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COMMUNICATIONS

**A CONTRIBUTION TO THE PATHOLOGY OF
PAPILLOEDEMA**

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Introduction

It is generally held that in papilloedema the swelling does not affect the whole disc at once, but starts at one or other part of it. Some, following Horsley,¹ state that the swelling is first seen at the upper and inner quadrant, while others believe that it appears first at the upper or lower border of the disc. It is universally agreed, and Gowers² was especially insistent upon this point, that the inner (nasal) edge of the disc is affected before the outer (temporal). No satisfactory explanation of this special site of commencement of papilloedema has been advanced. Another point which appeared to us to call for explanation is the reason why in papilloedema, considering the theories of its causation most widely held, practically speaking, only the disc and its immediate neighbourhood should be considered to be affected.

The theory of the method of production of papilloedema most widely adopted in this country is that based on the work of Deyl,³ of Dupuy-Dutemps⁴ and of Paton and Holmes,⁵ and may be stated shortly as follows. The increased intracranial pressure is transmitted to the subarachnoid space round the optic nerve since this

space is continuous with the intracranial subarachnoid space (Schwalbe⁶). As they cross the subarachnoid space the central retinal vein and its accompanying lymphatic vessels are compressed with resultant dilatation of the retinal veins, oedema of the disc, and later, exudates and haemorrhages.

But the central retinal vein is an end vein, apart from a very slight anastomosis at the entrance of the optic nerve which is not to any extent comparable with the arterial circle of Haller, and we are therefore led to inquire why the whole of the retina drained by the

FIG. 1. $\times 105^*$

Transverse section of human optic nerve to show the central retinal vessels in the peri-optic subarachnoid space.

central vein should not be equally affected. A venous anastomosis of any considerable extent at the nerve head would evidently tend to carry away excess of fluid rather than hinder its passage. The same criticism would apply to the theory that attributes papilloedema to the raised intracranial pressure damming back the lymph stream which normally is said to flow from the eye along the optic nerve towards the chiasma. (Parinaud,⁷ Ulrich,⁸ Sourdille,⁹ Kamphers-stein,¹⁰ Rochon-Duvigneaud,¹¹ Liebrecht,¹² Behr¹³).

Schieck¹⁴ is of the opinion that the subarachnoid space around the optic nerve communicates directly with lymphatic spaces around the central retinal vessels so that any increase in intracranial pressure would result in the *cerebrospinal fluid* being forced into the optic nerve along the central retinal vessels causing all the phenomena of papilloedema. Thus the swelling of the nerve head, produced by a distension of the perivascular lymphatic sheaths, will first be seen

* All microphotographs have been reduced one-third in reproduction.

at the bottom of the optic cup, pushing forward the internal limiting membrane, and subsequently the swelling will be visible at the places where the large vessels cross the edge of the disc. Schieck's theory of the method of production of papilloedema would thus present an explanation for the onset of papilloedema at a certain definite part of the nerve head. But the direct continuity of the subarachnoid space with the perivascular lymphatics about the central retinal vessels has not been definitely established, and the statement that the lymphatics of the retina open into the subarachnoid space requires further consideration. Indeed it is doubtful if true lymphatic vessels exist in the retina (which is part of the central nervous system). Schmidt-Rimpler¹⁵ first suggested that it was actually the cerebrospinal fluid which got into the nerve and caused the swelling of the disc. Papilloedema would then be a sort of (rather inefficient) safety valve for the escape of cerebrospinal fluid in cases of increased intracranial pressure. Schmidt-Rimpler injected Berlin blue into the intracranial subarachnoid space of rabbits, dogs and calves, and subsequently found the dye in the lamina cribrosa. Leber¹⁶ and others repeated these experiments but could not find the dye in the nerve and concluded that in Schmidt-Rimpler's experiments the dye must have got into a blood vessel. (See Fig 5, cat). Furthermore, Schwalbe,⁶ in his classical experiments, found that it was not possible to inject the retinal lymphatic vessels from the subarachnoid space, whereas the dye would pass into these vessels if the syringe needle were placed *under the pia mater*. Schieck himself repeatedly injected dyes into the subarachnoid space of human eyes (removed post-mortem with a length of optic nerve attached), and found that when a *non-diffusible* dye was used the particles of dye did not leave the subarachnoid space. This worker believed, however, that the fluid part of the dye passes into the nerve, as evidenced by the oedema of the spaces around the vessels similar to that which he noted in cases of papilloedema. But oedema has always been the bugbear of the histo-pathologist, and it is well known that oedema may not be evident in a microscopic section of an organ where oedema has been observed during life and, *vice-versa*, the microscopic appearance of oedema in a normal tissue may be produced in the process of its histological preparation (imbedding oedema). In his later papers Schieck admits the possibility of this interpretation of his results, though in one case¹⁷ of a freshly excised human eye he claims to have got the dye (Prussian blue—turpentine mixture of Baum¹⁸) into the retinal lymphatics by injecting it into the subarachnoid space around the attached length of optic nerve. So far as we are aware this is the only case on record in which the retinal lymphatic vessels have been injected directly from the peri-optic subarachnoid space. If there were a direct communication between the subarachnoid

