COMMON PATHOLOGICAL BASIS OF THE NERVOUS OCULAR SYMPTOMS IN CHRONIC GLAUCOMA

A PRELIMINARY NOTE*

BY

G. CRISTINI

Clinica Oculistica Universitaria di Bologna. Director, Prof. Z. Di Marzio

CLINICALLY the main symptoms of chronic glaucoma (such as optic atrophy and ocular hypertension) appear to be independent, and the latter may be absent or may appear late. It is, therefore, desirable to be able to ascribe most of the symptoms of this disease to a common pathology.

The pathogenesis of hypertension is difficult to establish, but that of optic atrophy and the field changes associated with a pathological tissue change is easier. This special form of atrophy of the nerve fibres, known as " lacunar or cavernous degeneration ", affects not only the pre- and retro-laminary portion of the optic nerve, but also spreads along the trunk into the brain.

This cavernous atrophy is known to be independent of the increase of ocular tension, being due to a trophic disturbance in the fibre. Duke-Elder (1940) thinks it to be an ischaemia due to a sclerosis of the nutritional vessels, and Wolff (1947) thinks it results from a reduction of blood flow. As the nerve fibre is the most differentiated, it is the first to be modified and to disappear.

The histo-pathological findings are not always in agreement, and it is not possible to say whether characteristic vascular alterations are present in glaucomatous atrophy. According to Elschnig (1928), the reduction of the number of capillaries distinguishes the glaucomatous from other forms of nervous atrophy. The meshes appear interrupted and the individual lumina are often obliterated. Loewenstein (1945) tried to correlate the findings of nervous atrophy in glaucoma with the histo-pathological vascular findings, and frequently found a thrombotic occlusion of the smallest vessels.

The purpose of this research, therefore, was to investigate the nature of the vascular alteration of the nerve fibre in glaucoma.

MATERIAL AND TECHNIQUE

An examination was made of forty eyes enucleated in a very advanced phase of the disease, where an ophthalmoscopic picture of glaucomatous atrophy was present, cases of haemorrhagic glaucoma being excluded. After being opened at the equator and fixed in a 10 per cent. formalin solution, thirty eyes were embedded in paraffin and the sections stained by the usual methods. Sections of the remaining ten freshly enucleated eyes were treated with the object of examining the capillary circulation in the optic nerve, by Pickworth's method, which is based on the property of benzidine to reveal very small quantities of haematic pigment, which becomes a deep red colour. This method seemed the best to reveal the extent of and spaces in the capillary network in glaucomatous atrophy ; other nerve sections of normal old people were prepared as controls.

The ten eyes were opened near the optic nerve and the small posterior cap containing the nerve was fixed for two days in a saturated solution of formalin, salt, and sugar (watery solution of kitchen-salt 40 ml.; watery solution of sugar 40 ml. ; formalin 10 ml.). The pieces were cut with a freezing microtome without rinsing into sections of 200 microns. These were rapidly rinsed in water and passed through a solution of sodium nitro-prusside and benzidine in the thermostat for about 2 hours (watery solution sodium nitro-prusside 0·1 per cent., 4 parts, added to 1 part 0·25 solution benzidine with 2 per cent. acetic acid in distilled water). They were again rinsed in water and passed through 0·5 per cent. hydrogen peroxide in the thermostat till they took on a blue colour. They were again rinsed in water, dehydrated in 90 per cent. absolute alcohol, cleared in xylene, and embedded in balsam.

Observations.—In microscopic sections prepared with ordinary stains, no pathological vascular picture differing from that normally found in old age can be observed. I found a thickening of the intima, and sometimes of the adventitia, but no real restriction and obliteration of the lumen. In most cases the difference between the nervous parenchymal and the vascular findings is striking.

In sections where the benzidine reaction was employed, a marked difference between them and the controls was evident. The number of small vessels was conspicuously reduced ; the meshes of the capillary network fragmented, and the individual capillary lumina obliterated, so that a diminution in the range of the capillary circulatory bed becomes obvious (Figs 1, 2, 3, and 4). This reduction of the number of capillaries is particularly severe in the laminary region (Figs 1 and 2), and in some cases in the peripapillar choroid also.

