THE RÔLE OF RIBOFLAVIN IN BLOOD REGENERATION*

BY H. SPECTOR, A. R. MAASS, L. MICHAUD, C. A. ELVEHJEM, AND E. B. HART

(From the Department of Biochemistry, College of Agriculture, University of Wisconsin, Madison)

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Several reports in the literature suggest a possible relationship between riboflavin deficiency and anemia. Intramuscular administration of purified flavin prepared from liver was reported by Stare and Thompson (1) to have no effect on hemoglobin, erythrocyte, or reticulocyte response in patients with pernicious anemia. However, Miller and Rhoads (2) were able to produce in dogs a syndrome similar to sprue by diets deficient in riboflavin. These investigators (3) later reported the finding of an antipernicious anemia principle in egg white and in a rice polishings concentrate low in riboflavin, which confirmed the view of other workers that riboflavin is not the extrinsic factor of the deficiency state in pernicious anemia. Kohls (4) found evidence in blood studies for the association of anemia with a deficiency of the vitamin G complex (presumably a riboflavin plus). A slight anemia was listed by Potter et al. (5) as one of the symptoms of this deficiency in dogs. György and coworkers (6) found that riboflavin causes a definite increase in hemoglobin production above the basal level when fed to standardized anemic dogs on a salmon-bread diet.

Studies in this laboratory (7) on hemoglobin regeneration in dogs with a synthetic ration free of the B complex vitamins, supplemented only with the crystalline B vitamins, have given ample proof of the adequacy of this ration for good hemoglobin production during long periods of phlebotomy. Such a ration, then, makes possible the investigation of the rôle of the B complex vitamins in blood regeneration, because it allows the use of a ration relatively free of any one member.

**Methods and Materials**

Seven mongrel dogs of heavy breed were used in this experiment. Four of these were recently weaned litter mate puppies (Dogs 251 to 254) approximately 8 weeks of age. Two dogs (Nos. 236 and 238), litter mates about 4 months of age, had previously been on a choline-deficient ration but had shown no outward signs of any deficiency. Dog 186 was an adult

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dog which had been on the synthetic ration for some time. The puppies were twice treated with an anthelmintic (tetrachloroethylene) before being placed on the synthetic ration. The synthetic ration had the following composition: sucrose 66, casein (acid-washed) 19, cottonseed oil 8, cod liver oil 3, Salts 4, 4 per cent. Salts 4 is the same as Salts 1 of Phillips and Hart (8) with an additional 1.21 gm. of MnSO₄·4H₂O per kilo of salt mixture. The ration was supplied ad libitum and daily food consumption records were kept. This ration was supplemented with the following crystalline vitamins: thiamine 100 γ, pyridoxine 60 γ, calcium pantothenate 500 γ, niacin 2 mg., and choline 50 mg. per kilo of body weight per day. These vitamins in aqueous solution were fed twice weekly by pipette. Body weights were taken regularly before the morning feeding.

Blood samples for analysis were always taken from the radial vein. A 20 cc. sample was drawn into a syringe, the dead space of which was filled with Wintrobe's non-shrinking oxalate. Hemoglobin determinations were carried out in duplicate by the method of Evelyn (9). In addition, routine red blood cell counts were made and hematocrit values were obtained with Wintrobe tubes. During the periods of phlebotomy blood was removed at regular weekly intervals from an external jugular vein. Whenever possible, 25 per cent of the estimated total blood volume was removed at each bleeding. The volume removed was then measured and the hemoglobin determined. The total blood volume was considered to be 8 per cent of the body weight and the total hemoglobin was calculated from the hemoglobin level of the blood. These values, together with the known amount of hemoglobin removed in the analysis sample and during the periods of phlebotomy, permitted the calculation of the total "hemoglobin made."

EXPERIMENTAL

Figs. 1, 2, and 3 give the complete data for the individual dogs on body weight, food consumption, hemoglobin per cent, total hemoglobin, and hemoglobin removed. Fig. 1 (Dog 251) is representative of the data obtained on the young growing dogs. Fig. 2 shows the response of Dog 236 and includes the results obtained with liver feeding. Fig. 3 (Dog 186) shows the typical results obtained with an adult dog. Fig. 4 summarizes the data on the amount of bleeding and the hemoglobin production according to periods of different levels of riboflavin feeding.