space and the retinal lymphatics it should be possible to inject a coloured dye (diffusible or non-diffusible) by this route into the nerve and eventually produce a coloured papilloedema the evolution of which could be observed with the ophthalmoscope. With this main object in view the present writers performed a series of injection experiments on living animals. During the course of the present work a number of interesting facts emerged which are recorded below.

Personal Observations

The animals used were dogs, cats and rabbits. They were anaesthetised with a chloroform-ether mixture and the anaesthesia maintained by means of urethane (one gram. per kilo. body weight) injected intra-peritoneally. A few drops of a one per-cent. solution of atropine were instilled into each conjunctival sac to dilate the pupils.

In our earlier experiments we used a needle and syringe and, while one of us injected the dye (Indian ink) into the subarachnoid space either through the posterior occipito-atlantal membrane or through the cranial dura mater after trephining the skull, the other examined the fundus oculi with an electric ophthalmoscope. In these experiments it was found that the dye always passed into the subarachnoid space around the optic nerve even if only light pressure were made on the syringe. No dye, however, appeared in the eye. These early experiments were made on three rabbits, five cats and one dog. This method of injection was considered unsatisfactory as it was not possible to judge the pressure under which the dye was injected and, further, the dye tended to escape around the entrance of the needle.

In a second series of experiments we excised the eyes of living animals including a length of optic nerve with its surrounding meningeal sheaths, and injected the dye (Indian ink) directly into the subarachnoid space by means of a needle and syringe. This series comprised four rabbits, two cats and one dog. The dye (non-diffusible) did not pass into the eye as determined both by ophthalmoscopic and by microscopic examination. When the dye was forced with great pressure into the subarachnoid space it burst through the side of the disc into the vitreous but no dye was found in the optic nerve on subsequent microscopic examination.

In our later work we adopted a method of injecting a dye into the cranial subarachnoid space which is a modification of that employed by von Schultén,¹⁹ and later by Cushing and Bordley,²⁰ in their attempts to produce papilloedema experimentally. A mid-line incision was made through the scalp down to the bone. A flap containing the temporal muscle was reflected to one or other side and a trephine opening, 10 mm. in diameter, was made over the

parietal eminence. The exposed circle of dura was excised (including the subdural layer of arachnoid) and a flow of cerebro-spinal fluid resulted. Into the trephine hole a tightly fitting metal cannula was screwed, and this was connected by means of rubber tubing and a Y-piece glass connection, to a mercury manometer and to a Woulfe bottle containing the dye. The Woulfe bottle was connected to a large bottle which in its turn was connected to the water tap.

At the beginning of the experiment the parts of the apparatus between the Woulfe bottle and the metal cannula were filled with the warmed injection fluid. Then by turning on the water tap the pressure in the apparatus could be raised to any desired amount and the dye forced into the cranial subarachnoid space. Further, through the cork of the large bottle passed a short piece of glass tubing to the upper end of which a short length of rubber tubing was attached. The rubber tubing was closed by a clip, removal of which immediately lowered the pressure in the whole apparatus. Thus, if the pressure were raised too high and the animal became distressed, removal of the clip was followed by drop in pressure and rapid revival of the animal. It was found that, unless the veins in the neck were tied, there was a variable and often rapid loss of injection fluid from the apparatus on raising the pressure, undoubtedly due to absorption from the subarachnoid space into the venous blood stream; but by regulating the flow from the water

FIG. 2.

