thoroughbred and 5 cold-blooded horses, shows that the cells of the thoroughbred carry less hemoglobin per cell because the cells are a little smaller and because the hemoglobin concentration is a little less. The thoroughbred, nevertheless, carries more hemoglobin per milliliter of blood than does the cold-blooded horse because there are more red cells per unit volume.

TABLE 2

	Thoroughbred	Cold-blooded
Red cells, millions/mm.^{3}	10.35	8.21
Hemoglobin, grams/100 ml.	13.89	12.06
Mean cell volume, μ^3	42.2	43.6
Mean corpuscular hemoglobin concentration, per cent	32.7	33.5
Mean corpuscular hemoglobin, $\gamma\gamma$	13.4	14.7

This combination of an increased red cell count, a decrease in red cell volume, a decrease in mean corpuscular hemoglobin concentration, but an increase in the hemoglobin content per milliliter of blood, is met with in animals (rabbits) subjected to low atmospheric pressures (*1*) and in other states in which the bone marrow is hyperactive, such as polycythemia vera in man. Since it is most improbable that thoroughbred horses suffer from an oxygen lack sufficient to keep their bone marrows in a state of hyperactivity, the higher red cell counts and hemoglobin contents in the blood of these animals is probably a genetic characteristic, as polycythemia sometimes is in man. The probability of the genetic explanation being right is increased by the fact that the high red cell counts are present at birth and are maintained in the weanling, yearling, and ensuing age periods. The elevated counts are therefore not the result of training or conditioning processes which prepare the animal for racing. It may very well be, of course, that the increased hemoglobin content and slightly smaller cell size confer an advantage on the thoroughbred when running at high speeds, and so these may be characteristics which have become accentuated in the process of the "improvement of the breed."

Reference

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[1] This study was made on the horses of Col. C. V. Whitney, to whom we are indebted for his courtesy. The expenses of the investigation were defrayed by the Grayson Foundation.

[2] Several references are given in Appendix A of Wintrobe's *Clinical hematology* (Philadelphia: Lea and Febiger, 1942).