After 9 to 12 weeks on the synthetic ration without riboflavin four of the dogs (Nos. 251, 252, 254, and 238) developed a severe anemia. The hemoglobin was reduced to about 6 gm. per 100 cc. of blood. In the same length of time the remaining three dogs showed a milder anemia, with the hemoglobin reduced to about 9 gm. per 100 cc. of blood. In all cases the anemia was hastened by phlebotomy, as indicated in Figs. 1, 2, and 3.
When, at the end of 9 weeks, a hemoglobin level of 5.9 gm. per 100 cc. was reached in Dog. 251, phlebotomy was restricted to analysis samples of 20 cc. volume. The anemia became stabilized at a level of 6.8 gm. per 100 cc. 5 γ of crystalline riboflavin per kilo of body weight per day were then administered orally. This low level of riboflavin fed over a week was obviously insufficient. There was a further reduction in the hemoglobin level and a loss of body weight. The response to riboflavin levels of 10 and 15 γ was also negligible. The severity of the riboflavin deficiency became obvious by this time and the dog was found prostrate and suffering from spasmodic muscular convulsions. An intravenous injection of 5 mg. of riboflavin caused a rapid recovery. The response in hemoglobin and weight and the increased food consumption during the remainder of the period of feeding 15 γ were probably due to this injection. The slow and erratic rise in hemoglobin continued during the feeding at the 20 γ level. It was not until an increase to 30 γ of riboflavin was made that the dog responded positively and continuously in hemoglobin production. In 3 weeks the hemoglobin rose from 9.6 to 12.5 per cent; a total of 45.5 gm. of hemoglobin was made. During 4 additional weeks the maximum hemo-

Fig. 1. Experimental history of a typical young growing dog (No. 251). The supplements of riboflavin are given as γ per kilo of body weight per day.
globin of 13.3 per cent, probably close to the normal for the animal, was reached.

This dog was then continued on 30 γ per kilo daily, having attained a stable normal hemoglobin level, and was bled at regular weekly intervals to the extent of about 25 per cent of the blood volume. During a period of 8 weeks of phlebotomy a total of 176 gm. of hemoglobin was removed (actual determination) and 133.3 gm. were made (as calculated).

The record of Dog 251 follows the same trend as that of Dog 251. This animal, however, responded poorly to the lower levels of riboflavin feeding. Even after 2 weeks on 20 γ per kilo daily, the hemoglobin remained at 5.9 gm. per 100 cc. of blood. When 30 γ of riboflavin were fed, there was an immediate and rapid response in hemoglobin production. During the first 6 weeks on 30 γ of riboflavin the average weekly hemoglobin made was 12.4 gm. Growth was also stimulated and a weight gain of 4100 gm. resulted. After this growth, body weight and hemoglobin rose slowly to plateaus at levels of 15.75 kilos and 11.8 gm. per 100 cc. of blood respectively.
Dog 253 also gave a picture very similar to that described in detail for Dog 251 and, unlike Dog 252, gave a better response to each level of riboflavin. During the period of depletion of riboflavin, however, this animal was not bled to the same extent as its litter mates, which would account not only for the milder anemia shown but also for the increased production of hemoglobin on the various levels of riboflavin. After 89 days on the experiment the dog had muscular spasms and collapsed. 5 mg. of riboflavin were injected and again a remarkably rapid recovery was observed.

![graph](image)

**Fig. 3.** Experimental history of an adult dog (No. 186). The supplements of riboflavin are given as γ per kilo of body weight per day.

Both Dogs 254 and 238 gave a typical deficiency picture during the period of riboflavin depletion. Death occurred after 10 weeks on the experiment. Evidence of a riboflavin deficiency was found on necropsy (5).

Dog 236 (Fig. 2) showed no response in hemoglobin per cent at any of the levels of riboflavin fed. Only after 8 gm. of 1:20 liver concentrate were mixed with the synthetic diet did the hemoglobin per cent rise to the normal level. However, on the assumption that 8 per cent of the dog's weight comprised the total blood volume of the animal, the dog responded typically to all lower levels of riboflavin. The hemoglobin made, as calculated, is shown in Fig. 4. But the response in hemoglobin made to
the feeding of 100 γ per kilo daily and 3 mg. daily of riboflavin was no better than that made by the other animals on the 30 γ per kilo daily level. When 1:20 liver concentrate was added to the diet, the total hemoglobin increased rapidly. It is necessary, therefore, to emphasize two facts. First, this animal was 4 months old at the beginning of the experiment and had previously been on a choline-deficient diet but had shown no outward signs of the deficiency. Second, the response to the liver concentrate powder is over and above that expected on the basis of the riboflavin content itself.

