Studies on Erythropoiesis. XI. Reticulocyte Response of Transfusion-Induced Polycythemic Mice to Anemic Plasma from Nephrectomized Mice and to Plasma from Nephrectomized Rats Exposed to Low Oxygen

By Leon O. Jacobson, Edna K. Marks, Evelyn O. Gaston and Eugene Goldwasser

Data are presented by Jacobson, Goldwasser et al. suggesting that the kidney may be the site of elaboration of erythropoietin(s). Mirand and Prentice and Erslev offer data to the contrary.

Plasma erythropoietic activity is demonstrable by a number of different but related assay methods, but the basic substance(s) has not been characterized chemically; nor have assay methods been refined sufficiently to yield information revealing whether a single substance or group of substances is involved. Erythropoietic activity can be demonstrated readily in plasma from normal rats and rabbits subjected to cobalt ion, anemic anoxia, or hypoxic anoxia. In our hands, bilateral nephrectomy regularly abolishes this capacity.

The capacity of mice to produce erythropoietin(s) in response to anemic anoxia and cobalt ion is described in this paper. Whether bilateral nephrectomy in mice significantly influences the response to these stimuli is also considered. The plasma or plasma extracts from nephrectomized animals were assayed in transfusion-induced polycythemic mice. Data are also presented showing the effect of bilateral nephrectomy on the capacity of the rat to produce a measurable increase in erythropoietin in response to hypoxic anoxia, using not only polycythemic mice for assay, but starved rats as well.

Material and Methods

CF No. 1 female and C57BL/6Jax mice of both sexes were used to study the reticulocyte response in transfusion-induced polycythemic mice following the injection of "anemic" mouse plasma or other plasma preparations. Sprague-Dawley male rats, weighing from 200 to 300 Gm. were used as donors for the low-oxygen rat-plasma experiments. All plasma injections were given to the mice intravenously by tail vein, intraperitoneally, or subcutaneously in 0.5 cc. amounts on 4 successive days. Rats received a 2-ml. dose of plasma on 2 consecutive days.

Preparation of the plasma—Anemic mouse plasma was obtained from adult mice with an anemia induced by subcutaneous injections of phenylhydrazine hydrochloride (1.25 to 1.50 mg. 3 or 4 times over a period of 6 days), or from mice in the last trimester of pregnancy. When the hematocrit was about 30 per cent, blood from the carotid arteries was collected in heparin immediately after the mice were killed by cervical fracture. The plasma was separated by centrifugation and stored at once at −17 C. "Cobalt plasma"

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Submitted July 28, 1958; accepted for publication Dec. 9, 1958.
was prepared by injecting adult mice subcutaneously with 5 μM cobaltous chloride in 0.5 ml of saline 8 or 9 hours before their blood was withdrawn. Blood was taken 10 hours after surgery from nephrectomized and sham-operated mice. Normal mouse plasma was obtained from normal untreated adult mice. Starved rat plasma was collected from animals that had been deprived of food for 4 days, but had had free access to water. Plasma was also obtained from rats after they had been exposed to low oxygen at a simulated altitude of 21,500 ft. for 8, 16, or 24 hours. Bilateral nephrectomy or bilateral ureter ligation was performed immediately before the animals were placed in low oxygen. Plasma for control purposes was obtained from unoperated rats exposed similarly to low oxygen and from normal untreated rats.

Operative procedures.—Bilateral nephrectomy was performed on mice (with a phenylhydrazine-induced anemia) and rats under Nembutal anesthesia. The kidneys were removed by making a median abdominal incision, tying the renal blood vessels with one suture, and removing the kidney from its capsule, leaving the adrenal gland intact. The incision was closed with silk. Sham operations were performed in which the capsule of the kidney was peeled off, but the kidney remained in situ.

