

## VASCULAR PERMEABILITY IN SOME DISEASES OF THE CENTRAL AND PERIPHERAL NERVOUS SYSTEMS

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In our previous investigations [1, 2] it was established that patients with lesions of the diencephalic area and with pain syndromes of various etiology showed considerable changes of permeability in cutaneous capillaries. The criterion for judging permeability in the direction tissue  $\rightarrow$  blood was the time taken for half-elimination of NaCl solution labelled with  $\text{Na}^{24}$ , introduced into the skin of the forearm (right and left). The technique used was that developed in I. A. Olvin's laboratory [3]. Allowance was made for the fact that the rate of absorption reflected the functional state of the capillary wall and depended not only on its permeability but also on the extent of absorbing surface and rate of blood flow.

In practically healthy subjects the time of half-elimination of  $\text{Na}^{24}$  was, on the average, 9.6 minutes both in the right and left forearms. Patients with diencephalic lesions were divided into three groups according to the rate of absorption of  $\text{Na}^{24}$ : 1) with increased permeability ( $3\frac{1}{2}$  - 6 minutes), 2) with lowered permeability (up to 20-28 minutes) and 3) with permeability corresponding to the lower level of the normal range (average of  $7\frac{1}{2}$  minutes).

Patients with pain syndromes (radiculitis, neuritis, neuralgia, vascular tumors etc.) exhibited marked asymmetry of the rate of absorption on the healthy and affected sides of the body. Pain syndromes were associated in the majority of cases with lowered permeability; the absorption curve showed a diphasic character slowing markedly during the course of investigation.

The work of L. S. Shtern and collaborators [4] has shown that the composition and properties of tissue fluid depend both on the passage of substances from the blood into the tissues and on the passage of products of metabolism from the tissues into the blood. The relative constancy of extra-cellular fluid can only be maintained when the movement of water, electrolytes and nutrient substances from the blood into the tissues is balanced by a reverse movement from the tissues into the blood. The amount, composition and properties of tissue fluids depend on the capillary wall permeability in both directions.

The present communication, which is one of a series of investigations of the state of cell blood barriers in certain diseases of the nervous system (work of G. N. Kassil and collaborators), is concerned with the results of studies on capillary permeability in the direction blood  $\rightarrow$  tissues.

### EXPERIMENTAL METHODS

$\text{Na}^{24}\text{Cl}$  with activity of approximately 70 microcurie was given intravenously in 55 ml 20% solution of glucose. Blood samples for determination of activity were taken from the finger (0.1 ml) at intervals of 1, 3, 5, 10, 20, 30, 60, 120, 180 minutes. Intensity of radiation was determined by a counter using installation "B". The rate of passage of  $\text{Na}^{24}$  from blood into tissues was expressed in percentage of maximal concentration of the isotope in blood, reached directly after its administration (in the course of the first minute).

In the case of control subjects (healthy, young persons) the rate of  $\text{Na}^{24}$  uptake from the blood by the tissues usually reaches 52% by the 5th minute, 70% by the 20th minute, the latter level being maintained for up to 3 hours.

Observations were carried out on patients with diencephalic lesions (14 cases) and with pain syndromes of various etiologies (15 cases).

Results of observations on patients with diencephalic disorders are given in Table 1.

TABLE 1

Rate of Removal of Intradermally Administered  $\text{Na}^{24}\text{Cl}$  in Patients with Diencephalic Syndrome