Diagram of INJECTION APPARATUS.

tap the pressure could be raised or kept constant as desired. Cushing and Bordley controlled the pressure at which they injected the fluids by the gravity method, namely, by raising and lowering a flask containing the dye. The experiments of this nature that we conducted comprised those on one rabbit, two cats and twenty-one dogs. We employed as injection material, substances of two types:—

(1) Those which were in suspension and were unable to pass through an animal membrane (*i.e.*, were non-dialysable); and

(2) Those which were in solution and were able to pass through an animal membrane (*i.e.*, were dialysable).

Substances in the first class we refer to as *non-diffusible* while those in the second class we label *diffusible*. The non-diffusible substances we used were Prussian blue and Indian ink and the diffusible substances were methylene blue, eosin and Wasserblau.

Since the normal cerebrospinal fluid for all practical purposes is an extremely dilute aqueous solution (in fact, under normal conditions the nearest approach to water in the body), to prove that it is possible for cerebrospinal fluid to be forced into the retina and optic nerve if the intracranial pressure is raised, it seems only necessary to demonstrate that a diffusible dye can be forced in the living animal from the cranial subarachnoid space into the optic nerve. But there is a great difficulty in establishing this, because the diffusible dye soon diffuses into the blood stream and appears in the vessels of the eye. Thus, when we injected methylene blue into the cranial subarachnoid space the dye soon appeared in the retinal vessels and their change to a bright blue colour formed a striking picture when viewed with the ophthalmoscope. However, if the dye actually passed from the subarachnoid space into the optic nerve and retina, it ought eventually to produce a coloured papilloedema, if the hypothesis of Schieck and Schmidt-Rimpler is to be sustained. But this we failed to produce even though we raised the pressure in one case to 350 mm. of mercury (a pressure evidently incompatible with life). Another unsatisfactory feature concerning the employment of diffusible dyes for injection is that subsequent microscopic examination teaches us very little regarding the distribution of the dye during life. In some of our experiments we employed the method Weed²¹ used in his studies of the cerebrospinal fluid. The injection fluid is a mixture of potassium ferrocyanide and iron ammonium citrate, in equal parts, made up to a strength of one per cent. in distilled water. After about three hours injection, the eye is removed and placed immediately into a solution of ten per cent. of formalin to which hydrochloric acid has been added to a concentration of five per cent. Only in two cases (one dog and one rabbit) in which, however, the pressure had been raised to 270 mm. of mercury, were any Prussian blue particles found in the optic nerve and (a very small amount) in the disc. Such a pressure had,

however, killed the animal so that it is probable that in these cases we are dealing with post-mortem diffusion. A negative result in these cases would have been evidence of the impossibility of forcing even a soluble dye into the nerve, whereas the positive result obtained is not conclusive evidence of the presence of direct communication between the subarachnoid space and the interior of the nerve (lymphatic vessels or tissue spaces). Certainly in those cases where the pressure was kept at a level compatible with life (70 mm. of mercury) no Prussian blue particles were observed, on subsequent microscopic examination, either in the nerve or in the disc.

The *non-diffusible* dye that we employed most frequently was Prussian blue, prepared immediately before the experiment by mixing equivalent amounts of potassium ferrocyanide and ferric chloride solutions, in this manner obtaining the finest particles of Prussian blue in suspension for injection. Using this injection fluid we found that, at pressures compatible with life (60 to 70 mm. of mercury), no blue colour appeared in the disc when viewed with the ophthalmoscope, nor were any Prussian blue particles seen on microscopic examination either in the optic nerve or in the disc. In some cases we raised the pressure to 270 mm. of mercury, and in one of these the particles were seen with the naked eye circulating in the episcleral blood vessels just beyond the edge of the cornea. In most of these cases the Prussian blue particles were found, on microscopic examination, in the choroidal vessels but not in the supra-choroidal space. In one case only (cat) a very minute quantity of the Prussian blue particles was seen, on microscopic study, in the optic disc, but they were contained in definite small vessels (apparently venules). (Figs. 5 and 6.) The presence of the particles of Prussian blue in the vessels is no doubt to be explained by the probability that the greatly increased intracranial pressure, in distending the subarachnoid space around the optic nerve, produces a rupture of some of the vascular trabeculae crossing this space. The Prussian blue particles would then pass into the torn vessels and thence into the choroidal vessels. Adamkiewicz²² similarly found the dye in the choroidal veins in the rabbit, and concluded that distension of the choroidal veins was an accompaniment in clinical cases of raised intracranial pressure. However, it must be noted that the pressure employed in our experiments in those cases in which the particles of Prussian blue appeared in the veins was incompatible with life.

