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PATHOGENESIS OF OEDEMA OF THE OPTIC DISC (PAPILLOEDEMA)*†

A PRELIMINARY REPORT

BY

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I HAVE used the term "oedema of the optic disc" instead of the conventional "papilloedema" because the term "papilloedema" originated from an erroneous impression that the normal optic disc was elevated like a papilla. Since the structure is usually flat, the term is a misnomer. It must, however, be conceded that there are considerable variations in the appearance of the disc, all of which may be "within physiological limits". For instance, it is not uncommon to encounter a pronounced prominence of the disc mainly at its upper and lower poles, accompanied by a forward curving of the branches of the central artery of the retina and the tributaries of the central vein of the retina. The so-called "pseudo-papilloedema", in which the entire disc is prominent and the edges obscured, typically (although not invariably) associated with a high degree of hypermetropia is more rare. It is also noteworthy that the so-called physiological depression may vary considerably in size or indeed may be entirely absent. Furthermore, although the colour of the normal disc is described as being pink, it may show relative pallor especially in high myopes and in elderly people.

von Graefe (1860) first described oedema of the optic disc in brain tumours and postulated that the oedema was due to pressure on the cavernous sinus by the tumour, producing congestion of the retinal veins. Since then, much work has been done on the subject but without any conclusive results. Most of the relevant literature is old and it seems the work was abandoned in frustration, because the problem had eluded solution. If one goes through the huge literature on the subject, one is often reminded of the words of Langley (1899):

> "Those who have occasion to enter into the depths of what is oddly, if generously, called the literature of a scientific subject, alone know the difficulty of emerging with an unsoured disposition. . . . . Much that he is forced to read consists of a record of defective experiments, confused statements of results, wearisome description of detail, and unnecessarily protracted discussion of unnecessary hypotheses."

Of nothing is this more true than of the pathogenesis of oedema of the optic disc. The literature on the subject is full of contradictory results and interpretations, resulting in complete confusion. In most of the old experiments, the techniques were so unnatural that similar conditions would never exist in man, while the anatomy of the experimental animals was so different from the human that the results obtained in the former had no relevance to the latter.

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I have tried to explore some of the fundamental factors concerning the subject which may help in its better understanding. To explore the whole subject is, perhaps, more than a lifetime's work.

Method

Before undertaking this study, certain preliminary problems had to be solved. First, it was essential to find a suitable experimental animal which would resemble man as closely as possible. Keeping this in view, the relevant anatomy of the optic nerve and its blood supply, and the vascular pattern of the entire orbit were explored in rhesus monkeys (Hayreh, 1964). These were found to be identical to the human pattern, with only minor differences (*vide infra*).

The second consideration was to devise a method which should simulate a rapidly growing intracranial space-occupying lesion in man. A balloon was introduced into the skull of the monkeys at different locations, *e.g.* in the posterior cranial fossa, and supratentorially in the occipital, temporal, and parietal lobes. A very fine rubber balloon was tied on one end of a metal cannula, to the other end of which was fitted a thick rubber cap so that the whole assembly was leak-proof. Under complete surgical asepsis, the smallest possible trephine hole was made in the skull in the respective regions, the dura incised, and the balloon gently introduced into the subdural space in a collapsed state (Fig. 1). During this procedure, the cerebrospinal fluid was usually freely leaking. The rubber cap end was placed in the subcutaneous tissue and the wound was closed in layers from the dura to the skin. The animal recovered well and the wound was allowed to heal completely. Then the balloon was progressively inflated by the addition of small quantities of a radio-opaque fluid at regular intervals through the subcutaneous rubber cap of the cannula, which could easily be felt under the skin; it was like giving an intravenous injection into a fat subcutaneous vein by a very fine needle. With this balloon and cannula *in situ*, the animal could be kept for months or years without the slightest inconvenience to either the animal or the experimenter. The presence of the balloon could not easily be made out externally. It entered the brain substance and slowly invaded the brain when it was inflated. Around the

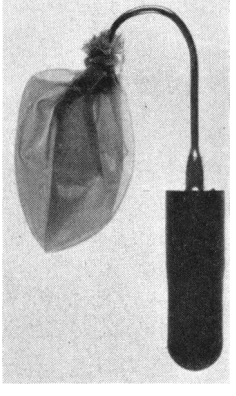


FIG. 1(*a*).—Balloon with cannula and rubber cap.

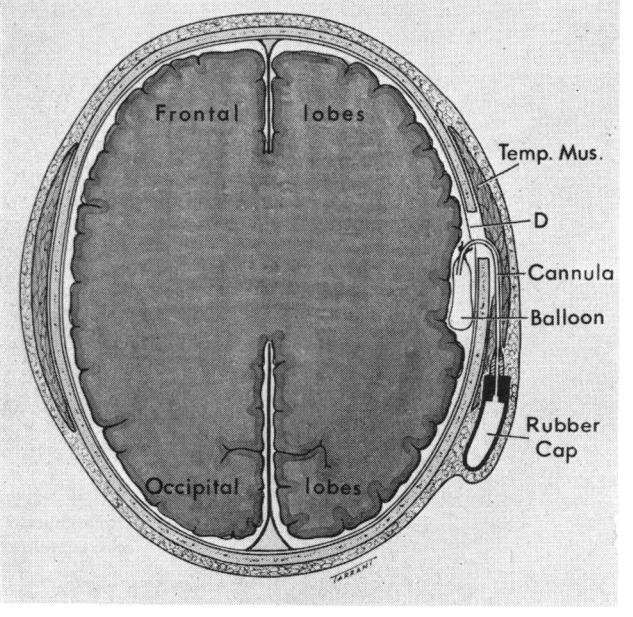


FIG. 1(*b*).—Schematic diagram showing the balloon and cannula *in situ* after its introduction.
D=Dura

cannula the dura and the superficial brain tissue were completely sealed and dense adhesions were seen between the brain and the dura at this site, allowing absolutely no leak of the cerebrospinal fluid from the cranial cavity. Thus the balloon exactly simulated a rapidly growing intracerebral or intracerebellar cyst. The site of this cyst and its rate of growth could be controlled at will.

Observations and Discussion

Infratentorial Balloons.—These entered the cerebellum posteriorly (Fig. 2).

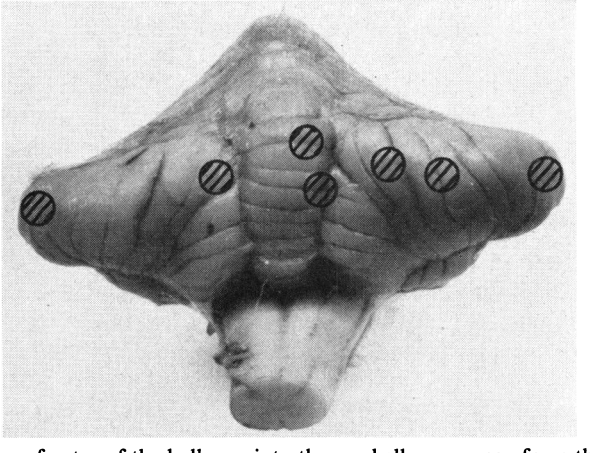
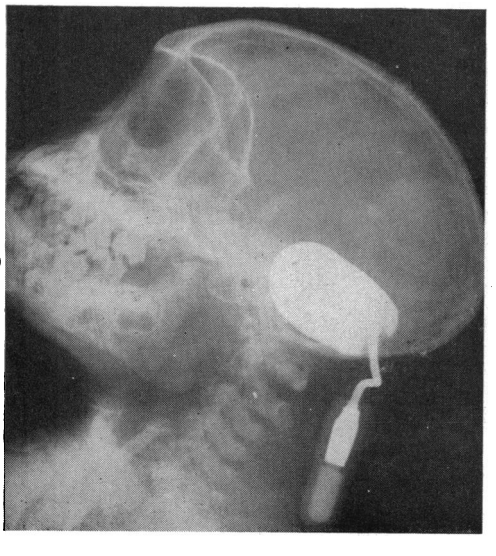
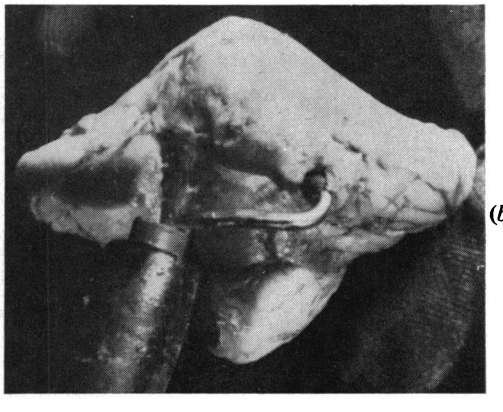


FIG. 2.—Various sites of entry of the balloons into the cerebellum, as seen from the posterior aspect.

