

exhibiting l.v.c. but otherwise with the same stage of the disease. It is proposed that l.v.c. favor rapid hematogenous spread of malignant cells and that patients with l.v.c. on lymphography should be classified as stage IV.

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T. Roxin, M.D., H. Bujar, M.D., "N. Gh. Lupu" Institute of Internal Medicine, Bucharest, Romania

Lymphostatic Ophthalmopathy*

M. Földi

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Lymphostatic encephalopathy has been described in certain patients and investigated in animal models. Among the many changes observed clinically and experimentally the alterations of the optic nerve and the papilla have not been adequately studied.

Material and Methods

In experiments performed with *Csanda* and *Zoltán* a cervical lymphatic blockade has been produced in 12 dogs.

One week after ligation of cervical lymph pathways the animals were sacrificed either by an overdose of hexobarbital or by means of decapitation. The skull was opened, the brain removed and the orbitae dissected; both eyes with the optic nerves were fixed in histological fixatives. Also the intracanalicular part of the optic nerve was used for histological studies; for this purpose, the optic nerve was transected

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orally from the optic chiasma. In some cases, the optic nerve was removed together with all the connective tissue within the orbitae; in other cases, the eyeball was opened by means of an equatorial incision made by a *Graefe* knife, right behind the limbus corneae and the oral third of the bulbus was circumsised with a pair of fine scissors and discarded. The posterior two-thirds of the bulbus and the optic nerve was then fixed in 10% neutral formalin and embedded, after dehydration, according to the combined methyl-benzoate-celloidine-paraffine impregnation technique. Before embedding, the lateral part of the bulbus was excised in the meridional plane.

In this plane, complete serial sections were cut from the eye, comprising the entire papilla and the optic nerve, respectively.

Sections were stained by haematoxyline-eosine, according to *van-Gieson*, *Crossman*, *Masson* and *Loyez*, or impregnated according to *Bodian-Holmes*. For nucleic acids, the gallocyanin stain of *Einarson* has been used.

Results

According to the regional sequence, the following alterations were observed: In sections stained for collagen, a hydropic swelling of the leptomeninx is observed. The cellular substance of the arachnoidea exhibits an isomorphic proliferation. Physiologically, the arachnothel consists of one or two cell layers; under the pathological conditions studied, however, the swollen cells, with their nuclei exhibiting light staining properties are arranged in 4-5 layers. This alteration is most characteristic, as a rule, in the vicinity of the eyeball, in the neighbourhood of the blind sac of the dura mater. The pia mater of the optic nerve is usually normal. The septal system in the continuation of the pia mater shows varying degrees of widening, and exhibits homogenous staining properties when studied by means of collagen stains. Between septa and parenchyma, varying gaps can be observed, especially in parts of the optic nerve more remote from the eyeball. The decreased staining of the cellular substance in the septal system, as well as the swollen, rounded nuclei result in long, continuous edematous stripes. Behind the eyeball, in the neighbourhood of the lamina cribrosa, glial cells show a proliferation in a columnar array. Especially in areas more remote from the eyeball, the myelin sheaths appear less strongly stained, sometimes slightly distorted, though usually their structure is entirely normal. In sections stained by hematoxyline-eosine, here and there paradoxical staining of nerve fibres can be seen, whereas in sections impregnated according to the *Bodian* technique axons or axonal groups exhibit an edematous loosening, fibrotization and dilatation. Swollen nerve fibers are located as a rule in the neighbourhood of the septum.

In the region of the lamina cribrosa, the impregnation pattern shows a less pronounced but characteristic axonal swelling. The lamina cribrosa itself closes hermetically between optic nerve and papilla. As a rule, alterations suggesting hydration or gap production cannot be seen, though in sections stained for collagen the grid structure of the lamina cribrosa appears to be slightly swollen. Since hydration and gaps regularly occur in the papilla of the optic nerve, the contrast between the lamina cribrosa and its neighbourhood becomes even more striking. Fibers of the papilla become loose and pushed apart. In low power views, the papillary loosening in the vicinity of the surface is even more conspicuous, due to the difference between the

compact lamina cribrosa and the less compact structure of more distal parts of the optic nerve. In serial sections, the pial funnels appear to be filled out. The edge fibers of the papilla appear to be loosened.