The effects of injecting fluids under pressure into the intracranial subarachnoid space may be considered under the following headings:—

1. Proptosis.
2. "Chemosis."
3. Dripping of fluid from the nose.
4. ? Papilloedema.

Proptosis.—Bilateral proptosis was observed in all the experiments in which a dye was injected into the intracranial subarachnoid space. It was due to oedema of the orbital tissues, as was shown by dividing the conjunctiva and ocular muscles and drawing the eyeball forwards thus exposing the retro-ocular orbital tissues (Fig. 7). In those experiments in which the pressure was kept about 70 mm. of mercury, the oedema fluid was found to be coloured when a diffusible dye was used and colourless with non-diffusible

FIG. 7.

Dog's eye drawn forward by dividing conjunctiva and ocular muscles to show retro-ocular oedema.

dyes. If the pressure was greatly raised and continued for some time after the death of the animal, even in those cases where a non-diffusible dye was used, particles of the dye were found in the oedema fluid. (Fig. 3.) Levinsohn,²³ who also noted this oedema of the orbital tissues, was of the opinion that the fluid passed from the subarachnoid space around the optic nerve through the dura mater at several places in the dog, whereas in the ape the place of exit was limited to the site where the central vessels pierce the dura. This experimentally induced oedema of the retro-ocular orbital tissues undoubtedly explains the proptosis which is not infrequently observed in clinical cases of cerebral tumour.

"*Chemosis*."—In many of our experiments there appeared what was apparently a marked swelling of the conjunctiva, the swelling

FIG. 3.

Horizontal section of dog's eye to show the effect of injecting potassium ferrocyanide into the cranial subarachnoid space at high pressure. Stained eosin.

The dye is in the subarachnoid space, outside the dura, in the orbital tissues, in the choroidal and scleral vessels and passes forward under Tenon's capsule to the conjunctiva.

FIG. 4. $\times 200$

High power view of choroidal vessel containing the dye. Note that the perichoroidal space is free from dye.

FIG. 5. $\times 55$

Longitudinal section of the optic nerve head of a cat injected as Fig. 3. The dye is in the subarachnoid space and in some vessels (? venules) in the disc.

FIG. 6. $\times 300$

High power specimen of injected vessels (? venules) in the disc seen in Fig. 5.

appearing in some cases as a roll between the eyelids (Fig. 8). On dividing the conjunctiva, however, it became evident that the fluid was not in the conjunctiva but under Tenon's capsule. When diffusible dyes were employed the fluid beneath Tenon's capsule was coloured in those cases where the pressure had been kept about 60 to 70 mm. of mercury. On the other hand, when non-diffusible dyes were used the fluid was colourless. In a few cases in which

FIG. 8.

Dog's eye to show "chemosis."

the pressure had been greatly increased (270 mm.) and maintained for some time (about two hours) after death, Prussian blue granules were found in the fluid under Tenon's capsule. (Fig. 3.)

Dripping of Fluid from the Nose.—A constant sequel of injecting fluids under pressure into the cranial subarachnoid space is an escape of fluid from the nose. In those experiments in which diffusible dyes were injected, the fluid dripping from the nose was coloured, and first appeared when the pressure employed was in the vicinity of 40 mm. of mercury. When Prussian blue was employed the fluid dripping from the nose was colourless at pressures compatible with life. In one case only, in which Prussian blue was injected at a pressure of 370 mm. of mercury for two hours after

death, the fluid dripping from the nose was blue in colour. In three experiments (dogs) potassium ferrocyanide, made up in a one per cent. solution in distilled water, was used as injection fluid, and the fluid which dripped from the nose when the pressure approached 40 mm. of mercury was allowed to drop on a filter paper moistened with ferric chloride solution. The resultant Prussian blue reaction showed that at this pressure the potassium ferrocyanide solution was passing from the cranial subarachnoid space into the nasal fossae. At the conclusion of these three experiments the heads of the dogs were cut (post mortem) in median sagittal section, the cut surfaces dried with blotting paper and subsequently touched at various points with a glass rod moistened with a solution of ferric chloride. An intense Prussian blue reaction was obtained all over the cut surfaces, including mucous membrane and muscles.