Preparation of polycythemic recipients.—CF No. 1 mice weighing 22 to 24 Gm., and C57BL/6Jax, 18 to 20 Gm., were made polycythemic by intraperitoneal injections of a 75 to 80 per cent concentration of washed homologous red cells suspended in saline. The suspension was given in 0.5 cc. amounts on 3 successive days and once again 2 days later. Seven days after the first injection of red cells, when the hematocrit was about 70 per cent and no reticulocytes were found in a peripheral blood smear, the mice were used as recipients for the various plasma preparations. Hematocrit determinations were made on a micro-hematocrit centrifuge, using heparinized capillary tubes. A modification of the technique described by Brecher and Schneiderman was used for counting the number of reticulocytes. Blood smears were made on slides coated previously with alcoholic brilliant-cresyl-blue; then the smears were transferred immediately to a moist Coplin jar and allowed to remain 15 to 20 minutes. They were then removed and whipped dry. By using a small drop of blood and holding the spreader slide at the proper angle, thin even smears were easily made. A Howard micrometer disc was inserted in the x10 ocular which superimposed 16 squares over the microscopic field. The red blood cells were counted in each corner square, the reticulocytes appearing in all of the 16 small squares were counted. Thus, 100 × the number of reticulocytes counted divided by the number of erythrocytes in the small squares × 4 gives the percentage of reticulocytes. At least 2000 red blood cells were counted when the reticulocyte range was 0.1 to 0.5 per cent, and 10,000 cells were counted as described above for counts in the 0.05 per cent range. Blood for hematocrit and reticulocyte determinations was drawn from the tail vein. The Fe assay procedure has been described previously.

Histologic studies.—In a previous publication we described the effect of the injection of anemic plasma on erythropoiesis in the hematopoietic tissues (bone marrow, liver and spleen) of the transfusion-induced polycythemic mouse. It was found that spleenic erythropoiesis in recipients was an excellent index of erythropoietic activity of injected plasma. In this present study, transfusion-induced polycythemic mice that were devoid of reticulocytes in the peripheral blood were divided randomly into 6 groups of 4 mice each as shown in table 1. The mice in each of the 6 groups were given four 0.5 cc. intravenous injections of plasma or plasma extract. On the fourth day after the first injection, hematocrit and reticulocyte determinations were done on all the animals in all 6 groups. The animals were then sacrificed. The spleens were removed immediately and fixed in Zenker-Formol. Embedding was done in nitrocellulose. Sections were cut at 6 μ and stained with hematoxylin, eosin, and azure. Saline-injected transfusion-induced polycythemic mice were sacrificed and similarly prepared for control histologic study.

Results

Polycythemic Recipients of Anemic Mouse Plasma

In this first experiment, recipients were divided into groups of 5 or more animals. As shown in table 2, groups 1 and 2 served as controls, receiving
TABLE 1.—Effect of Injection of Various Rat Plasma Preparations on the Hematocrit and Reticulocyte Values of the Peripheral Blood of Transfusion-Induced Polycythemic Mice and Histologic Evidence of Splenic Erythropoiesis

<table>
<thead>
<tr>
<th>Group</th>
<th>Source of plasma injected</th>
<th>Control reticulocyte count (%)</th>
<th>Average reticulocyte count (%) on day of sacrifice</th>
<th>Average hematocrit (%) on day of sacrifice</th>
<th>Estimate of erythropoiesis in the spleen</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Normal rat</td>
<td>0.0</td>
<td>0.0</td>
<td>76</td>
<td>0</td>
</tr>
<tr>
<td>B</td>
<td>Nephrectomized rat</td>
<td>0.0</td>
<td>0.0</td>
<td>75</td>
<td>0</td>
</tr>
<tr>
<td>C</td>
<td>Nephrectomized rat exposed to simulated altitude of 21,500 ft. for 24 hrs.</td>
<td>0.0</td>
<td>0.0</td>
<td>76</td>
<td>0</td>
</tr>
<tr>
<td>D</td>
<td>Untreated rat exposed to simulated altitude of 21,500 ft. for 24 hrs.</td>
<td>0.0</td>
<td>2.0</td>
<td>72</td>
<td>+</td>
</tr>
<tr>
<td>E</td>
<td>Extract of anemic sheep plasma†</td>
<td>0.0</td>
<td>1.3</td>
<td>72</td>
<td>+</td>
</tr>
<tr>
<td>F</td>
<td>Plasma from rats with ureter ligated and subjected to simulated altitude of 21,500 ft. for 24 hrs.</td>
<td>0.0</td>
<td>2.3</td>
<td>75</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>Saline</td>
<td>0.0</td>
<td>0.0</td>
<td>76</td>
<td>0</td>
</tr>
</tbody>
</table>

*These letters identify group from which photomicrographs were taken of representative spleen sections.

