Autocannibalism: The Etiology of Nerve-Resection Anemia

By Ernest Beutler and Diana Hofstra

RECENTLY, Hollán described a most interesting phenomenon: profound anemia in rats following unilateral section of the sciatic and femoral nerves. The hematologic features of this anemia were described in some detail. It was hypochromic, and the reticulocyte count was increased. There was erythroblastic hyperplasia of the marrow. Fecal urobilin excretion was normal, and serum bilirubin levels decreased with the anemia. Amputation of the denervated limb prevented onset of the anemia. Hollán concluded:

To sum up in brief how in our opinion nerve resection anemia develops, the following have been concluded from the experiments. After nerve resection, grave hyperemia and stasis develop in the almost totally denervated area. As a result, great masses of erythrocytes are congested in that area and are thus eliminated from systemic circulation. This mechanism may play a role in the rapid fall of red cell count and hemoglobin level following nerve resection. Stasis impairs circulation and nutrition of the denervated limb. From this area with impaired metabolism, humoral or neurohumoral effects induce (through as yet unknown routes, eventually by acting on various endocrine glands or internal organs) changes in reticuloendothelial function, grave disturbances in iron and nucleic acid metabolism and, as a result of all these, persistent anemia associated with extreme reticulocytosis.

She excluded bleeding as the cause of anemia because removing 3 to 5 ml. of blood from rats on 12 occasions in 34 days failed to produce a comparable anemia, and because no source of blood loss was discovered.

We were intrigued by Hollán's very interesting observations and had no difficulty reproducing them. We were impressed however, by the fact that the hematologic findings described by Hollán are highly suggestive of blood loss anemia. We therefore investigated this phenomenon in some detail, using radioiron. Our investigations show that anemia following nerve resection is due to bleeding from the denervated limb. Because the animal feeds upon this blood, the phenomenon may be called autocannibalism.

MATERIALS AND METHODS

Holtzman strain male rats, weighing 300 to 400 Gm. (retired breeders), were used. Sciatic and femoral nerve sections were carried out using clean, but not aseptic technics. Total-body counts on rats were obtained by placing the anesthetized animal over a scintillation crystal, as described elsewhere. Samples of feces, urine, cage washings and blood were counted in a Baird Atomic bench-type scintillation well counter, Model 810A. Hemoglobin determinations were carried out using the cyanmethemoglobin method. Plasma iron determinations were done by the method of Barkan and Walker. Sections of marrow were examined for iron as described previously. Iron-59 was obtained from Abbott Laboratories as FeSO₄.
Experimental and Results

Five rats were given approximately 4 μc. Fe⁵⁹ intravenously. After 20 days, nerve sections were performed on three rats and sham sections on two rats. Total-body radioactivity was determined at intervals before and after the operation. The results of this experiment are summarized in figure 1. It is evident that with the fall of the blood hemoglobin concentration, a concurrent decline in total-body radioactivity occurred. Examination of stools and urine from the animals whose nerves had been sectioned showed that the loss of radioiron from the body occurred through the feces. The stools also

Fig. 1.—The effect of femoral and sciatic nerve section and of sham operation on the hemoglobin level and total-body radioactivity of rats labeled with Fe⁵⁹.
gave a strong, positive reaction for occult blood with benzidine. Autopsy of the nerve-sectioned animal that died and sacrifice of the other animals failed to reveal any source of gastrointestinal bleeding. Radioiron was fairly evenly distributed along the gastrointestinal tract. No stainable iron was present in the marrow of the one nerve-sectioned animal whose marrow was examined, and the plasma iron of this animal was 30 μg per cent.

In a second experiment, balance studies were carried out on three nerve-sectioned and 3 sham-sectioned rats kept in metabolism cages. Four μc. of Fe⁵⁹ were given 6 days prior to surgery. Urinary, fecal and blood radioactivity was determined at intervals to quantitate the blood loss of the animals. No appreciable amounts of radioactivity were found in the urine, but, as shown in figure 2, large amounts of Fe⁵⁹ appeared in the stools of nerve-sectioned animals.

