

THE EFFECT OF INTRAVENOUS NOVOCAIN INJECTIONS ON THE BLOOD SYSTEM

COMMUNICATION II. CHANGES IN COMPOSITION OF THE BLOOD AFTER A SINGLE INJECTION OF NOVOCAIN

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An earlier report [11] was concerned with changes in the composition of the blood in rabbits and dogs resulting from repeated intravenous injections of 4-5 ml 1% solution of novocain. The present report presents data on the reaction of the blood system during the first few hours following injection of novocain.

EXPERIMENTAL METHOD

The experimental conditions and division of the animals into groups were the same as in the previous instance (see Communication I). Experiments were performed on 30 rabbits and 2 dogs. Blood was examined $\frac{1}{2}$, 1, 2, 3, and 4 hours after injection of novocain solution.

EXPERIMENTAL RESULTS

Leukocyte reaction. Changes in the number of leukocytes which arise in response to novocain injection are fairly consistent in character (Fig. 1 and 2) and consist of an initial drop in their number (in 22 out of 30 animals) with subsequent increase (in 27 cases). The increase in the number of leukocytes varied between 15.1 and 346.1% of the initial level or (in absolute figures) between 1000 and 20,645 cells per 1 mm³. Control observations showed that spontaneous fluctuations in the elements being studied could reach 69.1% and variations after injection of 4-5 ml physiologic solution 87.1% of the initial value. However, the characteristic curve described above with an increase in the number of leukocytes by the 2nd hour is only noted after injection of novocain. The reaction to novocaine was more marked than that to an injection of physiologic solution in 20 out of 30 rabbits and in both dogs, and in 10 animals the reverse was observed. In order to clarify whether repeated injection of novocain had any significance special investigations were undertaken; it was found that only in 12 out of 30 rabbits the maximal effect was observed after the first injection (unlike the previously established effect of novocain on conditioned reflex activity and arterial blood pressure). The increase in the number of leukocytes was not usually accompanied by changes in the differential leukocyte count.

Experiments in which novocain was administered to animals with previously (20-40 days earlier) denervated carotid sinuses and spleen throw some light on the mechanism of the changes observed by us. The significance of normal innervation of these organs for the regulation of hemoglobin and erythrocyte content has been repeatedly confirmed in recent years [4-10, 14, 13].

At the same time the leukocyte reactions in cases of impaired innervation of the spleen and carotid sinuses have remained practically uninvestigated. Experimental results showed that in 12 out of 14 animals, beginning from the 2nd-3rd month postoperatively, the increase in the number of leukocytes in response to novocain injection rose sharply (Fig. 1, IV-VII) and this could be observed during the next 12-18 months. Sometimes (in 3 cases; see table) the phase of enhanced reaction was preceded by a period of reduced reaction.

A similar reaction was observed also in animals with denervated spleens. Normal carotid sinus and spleen innervation is by no means the only factor on which the leukocyte reaction depends. A significant role was shown to be played by blood-letting (25-30 ml blood) sustained 25-30 days earlier. Thus, in 11 animals the average figures for increase in the number of leukocytes after injection of novocain before blood-letting varied within the range of 15.1-346%, after blood-letting from 33.4-420.7%. Enhanced intensity of leukocyte reactions was noted in 7 out of 11 rabbits (Fig. 2, III-V).

After blood-letting, unlike the situation before it, the most marked reaction occurred in response to the first injection of novocain (in 9 out of 11 animals).

For example, in rabbit No. 21 in experiment dated May 22, 1957 the increase amounted to 101.8% of the initial, and in experiment dated May 30, 1957 it was 46.2%. In rabbit No. 22 in experiment of May 24, 1957 the increase was 839.4%, in experiment of June 1, 1957 - 237.5% and in experiment of June 7, 1957 - 185%; the corresponding figures in the same rabbit prior to blood-letting were 346 and 419.8%.