The results obtained in an adult dog, No. 186, differ from those pre-
Previously described for the growing dogs. In 2 weeks without riboflavin the hemoglobin dropped from 13.2 to 11.1 gm. per 100 cc. of blood without bleeding. During the entire period of 9 weeks without riboflavin the average weekly removal of hemoglobin was 12.4 gm. The average amount made was 6 gm. per week. In 3 additional weeks without riboflavin in which only 20 cc. samples were removed for analysis, the hemoglobin production had dropped to a weekly average of 3.6 gm. Since the body weight dropped, the hemoglobin per cent actually rose slightly, even with this poor manufacture of hemoglobin.

4 days after administration of 5 \( \gamma \) per kilo daily of riboflavin was begun, and 108 days after the beginning of the experiment, this animal displayed a partial paralysis of the legs and 5 mg. of riboflavin were injected. This large amount of riboflavin resulted in a sharp rise in weight and in hemoglobin level. However, the average hemoglobin made for the 2 weeks on 5 \( \gamma \) per kilo daily was only 1 gm. per week. The riboflavin was increased to 15 \( \gamma \) and after 2 weeks phlebotomy was begun. In the 18 week period on this level of riboflavin, 424.0 gm. of hemoglobin were removed, or a weekly average of 23.9 gm. As a result of the increased and more regular food consumption, there was also an increase in body weight to slightly above the weight at the start of the experiment.

Erythrocyte Studies—Hemoglobin production may not be the only factor limiting recovery from hemorrhagic anemia, as there may also be a reduced capacity for building erythrocytes. An animal may be capable of building cells but have a limited capacity for producing hemoglobin, which would result in hypochromia. Any limitation in the capacity to manufacture cells could probably hinder the restoration of the hemoglobin to a normal level.

The normal values at the beginning of the experiment for total cell volume (hematocrit), erythrocyte count, and cell size in the dogs used were in the ranges of 33.0 to 45.3 per cent, 5.2 to 7.5 millions per c.mm., and 59.9 to 71.8 cu. microns, respectively. These values agree with those reported in the literature (10). From Table I it can be seen that the changes in total cell volume in the various periods are of the same order as those shown in the hemoglobin level. In all cases the hematocrit returned to normal when the riboflavin level was sufficient to raise the hemoglobin to normal.

The decrease in the number of erythrocytes during the period without the riboflavin supplement is also of the same order as the changes in the hemoglobin and hematocrit. The normal number of red cells was attained in each dog but one at the very low level of 5 \( \gamma \) per kilo daily of riboflavin feeding. Dog 236 showed a secondary decrease in the number of red cells at the higher levels of riboflavin. This may be explained by the great
increase in blood volume as already postulated. During the phlebotomy the number of red cells also showed a decrease of the same order as the decrease in hemoglobin per cent.