†Plus sign signifies only that erythropoiesis in the spleen red pulp is at least as active as in the normal mouse.

†Prepared by Armour Laboratories (White).

TABLE 2.—Effect of 4 Injections of Plasma from Anemic-Nephrectomized, Sham-Operated, or Anemic Mice on the Reticulocyte Response of Mice with a Transfusion-Induced Polycythemia

<table>
<thead>
<tr>
<th>Group</th>
<th>Source of plasma injected</th>
<th>Control Reticulocytes (%)</th>
<th>4 days</th>
<th>Number of mice at termination of experiment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Saline</td>
<td>0.00</td>
<td>0.0 (0.00)*</td>
<td>12</td>
</tr>
<tr>
<td>2</td>
<td>Normal</td>
<td>0.00</td>
<td>0.0 (0.00)</td>
<td>12</td>
</tr>
<tr>
<td>3</td>
<td>Anemic (phenylhydrazine)</td>
<td>0.00</td>
<td>2.35 (1.28)</td>
<td>8</td>
</tr>
<tr>
<td>4</td>
<td>Anemic nephrectomy</td>
<td>0.00</td>
<td>0.11 (0.10)</td>
<td>8</td>
</tr>
<tr>
<td>5</td>
<td>Anemic sham-operated</td>
<td>0.00</td>
<td>1.79 (0.46)</td>
<td>7</td>
</tr>
</tbody>
</table>

*Figures in parentheses are standard deviations.

saline and normal plasma, respectively. Those in group 3 received anemic mouse plasma; those in group 4, plasma from mice nephrectomized after phenylhydrazine-anemia induction; and those in group 5, plasma from sham-operated anemic mice. It is apparent that plasma obtained from mice made anemic by phenylhydrazine elevated the reticulocyte values of the recipient polycythemic mice from the zero baseline to 2.35 per cent. Plasma obtained from mice with a phenylhydrazine-induced anemia 10 hours after sham-nephrectomy, increased the reticulocyte values in polycythemic recipients to 1.79 per cent, whereas plasma from the anemic nephrectomized mice increased
Table 3.—Effect of 4 Injections of Anemic Plasma from C57BL/6ax mice; Plasma from Cobalt-Injected Mice; Plasma from Pregnant Anemic Mice; or Normal Mouse Plasma with Cobalt Added on the Reticulocyte Response of Mice with a Transfusion-Induced Polycythemia

<table>
<thead>
<tr>
<th>Group</th>
<th>Source of plasma injected</th>
<th>Control</th>
<th>Reticulocytes (%) 4 days</th>
<th>Number of mice at termination of experiment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Saline</td>
<td>0.00</td>
<td>0.00 (0.00)†</td>
<td>12</td>
</tr>
<tr>
<td>2</td>
<td>Normal (C57BL/6ax)</td>
<td>0.00</td>
<td>0.07 (0.007)</td>
<td>13</td>
</tr>
<tr>
<td>3</td>
<td>Normal (CF No. 1)</td>
<td>0.00</td>
<td>1.59 (0.82)</td>
<td>6</td>
</tr>
<tr>
<td>4</td>
<td>Anemic (C57BL/6ax) with trace cobalt added</td>
<td>0.00</td>
<td>1.59 (0.82)</td>
<td>10</td>
</tr>
<tr>
<td>5</td>
<td>Cobalt</td>
<td>0.00</td>
<td>1.92 (0.83)</td>
<td>4</td>
</tr>
<tr>
<td>6</td>
<td>Pregnant (anemic)</td>
<td>0.00</td>
<td>1.59 (0.82)</td>
<td>10</td>
</tr>
</tbody>
</table>

*Figures in parentheses are standard deviations.