As a rule histological alterations can be observed also in the retina. Most conspicuous is the edema in the ganglionic cell layer. The edema belongs to the "interstitial" type: the entire "ground substance" becomes loose and the histological structure becomes honey-comblike. Cells are surrounded by smaller or larger holes. Also the external granular layer becomes loose and appears to be less strongly stained than the controls. Loose areas can be observed also in the layer of cones and rods, without any other structural alterations.

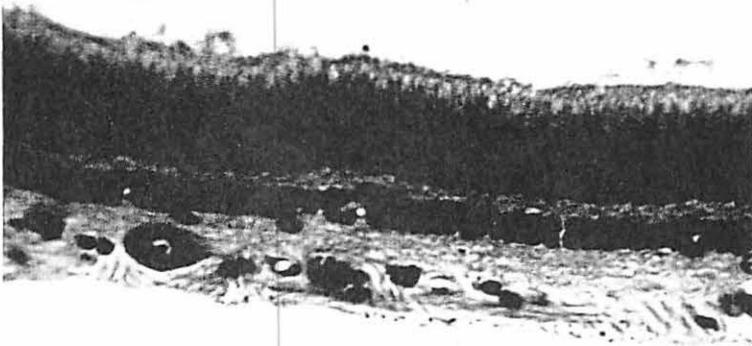


Fig. 1 Normal retina of the dog.

Most conspicuous is the retinal edema in the internal layers and parapapillary; alterations of varying grades can, however, be observed in areas more remote from the papilla and also in the entire width of the papilla; too; sometimes even these alterations are extremely severe. Edema of the retina can be observed even in those cases when the papilla does not show alterations. The histological structures of the chorioidea and the sclera are normal (Fig. 1 and 2).

Discussion

According to these studies it can be stated with certainty that the blockage of the cervical lymph circulation results in oedematous alterations of the optic nerve, the papilla and mainly, the retina.

Alterations in the optic nerve are striking in the impregnation pattern of the axons; slighter loosening and interfascicular glial proliferation can, however, also be observed.

From this point of view, more distal parts of the optic nerve, or, more properly, those in the vicinity of the chiasma, are usually more severely damaged than others, whereas in the neighbourhood of the eyeball the degree of alterations varies with intermingled entirely normal parts. The area before the lamina cribrosa is again usually edematous; the cell columns belonging to this area are proliferating.

The above distribution of the edematous alterations suggests that the papillary edema is not due to a simple propagation of the lymphostatic cerebral edema to the papilla. On the other hand also the fact appears to be proven that papillary edema is a consequence of alterations in the papilla itself and its neighbourhood; disturbances of this area are more or less independent of alterations in more remote areas of the optic nerve.

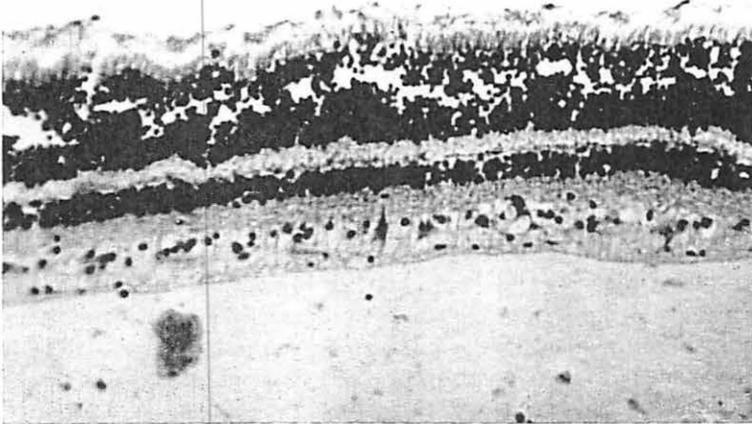


Fig. 2 Edematous retina of the dog after cervical lymphatic blockage.