In the experiments the area of the cerebellum destroyed by the balloon was its central part (Fig. 3), the lateral lobes being mostly spared, except in two instances so far, in which the balloon entered the lateral aspect of the cerebellum so that the greater part of the lateral lobe was destroyed including a little of the opposite side beyond the midline. As a rule the walls of the resulting cavities were formed by a thin shell of brain matter.

(*a*)





(*b*)

FIG. 3(*a*).—Skiagram (lateral view) of a midline posterior cranial fossa distended balloon.

(*b*) Cerebellum in the same animal, showing the cannula entering the substance of the cerebellum. The balloon is embedded in the substance of the cerebellum.

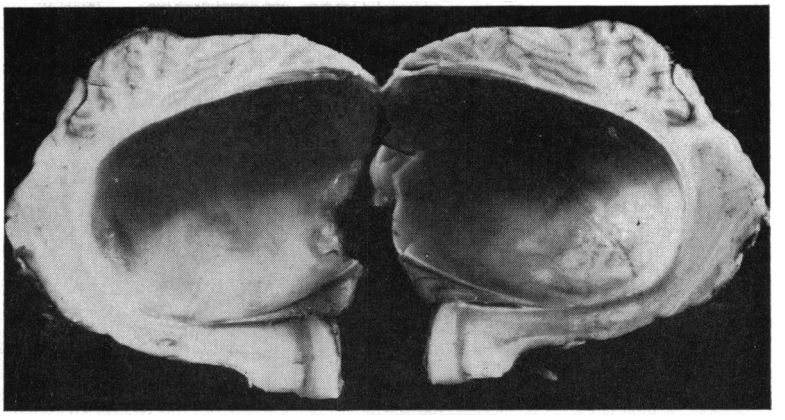
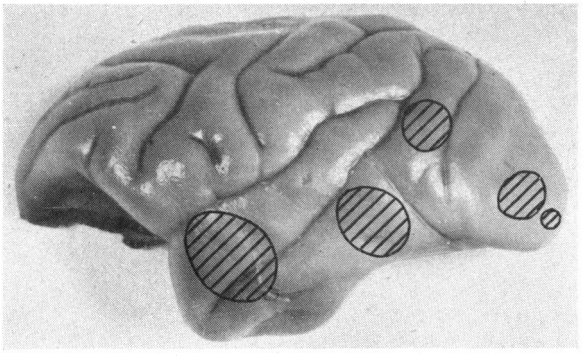


FIG. 3(*c*).—Midline sagittal section of the above cerebellum, showing the cavity of the balloon.



Supratentorial Balloons.—These entered the cerebral hemisphere on its supero-lateral surface as shown in Fig. 4.

FIG. 4.—Various sites of entry of the balloons into the cerebral hemispheres, as seen from the supero-lateral aspect.

Temporal Region.—The balloon lay in a cavity occupying most of the temporal and parietal lobes (Fig. 5 and Fig. 6 *a*, *b*, overleaf), and rarely small portions of the adjoining occipital and frontal lobes.

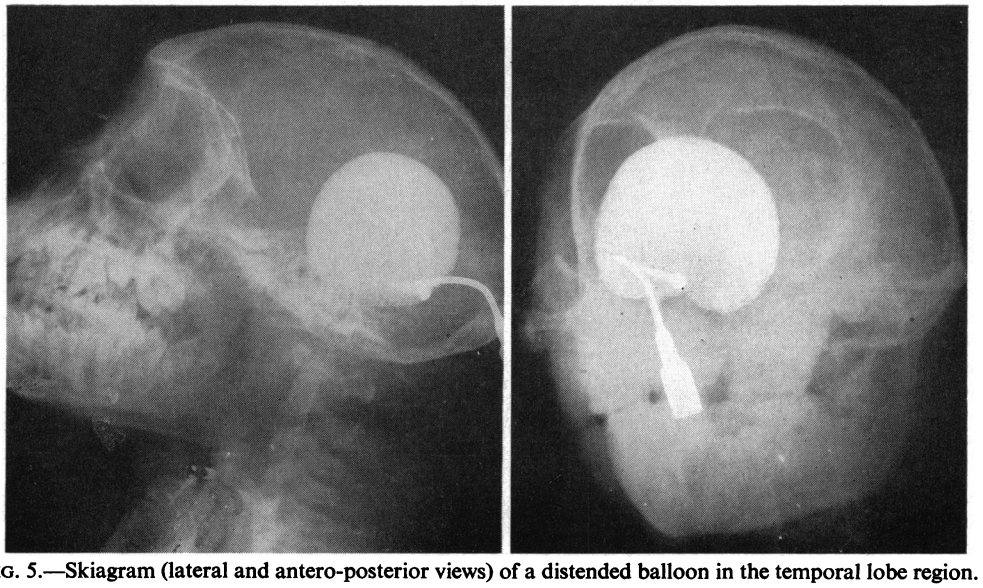
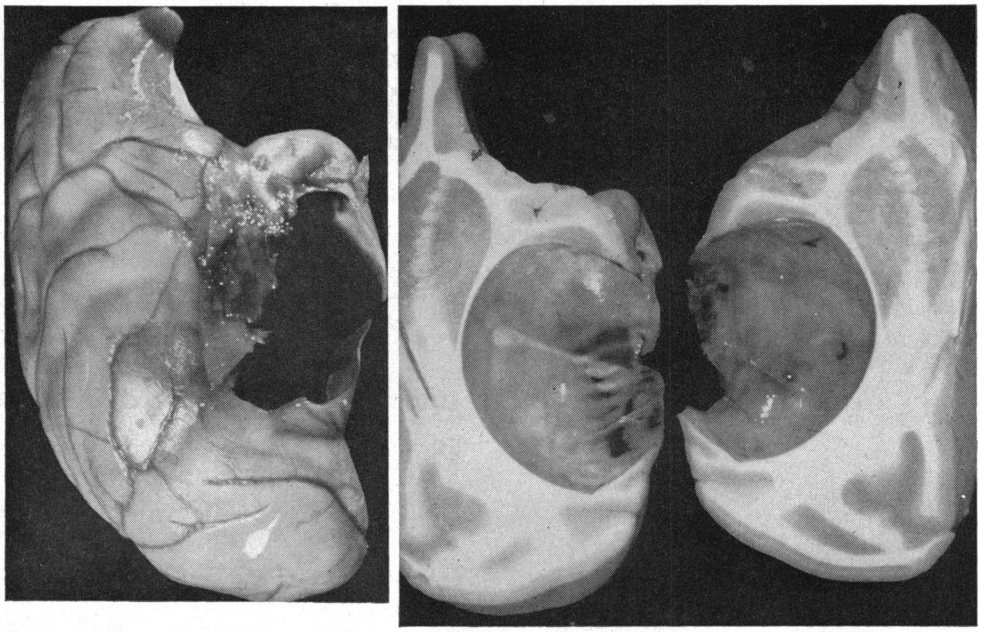


FIG. 5.—Skiagram (lateral and antero-posterior views) of a distended balloon in the temporal lobe region.



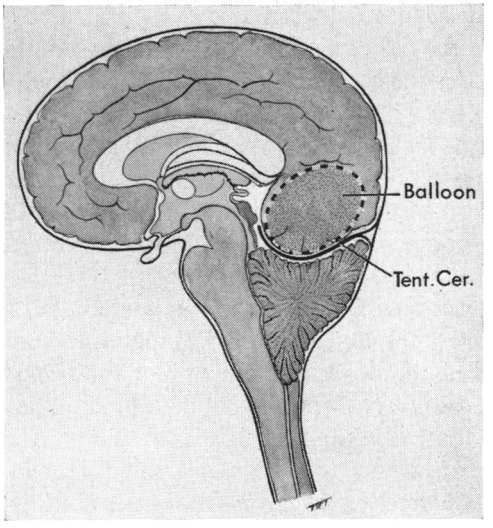
(*a*) (*b*)

FIG. 6.—Cavity of a temporal lobe balloon. (*a*) In cerebral hemisphere, (*b*) In horizontal section of the same.

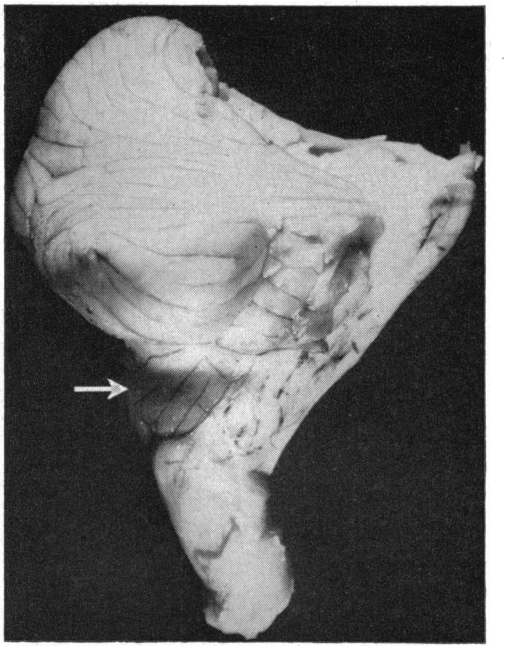
Occipital Region.—The balloon occupied most of the occipital lobe with a varying degree of encroachment on the adjoining temporal and parietal lobes.