A similar change in the capillary network, though in a lesser degree, is encountered in the extra-ocular portion of the optic nerve. These histo-pathological findings do not explain the lesion of the capillary segment peculiar to glaucomatous atrophy. One can but assert that the reduction of the number of capillaries seems to be independent of the increase of tension, since it is also present in the extra-ocular portion of the optic nerve. These findings do, however, confirm the observations of Elschnig who classified this reduction of the nervous capillary bed as the essential characteristic of glaucomatous atrophy.

DISCUSSION

We may now proceed to demonstrate that this vascular alteration is the cause of the two main optic-nerve changes : the lacunar or cavernous degeneration of the nerve fibres, and the bending and
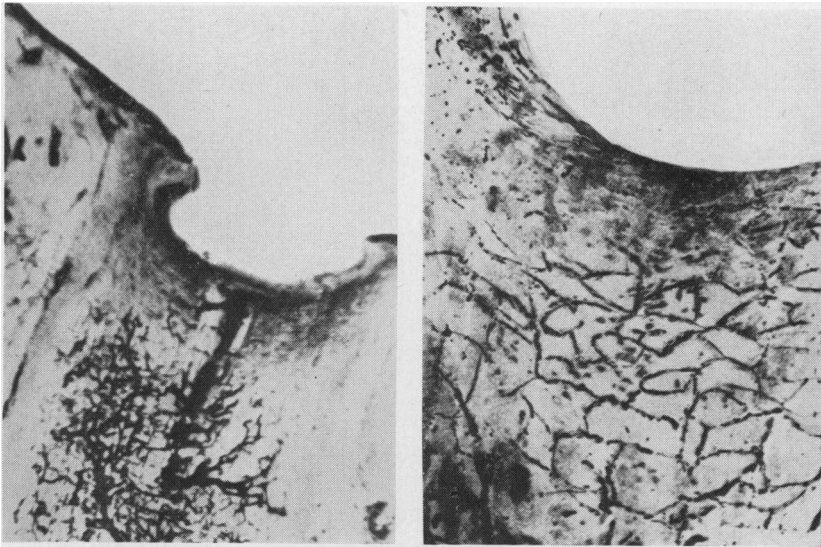
FIGS 1 and 2.—In glaucomatous nervous atrophies the number of blood capillaries is reduced, the meshes of the network are fragmentary and the flow of blood irregular.
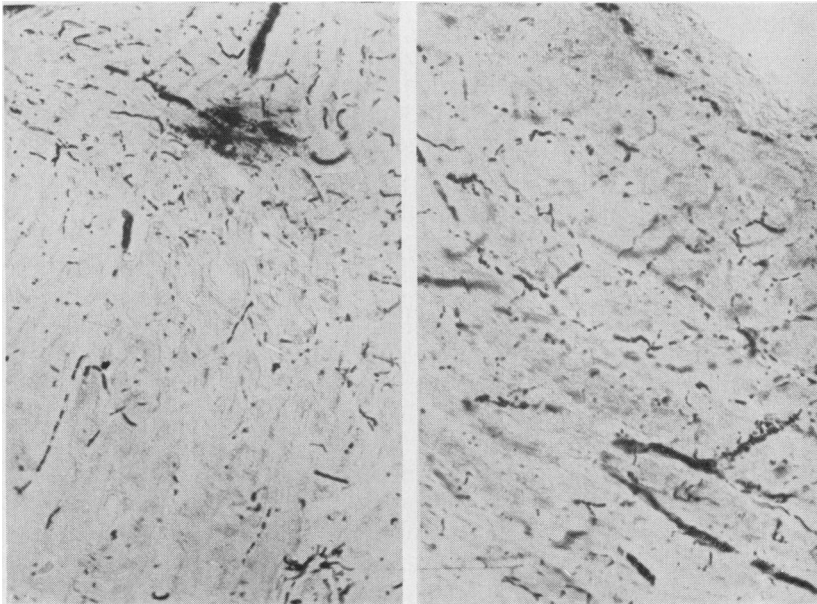