Changes in hemoglobin, erythrocyte and reticulocyte content. The view that these blood elements are relatively little subject to rapid fluctuations has become fairly firmly established in the literature.

In this connection investigations have recently appeared [12] in which changes in the number of erythrocytes and the amount of hemoglobin occurring 3-4 hours after administration of test substances serve as an indication of whether the latter contain hemopoietic or anemia-inducing agents.

Our investigations showed that injections of both physiologic solution and novocain could produce fluctuations in the numbers of erythrocytes in excess of spontaneous variations (Fig. 1, I); so-called spontaneous fluctuations in erythrocyte content, according to our data (repeat examinations performed on 30 rabbits) amounted to 0-15.9% of the initial, or from 0 to 600,000 erythrocytes per 1 mm³. Reduction in the number of erythrocytes was noted within the limits of 4.8 to 16% of the initial, or from 100 to 620,000 erythrocytes per 1 mm³ (the latter was only observed in one case).

Intravenous injection of physiologic solution (4-5 ml) can lead to decrease or increase in the number of erythrocytes (to 24.6% of initial, or to 1,290,000 per 1 mm³ in the latter case, and to 35.2% of initial or 1,950,000 per 1 mm³ in the former). Reduction in the number of erythrocytes was observed in 24 out of 30 animals, increase in their number in 16. Injection of novocain produced approximately the same reaction with the difference that reduction in the erythrocyte content was somewhat more pronounced than that seen after injection of physiologic solution to the same animals (in 21 out of 30 cases). Increase in the number of erythrocytes fluctuated (average figures) from 0 to 32%, decrease in their numbers varied from 1 to 23% of the initial.

In absolute figures variations in the number of erythrocytes constituted 90,000-1,400,000 cells (increase) and 40,000-1,240,000 (decrease).

We are thus led to state that injections of physiologic solution (if they are not "extinguished" by multiple repetition) and of novocain give rise to fairly marked changes in the number of erythrocytes during the first 4 hours after injection. This suggests that changes in the number of erythrocytes immediately following injection of any substance cannot serve as an indication of the presence in it of stimulators or inhibitors of erythropoiesis.

Denervation of the carotid sinuses affected the reaction under consideration in such a way that 1-2 months after the operation, when normalization of the blood composition had apparently taken place, injection of novocain produced, as a rule, no erythrocytosis, while the reduction in the number of erythrocytes was more marked. Sometimes this phenomenon lasted for 9 months postoperatively (rabbits No. 4 and 5). This altered reaction to novocaine may be related to the reflex character of erythrocytosis noted by M. L. Belenkii and Iu. N. Stroikov [2], to the facts concerning the role of the carotid sinuses in the onset of erythrocytosis during hypoxemia established by N. N. Beller [3] and to the work of W. Grant [12] and M. Terzioğlu [16].