Table I

Effect of Various Levels of Riboflavin Feeding on Blood Values

| Dog No. | Normal | Per kilo body weight per day | Per day |  |
|---------|--------|------------------------------|---------|
|         | Hb     | None | 5γ | 10γ | 15γ | 20γ | 30γ | 50γ | 100γ | 3 mg | 1 mg* | 1 mg* |
| 251     | Hb     | 13.1 | 6.8 | 6.5 | 7.6 | 8.3 | 9.7 | 12.8 | 9.38† |       |       |
|         | Ht     | 38.0 | 18.8 | 20.2 | 24.7 | 27.3 | 34.3 | 40.0 | 28.6 |       |       |
|         | R.b.c. | 5.3  | 3.7  | 4.4  | 5.4  | 5.7  | 5.9  | 5.6  | 3.8  |       |       |
|         | M.c.v. | 71.8 | 50.7 | 45.9 | 45.7 | 47.9 | 53.2 | 52.7 | 75.2 |       |       |
| 252     | Hb     | 10.7 | 6.5  | 5.8  | 6.0  | 6.1  | 5.9  | 11.8 |       |       |       |
|         | Ht     | 33.0 | 20.3 | 22.7 | 23.2 | 21.8 | 22.0 | 37.2 |       |       |       |
|         | R.b.c. | 5.2  | 4.5  | 5.5  | 5.4  | 5.5  | 4.9  | 6.5  |       |       |       |
|         | M.c.v. | 63.5 | 45.1 | 41.3 | 42.8 | 39.6 | 44.9 | 57.2 |       |       |       |
| 253     | Hb     | 13.0 | 9.41 | 10.2 | 10.2 | 10.7 | 13.9 | 11.6† |       |       |
|         | Ht     | 43.8 | 32.8 | 36.0 | 35.9 | 35.5 | 44.6 | 41.0 |       |       |       |
|         | R.b.c. | 6.3  | 6.7  | 6.6  | 7.2  | 7.0  | 6.7  | 5.6  |       |       |       |
|         | M.c.v. | 69.5 | 48.9 | 54.5 | 49.9 | 50.7 | 66.5 | 57.3 |       |       |       |
| 236     | Hb     | 13.5 | 9.7  | 9.3  | 8.8  | 8.6  | 8.7  | 9.0  | 13.4 | 10.1† |       |
|         | Ht     | 45.3 | 32.9 | 31.7 | 32.0 | 30.2 | 30.3 | 32.0 | 44.5 | 34.7  |       |
|         | R.b.c. | 6.6  | 5.2  | 6.6  | 6.1  | 5.1  | 4.8  | 4.8  | 6.5  | 6.0   |       |
|         | M.c.v. | 68.7 | 50.1 | 48.0 | 51.5 | 59.2 | 63.1 | 66.7 | 68.4 | 57.8  |       |
| 186     | Hb     | 13.2 | 9.9  | 10.9 | 9.8† |       |       |       |       |       |       |
|         | Ht     | 43.9 | 34.1 | 36.0 | 33.6 |       |       |       |       |       |       |
|         | R.b.c. | 6.8  | 6.0  | 6.0  | 4.9  |       |       |       |       |       |       |
|         | M.c.v. | 64.6 | 56.8 | 60.0 | 68.5 |       |       |       |       |       |       |
| 254     | Hb     | 12.3 | 6.3  |       |       |       |       |       |       |       |       |
|         | Ht     | 41.4 | 21.4 |       |       |       |       |       |       |       |       |
|         | R.b.c. | 6.9  | 4.6  |       |       |       |       |       |       |       |       |
|         | M.c.v. | 60.0 | 46.5 |       |       |       |       |       |       |       |       |
| 238     | Hb     | 11.1 | 6.5  |       |       |       |       |       |       |       |       |
|         | Ht     | 36.5 | 23.7 |       |       |       |       |       |       |       |       |
|         | R.b.c. | 5.8  | 4.1  |       |       |       |       |       |       |       |       |
|         | M.c.v. | 62.9 | 57.8 |       |       |       |       |       |       |       |       |

Hb represents blood hemoglobin in gm. per cent; Ht, hematocrit in per cent; R.b.c., erythrocyte count in millions per c.mm.; M.c.v., erythrocyte volume in cu. microns.

* Plus 8 gm. of 1:20 liver concentrate daily.
† Phlebotomy.

The most striking changes were observed in the size of the red cells. There was a reduction in the size of the erythrocytes during the low levels of riboflavin feeding. As with the hematocrit, the red cells were of normal size when the riboflavin fed was sufficient to raise the hemoglobin to normal. Strangely enough, the red cells were of normal size during phlebotomy, even
though there was a reduction in the hemoglobin, hematocrit, and number of cells. Dog 236 produced cells only 85 per cent of the normal size during phlebotomy. This dog, however, was bled to a greater extent than the other dogs. These results are contrary to the reports found in the literature (10–14), which describe a decrease in the size of the cells during any great production of blood.

DISCUSSION

All the dogs displayed the usual symptoms of a riboflavin deficiency, but, in addition, one of the earliest changes observed was the failure to regenerate blood with phlebotomy. These experiments also indicate a definite decrease in food consumption in a riboflavin deficiency. The food consumed was sufficient only to maintain the body weight in the younger dogs (Nos. 251 to 254). The larger dogs (Nos. 186 and 236) showed a loss in body weight in the depletion period. In Dog 186 this loss in body weight was observed while the food consumption was fairly high, whereas in Dog 236 the food intake was extremely low.