FIGS 3 and 4.—In chronic glaucoma a marked reduction in the number of blood capillaries is also noticed behind the laminary region, along the trunk of the optic nerve.
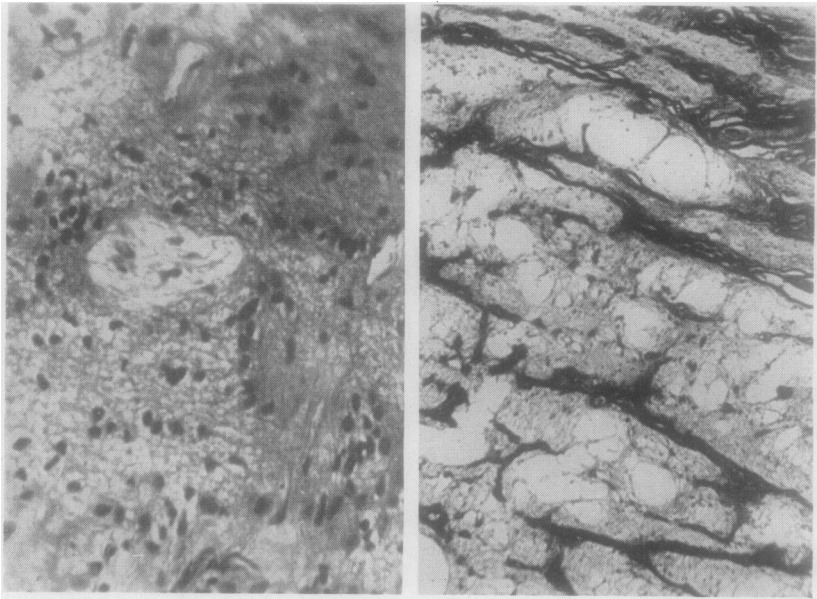
FIGS 5 and 6.—Sections of glaucomatous optic nerves at the entrance of
the central vessels, showing spongy and cavernous degenerations of the
nerve fibres.

fragmentation of the laminary scaffolding. The severity of the
atrophic papillary excavation depends on both changes ; the
essential problem is whether a reduction of the capillary bed may in
itself be sufficient to cause these changes in the nerve fibres and in
the laminary scaffolding.

LACUNAR DEGENERATION.—The spongy degeneration of Garrow and
Loewenstein (Fig. 5) directly precedes the appearance of Schnabel's
lacunar degeneration (Fig. 6). The latter makes the nerve fibres
appear skeletonized, because only the glial framework is left.
According to Schnabel (1905), no other atrophic process, apart from
the glaucomatous one, provides a better preparation of glia. Though
the histolytical action of the vitreous and the effect of the hyper-
tension on the nerve fibres of the prelaminary portion cannot be
wholly excluded, the reduction of the capillary bed alone can produce
lacunar degeneration. This degeneration can be brought about only
by an anoxaemic condition following chronic ischaemia, caused by
the reduction of the capillary network. Wolff (1947) concluded that
the reduction of the blood flow is essential for atrophy of nerve
fibres, independent of an increase in ocular tension. Owing to the
higher metabolism of the nerve fibres compared to that of the glia,
the former will be affected first and more severely. The various
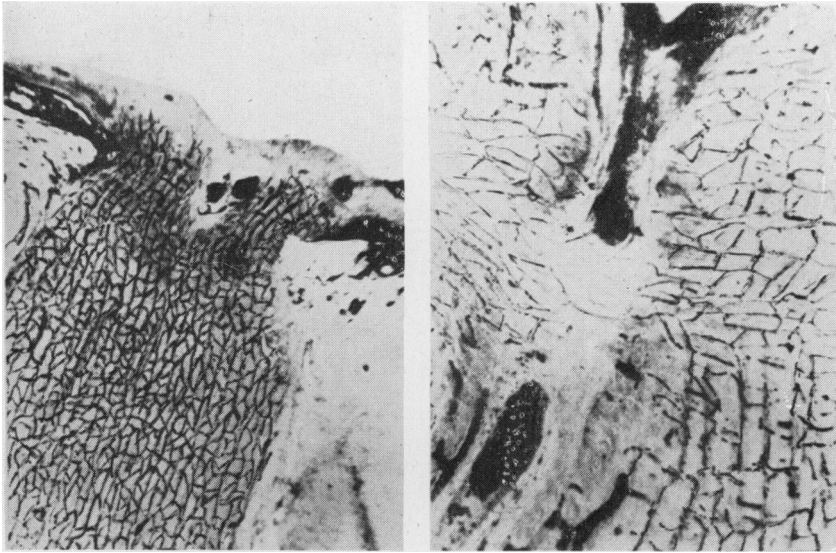
FIGS 7 and 8.—Capillary network (benzidine method) of the optic nerve in a normal individual; magnification of the capillary meshes in the laminary region.

stages of this anoxaemic condition of the nerve fibres may be followed microscopically : first Garrow and Loewenstein's nervous degeneration and later Schnabel's lacunar degeneration. The recognition of these histo-pathological stages enables us to exclude any others of a vascular nature. If an occlusion of vessels with larger lumina than those of the capillaries occurred, the malacic foci well known in cerebral pathology would be apparent. The active perifocal diapedesis in the collateral vessels would produce a malacic focus with ecchymotic borders.