Inflation of Balloons.—The maximum size attained varied according to the site and rate of growth of the balloon and the cranial capacity of the animal. In the cerebellar region, in small animals of about 3 kg., it could be inflated to about 4 to 6·5 ml., while in two big animals, weighing about 7 kg., a capacity of 6·2 and 12 ml. could be attained. In the latter two, the balloon occupied one half of the cerebellum while in the former it usually occupied the central part of the cerebellum. This may explain the difference in the size attainable. Among the supratentorial balloons, those in the temporal region could attain a size of 13 to 16·3 ml. in animals of 3 to 5 kg.; and in the occipital region 6·2 to 11 ml. in animals of 6 to 7 kg.

The balloons in the cerebellar region did not attain a large size because of the restricted space available in the posterior cranial fossa and early pressure on the vital medullary centres, particularly the respiratory centre; in the occipital lobe the degree of inflation was limited because of pressure on the tentorium cerebelli from above (Fig. 7, opposite), which in turn pressed the hind brain down into the foramen magnum (particularly the cerebellum), thus pressing on the medullary centres and causing respiratory failure. It was interesting to observe that in these animals the addition of about 0·75 to 1 ml. of fluid in the balloon would stop respiration and abolish the corneal reflex so that the animal lay virtually dead, except that the heart was still beating, whereas aspiration of that much fluid immediately revived the animal. Thus a critical balance existed. In contrast to these, because of the absence of such immediate complications, the balloons in the temporal region could be made to attain a greater size at a faster rate.



(*a*)



(*b*)

FIG. 7(*a*).—Schematic diagram showing pushing down of cerebellum into foramen magnum by a distended occipital lobe balloon.
Tent. Cer. = Tentorium cerebelli.
(*b*) Hind brain from a monkey with an occipital lobe balloon, showing herniation of the cerebellum into the foramen magnum with a marking of the foramen on the brain (arrow).

I have tried to work out an average rate of growth of the balloon per day in these animals:

Site of Balloon	Rate of Growth per Day (ml.)	Total Days of Balloon Growth
Temporal lobe	0·43 to 0·54	25–38
Occipital lobe	0·2 to 0·34	20–46
Cerebellum	0·11 to 0·21	30–51

The slower the growth of the balloon in a particular region, the longer the animal lived. In one of the cerebellar cases with growth of 0·04 ml. per day, the animal survived for 78 days.

Cerebrospinal Fluid Pressure Changes

The normal cerebrospinal fluid pressure (CSFP) was measured in all the cases before operation and fluctuated widely, being usually about 50–100 mm. of water. Frequent CSFP measurements were not done because it was not considered desirable to do so with a distended intracranial balloon and because of the dangers of repeated deep anaesthesia. Moreover, the CSFP also depended upon the level of anaesthesia which was not uniform in all the animals at different occasions and made a difference in their readings, so that a critical comparison was not possible. Whenever it was measured with marked fundus changes it was found to be raised. The CSFP seemed to depend on the rate of growth of the balloon rather than on its size, the more rapidly a balloon was expanded, the higher was the CSFP. On the other hand, when the balloon was not inflated for a long period even although the size of the

balloon was near its maximal limits, the CSFP started to fall and even returned to normal after some time. It was noticed that if the balloon size was then increased, the CSFP rose sharply because of the lack of compensation at this stage. The fundus changes also fluctuated in the same way. As the balloons were inflated, the CSFP was found to be 200–500 mm. of water in temporal lobe cases, while its maximum was 250 mm. of water in cerebellar cases. In occipital cases this was never attempted because of the greater tendency of the hind brain to herniate down in the foramen magnum. The higher pressures recorded in compression of the temporal lobe were presumably due to their rapid rate of inflation.

When the CSFP was high, fundus changes were invariably seen. In general, these tended to vary with the pressure although there were considerable differences. This, I feel, was most probably due to a variation in the degree of patency of the sheath of the optic nerve in the optic canal region in different animals (p. 537) leading to a difference in the ease of communication of the intracranial CSFP into the sheath, and a variation in individual response, in addition to other unknown factors. Although the CSFP was not frequently measured in every animal, the findings pointed towards its being high in every case at one time or the other.

In the temporal lobe balloons, where the CSFP was repeatedly measured at frequent intervals, it was observed that during the last stages the CSFP showed a fall to normal or even to a sub-normal level although the fundus changes were marked or even progressive in severity. This fall in pressure was usually quite sudden because at two subsequent recordings, at an interval of about 2–3 days, the CSFP fell from the maximum to a normal or sub-normal level. In these cases, no pressure could be recorded by cisternal puncture during the latter recording, although it had been possible earlier. At autopsy later on, the cerebellum showed a varying degree of herniation into the foramen magnum (Fig. 7), which explained the inability to record the CSFP at cisternal puncture (because of complete obliteration of the cerebello-medullary cistern), and a low pressure at the lumbar puncture (due to a block at the foramen magnum). Thus, in these, even although there was still high CSFP in the cranial cavity, as indicated by marked or even progressive fundus changes, the lumbar puncture showed a normal or even sub-normal pressure. Therefore a low CSFP reading in the lumbar region is likely to mislead, misrepresent, and confuse the entire issue in such cases, and is no index of the intracranial pressure during their last stages.

Fundus Changes

In the majority of animals, the fundus changes started to appear about 3 to 7 days after the introduction of the balloon but sometimes later. Commonly the ipsilateral side was the first to show these changes, particularly in the supratentorial cases, the other side being affected after a variable interval. Occasionally both sides showed changes simultaneously, particularly in the cerebellar cases. Invariably the first sign was hyperaemia of the optic disc, slight at first but slowly progressive. The hyperaemia did not affect the temporal sector of the disc (lying lateral to the temporal retinal vessels), through which the lamina cribrosa could be seen. The temporal sector was involved only in advanced cases, when the disc looked somewhat juicy and swollen, with obliteration of the physiological pit. In a few rare cases the changes did not progress beyond the stage of hyperaemia.

Striation of the nerve fibres on the retina around the optic disc appeared shortly after the hyperaemia (Fig. 8). The striation, whenever present, was particularly prominent near the upper and lower margins of the disc along the retinal vessels running up and down to the temporal side, a circumstance which accounted for the early blurring of these margins of the disc. Later on the striation involved other areas around the disc as well, depending upon the degree of change and the margins involved (Fig. 8).

(*a*)

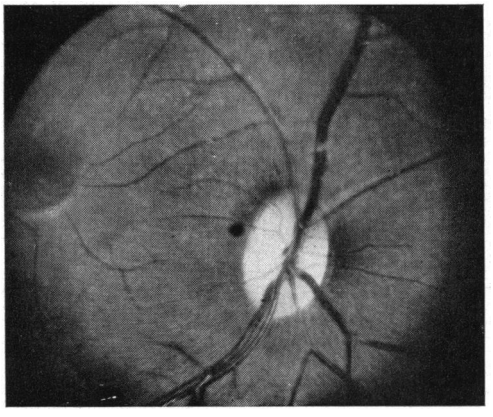


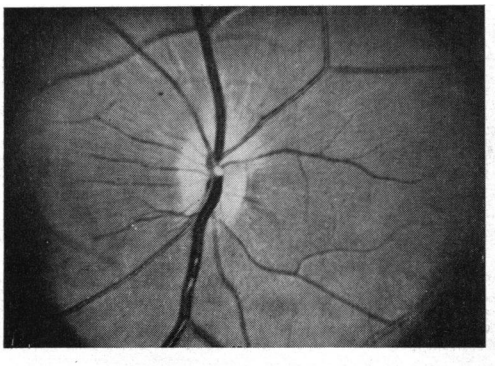
FIG. 8(*a*).—Normal fundus of rhesus monkey.

(*b-e*) Oedema of optic disc of varying degrees—mild in (*b*) and most marked in (*e*).

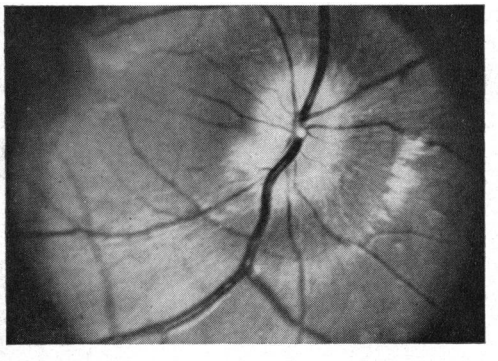
(*d*) Haemorrhages in the retina on the nasal side of the optic disc (arrow), with oedema of the disc.

Note that *b*, *c*, and *d* are all from the same eye.