In essence, the oedematous alterations of the optic nerve are identical with those of the brain of a lesser extent. The normal structure of the pia mater and the surface-near septal system is conspicuous, in contrast to the subpial edema of the cortex cerebri. In the leptomeningeal compartments, signs of an arachnoideal cell excitation can be observed.

The interpretation of papillary alterations is, due to the possibility of technical failures, very difficult. An entirely normal papilla may exhibit signs of prominence in an unfavourable histological section, whereas pathological alterations may be obscured by histological artifacts. Therefore, the utmost caution should be exerted when interpreting the microscopic slides.

One of the real characteristics of papillary prominence is the distance between lamina cribrosa and papillary surface, as measured in serial sections. Loosening of the fibers usually accompanies the prominence.

It should be noted that, even in the most severe cases, the degree of papillary prominence did not equal that seen in cases of volume displacement edema of the brain. The pattern observed after ligation of cervical lymphatics is similar to that seen after an experimental iodoacetate poisoning. In both cases, hydration and papillary alterations are of medium size; and, in both cases, papillary oedema is accompanied by edema of the retina, too.

In electron microscopic studies performed unit *Várkonyi* and *Csillik*, these results could be confirmed.

Summary

Lymph drainage plays an important part in the fluid circulation of the optic nerve and the retina: One week after cervical lymph blockage, oedema of the optic nerve and the retina can be seen.

M. Földi, M.D., 338 Goslar/Harz, Marienbader Weg 31

ABSTRACTS

Basic Science

BACH, J. F., J. DORMONT, M. DARDENNE, H. BALNER (Hôp. Necker, 151 rue de Sèvres, Clin. Néphrol. Paris, France, and Radiobiol. Inst. TNO, Rijswijk, The Netherlands): **In Vitro Rosette Inhibition by Antihuman Antilymphocyte Serum**. *Transplantation* 8 (1969), 265 or 280

A major difficulty in the clinical use of antihuman antilymphocyte serum (ALS) is the lack of an *in vitro* test whereby its immunosuppressive power can be evaluated. The authors correlate the results of an *in vitro* rosette inhibition test, with the time of survival of skin allografts in subhuman primates.

Normal unimmunized peripheral lymphocytes of 25 individuals from 43 volunteers, formed rosettes when brought into contact with sheep red blood cells (SRBC). A rosette is defined as the agglutination of more than 3 SRBC around a lymphocyte. The number of rosette forming cells varied from 4 to 26 per 1000 lymphocytes.

Incubation of lymphocytes with ALS before addition of SRBC, inhibited rosette formation. This inhibition is increased by the presence of guinea pig complement. The titres obtained with this test were always higher than those

of leukoagglutination and cytotoxicity obtained with the same ALS. Reasonable correlation was found with rosette inhibition and skin graft survival in chimpanzees ($P < 0.01$) and macaques ($r = 0.78$).

The authors have devised a test which may lead to a standardized method by means of which the immunosuppressive potency of ALS could be established *in vitro*.

S. V. Jooste

REICHEL, A. (Physiol. Inst. der Universität x22 Greifswald, Rubenowstr. 3): **Comparison of Protein Components between Lymph and Blood in Frog**. *Pflügers Arch. ges. Physiol.* 310 (1969), 167-181

The protein fractions in lymph and plasma of the frog species *Rana esculenta* and *Rana temporaria* were examined by agar-gel electrophoresis on microscope slides that had a format of 75 x 25 x 0.8 mm. The electrophoresis was done in a unit manufactured by Vitraton, in Dieren, Holland. Temperature was kept at 8 Centigrade and an electrical field of 30 mA and 200 volts was applied. Difco Agar Special Noble or Difco Bacto Agar (1 per cent) buffered with veronal sodium was used as the