BENDING AND FRAGMENTATION OF LAMINARY SCAFFOLDING.—It is theoretically impossible to exclude absolutely either Schnabel's hypothesis of primary cavernous retro-laminary degeneration or the hypothesis of the hypertensive effect. A reduction of the capillary network with a severe circulatory impairment at this level may also cause changes in the laminary tissue (Reid, 1937), and thus produce Schnabel's lacunæ between and behind the connective laminary scaffolding. Of the laminary scaffolding and the cause of its horizontal disposition, Wolfring (1872) wrote :

The difference between the lamina cribrosa and the sclera is that the former is constituted partly by vascular connective tissue belonging to the small vessels of the scleral circle and partly by the one belonging to the perineurium of the optic nerve.

He also pointed out the particular direction of these small vessels belonging to the scleral circle which force the laminary scaffolding into its characteristic horizontal architecture (Figs 7 and 8). A
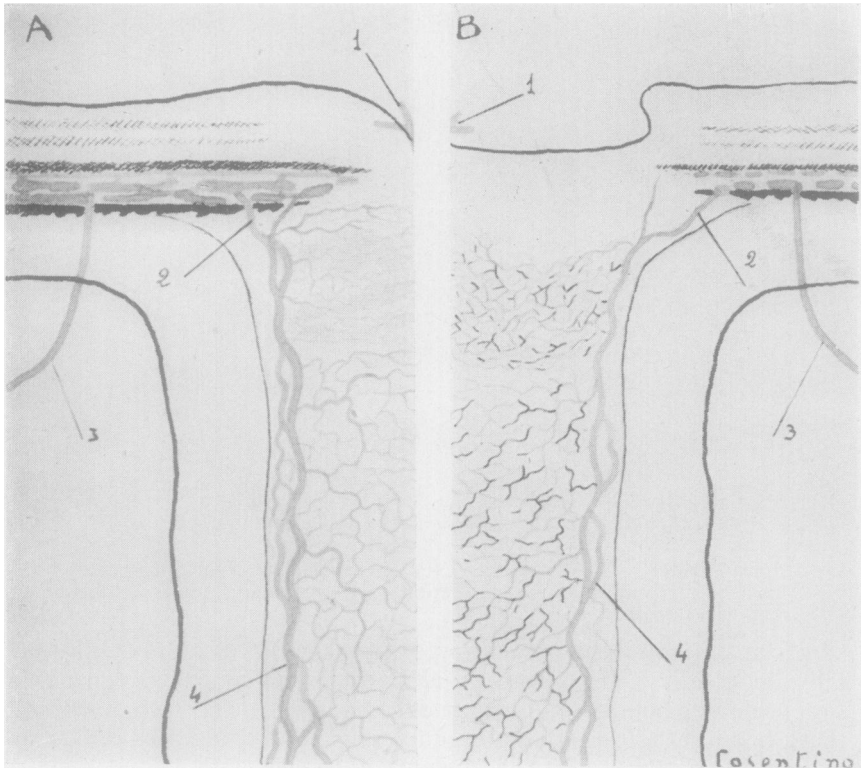
FIG. 9. (Partly schematic drawing).—Blood circulation: (A) in normal conditions; (B) in glaucoma. Note global reduction of the capillary bed, especially in the laminary region, and simultaneously in the choriocapillaris of the peri-papillary region. These regions both belong to arterial district (2).

  (1) Central artery of the retina. (2) Arteriole of the scleral circle.
  (3) Short posterior ciliary artery. (4) Arteria vaginalis.

reduction of the capillary bed in the laminary region must produce the typical changes noticed in glaucoma. Such an alteration developing on this pathological ground is accompanied, as was already mentioned, by obliteration of the choriocapillaris and atrophy of the peripapillary choroid. This is not surprising since the peripapillary choroid and the laminary region have a close physio-logical vascular solidarity, in that both belong to the same circulatory scleral district (Leber, 1872 ; Wolfring, 1872).