These experiments demonstrate that, whereas diffusible dyes pass readily from the subarachnoid space into the nasal fossae at pressures compatible with life, particulate matter does not pass under these circumstances. This is evidence against the presence of direct communications between the cranial subarachnoid space and the nasal fossae. In this connection the work of Le Gros Clark²⁴ is of interest. This observer found that a solution of potassium ferrocyanide and iron ammonium citrate, dropped into the nasal cavities of living rabbits, reaches the cranial subarachnoid space by way of the perineural sheaths of the olfactory nerves, and he postulates the existence of a current running centripetally in these sheaths under normal conditions. Clark states that the evidence indicates that the perineural spaces are directly continuous above with the cranial subarachnoid space, though it must be remembered that he was dealing with diffusible substances and not with particulate matter.

? *Papilloedema*.—Before we could assess the value of any changes in the optic nerve head that might be produced by our experimental injections, it was necessary to determine the normal appearance of the "papilla optica" in these animals* and compare it with that of the human nerve head. The descriptions of the latter in our classical text-books differ to a marked extent, and it is therefore appropriate to give here some of the views expressed with regard to the appearance of the human nerve head.

The Human Nerve Head.—Briggs²⁵ in his "Ophthalmographia" (1676), was the first to describe the human nerve head and called it the *papilla optica*. This description was undoubtedly based on the examination of post-mortem material, in which a swelling of

* Up to the present it has only been possible to make a detailed study of the nerve head in the dog (and man).

the disc is normally present. Merkel²⁶ in the first edition of Graefe-Saemisch (1874), states: "Papilla nervi optici is a name which to-day has only a conventional meaning, as it has long been shown that during life there is no elevation of the nerve head above the level of the retina which justifies it." Fuchs,²⁷ in his text-book of Ophthalmology (1917) says: "The name 'Papilla' was selected by the older authors under the *erroneous* impression that the head of the nerve represented a projection into the interior of the eye . . . In the normal state it is perfectly flat so as to lie in the same plane as the retina." Testut²⁸ (1923) states that "the region of the papilla does not project as one would suppose from the name 'papilla.' Normally it is flat and situated exactly in the same plane as the retina of which it forms a part. But custom has made this name (papilla) sacred and for a long time yet we shall have to accept it (*s'incliner devant elle*)."
Most modern text-books of anatomy and of physiology describe the nerve head as a projection and call it a papilla without qualification. It would seem, therefore, that the nerve head described as a papilla in 1676, became flat somewhere about 1870, and has now become a projection again! The present writers are of the opinion that this varied description of the nerve head is due mainly to the time and the method of examination of the disc. On ophthalmoscopic examination of the normal eye in the living subject, no swelling of the disc is seen and the vessels pass across the edge of the disc *without loss of their light reflex*. Also, if a freshly enucleated normal human eye be divided equatorially and the disc be examined by direct vision, no swelling of the disc is seen. If, however, the eye be first fixed in Zenker-acetic fluid for about 24 hours, sufficient swelling of the disc is produced to be just visible to the naked eye. It is to be noted, however, that the outer (temporal) side of the disc does not show any appreciable swelling. Microscopically, also, after the eye has been fixed as above described, the nerve fibres are seen to bulge in slightly towards the vitreous, not, however, sufficiently to deserve the name "Papilla" (*cf.* Salzmann²⁹), and here again the fibres on the temporal side of the disc are seen to be on the same level as the neighbouring retina.

The Canine Nerve Head.—After fixation in Zenker-acetic solution we noted that the nerve head in the dog appears distinctly swollen to the naked eye. The swelling is greater than in the human, and differs from that in the human in that the projection is equally prominent on all sides of the disc, the temporal side being quite as prominent as the remainder. The absence of a thinner temporal side of the disc is undoubtedly to be correlated with the absence of a macula in the dog. It is essential to bear in mind the microscopic appearance of the normal canine disc after fixation in Zenker-acetic for the proper appreciation of the condition of the nerve head in

FIG. 9.

Normal dog's eye fixed within half an hour after death in Zenker-acetic to show the "swelling" of the disc that occurs.

those cases in which the intracranial pressure has been increased. The fluid used for histological fixation has also to be borne in mind as the appearance of the disc varies with the fixative employed, for example, Fig. 12 shows a section through the disc of a dog whose intracranial pressure had been raised to 70 mm. of mercury for two hours, by injecting Weed's fluid, the eye then being removed and fixed in 10 per cent. formalin and 5 per cent. HCl. Despite the increased intracranial pressure the disc does not project towards the vitreous like that of a normal dog whose eye has been fixed in

FIG. 10.