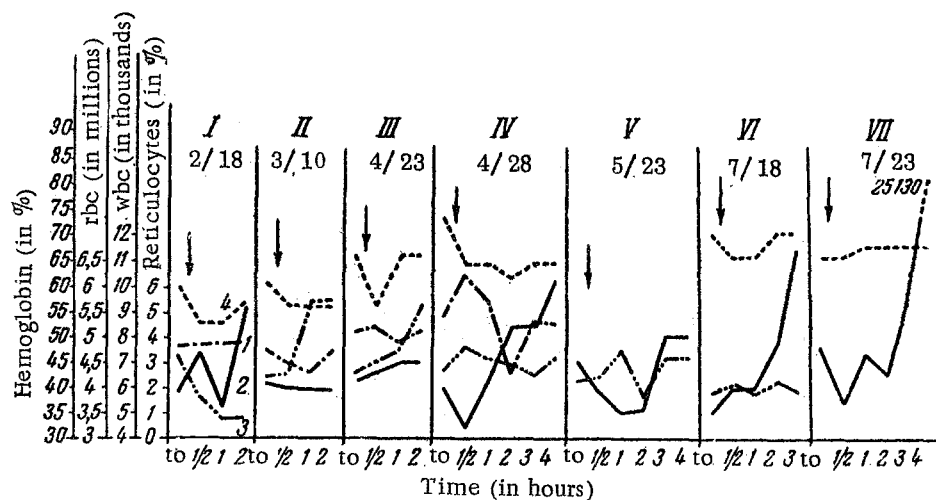


Fig. 1. Changes in composition of the blood in rabbit during 4 hours after intravenous injection of 5 ml 1% solution of novocain . I) Before denervation of carotid sinuses (denervation performed February 19, 1956); 1) erythrocyte content, 2) leukocyte content, 3) reticulocyte content, 4) hemoglobin content ↓) novocain injection.

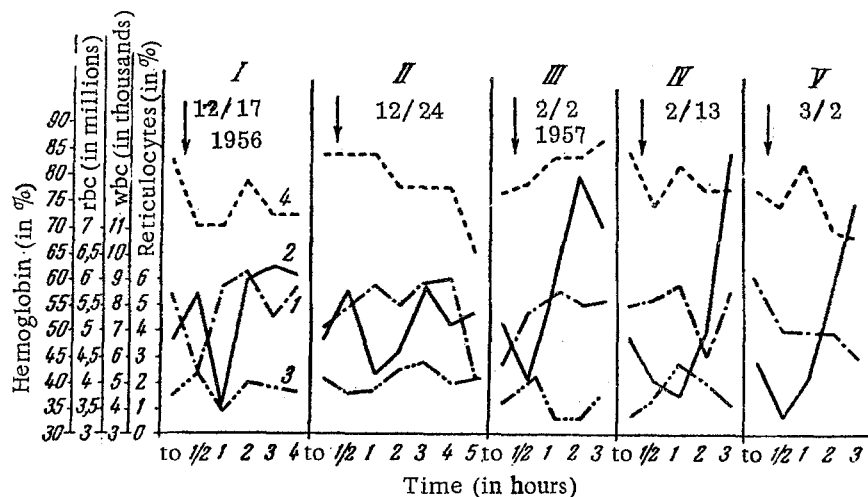


Fig. 2. Changes in composition of the blood in rabbits during 4 hours after intravenous injection of 5 ml 1% solution of novocain . I-II) Before blood-letting, III-V) after blood-letting (blood-letting January 9, 1957, 20 ml blood). Records the same as in Fig. 1.

The effect of preceding blood-letting was reflected in that injection of novocain caused a more marked drop in the number of erythrocytes in 7 out of 11 animals than was observed prior to this procedure; at the same time less marked increase in the number of erythrocytes was also seen in 7 animals. Thus, rabbit No. 20 showed an average drop in the number of erythrocytes following injection of novocain without previous blood-letting amounting to 13.5%, and an increase by 7% (after 2 months); after blood-letting the corresponding figures were 30.6% and 6.7%.

Fluctuations in hemoglobin content in healthy animals following injection of novocain are not very large, but there is a predominant tendency toward its reduction (Fig. 1, I and Fig. 2, I). The increase, according to our data, amounts to +10 units, and the decrease to -16 units. We, like a number of other authors [1, 5, 14] observed in more than half the cases no parallelism in the course of changes in the number of erythrocytes and of hemoglobin content (in 16 out of 30 animals).

Changes in the Number of Leukocytes in Rabbit No. 5 on Injection of 1% Novocain Solution Before and After Carotid Sinus Denervation

1/5 1956	A	B	1/12 1956	A	B	1/16 and 1/31 1946. Denervation of carotid sinuses	3/18 1957	A	B	3/10 1957	A	B	4/24 1957	A	B	5/14 1957	A	B	6/5 1957	A	B	7/24 1957	A	B	8/10 1957	A	B	8/24 1957	A	B	9/27 1957	A	B
	+1200	21.1	+2800		+35.1		+1400		+17	0	0	0	0	0	0	+6000	+74	+6470	+71	+20 670	+198	+35 200	+379	+10 900	+119	+11 730							
	-0	0	-720		-17.5		-0		0	-3340	-27	-6360	-48	0	0	0	0	0	0	0	0	0	0	0	-2700	-3.2	-2530						

Note: A) Absolute number in thousands per 1 cm³, B) percentage of initial level.