![Fig. 2.—Blood hemoglobin levels and fecal Fe⁵⁹ excretion of nerve-sectioned rats.](image-url)
as they became anemic. Sham-operated controls excreted only small amounts of "radioiron" in the stools (fig. 3). While radioiron loss has been expressed in terms of milliliters of blood, the small amounts of radioiron lost prior to surgery and subsequently in the sham-sectioned animals probably actually represents largely enzyme iron from desquamated mucosal cells. This supposition is supported by the gradual decrease in the amount excreted, blood radioactivity remaining relatively constant. At autopsy of the two rats that died during the course of the experiment and of the four rats that were sacrificed at the conclusion of the experiment, no source of gastrointestinal bleeding could be detected, grossly or on microscopic examination of sections of the gastrointestinal tract. The plasma iron of the nerve-sectioned animal sacrificed at the end of the second experiment was 30 γ per cent, that of the three sham-sectioned animals 150, 170, and 245 γ per cent.

In contrast to the findings of Hollán,¹ no animal we studied in these experiments or of eight others on which nerve sections have been carried out developed anemia unless excoriations of the affected foot were also present. In some animals which failed to develop any anemia at all for a week after nerve section, anemia could be precipitated by removal of food from the cage for 48 hours. Excoriations and severe anemia then resulted immediately. Excoriations of the feet of anemic, nerve-sectioned animals varied from fairly small breaks in

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Fig. 3.—Blood hemoglobin levels and fecal Fe⁵⁹ excretion of sham-operated rats.
the skin with scabbing to amputation of all of the toes (fig. 4). Occasionally, frank bleeding occurred and blood was found in the cage; more often, little blood was seen, and it is thus quite understandable that bleeding from this source was considered negligible by Hollán.¹

**Discussion**

The experiments presented demonstrate that nerve-resection anemia is due to blood loss. The loss of body radioactivity through the stools cannot reasonably be explained in any other way: in nonbleeding animals only minute amounts of iron are lost in the feces, even during acute hemolysis.⁶ Our interpretation of the cause of this anemia is confirmed by the profound hypoferremia that occurs and by the absence of stainable iron from the bone marrow.

Autopsies failed to show any source of bleeding within the gastrointestinal tract; however, excoriations have been observed invariably on the denervated foot of the nerve-sectioned animals. This, together with the fact that withdrawal of food rapidly induces the anemia, and that amputation of the involved leg prevents onset of the anemia,¹ appears to establish clearly that blood eaten from the denervated foot of the rat is the source of the blood found in its stools. Anyone who has worked with the laboratory rat is familiar with its cannibalistic tendencies. The rat apparently does not recognize the denervated foot as its own. Once it tastes blood from its foot, it continues to lick and bite the affected limb. Frequently, several toes are amputated in this process. Our estimates of the quantity of blood lost, based on fecal radioiron excretion, represent minimum figures: part of the hemoglobin iron ingested is undoubtedly reabsorbed.⁷ Only a part, perhaps 70 to 80 per cent, of the hemoglobin iron ingested is re-
covered in the feces. The amount of blood lost in the process of autocannibalism is, therefore, quite considerable, and accounts clearly for the anemia that occurs when a limb is denervated.

**Summary**

1. The finding of Hollán that severe anemia follows nerve resection in rats has been confirmed.
2. By the use of total-body labeling with radioiron, it has been demonstrated that this anemia is due to blood loss.
3. The blood lost by the nerve-sectioned rat is found in the stools, but autopsy reveals no source of gastrointestinal bleeding.
4. Anemia occurs only in animals with excoriation of the denervated foot. Anemia may be precipitated by withdrawing food for 48 hours. Hollán has found that amputation of the denervated limb prevents onset of the anemia.
5. It is concluded that nerve-resection anemia in the rat is due to autocannibalism of the denervated foot.

**Summario in Interlingua**

1. Le constatation de Hollán que anemia sever seque le resection de nervos in rattos esseva confirmate.
2. Per le uso de marcation del corpore total con ferro radioactive il ha essite possibile demonstrar que iste anemia es le effecto de un perdita de sanguine.
3. Le sanguine perdite per le rattos subjicite a section de nervos es trovate in le feces, sed necropsia revela nulle sanguination gastrointestinal.
4. Anemia occurre solmente in animales con excoriation del pede disnervate. Anemia pote esser precipitate per non-alimentation durante 48 horas. Hollán ha trovate que le amputation del disnervate extremitate preveni le disveloppamento de anemia.
5. Es concludite que anemia post resection de nervos in rattos es le effecto de autocannibalismo del pede disnervate.

**References**

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