Longitudinal section of nerve head from normal dog's eye removed during life and fixed immediately in Zenker acetic. Note the "swelling" of the nerve head.

Zenker-acetic (Fig. 10). It is evident, therefore, how important is the method of fixation in judging the presence or absence of swelling of the disc from a microscopic section. If the eyeball of a living dog be removed, divided equatorially, and the vitreous taken

FIG. 11. X 55

As Fig. 10 but fixed in 10 per cent. formalin. There is no "swelling."

FIG. 12.

Longitudinal section of nerve head of dog whose intracranial subarachnoid space had been injected under high pressure. (250 mm. Hg) with Weed's fluid and then fixed in 10 per cent. of formalin + 5 per cent. HCl. Compare Figs. 10, 11 and 12.

out, no swelling of the disc can be seen either with the naked eye, a loupe, or with the slit lamp, whether the disc be looked at directly or after examining a section passing through it. With the slit lamp, the edge of the disc is seen to be markedly irregular with short whitish processes extending centrifugally from its entire circumference, giving the frayed appearance of opaque nerve fibres. The

blood in the retinal vessels is also seen by this method to move with gravity long after the eye has been removed. This, as Salzmann²⁹ pointed out, is important to bear in mind in interpreting congestion in a microscopic section of the eye. Thus with a slowly acting fixative the lowermost part of the eye will show vascular engorgement and the upper part anaemia, whereas both parts may have been perfectly normal during life. *No swelling (or projection) of the nerve head is observed in frozen sections of the dog's eye.*

On ophthalmoscopic examination of the fundus oculi of the living dog, the disc is seen to be oval (sometimes triangular) in shape. An

FIG. 13.

High power view portion of normal nerve head of dog to show the pseudo-oedema (vacuolation) that takes place if fixative is 4 per cent. of formalin in distilled water.

outstanding feature of the canine disc is the almost complete ring of large veins on it. To this venous ring the retinal veins converge, and as they pass across the edge of the disc they do not lose their light reflex. The arteries are all cilio-retinal, so that no true arteria centralis exists. (Fig. 14.)

The ciliary vessels pierce the sclera immediately around the optic nerve and pass inwards to the nerve head just in front of the subarachnoid space, where they give off the retinal branch. This enters the nerve at the level of a ledge of retino-choroidal pigment (usually present in the dog) to appear at the periphery of the disc. A central retinal vein (or veins), on the other hand, is often present but is exceedingly short, in fact it leaves the nerve head where the arteries enter it and then passes in front of the subarachnoid space. *In no case have we seen the main retinal vessels actually crossing the subarachnoid space of the dog* (Figs. 16-19).

FIG. 14. $\times 70$

Transverse section of canine optic nerve still within the globe to show cilio-retinal arteries (no central vessels).

FIG. 15. $\times 500$

High power view of a cilio-retinal artery in Fig. 14 to show *normal* pigment round the vessel which gives rise to a bluish halo when seen with the ophthalmoscope.

FIG. 16. X 75

Transverse section of canine optic nerve still in the globe, to show cilio-retinal vessels outside nerve with one C.R. entering it.

C = Ciliary artery dividing into cilio - retinal and choroidal branches.

S = Subarachnoid space.

FIG. 17. X 60

Longitudinal section of canine optic nerve to show cilio-retinal vessels entering nerve at level of ledge of choroidal pigment. Note subarachnoid space further back.

FIG. 18. $\times 75$

Transverse section of canine optic nerve still in the globe to show main retinal vein V leaving the nerve.

FIG. 19. $\times 75$.

Longitudinal section of canine optic nerve to show cilio-retinal vessels passing in front of subarachnoid space.

The arteries are very much smaller than the veins and it is often difficult to follow their light streak as they pass across the edge of the disc. Hirschberg explains this as a contrast phenomenon due to the green colour of the tapetum. Under the best of circumstances the light streak on the arteries is narrow and not at all easy to follow. In many cases the edge of the disc is not very sharply defined, a fact also noted by Schieck (14 c.), and this circumstance makes it difficult to assess slight changes in it.