(*b*)



(*c*)



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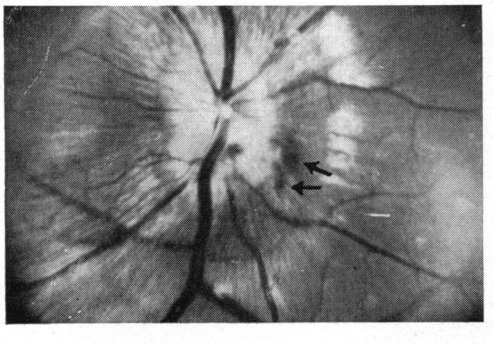
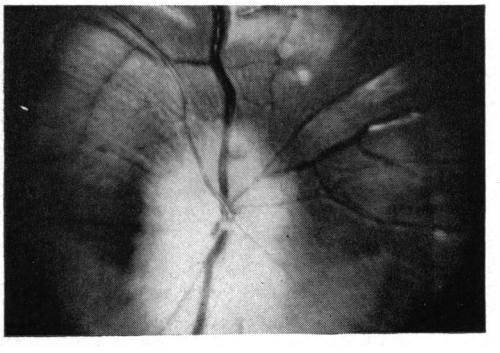


(*e*)



Blurring of the margins of the disc appeared as the changes progressed and after the hyperaemia had developed (Fig. 8). The upper and lower margins, particularly the latter, were involved first and most markedly; the temporal margin came next in sequence and degree; and the nasal margin was affected least and last or not at all. This is unlike man in whom the nasal margin is involved more than the temporal; only rarely was this sequence seen in monkeys. When the changes were advanced, the upper, lower, and temporal, and even the nasal margins were completely obliterated and nearly to the same extent (Fig. 8*e*), whereas in mild cases the upper and lower, or only the latter, were affected leaving the others clear and well defined (Fig. 8*b*). The blurring of the disc margins was due to striation of the nerve fibres extending for some distance onto the retina, so that the surrounding retina, instead of being darkly pigmented, became whitish and the disc had no clear margins (Fig. 8*e*).

Haemorrhages were sometimes seen in the retina adjoining the optic disc (Fig. 8*d*), being much more common in the cerebellar than in the supratentorial cases. These were small, superficial, and flame-shaped. They appeared on the same side as that on which the disc changes were most marked and generally after some violent straining by the animal. No such haemorrhages were seen in the animals with intracranial balloons, in which the fundus was almost normal, and their occurrence thus indicates a high retinal venous pressure.

In monkeys a mild swelling of the disc with filling of the central pit was seen only in very advanced cases in which a reddish, juicy-looking disc was seen to protrude forwards (Fig. 9, opposite). It was never so marked as to be of measurable height ophthalmoscopically.

No appreciable change in the size of the retinal veins or spontaneous venous pulsation was seen in these animals with oedema of the disc.

In one monkey, which had optic atrophy initially, no changes were seen on inflation of the balloon.

Cerebellar Group.—Fundus changes of mild to moderate degree always appeared on introduction of the balloon and even before its inflation. When this was started, in midline cases the changes progressed initially to a moderate degree but regressed to normal at the terminal stages. This regression seems to me to be due to two factors:

(*i*) The main rise in pressure occurs in the ventricles because of obliteration of the fourth ventricle by the pressure of the balloon (Fig. 3*c*), leading to marked internal hydrocephalus without any corresponding rise in the CSFP in the subarachnoid space.

(*ii*) An upward herniation of the cerebellum into the tentorial notch (Fig. 10, opposite) leads to its closure, and this entails a fall in the CSFP in the supratentorial space since little CSF can enter from beneath. The mechanism being comparable to the low CSFP on lumbar puncture in cases of cerebellar herniation into the foramen magnum (Fig. 7), as discussed above.

In contrast to these midline cerebellar cases, in one monkey in which the balloon was mainly unilateral, the fundus changes did not subside at a later stage but were maintained or even progressed. The fundus findings in the cerebellar group in monkeys, particularly those of midline cases, do not correspond with the common clinical experience in man.

Occipital Group.—The changes were always more marked than in the cerebellar group. In these, it was not possible to inflate the balloon rapidly because of pressure on the underlying cerebellum, which pushed the hind brain into the foramen magnum, resulting in

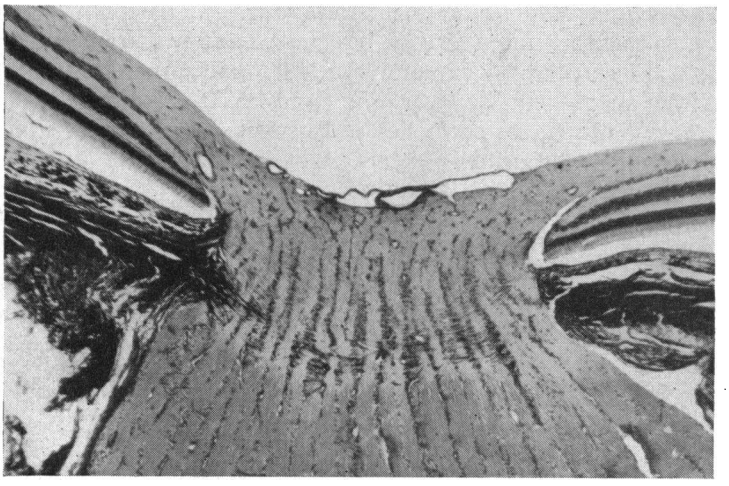
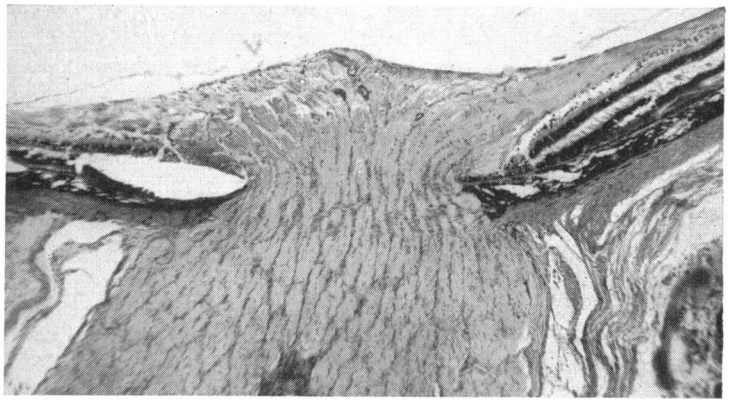


FIG. 9.—Longitudinal section of optic nervehead in the monkey

(*a*) Normal.



(*b*) With swelling of the disc. Fundus pictures of this eye are shown in Fig. 8*b*, *c*, *d*.

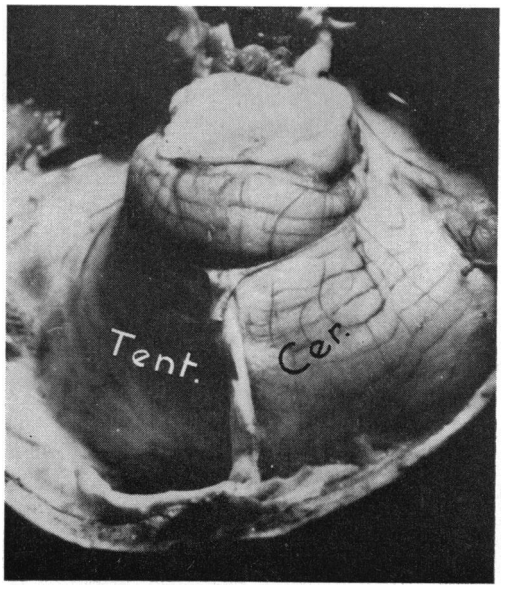


FIG. 10.—Herniation of cerebellum through the tentorial notch in a posterior cranial fossa balloon.

Tent. Cer.=Tentorium cerebelli.

pressure on the vital medullary centres and respiratory failure (Fig. 7). Therefore the balloon was inflated gradually, so that the fundus changes progressed slowly and were not so marked as when the balloon was located in the temporal lobe. If, on the other hand, the balloon was inflated comparatively quickly, the changes progressed rapidly but the animal soon died. Because of the above hazards, the cerebellar and occipital regions were not considered suitable sites for prolonged and safe experiments, and were discarded.

Temporal Lobe Group.—The changes were always more marked than in the previous groups and generally progressed more rapidly to their maximum because the balloon could be inflated much more rapidly and to a bigger size, without causing any immediate complication, although the terminal complications like those of the occipital region were seen at a much later stage. In these and the occipital group, the fundus changes mostly corresponded to the rate of the growth of the balloon, till the fundus changes reached their maximum. In the vast majority, the changes in the latter stages were well maintained but in a few cases regressed to a variable degree in spite of the growth of the balloon, particularly so on the contralateral side.

In the supratentorial group, the changes always occurred earlier and were more marked on the ipsilateral side. No such clear-cut distinction was seen in the cerebellar lesions.