Clearly then the fibre degeneration, the laminary changes, and the glaucomatous halo, may be brought about by a common pathological vascular denominator : the reduction of the capillary bed (Figs 9 and 10). It is, however, more difficult to relate the various
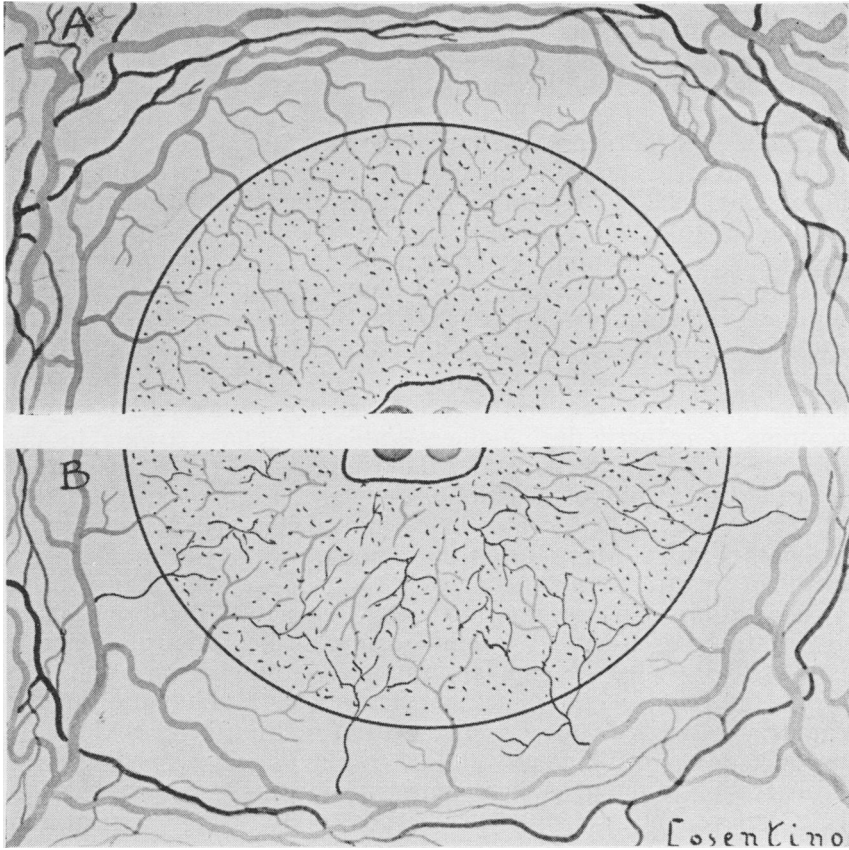
FIG. 10.   (Partly schematic drawing).—Blood circulation in the optic-nerve
head : (A) in normal conditions ; (B) in glaucoma.   Note afferent arterioles
reduced in number and capillary meshes interrupted and fragmentary.

campimetrical changes to this common pathological denominator,
because their semeiology and their relationship to papillary atrophy
have not so far been sufficiently elucidated. Traquair (1927)
affirmed papillary pallor to be more closely related to the severity of
the campimetrical changes than the excavation.   Clinical experience
enables me to confirm this observation and to add that not only
pallor but a glaucomatous halo can contribute to field changes.

Without reporting the different perimetrical and campimetrical
defects in glaucoma, modern workers have tried to unify the various
conceptions, admitting that the typical neuroscotomata (Roenne's
nasal step, the peripheral reduction of the infero- and supero-internal
nasal isopters, and Bjerrum's arcuate scotoma) develop through the

enlargement and fusion of the angioscotomata (Evans, 1938 ; Humblet and Weekers, 1948). Though the physiological nature of the angioscotomata has not been fully explained, a series of important experimental results is available. The researches of Evans and McFarland (1938) and of Bietti and de Gaspare (1950) show that the fluctuation in the density and extensions of the angioscotomata is related to the quantity of oxygen inspired. In conditions of anoxaemia, such as flight at high altitude, the angioscotomata show a tendency to extend and fuse. In glaucomatous patients a similar spontaneous fluctuation may be seen, which is unrelated to tensional variations. In earlier researches I observed that *X*-ray irradiation on the sympathetic medullary centres causes a reduction of the extension and density of the angioscotomata through an improved arterial " debit " in the optic nerve. This has been confirmed by Sanna (1950) ; it was demonstrated that the glaucomatous angioscotoma is reduced during the vasodilatory phase, owing to the inspiration of amylnitrite, and extends during the vaso-constrictory phase independently of variations in ocular tension.