The stimulus for increased food consumption was variable at the lower levels of riboflavin feeding. 15 γ per kilo per day resulted in a noticeable increase in food consumption and a rise in body weight. 30 γ produced a greater and more regular food intake and gave excellent growth. Increasing the riboflavin to 100 γ per kilo daily resulted in a still larger food intake and a more rapid gain in weight. It should be remembered, however, that the depletion of the tissues of their riboflavin and also the consequent stunting of the growth gave the dog a larger capacity for growth than would be manifest in a normal dog on the same high level of riboflavin. The adult dog (No. 186) responded with a maximum food intake at a level of 15 γ per kilo daily, which was sufficient to restore the body weight to the initial level and to allow for a slight increase. These data suggest that 30 γ are the minimal level for food consumption and good growth in young growing dogs under the conditions of our experiment. In adult dogs 15 γ per kilo daily may suffice for good food consumption and maintenance of body weight.

Investigators who observed a mild anemia in riboflavin deficiencies made no attempt to determine this relationship quantitatively. György et al. (6) measured hemoglobin production in standardized anemic dogs and found an increase above the basal level of 28 gm. per 2 weeks with daily doses of 0.1 to 0.5 mg. per kilo. As these investigators themselves point out, their basal salmon-bread diet may be open to criticism because of its high content of riboflavin which provided 0.8 to 1.5 mg. daily. Using a highly purified synthetic ration, we were able to limit the riboflavin content to 5.7 γ per 100 gm. of ration. This ration supplemented with the
crystalline B vitamins will produce an uncomplicated riboflavin deficiency when riboflavin is not included in the supplement.

Mild anemia is produced in the absence of riboflavin and a severe anemia is readily induced with slight bleeding. The dogs cannot recover from this anemia unless riboflavin is fed and show only a slight and variable hemoglobin production below a level of 15 \( \gamma \) per kilo daily for growing dogs. 30 \( \gamma \) are necessary in growing dogs for good hemoglobin production and rapid recovery from anemia. The rate of hemoglobin production is proportional to the amount fed between the levels of 15 and 30 \( \gamma \). An adult dog was able to show good hemoglobin regeneration at a level of 15 \( \gamma \) per kilo daily. A level of 5 \( \gamma \) gave an insignificant amount of hemoglobin production.

These results suggest that in growing dogs there is a competitive need for riboflavin for growth and hemoglobin production. While in an adult dog 15 \( \gamma \) were sufficient for good hemoglobin regeneration, the added burden of growth decreased considerably the hematopoietic response of young dogs to this same level. It is unlikely that the dog shows a preferential use of the riboflavin at the low levels, for 15 \( \gamma \) give both a noticeable gain in weight and hematopoietic response, and higher levels of riboflavin show a proportional increase in both growth and hemoglobin regeneration.

The strain of phlebotomy is borne by the adult dog at the level of 15 \( \gamma \) per kilo daily, and the hemoglobin regenerated is equal to the amount removed, maintaining a normal hemoglobin level. The hematopoietic response in the younger dogs on 30 \( \gamma \) per kilo daily was not able to keep pace with the blood removed. At the same time there was a drop in body weight with the induction of phlebotomy. The body weight quickly reached a plateau at about 1 kilo below the level attained before phlebotomy was begun. Thereafter the body weight was maintained at the same level. This indicates that 30 \( \gamma \) are a marginal level and do not satisfy the increased requirement when the animal is put under any great strain of blood formation. Again we observe no preferential use of riboflavin and find the animal meets the competitive needs of weight gain and hemoglobin regeneration by impartially limiting both activities.

Dog 236 was able to maintain good growth during phlebotomy, owing to the higher riboflavin intake. The drop in hemoglobin is probably due to purely physiological reasons, the amount of blood removed being greater than the limit of the dog’s capacity to regenerate it in 1 week. This dog manufactured 1.76 gm. of hemoglobin per kilo of body weight as compared to 1.67 for Dog 251 and 1.5 for Dog 186. Dog 253 demonstrated a greater hematopoietic ability throughout and produced an average of 1.91 gm. of hemoglobin per kilo of body weight during phlebotomy.