It is interesting to note that in one animal, when the balloon was first introduced into the posterior cranial fossa, the post-operative reactionary changes in the fundus were equal on the two sides. This balloon had to be removed because the cannula broke. Later on, after the animal had recovered, a new balloon was introduced into the temporal lobe region, and the reactionary changes in the fundus were more marked on the ipsilateral side. Thus, in the same animal, the pattern of fundus changes varied with the location of the balloon.

On the whole, when the CSFP was high, the fundus was never normal but always showed changes. Similarly when the fundus changes were present, the CSFP was found to be high, the height varying directly with the degree of change. Thus a correlation existed between the changes in the fundus and the height of the CSFP in the cranial subarachnoid space, though there were individual variations. The raised intraventricular pressure, which is independent of that in the cranial subarachnoid space as in obstructive internal hydrocephalus, however, seemed to have no relationship to the fundus changes. Marked obstructive internal hydrocephalus was seen in some cases with normal CSFP on lumbar puncture and a normal fundus.

The fundus changes regressed under certain conditions.

(*i*) A decrease in the size of the balloon due to any reason caused a rapid regression of the changes.

(*ii*) When the size of the balloon was kept stationary for some length of time after it had been increased. In such cases the actual size of the balloon did not seem to matter.

(*iii*) In some cases when the rate of distension of the balloon was slowed considerably, the changes started to regress.

(*iv*) In midline cerebellar cases the changes started to regress during the last stages, as mentioned above (p. 530).

In some cases, however, it was difficult to explain the regression of fundus changes in the later stages despite a continuous growth of the balloon and normal vision. In supratentorial cases, this may have been due to a block at the tentorial notch caused by downwards herniation of the hippocampus through it and a marked distortion

and displacement of the midbrain. In addition to this, it may be due to a block in the outlet of the CSF from the ventricular system at the aqueduct in a distorted and displaced midbrain (Fig. 11).

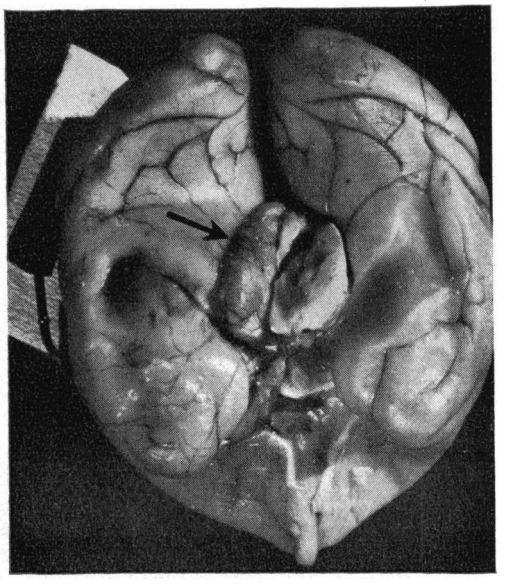


FIG. 11.—Inferior surface of cerebral hemispheres with a temporal lobe region balloon, showing hippocampal herniation into the tentorial notch (arrow), and displacement of the midbrain to the opposite side.

The regression of changes occurred in reverse order to their appearance.

It seems that a continuous growth of the intracranial space-occupying lesion, particularly the supratentorial lesion, causes a rise in the CSFP and its maintenance at a high level.

The post-operative reactionary changes in the fundus following the introduction of the balloon into the cranial cavity seem to be due to raised CSFP as a result of the reactionary oedema of the brain and the surrounding tissue caused by the surgical interference and the initial foreign body reaction to the balloon. The fundus changes started to regress within a week or two, if the balloon was not inflated meanwhile.

Effects of Opening the Optic Nerve Sheath on the Oedema of the Optic Disc

To investigate further the mechanism of the action of the raised CSFP in producing oedema of the optic disc, the optic nerve sheath was opened on the ipsilateral side by lateral orbitotomy (Fig. 12) when a balloon was inserted, usually into the temporal lobe. The ipsilateral side was chosen because of its proven involvement.

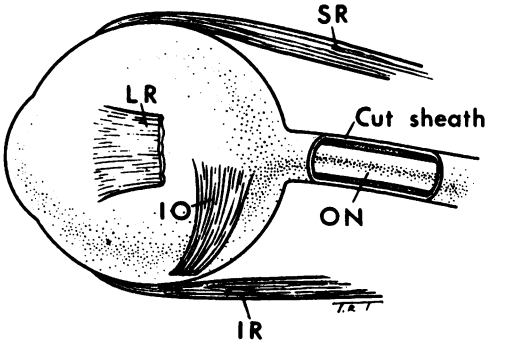


FIG. 12.—Schematic diagram, showing opened optic nerve sheath.

LR=Lateral rectus
IO=Inferior oblique
IR=Inferior rectus
ON=Optic nerve
SR=Superior rectus

In these cases, in contrast to the normal cases, practically no fundus changes were seen on the side with the opened sheath. The contralateral side showed changes, progressing with the increase in size of the balloon. These cases were divided into three groups (Table):

(*i*) The optic nerve sheath was opened on the ipsilateral side when the balloon had reached almost its maximum size and the fundus changes were prominent on both sides. After opening the sheath and further inflating the balloon, the fundus on the ipsilateral side regressed to nearly normal while on the contralateral side the changes progressed.

(*ii*) The balloons were introduced first and not inflated. The post-operative reactive changes in the fundus were more marked on the ipsilateral side than on the contralateral side. The fundus changes were allowed to regress to the normal on both sides. Then the sheath was opened on the side of the balloon, and after this inflation was started. Changes appeared in the fundus and progressed only on the contralateral side, little or no changes being seen in the ipsilateral fundus. Thus complete reversal of the oedema of the optic disc was brought about in the same animal on opening the sheath.

(*iii*) The optic nerve sheath was opened simultaneously with the introduction of the balloon; no post-operative reactionary fundus changes were seen on the ipsilateral side with the sheath opened, whereas changes of variable degree appeared on the contralateral side. Normally, one would have expected more changes on the ipsilateral side and fewer on the contralateral. In this third series, on inflating the balloons, no changes were seen on the side with the opened sheath, whereas changes were seen on the contralateral side, though comparatively less in some cases than usual, a circumstance which may be due to a leakage of the CSF at the site of the opened sheath acting as a safety mechanism to some extent. The CSF was also comparatively lower in cases with opened sheaths than those with intact sheaths.

TABLE

EFFECTS OF OPENING THE OPTIC NERVE SHEATH ON OEDEMA OF THE OPTIC DISC

Stage of Fundus Changes	Group I		Group II		Group III	
	Ipsi-lateral	Contra-lateral	Ipsi-lateral	Contra-lateral	Ipsi-lateral	Contra-lateral
Post-operative Reaction	+	+	+ +	+	−	+
At the Time of Opening the Sheath	+ +	+ +	−	−	−	−
Terminal	±	+ + ±	±	+ + ±	±	+ + ±

These observations seem to establish that *a rise in pressure in the optic nerve sheath was essential for the development of oedema of the disc and the associated changes. It thus seems highly probable that the oedema is mechanical in origin.*

The mechanical nature of the oedema of the optic disc solves the age-old mystery of the varying pattern of the oedema in hydrocephalus in infants. The usual cause of the hydrocephalus in infancy is due to a block either in the ventricular system or in the subarachnoid space in relation to the basal cisterns. The block may be as far

forward as the interpeduncular cistern. In these cases, therefore, the raised intracranial CSFP is not communicated to the optic nerve sheath, and this explains the absence of oedema of the optic disc. In contrast to this, oedema of the optic disc occurs in infants when the raised CSFP is due to an intracranial tumour or rarely to hypertrophy of the choroidal plexus resulting in overproduction of CSF. This is because in these two latter conditions the intracranial CSFP is communicated forward to the optic nerve sheath.

In monkeys, the difference in the reaction of the fundus on the two sides with raised intracranial tension, strongly suggests that the pressure in the different compartments of the cranial cavity, divided by the falx cerebri and the tentorium cerebelli, were not the same, particularly when the brain was displaced from its normal position.

In old monkeys, the initial post-operative reaction differed from that in young and adult monkeys. The aged group invariably gradually lapsed into a state of coma 2 to 4 days after the operation, but the others showed no such reaction. The fundus was normal during this coma. Complete recovery followed within 24 hours of administration of intravenous urea in all these animals. Thus the coma seems to be as a result of oedema of the brain resulting from the introduction of the balloon.

Ventricular Changes

In the cerebellar group, a moderate to marked distension of the lateral and third ventricles and of the aqueduct was seen because of the obliteration and distortion of the fourth ventricle by the balloon (Fig. 3*c*). In the supratentorial group, moderate distension of the contralateral lateral ventricle and the third ventricle was seen with obliteration of the aqueduct because of distortion of the midbrain by hippocampal herniation (Fig. 11). The fourth ventricle in these latter cases was more or less normal and the ipsilateral lateral ventricle was compressed and obliterated to a potential cavity in most of its extent by the pressure of the balloon.