| No. of experiment | Date of experiment, 1956 | Subjects |    | Age, in years | Removal of $\text{Na}^{24}$ from blood (as % of its maximal value) in course of min. |    |    |    |    |    |     |     | Time of $\text{Na}^{24}\text{Cl}$ admin. in-<br>traderm. ab-<br>sorp. (min) |
|-------------------|--------------------------|----------|----|---------------|--|----|----|----|----|----|-----|-----|---|
|                   |                          |          |    |               | 3  | 5  | 10 | 20 | 30 | 60 | 120 | 180 |   |
| 1                 | 23/XII                   | S.       | F. | 20            | —  | —  | 5  | —  | 15 | 20 | 38  | 40  | 5.5   |
| 2                 | 22/XII                   | K.       | M. | 20            | —  | —  | 9  | —  | 40 | 46 | 46  | 46  | 6.0   |
| 3                 | 19/I                     | F.       | »  | 27            | 5  | —  | 10 | —  | 25 | 30 | 33  | 40  | 6.0   |
| 4                 | 20/I                     | M.       | F. | 32            | —  | 10 | —  | 18 | 22 | 33 | 40  | 40  | 11—14.5   |
| 5                 | 23 II                    | K.       | »  | 44            | 10   | —  | 21 | 27 | —  | 33 | 38  | —   | 5.5   |
| 6                 | 23/III                   | P.       | M. | 30            | —  | 15 | —  | 26 | 27 | 46 | 48  | —   | 5.5   |
| 7                 | 9/V                      | Z.       | »  | 18            | 5  | 10 | 24 | 30 | 34 | 46 | —   | 48  | 8.0   |
| 8                 | 1/III                    | D.       | F. | 42            | 15   | —  | 54 | 55 | 60 | 62 | 62  | —   | 7.5   |
| 9                 | 24/V                     | M.       | »  | 35            | 27   | 39 | 50 | 59 | 60 | —  | 60  | —   | 7.5   |
| 10                | 31/V                     | G.       | »  | 57            | —  | 20 | 35 | 36 | 55 | 60 | 62  | —   | 12.0  |
| 11                | 29/III                   | B.       | M. | 53            | 52   | 62 | 66 | 74 | 83 | 83 | —   | —   | 20.0  |
| 12                | 6/IV                     | B.       | F. | 37            | 26   | 50 | 60 | 60 | 88 | 80 | —   | —   | 10.0  |
| 13                | 1/IV                     | L.       | »  | 32            | 47   | 52 | 53 | 69 | 71 | 72 | 72  | —   | 20.0  |
| 14                | 31/V                     | K.       | »  | 33            | 13   | 49 | 56 | 60 | 66 | —  | 67  | —   | 10.0  |

As can be seen from these data, the rate of removal of  $\text{Na}^{24}$  from the blood was considerably slowed in the case of the first 7 patients. At 20 minutes only 18-30%  $\text{Na}^{24}$  had been removed, and up to 40-48% subsequently. Slowed removal of  $\text{Na}^{24}$ , though less marked, was also seen in the next three patients (at 20 minutes 36-59% and then 60-62% was removed). Cases No. 11 and No. 12 showed, in contrast, accelerated removal of  $\text{Na}^{24}$  which reached, at 5 minutes, 50-62% and 80-83% at 30 minutes. The two last patients showed rates of  $\text{Na}^{24}$  removal which were within normal limits. Thus, of 14 patients investigated, 10 exhibited slowing of the passage of  $\text{Na}^{24}$  from blood to tissues and accelerated (except the fourth patient) absorption of  $\text{Na}^{24}$  from the tissues into the blood (average 5.7 minutes).

The rate of  $\text{Na}^{24}$  removal from blood is presented graphically in the figure. The curve for  $\text{Na}^{24}$  removal from blood shows in its first part (up to the 10th minute) the intensity of  $\text{Na}^{24}$  exchange between blood and extra-cellular fluid, and in its second part the onset of a relative state of equilibrium between these systems. While the normal removal of  $\text{Na}^{24}$  from blood reaches 70-74% by the 20th minute, in the first group of patients with diencephalic disorders only 18-30% is removed during this time (see Figure) which indicates retention of  $\text{Na}^{24}$  in the blood. Accelerated absorption of  $\text{Na}^{24}$  from the tissues into the blood is usually observed in these patients as has already been reported in a previous communication [1]. Clinical and physiological examination of the patients revealed, as a rule, accelerated excretion of water from the organism, dryness of skin and tissues and tendency to wasting. Curve 3 (see Figure) is characteristic for rapid removal of  $\text{Na}^{24}$  from the blood which is evidently accompanied by its accumulation in extra-cellular fluid. These patients not infrequently show slowed uptake of  $\text{Na}^{24}$  from the tissues by the blood [1] as well as retention of water in the body, edema and excessive deposition of adipose tissue. The material presented thus indicates that patients