With regard to the possibility of producing papilloedema by injecting fluids under pressure into the cranial subarachnoid space, the results of the following workers may first be considered. Manz,³⁰ (1870), stated that injection of fluids under pressure into the cranial subarachnoid space in rabbits produces dilatation and tortuosity of the retinal veins and hyperaemia and swelling of the optic nerve head. This author's results are often quoted but they have been criticised by von Schultén,¹⁹ and it may be noted here that these experiments were performed on animals most of which were not anaesthetised, whose pupils were not dilated, and whose eyeballs rolled about during the observations. It is impossible to assess fine changes in the retina under such conditions. von Schultén¹⁹, (1885), found that raising the pressure in the subarachnoid space in rabbits resulted in narrowing of the retinal arteries and dilatation of the retinal veins, but never in swelling of the disc. Merz,³¹ (1900), on the other hand, stated that in dogs, raising the intracranial pressure 15 to 20 mm. of mercury produces typical papilloedema. Kampherstein and Heine,³² (1905), however, repeated Merz's experiments and found that they could not produce papilloedema, at least so long as the animal was alive. (Some of these experiments were performed under the supervision of Uhthoff.) Adamkiewicz,²² (1895 and 1905), working with rabbits, found that injecting coloured fluid (Berlin blue saline) under pressure into the subarachnoid space produced no change in the fundus oculi until just before death, when the vessels disappeared and the disc went white. If the raised pressure was maintained after death, the coloured fluid entered the choroidal veins. Cushing and Bordley²⁰, (1909), experimenting with dogs, state that by injecting fluid at a pressure of 30 mm. of mercury into the cranial subarachnoid space, a swelling of six dioptries was observed in the disc in eleven minutes (observation 6). In another experiment (observation 5) they made a one-inch trephine hole in the midline, just anterior to the occipital protuberance, thus exposing the superior longitudinal sinus and a portion of dura over each cerebral hemisphere. A few minutes' pressure exerted with the finger against the exposed dura sufficed to produce a swelling in the disc of two dioptries. A stronger

pressure continued for some time increased the swelling to seven dioptries! Schieck,¹⁴ (1910-1911), is of the opinion that dogs, cats and rabbits are unsuitable for these experiments as they have optic discs whose edges are normally ill-defined. This worker produced papilloedema by this method in apes and dogs, the latter being used only as controls. Contrasted with Schieck's results, Levinsohn,²³ (1912), failed to produce definite papilloedema in apes, dogs and cats by the above means. von Hippel,³³ (1923), reviewing the above experiments, is at a loss to find a satisfactory explanation of the contradictory results.

Of the above workers, only Cushing and Bordley reproduce a microscopic section showing distinct swelling of the optic disc, but the method of histological preparation of this section needs careful consideration. The authors state that with the object of fixing the oedematous retinal tissues under the conditions of the experiment so as to obviate in a measure the inevitable shrinkage of subsequent fixation, a solution of 4 per cent. formalin (? 4 per cent. formalin; ? 4 per cent. formaldehyde) was employed instead of salt solution for the injection fluid. The eye was removed post-mortem. The formalin used was obviously not strong enough to fix immediately the living tissues with which it came into contact, for the animal lived for one and a half hours with the fluid presumably in contact with the medulla. Even if the formalin entered the optic nerve head (and our injection experiments showed the diffusible dyes did not enter the disc) it would undoubtedly be only strong enough to act here as an irritant to the living tissues and may quite well have produced oedema in this way.

In many of our experiments, in which we kept the pressure of the injection fluid about 70 mm. of mercury, we could not convince ourselves that any visible change occurred in the fundus oculi, although post-mortem we always found the subarachnoid space around the optic nerve distended with dye. In some cases we thought that there was possibly some dilatation of the retinal veins. Slight changes in the arteries are very difficult to judge since they are normally narrow. In some cases the pressure of the injection fluid was gradually raised and it was observed that when the pressure reached 100 to 200 mm. of mercury (varying with different animals) the animal would stop breathing and the heart's action would become so weak that the retinal arteries practically disappeared and the fundus became pale and the disc dead white. The pressure would then be lowered (by releasing the clip on the tube leading from the large bottle) and the animal gradually commenced breathing. Sometimes artificial respiration had to be resorted to in order to re-establish respiration. The retinal arteries rapidly reappeared and the colour of the fundus and disc soon returned to normal. In most of our experiments we noted that,