Posterior Drainage of the Ocular Fluid Along the Optic Nerve and its Role in the Pathogenesis of Oedema of the Optic Disc

One of the theories of the pathogenesis of oedema of the optic disc regards the process as a stasis and oedema due to blockage of the tissue-fluid drainage from the eye along the optic nerve as a result of the raised intracranial tension. Such a flow of fluid has never been adequately demonstrated in the monkey or in man, and much ambiguity exists about the question. It was therefore considered important to investigate this flow, which was studied in rabbit, monkey, and man.

The major part of this investigation was done on rabbits by injecting various substances into the vitreous, *e.g.* Dextran, haemoglobin, nitroblue tetrazolium, and colloidol iron. The most conclusive results were obtained with colloidol iron, and most of the study was carried out with this. The iron was injected into one eye of the animal, into the retrolenticular space or near the equator of the eyeball in the vitreous. The animals were killed at intervals varying from 10 minutes to 72 hours.

The distribution of the colloidol iron in the optic nerve was very characteristic (Fig. 13). From the vitreous, it entered the nerve at the optic nervehead in the loose tissue surrounding the central retinal artery and travelled back in the perivascular space of the artery all the way. It accompanied the artery into the orbit, out of the optic nerve. In the nerve substance, the iron was seen in the septa of the anterior segment (*i.e.* the part of the nerve containing the central retinal artery), usually in the perivascular spaces of the small septal vessels. Most of it lodged near the central part of the nerve but sometimes it reached up to the pia. Immediately behind the anterior segment, it was seen in some cases in the septa, and nearly always in the pia on the inferior surface of the posterior part of the nerve, where a branch from the central retinal artery was seen to run. The iron was distributed perivascularly around this latter branch. In addition, the iron entered the optic nervehead from its vitreal surface for a short distance along the fine capillaries; no such penetration was seen in the retina anywhere in the eyeball but it was strictly localized to the nervehead.

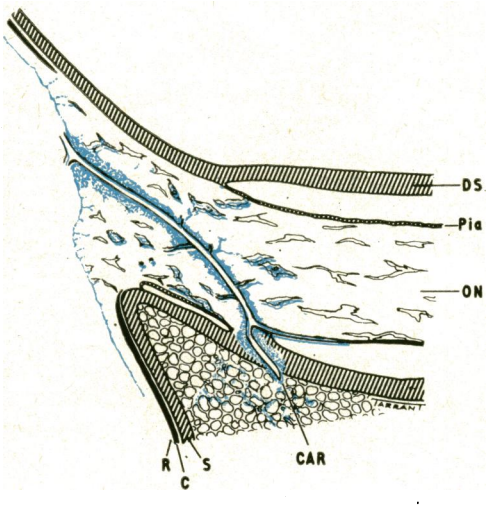


FIG. 13.—Schematic diagram, showing distribution of colloidol iron (blue) in optic nerve in the rabbit.

C=Choroid
CAR=Central artery of the retina
DS=Dural sheath
ON=Optic nerve
R=Retina
S=Sclera

The distribution of this iron in the nerve was a replica of the distribution of the central artery of the retina in the optic nerve and the two patterns were exactly similar. Therefore, the distribution of the iron in the optic nerve depended upon the distribution of the central retinal artery in that region. No central retinal vein was seen in the rabbits. At the site of penetration of the central retinal artery into the dura of the optic nerve sheath, colloidol iron was plainly seen lying in the dura surrounding the artery. Outside the nerve, in the orbit, the iron travelled for a very short distance with the central retinal artery but was mainly seen to be diffusely scattered in the intercellular spaces of the surrounding loose connective tissue. It may be assumed that it is then drained away by the tissue fluid channels of the orbit. The iron reached the nervehead in less than one hour and progressed outside the nerve in as little as 1¼ hrs in some specimens and in about 24 hours in all of them.

No connexion was seen between this perivascular space of the central retinal artery and the subarachnoid space of the nerve sheath. Therefore this ocular fluid and the CSF did not mix with one another, as has been thought by most previous workers.

An intracranial hypertension would lead to distension of the optic nerve sheath, so that the raised CSFP in the subarachnoid space could compress the perivascular space of the central retinal artery (through which the fluid from the eye flows into the orbit). This would lead to stasis and oedema of that part of the nerve which contained this ocular fluid, *i.e.* the whole of the anterior segment of the nerve with the

adjoining part of the posterior segment and the optic nervehead, without involving the retina. This seemed to explain very nicely the entire pathology of the oedema of the optic disc and its localization to the disc only, without involving the surrounding retina. But subsequent observations did not support this hypothesis, because no such flow of the fluid had been seen in the monkey and man. Moreover, when intracranial balloons were introduced (Fig. 14) into the rabbit and gradually inflated at different rates in different animals to simulate growing intracranial tumours, no definite case of swelling of the optic disc could be observed. Although the initial observations seemed very promising, subsequent work ruled out the possibility that the oedema of the optic disc was due to blockage of the tissue fluid drainage from the eye along the optic nerve.

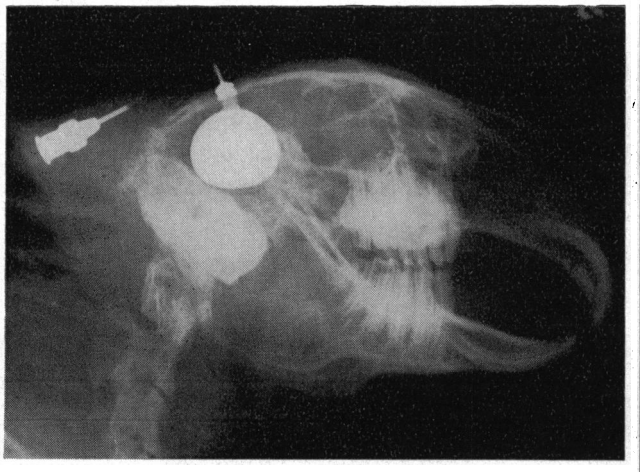


FIG. 14(*a*).—Skiagram (lateral view) of the rabbit skull with a distended balloon.

FIG. 14(*b*).—Rabbit brain, showing dorsal aspect of cerebral hemisphere with the site of entry of the balloon and adjoining bone and connective tissue.

Patency of the Optic Nerve Sheath in the Region of the Optic Canal

It has always been considered that a free communication exists between the cranial cavity and the optic nerve sheath. While studying the intracanalicular part of the ophthalmic artery in human beings (Hayreh and Dass, 1962), it was found that the optic nerve was markedly adherent to the surrounding optic nerve sheath in the region of the optic canal; this made me wonder how free a communication exists between the intra-orbital part of the nerve sheath and the cranial cavity. With this question in view, this communication was investigated in rabbit, monkey, and man.

In the rabbit, the nerve usually showed no adhesions in the canal and a free communication existed. In the monkey, a variable degree of adhesion was seen in the optic canal region but a communication between the two was made out by injection of dye in the cranial cavity. This communication was further investigated in sixty

human specimens by injecting a dye into the optic nerve sheath in the orbit and observing its flow into the cranial cavity. In all these a communication was seen, although its extent differed in different specimens. In some the communication was free but in others a very high pressure was required to force the fluid into the cranial cavity on injection. In all cases dense adhesions were seen in the optic canal region (Fig. 15), in some extensive but in others sparse, and in all particularly marked at the floor of the canal. The orbital part of the sheath was loose enough to be capable of marked distension, especially near the eyeball, but in the optic canal region the bony canal and the optic nerve fitted tightly and were fixed to each other by fibrous adhesions (Fig. 15). Therefore the CSF from the cranial cavity had to percolate through the narrow meshed trabecular meshwork formed by these adhesions to reach the orbital part of the sheath. I feel, therefore, that *the region of the optic canal plays a crucial role in the dynamics of conveying the CSFP of the cranial cavity into the optic nerve sheath*, both in monkey and in man, particularly in the latter. Unilateral or bilateral absence of oedema of the optic disc or variations in its degree with the level of CSFP, may be due to differences in the facility of communication from the cranial cavity forwards. The distortion of the optic nerves in intracranial pathology and intracranial hypertension and adhesions in the interpeduncular cistern may interfere with the communication of the intracranial pressure to the optic nerve sheath, leading to the many variations which may be observed.