When carotid sinuses were denervated the animals no longer (from the 30th-40th postoperative day) showed an increase in hemoglobin content, and in some cases a decrease in the latter was observed.

Studies of the reticulocyte content of peripheral blood and of bone marrow contribute toward the solution of the question concerning the mechanism of changes elicited in response to injection of novocain. It was found that novocain administration to healthy animals produced no increase in blood reticulocytes; fluctuations in their number were diphasic in character in 14 out of 30 animals.

In absolute figures the fluctuations were from 1 to 22 per 1000 erythrocytes. In 3 experiments a decrease in the number of reticulocytes (to 27 per 1000 erythrocytes by the 4th hour of investigation; Fig. 1, I) was marked. In 2 experiments it could still be seen that following a preceding injection of novocain the reticulocyte content remained high even after 5 days, amounting to 59 per 1000 (with an initial level of 21 per 1000 erythrocytes). Carotid sinus denervation is known to be accompanied during the first 3-4 weeks by marked reticulocytosis, which then usually disappears. However, if novocain is injected at this time it produces marked increase in the number of reticulocytes in the peripheral blood (Fig. 1, II, III).

Attempts to elicit such an increase in the number of reticulocytes in rabbits at a later period proved unsuccessful. It should be recalled that during this period the bone marrow [3, 4] shows inhibition of erythropoiesis and absence of enhanced reticulocytosis. It seems probable that in the period between the 2nd and 4th month after denervation the injection of novocain may encourage egress of reticulocytes from the bone marrow. As regards the effect of preceding blood-letting, injection of novocain after normalization of the composition of the blood and the number of reticulocytes had dropped, not only did not cause an increase in their number, but was associated with less marked reticulocytosis than prior to blood-letting (rabbits No. 29, 30 and 32; Fig. 2, III, V).

The experiments carried out permit the following conclusions:

1. Intravenous administration of 4-5 ml 1% novocain solution to rabbits elicits, in healthy animals, marked leukocytosis beginning with the 2nd hour after injection, with frequently a preceding phase (during the first 30-60 minutes) of reduction in the number of leukocytes. Carotid sinus and spleen denervation leads to marked enhancement of the leukocyte reaction under consideration beginning from the 2nd postoperative month and lasting up to 1-1½ years. Blood-letting also enhances this reaction.
2. Changes in erythrocyte and hemoglobin content during 4 hours after injection of novocain are not consistent but are fairly marked both in the direction of decrease and increase of these indices. Denervation of the carotid sinuses leads to the disappearance of erythrocytosis in response to novocain.

3. Healthy animals do not usually show a reticulocyte reaction to novocain injection. After denervation of carotid sinuses, when the reticulocyte content of bone marrow is raised, injection of novocaine elicits an appreciable increase in the number of reticulocytes in peripheral blood.

SUMMARY

The author studied the changes which took place in the composition of the blood within 4 hours following the injection of 4-5 ml of 1% novocain solution to 30 rabbits. The number of leukocytes was increased in healthy animals in 2 to 4 hours.

After denervation of carotid sinuses and spleen this reaction was considerably intensified (for 2-18 months after the operation). Blood-letting acts in the same way but its effect is shorter. Changes in the number of erythrocytes and in the hemoglobin content are not consistent, but are rather pronounced. In $\frac{2}{3}$ of all cases this response to injection of novocain was more marked than that due to injection of physiological saline. 3-4 weeks after denervation of carotid sinuses novocain injection caused an increase in the number of reticulo-cytes in the peripheral blood due to their egress from the bone marrow.

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* In Russian.

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