Table 4.—A. Effect of Plasma from Normal Unoperated, Nephrectomized, or Ureter-Ligated Rats Exposed to a Simulated Altitude of 21,500 Feet for 8, 16, or 24 Hours on the Reticulocyte Response of Mice with a Transfusion-Induced Polycythemia as Compared with Plasma from Normal and Starved Rats. B. Effect on Fe* uptake in Starved Rats

<table>
<thead>
<tr>
<th>Group</th>
<th>A. Reticulocytes (%) in polycythemic mice</th>
<th>B. Fe* uptake (%) in starved rats</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Time in low O2 (hrs)</td>
<td>Normal untreated</td>
</tr>
<tr>
<td></td>
<td>Normal untreated</td>
<td>Nephrectomy</td>
</tr>
<tr>
<td>8</td>
<td>0.9 (0.33)†‡</td>
<td>0.18 (0.36)§</td>
</tr>
<tr>
<td>16</td>
<td>1.71 (0.49)†</td>
<td>0.11 (0.14)§</td>
</tr>
<tr>
<td>24</td>
<td>1.78 (1.47)*</td>
<td>0.00 —</td>
</tr>
</tbody>
</table>

*Figures in parentheses are standard deviations.
†Superscript figure gives number of animals in group.
‡Figures in parentheses are standard errors of the mean.

the reticulocytes to 0.11 and normal plasma had no apparent effect (0.00 per cent).

Comparison of Anemic, Cobalt and Pregnant Plasma

A second experiment was performed which was similar to the first (table 3) except that the erythropoietic activity of anemic plasma obtained from C57BL/6ax mice with a phenylhydrazine-induced anemia was compared with that of the cobalt mouse plasma and plasma obtained from pregnant mice in the third trimester. It is apparent that anemic plasma, cobalt plasma, and pregnant mouse plasma had considerable erythropoietic activity because the reticulocyte values were elevated to above 1.5 per cent. On the other hand, saline had no erythropoietic effect and normal plasma, with or without a trace of cobalt added, had only a minimal one.

Nephrectomy and Hypoxic Anoxia

In the third experiment, the polycythemic recipient mice were given plasma from rats exposed to low O2. As shown in table 4, groups of rats were exposed for varying lengths of time to low O2 (8, 16, or 24 hours) and another group of
rats was neither operated upon nor exposed to low O₂. Thus group 1 received plasma from normal rats exposed to low O₂; those in group 2, plasma from rats with bilateral nephrectomy and exposure to low O₂; and those in group 3, plasma from rats with ureters ligated and exposure to low O₂. Group 4 consisted of 3 control subgroups that received plasma from normal rats or starved rats or were given normal saline.

The reticulocyte response in polycythemic mice that received plasma from normal rats exposed to low O₂ for 8, 16, or 24 hours was respectively, 0.9, 1.71, and 1.78 per cent by 4 days after the first subcutaneous injection. Plasma from rats that were nephrectomized before subjection to low O₂ caused a slight reticulocyte response in polycythemic mice. By 4 days, the reticulocyte values in the animals that received nephrectomized-low-O₂ rat plasma were 0.18, 0.11, and 0.00 per cent, respectively (table 4). The reticulocyte value of polycythemic mice that received normal rat plasma was 0.01 per cent. Mice that received starved rat plasma or saline remained essentially reticulocyte-free.

Table 4 also includes data on Fe⁵¹ red cell incorporation that have been published elsewhere. These data are included to permit a comparison of the sensitivity of that means of assay with the one we have used in these experiments. No erythropoietic plasma activity was found in the plasma of nephrectomized rats exposed to low O₂, whereas definite erythropoietic activity was apparent when plasma from the normal unoperated or ureter-ligated rats exposed to low O₂ was assayed in starved rats.

**Histologic Findings**

As had been our previous experience, transfusion-induced polycythemia reduces erythropoiesis to zero, as judged by the number of reticulocytes in the peripheral blood and histologic study of the spleen. Four 0.5 cc. injections of saline, normal rat plasma, nephrectomized rat plasma, or nephrectomized hypoxic anoxic rat plasma produce neither an increase in reticulocytes nor an increase in splenic erythropoiesis, whereas hypoxic anoxic rat plasma, hypoxic anoxic ureter-ligated plasma, or an extract of anemic sheep plasma produces both an increase in the per cent of reticulocytes in the peripheral blood and a marked splenic erythroblastic reaction (table 1 and fig. 1).