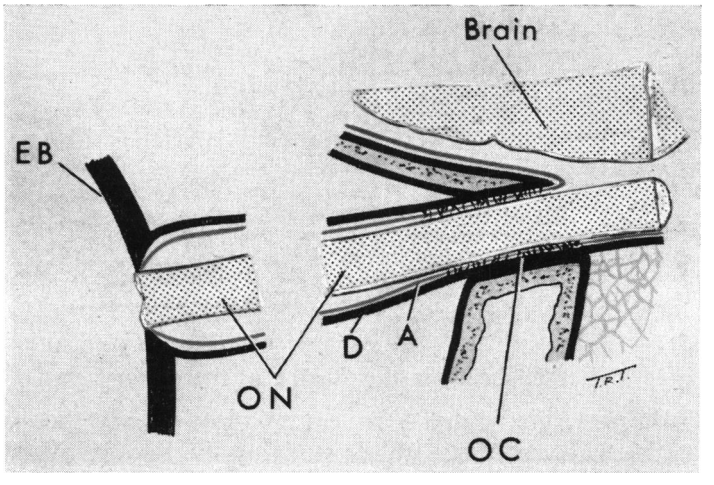


FIG. 15(*a*).—Schematic diagram, showing various regions of optic nerve sheath.

FIG. 15(*b*).—Longitudinal section of a normal human optic nerve, showing the sheath in its different parts. ×5. Explanatory diagram below.

FIG. 15(*c*).—Longitudinal section of monkey optic nerve in region of optic canal, showing a capillary subarachnoid space and fibrous bands connecting the optic nerve with the surrounding sheath. ×100.

A Arachnoid	FB Fibrous band	R Retina
C Choroid	OC Optic canal	S Sclera
D Dura	ON Optic nerve	SA Subarachnoid space
EB Eyeball	P Pia	

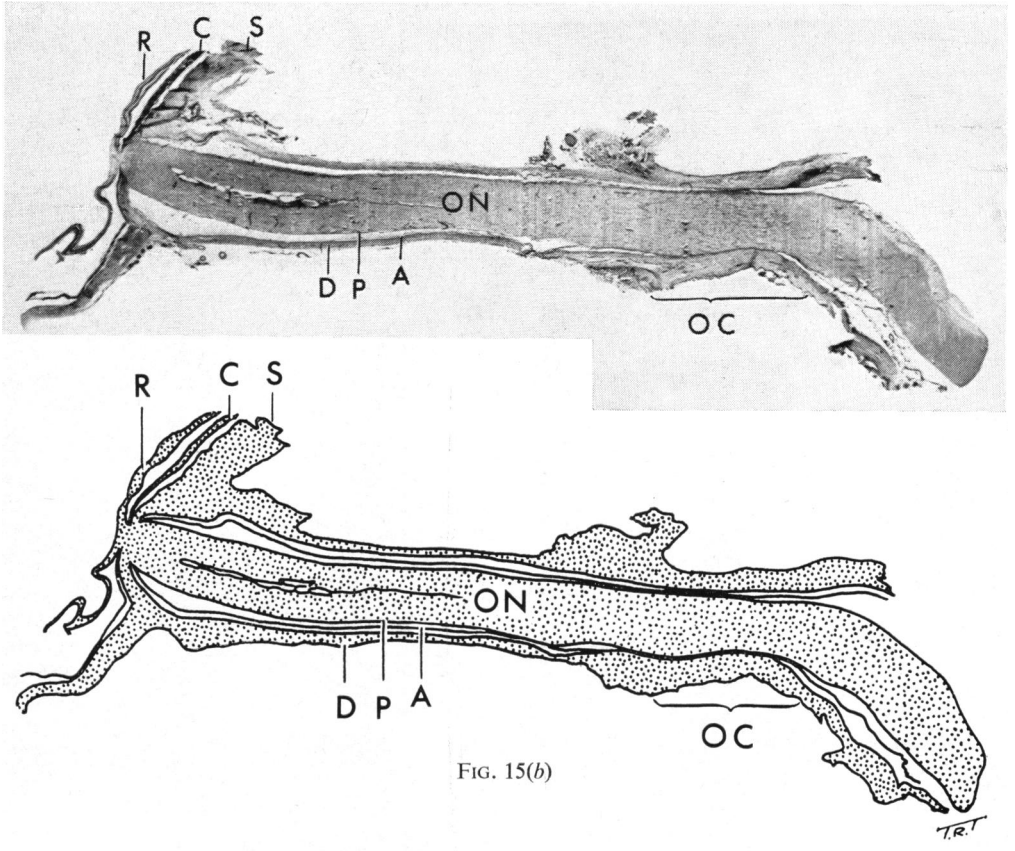


FIG. 15(*b*)

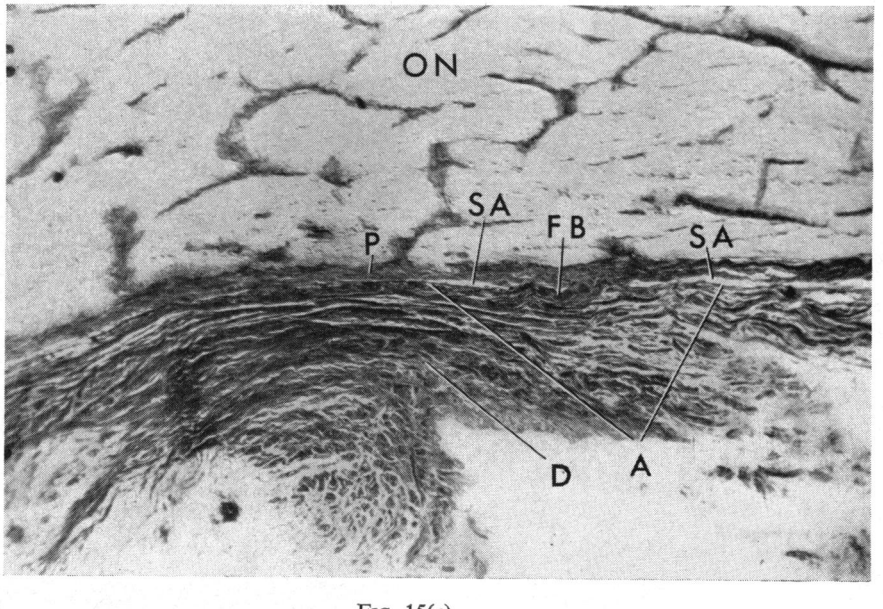


FIG. 15(*c*)

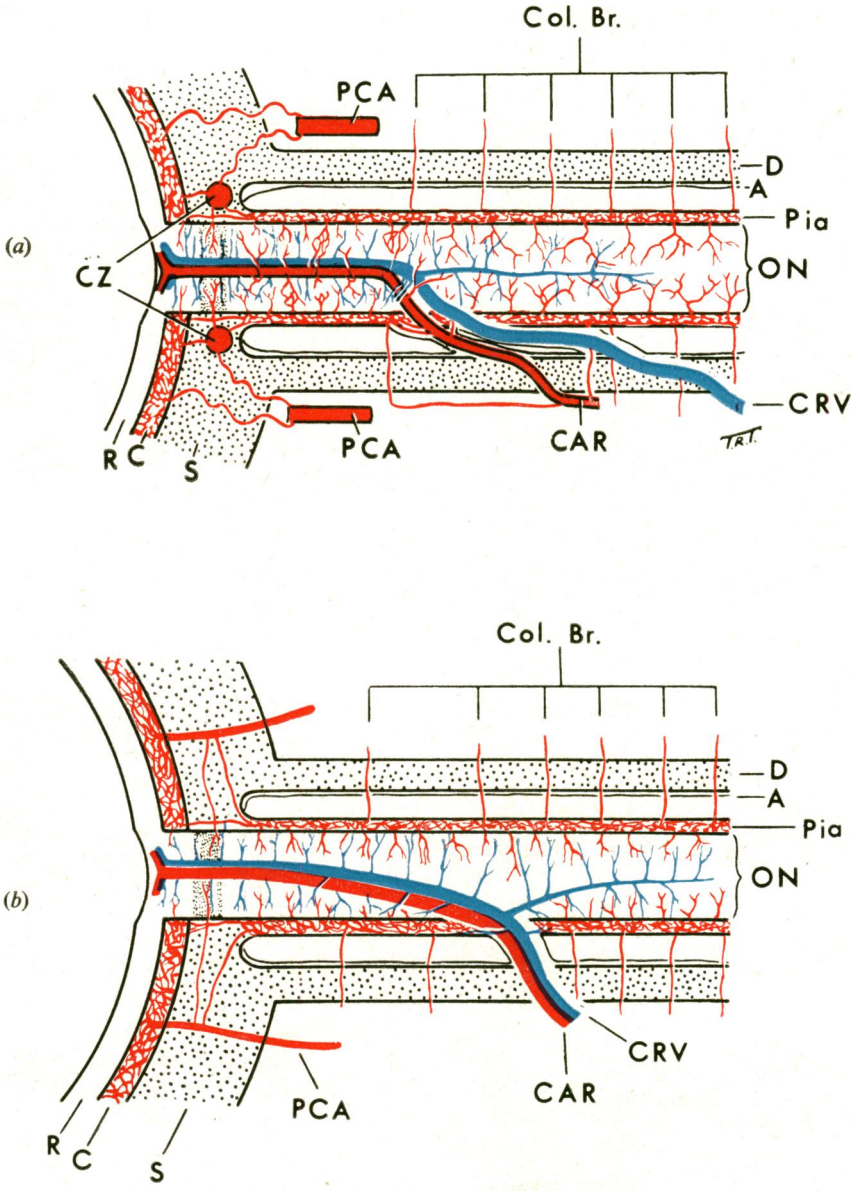


FIG. 16.—Blood supply of optic nerve.
(*a*) In human being.
(*b*) In rhesus monkey.