The anoxaemia factor, mentioned above, may also play a part in the pathogenesis of the fusion of angioscotomata and the development of glaucomatous neuroscotomata. The fluctuations of a glaucomatous angioscotoma in the early stages of the disease may give warning of a circulatory claudication in the optic nerve, and it is easy to see why the papillary pallor and the glaucomatous halo are so important in campimetrical changes. An obliteration of the capillary network in the vascular district of the scleral circle must produce the known laminary and peripapillary changes and a severe degeneration of the nerve fibres in this region. The laminary region is, therefore, the probable seat of most of the campimetrical and perimetrical defects in glaucoma (Beauvieux, 1948).

It also seems possible to relate even the perimetrical defects to the same pathological denominator as optic atrophy and the glaucomatous halo. This conclusion, though not to be regarded as decisive, is worthy of consideration. The following two questions arise :

(1) May this common pathological denominator, found for the nervous symptoms, apply to glaucomatous hypertension ?

(2) What is the pathological nature of the lesion in the arteriolo-capillary segment ?

With regard to the first, I have at my disposal anatomo-pathological findings which enable me to reply in the affirmative. These conclusions were expressed at the XVI International Congress of Ophthalmology in London (1950). The most striking vascular changes in the uvea are those affecting the choriocapillaris. The

meshes of the network appear fragmented and the individual lumina of the capillaries are often obliterated. This change is the more marked, the more advanced the affection. In recent glaucomatous forms, areas with an increased number of capillaries showed dilated lumina alternately with those mentioned above, almost as if the former had assumed a compensatory function. Thus the most characteristic histo-pathological vascular change in the uvea of glaucomatous eyes consists in a global reduction of the capillary network.

The second question leads to the aetiological problem of glaucoma.

Previous studies undertaken in Bologna suggested that most of the glaucomatous symptoms are attributable to a change in the internal carotid or its cerebral branches. The same significance is attached to this change as to those of the corresponding large vascular trunks in other distal vascular syndromes. The researches of Leriche and Policard (1918; 1930; 1945) and of Ricker (1927) strongly suggest that isolated diseases of the arterio-capillary system are but a nosographic creation of our own, and that a close pathological relationship between the large arteries and the corresponding arteriolo-capillary districts exists in most vascular syndromes of this type.

SUMMARY

The opinion of Elschnig (1928) that the pathognomonic histo-pathological change of the optic nerve in glaucoma consists in a diminution of the number of small vessels (*i.e.*, by a global reduction of the capillary network) is confirmed. This change seems to be independent of the increase in ocular tension, because it is also encountered in the extra-ocular portion of the optic nerve. As was also pointed out by Wolff (1947), the consequence is a diminution in blood flow and, therewith, a state of chronic anoxaemia of the nerve fibre. This process is essential for the development of Schnabel's cavernous atrophy.

This change in the smallest vessels also constitutes the common pathological basis of the other nervous signs and symptoms in glaucoma, *e.g.*, laminary changes, glaucomatous halo, field defects.

A change in the capillary circulation, establishing itself chiefly in the area of the circle of Haller, produces both an atrophy of the peripapillary choroid, and sclerosis and degeneration in the laminary scaffolding, regarded by Wolfring as adventitious connective tissue.

An anoxaemic condition of the nerve fibres caused by claudication of the capillary blood circulation must determine the occurrence of neuroscotomata. Physio-pathological and clinical reasons lead one to think that the most probable site of perimetrical defects is the lamina.

In the uvea of glaucomatous patients, a global reduction of the

capillary network and morpho-structural changes are found in relation to a state of relative chronic ischaemia (this may be the pathological basis of the increase in ocular tension, depending upon the consequent modification of the haemodynamic regimen).

Most glaucomatous manifestations may be attributed to a common vascular pathology.

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