**Discussion**

Present methods of assay for erythropoietin(s) are at best semiquantitative. Of the available assay preparations, we found the transfusion-induced polycythemic mouse to be the most reliable, and we use it routinely to check results obtained by other means. In a sense, the polycythemic mouse is ideal for bioassay because erythropoietin production is presumably shut off by a "nontoxic" physiologic mechanism (increased O₂ supply in the presence of a normal O₂ demand). Consequently, erythropoiesis drops for all practical purposes to zero as judged by the absence of reticulocytes in the peripheral blood and the absence of recognizable erythroblasts in the blood-forming tissue. Thus, any exogenous erythropoietin(s) (if one assumes that an erythropoietin is required to initiate erythropoiesis) must initiate erythropoiesis from the reticulum itself, from early erythroblasts, or from multi-
Fig. 1.—Histologic effect of four 0.5 ml. injections of rat plasma on splenic erythropoiesis in mice with a transfusion-induced polycythemia. Tissues were taken for study 4 days after the first injection of plasma.*

A. Spleen of normal plasma-injected mouse. Red pulp is devoid of erythropoietic foci.

B. Spleen of mouse injected with plasma from nephrectomized rat. Red pulp is sparsely cellular and no islands of erythropoiesis are apparent.

C. Spleen of mouse injected with plasma from nephrectomized rat exposed to a simulated altitude of 21,500 feet for 24 hours. Red pulp is very sparsely populated and no islands of erythropoiesis are seen.

D. Spleen of mouse given plasma from unoperated rat exposed to a simulated altitude of 21,500 feet for 24 hours. Marked erythropoietic activity in the red pulp and a moderate reduction in lymphopoietic cells in the white pulp.

E. Spleen from mouse injected with a sheep plasma extract known to have erythropoietic activity. Extreme erythropoietic activity is evident in the red pulp.

F. Spleen of mouse that received plasma from rat with ureters tied and exposed to a simulated altitude of 21,500 feet for 24 hours. Red pulp shows numerous islands of erythropoiesis.

*Spleen of saline-injected polycythemic mice not shown.
potential” blast forms that are available in the marrow; perhaps from all three. Following the administration of anemic plasma, cobalt ion or cobalt plasma, or extracts made from known active anemic plasma to the transfusion-induced polycythemic mice, erythropoiesis proceeds from none at all to a hyperplastic erythroblastic stage in 3 to 4 days. Histologically, this transition appears to be orderly, and the various maturation stages appear quite normal.

It is our belief that the data presented are evidence in favor of the renal origin of erythropoietin(s). But, if the minimal reticulocyte values (about 0.2 per cent or less) found in the polycythemic mice in response to plasma from nephrectomized rats that have been subjected to hypoxic anoxia can be considered to be the result of the introduction of erythropoietin(s) into the system, then it would be necessary to state that erythropoietin production can occur in the absence of the kidneys. Accepting this for purposes of discussion, then two possibilities should be considered; namely, that (1) the kidneys do not produce erythropoietin and the reduced production in nephrectomized animals is a result of the toxicity, and (2) in the absence of the kidneys, another site, in response to a severe stimulus (hypoxic anoxia), produces a minimal amount of erythropoietin. This latter concept might be considered analogous to the production of other substances such as androgens and estrogens, which are principally gonadal in origin, but which may be synthesized on a small scale (roughly less than 10 per cent of normal production) by the adrenal. On the other hand, Erslev5 may be right in his suggestion that erythropoiesis in the normal, steady state is under the control of erythropoietin produced in some as yet unknown site, and that in the presence of renal disease, with uremia or after bilateral nephrectomy, some toxic effect interferes with the normal production or utilization, or both.

It is worthy of note that the plasma of rats starved for 4 days, contains no erythropoietic activity when assayed in the polycythemic mouse. This was to be expected since the starved rat in our hands is sensitive to plasma with erythropoietic activity.9 We have previously assumed this indicated a reduced erythropoietin titer in the plasma of starved rats.

It is also worthy of note that increased erythropoietic activity is found in the plasma of the mouse during the last trimester of pregnancy. Mice are almost universally anemic in late pregnancy. This substantiates the report of Contopoulos et al.14 on the erythropoietic activity of plasma from pregnant rats.

**SUMMARY AND CONCLUSIONS**

Mice with transfusion-induced polycythemia have been used to assay erythropoietic activity in plasma derived from mice and rats subjected to various stimuli and experimental procedures.