A	= Arachnoid	D	= Dura
C	= Choroid	ON	= Optic nerve
CAR	= Central artery of the retina	PCA	= Posterior ciliary arteries
Col. Br.	= Collateral branches of ophthalmic artery	R	= Retina
CRV	= Central retinal vein	S	= Sclera
CZ	= Circle of Zinn		

Vascular Supply of the Optic Nerve

Sometime ago I investigated the vascular pattern of the human optic nerve in over a hundred specimens (Hayreh, 1958, 1962, 1963a, 1963b; Singh and Dass, 1960a, 1960b), see Fig. 16*a*. In the rhesus monkey I found the arrangement shown in Fig. 16*b* (Hayreh, 1964). There are some obvious similarities and differences between the two. In some human specimens a similar type of arterial pattern was seen. It is worth noticing that the central retinal vein in the monkey passes quickly through the intervaginal space of the optic nerve sheath, whereas in man it generally runs a long course in this space. This means that a long segment of the vein is subjected to the CSFP in man while a very small segment is subjected to that pressure in the monkey.

Marked elevation of the optic disc and marked haemorrhages comparable to those in man were never seen in the monkeys, even in the most severe cases. This is, perhaps, due to this anatomical difference in the course of the vein. In oedema of the optic disc, no appreciable distension of the retinal veins was seen in the monkey as compared with man.

The rabbit has no central retinal vein and the retinal veins leave at the margin of the optic disc, so that none is seen in the subarachnoid space of the optic nerve sheath. This may be a reason for the absence of oedema of the optic disc in these animals when the intracranial tension is raised.

Oedema of the Optic Disc due to Forcing the Cerebrospinal Fluid along the Central Artery of the Retina

If any CSF were to be forced into the optic nerve and the disc along the central retinal artery when the intracranial tension is raised, it would be essential that the subarachnoid space of the optic nerve sheath should communicate with the perivascular space of the central retinal artery. No such communication has been observed in rabbit, monkey, or man. Therefore, in the absence of any communication between the two spaces, it is impossible to imagine any such forcing of the fluid into the optic nerve.

Oedema of the Optic Disc a Manifestation of the Oedema of the Brain

In all the monkeys in which oedema of the brain developed after operation and the animals responded dramatically to the intravenous injection of urea (*vide supra*), no oedema of the optic disc was seen. On histological examination of the material in the monkeys with oedema of the optic disc, no oedema of the optic disc was seen in the posterior part and in the region of the chiasma. Therefore, there is no evidence that oedema of the disc in cases of raised intracranial tension is due to descending oedema of the brain. This seems to be further confirmed by the fact that disappearance of oedema of the disc on opening the sheath was seen.

Oedema of the Optic Disc an Inflammatory Process

The old concept that the oedema of the optic disc is inflammatory in origin has been discarded long ago because of the absence of signs of inflammation in such cases; this was also confirmed in the present experimental study. Therefore to describe "oedema of the optic disc" as "optic neuritis" has no justification whatever.

Oedema of the Optic Disc associated with Raised Cerebrospinal Fluid Proteins

Oedema of the optic disc in cases of the Guillain-Barré syndrome, spinal neurofibromata, and small acoustic neuromata, *etc.*, has been reported in the literature. It is generally postulated that in such cases the CSF proteins are increased and that these block the drainage channels of the CSF, leading to raised intracranial tension and oedema of the optic disc. To investigate this in monkeys, their own serum was injected by cisternal puncture into the cerebello-medullary cistern, 2–3 ml. of the serum being injected at a time. In some the injection was done every day, and the CSF proteins showed a rise as the serum was being injected but immediately settled down on discontinuing the injection. In others it was injected on alternate days or at longer intervals, and no significant rise in the CSF proteins was noticed. None of the animals showed any rise in the CSFP, as measured by cisternal puncture. In spite of continuous injections, almost daily for more than 3 weeks in one animal, amounting to 40 ml. serum intracranially during this period, no change was seen in the level of the cerebrospinal fluid pressure and the appearance of the optic disc. It therefore seems improbable that, in these clinical conditions, a simple increase in the CSF proteins is responsible for the high CSFP and consequently for the oedema of the optic disc.

Conclusions

(1) Oedema of the optic disc has been produced experimentally in the rhesus monkey by introducing and progressively distending intracranial balloons, thus simulating a growing intracranial space-occupying lesion in man.

(2) The maximum size attained by the balloon depended upon its site, the rate of distension, and the size of the cranial cavity.

(3) The level of the cerebrospinal fluid pressure in the cranial subarachnoid space depended more upon the rate of distension of the balloon than upon its size. Therefore the more rapidly the balloon grew the higher was the cerebrospinal fluid pressure and the more marked the oedema of the optic disc.

(4) High intraventricular pressure in obstructive hydrocephalus was independent of the cerebrospinal fluid pressure in the cranial subarachnoid space and had no relationship with the oedema of the disc.

(5) The occurrence and course of the oedema of the optic disc depended upon the raised cerebrospinal fluid pressure in the cranial subarachnoid space and its successful transmission into the optic nerve sheath. The fundus change showed a definite relationship with the raised pressure. This is firmly established by the fact that, in such cases, if the optic nerve sheath was opened on one side to relieve the pressure unilaterally, no oedema of the optic disc developed on that side.

Similarly in hydrocephalus in infants the oedema is absent when the raised intracranial pressure is not transmitted forward on to the optic nerve sheath, whereas it is present when the pressure is conveyed forward.

(6) In the supratentorial group, the oedema of the optic disc generally appeared first on the ipsilateral side and was more marked on that side. No such phenomenon occurred in the midline cerebellar group.

(7) In the rabbit one could observe a definite flow of tissue fluid from the eye along the central retinal artery, through the optic nerve, and into the orbital tissues, but no such flow was seen in monkey or man.

(8) The cranial cavity communicates with the optic nerve sheath but the degree of communication in the region of the optic canal varies in different species, and in man in different individuals. This difference in ease of communication may be responsible for the variations in optic disc oedema seen in different individuals under similar conditions.

(9) No evidence was found to support the hypothesis that oedema of the optic disc is a manifestation of oedema of the brain.

(10) The segment of the central retinal vein in the subarachnoid space of the optic nerve sheath is very small in the monkey but extensive in man.

(11) The perivascular space of the central retinal artery in the optic nerve does not communicate with the subarachnoid space of the nerve sheath.

There is thus strong evidence that *in intracranial space-occupying lesions the raised cerebrospinal fluid pressure in the subarachnoid space is transmitted into the optic nerve sheath, where it presses upon the central retinal vein and produces oedema of the optic disc. Therefore, in such cases, it seems probable that the oedema is mechanical in origin.*

In conclusion, I am fully conscious of the fact that there remain many lacunae in our knowledge of the exact mechanism of oedema of the optic disc in various disorders, but this modest effort may help towards a better understanding of some of the aspects of this intricate and baffling subject and provide a stimulus for further work.

I owe a debt of gratitude to Sir Stewart Duke-Elder for his help, guidance, and encouragement. I am grateful to Prof. E. S. Perkins and Dr. J. Gloster for providing facilities for experimental work in their department and for their interest, and to Mr. T. Keith Lyle, Prof. N. Ashton, Prof. B. Jones, Dr. C. M. H. Pedler, Dr. C. N. Graymore, Dr. D. F. Cole, and Dr. D. M. Maurice for their help and interest. It is a pleasure to acknowledge with thanks the help and co-operation of Prof. R. E. M. Bowden of the Royal Free Hospital School of Medicine, London, Prof. D. V. Davies of St. Thomas's Hospital Medical School, London, and Prof. E. W. Walls of the Middlesex Hospital, Medical School, London, for providing facilities to investigate the optic nerve sheath in their departments; and that of Mr. G. H. MacNab, of the Hospital for Sick Children, Great Ormond Street, London, for his opinions on hydrocephalus in infants. My special thanks are due to Mr. J. Edwards, Mr. M. S. Bass, Miss Margaret Boyle, and Miss Hazel Jollife for technical assistance; to the Medical Illustration Department for the illustrations; to the animal technicians for their great care of the animals; to Miss B. Jenkins for secretarial help; to Mr. S. Downing for the cannulae; to the Department of Anatomy of the Royal Veterinary Hospital, London, for *x*-ray facilities; and to London Rubber Industries Ltd. and Parke, Davis and Co. for supplying the balloons and Phencylidine injections respectively free of cost. Finally, I am extremely grateful to Miss Eva Maria Harms of Salzhausen (Germany) for her painstaking help in translating some of the important German literature.

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