**TABLE 2**  
Rate of Na<sup>24</sup> Removal in Patients with Pain Syndrome

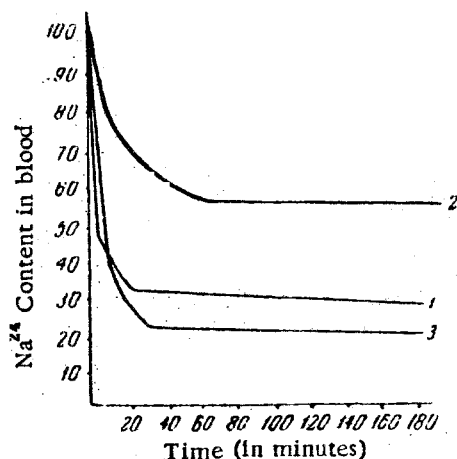
| No. of ex-<br>periment | Date of ex-<br>periment,<br>1956 | Subjects | Sex | Age | Removal of Na <sup>24</sup> from blood<br>(in % of its maximal value)<br>in course of min. |    |    |    |    |    |     |     |       | Absorption<br>time in<br>min.                     | Diagnosis |
|------------------------|----------------------------------|----------|-----|-----|--|----|----|----|----|----|-----|-----|-------|---|-----------|
|                        |                                  |          |     |     | 3  | 5  | 10 | 20 | 30 | 60 | 120 | 180 |       |   |           |
| 1                      | 24/XI                            | K.       | M.  | 57  | 27   | 39 | 51 | 55 | —  | 55 | 57  | —   | 15    | Right-sided lumbo-sacral<br>radiculitis           |           |
| 2                      | 1/III                            | P.       | »   | 66  | 20   | —  | 25 | 37 | 42 | 46 | 48  | 49  | 11    | Left-sided lumbo-sacral<br>radiculitis            |           |
| 3                      | 15/III                           | K.       | »   | 41  | —  | 30 | 36 | 39 | 45 | 59 | 61  | 61  | 11—20 | Trigeminal neuralgia                              |           |
| 4                      | 22/III                           | F.       | »   | 26  | 23   | —  | —  | —  | 59 | 62 | —   | —   | 11    | Right-sided lumbo-sacral<br>radiculitis           |           |
| 5                      | 10/V                             | P.       | »   | 70  | 28   | —  | 35 | 50 | 55 | 58 | 61  | 61  | 19—25 | Bilateral lumbo-sacral<br>radiculitis             |           |
| 6                      | 9/II                             | K.       | »   | 62  | 30   | 49 | —  | 70 | 75 | 78 | 78  | 77  | 24    |   |           |
| 7                      | 24/II                            | R.       | »   | 31  | 32   | 37 | 49 | 55 | 67 | 70 | 72  | —   | 13    | Vascular pains. Angioneurosis                     |           |
| 8                      | 14/III                           | O.       | F.  | 32  | 30   | 56 | 57 | 60 | 66 | 67 | —   | 67  | 11    | Autonomic polyneuritis.<br>Angioneurosis          |           |
| 9                      | 15/III                           | L.       | M.  | 32  | —  | 38 | 59 | 65 | 65 | 70 | 72  | 72  | 9     | Chronic headaches —<br>otic etiology              |           |
| 10                     | 5/IV                             | B.       | »   | 25  | 40   | 52 | 63 | 70 | 70 | 72 | 75  | —   | 6     | Chronic headaches — angio-<br>neurotic etiology   |           |
| 11                     | 9/V                              | G.       | »   | 51  | —  | 35 | 50 | 60 | 67 | 69 | 69  | —   | 20    | Pain syndrome-multiple<br>sclerosis Angioneurosis |           |
| 12                     | 29/II                            | M.       | F.  | 56  | 64   | —  | 80 | —  | 82 | 88 | —   | 88  | 7     | Right-sided lumbo-sacral —<br>radiculitis         |           |
| 13                     | 12/IV                            | T.       | M.  | 33  | 52   | 62 | 65 | 70 | 74 | 83 | 83  | —   | 6     | Thoracic ganglion infla-<br>mmation. Sympathalgia |           |
| 14                     | 16/V                             | C.       | F.  | 46  | —  | 50 | 62 | 68 | 72 | 77 | 83  | —   | 25    | Pain syndrome — spon-<br>dyloarthritis            |           |
| 15                     | 24/V                             | K.       | »   | 45  | 58   | 70 | 75 | 77 | 80 | 85 | 88  | —   | 9     | Severe headaches —<br>angioneurosis               |           |