1. Anemic, anoxic, or cobalt mouse plasma increased erythropoiesis from the zero baseline to about the normal range after four 0.5 cc. injections. No significant effect is observed from the same number of injections of normal rat or mouse plasma or normal saline. Similarly, plasma from rats starved for 4 days had no erythropoietic activity, but erythropoietic activity was
present in the plasma of pregnant mice during the last trimester of pregnancy.

2. Plasma from mice made anemic by phenylhydrazine and then subjected to bilateral nephrectomy contained slight erythropoietic activity (less than 0.2 per cent reticulocytes). The plasma of sham-operated anemic animals had considerably more erythropoietic activity (2.0 per cent). The plasma was collected for assay 10 hours after the operative procedures.

3. Plasma from nephrectomized rats exposed to hypoxic anoxia for 8, 16, or 24 hours, had slight erythropoietic activity when measured by the peripheral reticulocyte response of the recipients (0.18, 0.11, and 0.00 per cent reticulocytes, respectively). The same plasma had no erythropoietic activity when judged by the Fe59 red cell incorporation response in starved rats.

Plasma from rats subjected to bilateral ureter ligation and similarly exposed had an erythropoietic activity (0.7, 1.38, and 1.26 per cent reticulocytes, respectively), comparable with that of the plasma from normal rats exposed to hypoxic anoxia (0.9, 1.71, and 1.78 per cent, respectively). The low and inconstant erythropoietic activity in the plasma of nephrectomized mice and rats subjected to anemic or hypoxic anoxia is more or less comparable with the response occasionally produced by normal plasma. We are, therefore, disinclined to consider the data as evidence against the renal origin of erythropoietins, but the alternative possibilities are discussed.

**SUMMARY IN INTERLINGUA**

Muses con polycythemia inducite per transfusion esseva utilisate pro essayar le activitate erythropoietic in plasma derivate ab muses e rattos que esseva subjicite a varie stimulos e procedimentos experimental.

1. Plasma ab muses anemic, anoxic, o tractate con cobalt augmentava le erythropoiese ab le nivello zero usque a un nivello approximativemente normal post 4 injectiones diurne de 0,5 cm³. Nulle effecto significative esseva observate ab le mesme numero de injectiones de plasma ab rattos o muses normal o de solution salin physiologic. Similemente, plasma ab rattos que habeva jejunate 4 dies habeva nulle activitate erythropoietic, sed activitate erythropoietic esseva presente in plasma prendite ab muses in le ultime trimestre del pregnantia.

2. Plasma ab muses que esseva facite anemic per phenylhydrazina e alora subjicite a nephrectomia bilateral habeva pauc activitate erythropoietic (minus que 0,2 pro cento de reticulocytos). Le plasma ab animales anemic que habeva essite subjicite a pseudo-operationes monstrava un activitate erythropoietic considerablemente plus grande (2,0 pro cento). Le plasma esseva colligite pro le essayage 10 horas post le interventiones chirurgic.

3. Plasma ab rattos nephrectomisate que esseva exponite a anoxia hypoxic pro 8, 16, o 24 horas, habeva pauc activitate erythropoietic in comparation con le responsa del reticulocytos peripheric del recipientes (0,18, 0,11, e 0,00 pro cento respectivemente). Le mesme plasma habeva nulle activitate erythropoietic quando isto esseva mesurate per le incorporation de Fe59 in le erythrocytos de rattos jejun.

Plasma ab rattos nephrectomisate e exponite a anoxia hypoxic pro le mesme periodos habeva un activitate erythropoietic (0,7, 1,38, e 1,26 pro
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cento de reticulocytos respectivamente) que es comparabile con illo del plasma ab rattos normal que esseva exponite a anoxia hypoxic (0,0, 1,71, e 1,78 pro cento respectivemente). Le basse e inconstante activitate erythropoietic in le plasma de muses e rattos nephrectomisate e subjicite a anoxia anemic o hypoxic es plus o minus comparabile con le responsa que es a vices producute per plasma normal. Consequentemente nos non es inclinate a considerar le datos como evidentia contra le origine renal del erythropoietinas. Le possibilitates alternative es discuttite.

REFERENCES


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