It is advisable to consider the matter of decreased food consumption
during the depletion period and to satisfy ourselves that the low food intake is not a factor in the development of the anemia. Fasting experiments have been studied in Whipple's laboratory (15). A standard anemic dog fed an optimum dose of iron with sugar and fat but no protein produced 40 to 50 gm. of new hemoglobin each week for several weeks. "Obviously [there is] a rather extensive shift of important protein material from various body depots into red cells" (15). In our experiments, anemia developed, even though the food consumed was sufficient to maintain body weight in the young dogs. The anemia is, therefore, a direct result of a riboflavin deficiency.

Studies of the red blood cells give an indication of the type of anemia produced and may perhaps offer an insight into the rôle played by riboflavin in the regeneration of blood. During the depletion period the anemia produced is of the microcytic, hypochromic type. There was also a decrease in the number of cells and, while the rate of return to normal of the hemoglobin, hematocrit, and mean cell volume is proportional to the level of riboflavin fed, the red cell count was readily restored to normal at the low level of 5 \( \gamma \) per kilo daily. During phlebotomy with riboflavin administration there is again a decrease in hemoglobin, hematocrit, and erythrocyte count, but the size of the erythrocytes, surprisingly, is normal. Reports in the literature of hemorrhagic anemias and of conditions in which there is an increased production of erythrocytes describe a decreased cell size (10). An inescapable suggestion from our data is that riboflavin plays some rôle in determining the size of new red blood cells formed.

The development of a satisfactory method for the determination of riboflavin has stimulated investigations of the distribution of this vitamin in various tissues. The riboflavin level of the blood (0.5 \( \gamma \) (16) per 100 cc. of whole blood) and the flavin-nucleotide levels of the cells and plasma are fairly constant (17). Relatively large amounts are found in the liver. It is doubtful, however, that this organ serves as a storage depot for riboflavin. Intake of large amounts of riboflavin does not increase the riboflavin content of the liver to any appreciable extent (18). Klein and Kohn (17) found a synthesis both \textit{in vitro} and \textit{in vivo} of flavin-adenine dinucleotide from riboflavin, in human blood cells. Although the dinucleotide occurs in plasma, its level in the plasma is not affected by incubation with riboflavin. A deficiency of riboflavin causes a decrease in the blood of riboflavin values (19).

The fundamental action of riboflavin in living tissue is to take part in enzyme systems which regulate cellular oxidations: carbohydrate and fat metabolism. The necessary participation in, and the direct influence of, riboflavin on growth and body weight gain is, therefore, obvious. Riboflavin may bear an important relation to amino acid metabolism, since
d-amino acids are deaminated by an enzyme system which contains the flavin-adenine dinucleotide. An inviting speculation is that riboflavin may be concerned in the metabolism and arrangement of the amino acids of the protein of the hemoglobin molecule.

SUMMARY

Dogs were kept on a highly purified synthetic ration supplemented only with the crystalline B vitamins, exclusive of riboflavin. Blood analyses were carried out at various levels of riboflavin feeding, with and without phlebotomy, and the rate of hemoglobin regeneration was followed.

1. Food consumption was poor and irregular in a deficiency of riboflavin and typical symptoms were observed. 30 γ per kilo of body weight per day were the minimal level for good food consumption and good growth in young dogs. In adult dogs 15 γ may be sufficient for good food consumption and maintenance of body weight.

2. A mild anemia developed on a synthetic ration without riboflavin and a severe anemia was readily induced with slight bleeding.

3. The dogs cannot recover from this anemia unless riboflavin is fed. Only a slight and variable hemoglobin production was observed below a level of 15 γ per kilo of body weight per day in growing dogs. 30 γ were necessary in growing dogs for good hemoglobin production and rapid recovery from anemia. The adult dog was able to show good hemoglobin regeneration at a level of 15 γ per kilo daily.

4. An adult dog can maintain a normal hemoglobin level under the strain of phlebotomy with 15 γ per kilo daily. The hematopoietic response in growing dogs on 30 γ was not sufficient to replace the blood removed.

5. In the absence of riboflavin a microcytic, hypochromic type of anemia was produced. During phlebotomy with riboflavin feeding there was a normocytic, hypochromic type of anemia. Riboflavin plays a rôle in determining the size of new cells.

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