**TABLE 3**  
Absorption Time for Intradermally Introduced Na<sup>24</sup>Cl in Patients with Diencephalic  
Syndrome, Following Administration of Sympatol

| No. of ex-<br>periment | Date of ex-<br>periment | Subjects | Sex | Age | Absorption time in min.             |                             |
|------------------------|-------------------------|----------|-----|-----|-------------------------------------|-----------------------------|
|                        |                         |          |     |     | before ad-<br>min. of sym-<br>patol | after admin-<br>of sympatol |
| 1                      | 17/IX 1955              | P.       | F.  | 26  | 4.4                                 | 16.0                        |
| 2                      | 12/X.                   | T.       | »   | 33  | 6.5                                 | 12.5                        |
| 3                      | 23/XI                   | Kh       | »   | 42  | 4.7                                 | 7.5—13                      |
| 4                      | 1/XII                   | S.       | M.  | 43  | 5.5                                 | 11.0                        |
| 5                      | 15/XII                  | S.       | F.  | 22  | 5.5                                 | 5.5                         |
| 6                      | 15/XII                  | K.       | M.  | 20  | 6.0                                 | 8.0                         |
| 7                      | 21/XII                  | B.       | F.  | 23  | 6.0                                 | 9.5—14                      |
| 8                      | 29/XII                  | P.       | »   | 33  | 3.7                                 | 4.5                         |
| 9                      | 19/I 1956               | K.       | »   | 44  | 5.5                                 | 6.0                         |
| 10                     | 8/III                   | K.       | »   | 35  | 6.0                                 | 12.5                        |
| 11                     | 15/III                  | D.       | »   | 42  | 9.5                                 | 14.0                        |

with diencephalic disorders show definite, consistent changes of vascular permeability both in the direction tissues  $\rightarrow$  blood and blood  $\rightarrow$  tissue.

Changes of permeability in both directions were also studied in patients with pain syndromes. The results are presented in Table 2. These data show that patients with lumbo-sacral radiculitis and neuralgias have a diminished rate of  $\text{Na}^{24}$  removal from blood into tissues. By the 20th minute 37-50% was removed and a state of equilibrium was attained when 49-61%  $\text{Na}^{24}$  had been removed. Patients with pain caused by various conditions (Nos. 6-11) showed  $\text{Na}^{24}$  removal rate which was within normal limits (67-78%); in 4 patients (Nos.



Rate of  $\text{Na}^{24}$  removal from blood in the normal (1) and in patients with diencephalic disorders (2 and 3). Initial  $\text{Na}^{24}$  content of blood taken as 100.

12-15) accelerated removal of  $\text{Na}^{24}$  from blood was observed (83-88%). In 7 patients out of 15 the time of absorption of  $\text{Na}^{24}\text{Cl}$  from the tissues into the blood was considerably prolonged while in the others it was within limits of normal. In this group of patients, unlike those of the diencephalic disorder group, it proved to be impossible to reveal strict dependence of movement of  $\text{Na}^{24}$  in the direction blood  $\rightarrow$  tissues and tissues  $\rightarrow$  blood. It is connected apparently with different etiology of the pain syndrome in various disorders of the central and peripheral nervous systems. The pain syndrome as such does not produce characteristic changes of vascular permeability in the direction blood  $\rightarrow$  tissues as distinct from the data obtained in studies on permeability in the direction tissues  $\rightarrow$  blood. It must be supposed that the rate of removal of  $\text{Na}^{24}$  from the blood depends on the main disease and may be of definite significance for differential diagnosis and therapeutic considerations.

Dynamic studies of vascular permeability on some patients revealed that improvement in the general condition under the influence of therapy was accompanied by normalization of the movement of  $\text{Na}^{24}$  from the blood into tissues and vice versa. In the case of patient K., aged 44 years, with marked manifestations of diencephalic disorder vascular permeability to  $\text{Na}^{24}$  in the direction of tissues  $\rightarrow$  blood was increased on first examination, when its removal from the blood was slowed. Following 8 irradiations of the diencephalic area with roentgen rays the vascular permeability to  $\text{Na}^{24}$  in both directions was normalized against a background of general improvement in the patient's condition.

Taking these data into consideration, it was decided to study the problem of possible directed alteration of capillary permeability. Certain "vegetotropic" substances, widely used in clinical practice, were chosen for study (sympatol, proserine).

Results of these investigations are presented in part in Table 3.

The data obtained show that absorption time for  $\text{Na}^{24}$  after preliminary administration of sympatol was considerably increased in most patients, in some cases 2-3 fold. Apparently, the sympathetic reaction which occurs on administration of sympatol and is accompanied by vaso-constriction, rise of blood pressure, acceleration of blood flow and slowing of absorption favors change in capillary permeability.

When proserine was given to the subjects under investigation it was thought that depression of cholinesterase activity and accumulation of acetylcholine connected with this would cause a parasympathetic effect and, unlike sympatol, lead to acceleration of  $\text{Na}^{24}$  absorption. However, acceleration of absorption was noted in only 2 out of 7 cases. This was associated with pronounced increase of parasympathetic tonus (slowing of pulse, pupillary constriction, increased peristalsis, nausea). In the remaining cases administration of proserine did not produce any appreciable parasympathetic effect or any changes in the permeability of skin capillaries. Investigations along these lines are being continued.

• Russian trade name.

## SUMMARY

Permeability of blood vessels to  $\text{Na}^{24}$  was studied in the direction of tissues to blood and vice versa. These investigations were conducted in healthy individuals as well as in patients with diencephalic lesions and with pain syndromes of various etiology.

Pronounced delay of removal of  $\text{Na}^{24}$  from the blood into the tissues was noted in diencephalic patients with increased permeability in tissue to blood direction. A more rapid removal of  $\text{Na}^{24}$  from the blood was revealed in patients with reduced permeability from the tissues into the blood. The rapidity of  $\text{Na}^{24}$  removal from the blood into the tissues in the patients with pain syndromes of various etiology is different (its velocity is increased in one case and decreased in the other). Certain vegetotropic substances widely used in the clinic (such as sympatol, and proserine) were used for directed change of permeability. It was established that following administration of sympatol absorption of  $\text{Na}^{24}$  which was injected subcutaneously is greatly delayed.

## LITERATURE CITED

- [1] I. L. Vaisfeld, and G. N. Kassil, Doklady Akad. Nauk SSSR, 109, No. 5, 1956.\*
- [2] I. L. Vaisfeld, A. M. Vein, N. I. Grashchenkov and G. N. Kassil. Reports of the All-Union Conference on Medical Radiology,\*\* 1956, p. 128.
- [3] I. A. Olvin, In the book: Materials on the Pathogenesis of Inflammation and Pathology of Vascular Permeability,\*\*3, Stalinabad, 1956.
- [4] L. S. Shtern, In the book: Transactions of the Institute of Physiology, Academy of Sciences USSR,\* • Vol. IV, 1947.

\* Original pagination. See C. B. Translation.

\*\* In Russian.