not long after the commencement of the experiment, the disc appeared to become hazy. At first we thought that this was due to swelling of the disc, but we soon observed that this appearance resulted from small areas of clouding of the cornea which are liable to occur under experimental conditions and are no doubt due to exposure. Owing to refractive changes which they produce they may give rise to all kinds of distortion of the disc. It was noted that when the disc was looked at through another (unclouded) part of the cornea, the disc appeared normal. von Schultén's¹⁹ words are appropriate here: "(as) I know the difficulties of estimating the value of what is seen with the ophthalmoscope and the part fancy may play therein" These observations evidently indicate that it is unsatisfactory to regard simple blurring of the edges of the disc as proof of the presence of papilloedema. The criterion we employed in the diagnosis of swelling of the disc was disappearance of a previously present light reflex on the veins as they crossed the edge of the disc. The light reflex on the arteries, as aforesaid, is normally very difficult to follow. The light reflex is the image of the source of light (used in the examination of the fundus) which reaches the eye of the observer through the pupil. It is obvious therefore that the slightest swelling of the disc would cause a bending in the vessels and thus throw the image of the source of light beyond the pupil so that the bent portion of the vessel would appear dark (*i.e.*, it would lose its light reflex). Clouding of the cornea, although it may produce a blurred appearance of the disc, does not lead to a vessel losing its light reflex in one place while retaining it in another. It is remarkable that, in the extensive work that has been carried out on the *experimental* investigation of the method of production of papilloedema, this essential sign (loss of light reflex) has apparently not been employed in the diagnosis of swelling of the nerve head. Using this criterion in the diagnosis of swelling of the disc, in none of our experiments, in which the pressure of the injection fluid was kept at 70mm. of mercury for two to three hours, did we observe papilloedema.

In one case only did we see the disappearance of the light reflex. Here, however, the pressure had been put up so high that the animal stopped breathing and its* heart's action almost ceased. The vessels in the disc disappeared and the disc became quite white. On reducing the pressure to zero and after artificial respiration had been resorted to for some time the animal recovered. At first the disc went pink with each inspiration and white again with each expiration, and then finally regained its colour. It is possible that here

* Mr. Wilfred Trotter tells us of an almost exact human equivalent of the above experiment. Those cases who, apparently dead, have recovered after cardiac massage, often die subsequently, and on post-mortem examination, an *oedema of the brain is found*. Up to the present we have not been able to ascertain whether papilloedema was diagnosed during life in these cases.

we unconsciously repeated Starling's classical experiment on the production of oedema of the legs. He tied the femoral vein, no oedema resulted. He then tied the femoral artery, and when after some time he released it, oedema was produced. The cutting off of the blood supply had injured the endothelium of the capillaries and when the pressure in them become normal again they allowed an excessive amount of fluid to pass through their walls and oedema resulted.

It is possible that in our experiment the blood supply from the capillaries was cut off for a sufficient time to injure their endothelium and when the pressure came back to normal an excessive amount of fluid passed through their walls as occurred in Starling's experiment.

It is interesting to note that, as long ago as 1887, Deutschmann,³⁵ in criticising von Schulten's results, stated that the failure of the latter to produce papilloedema experimentally was due to the fact that he had not cut off the *arterial* supply to the retina.

We have seen that it is possible to get only a non-diffusible dye into the eye at pressures incompatible with life. Moreover, the dye is found in definite vessels and not in the tissue spaces where one finds the oedema in papilloedema. Also we could not produce a coloured papilloedema either with diffusible or non-diffusible dyes. It would thus appear that, at any rate, in the dog, there is no communication between the peri-optic subarachnoid space and the optic nerve.

With regard to man the only evidence of a communication is the solitary experiment* described by Schieck. What seems certain to us, however, is that whether the papilloedema is produced directly or indirectly by the cerebrospinal fluid there is no reason why the whole of that part of the retina drained by the central vein should not become oedematous. If we take it that the vein is obstructed in the intervaginal space then the tendency to oedema must be the same in the whole area which it drains; the slight venous anastomosis at the entrance of the nerve would in fact, as suggested above, tend to carry the oedema fluid away and therefore make it less likely for the area to become oedematous.

We believe, then, that in papilloedema the entire area drained by this vein does contain an excess of fluid (oedema), but that the amount of fluid in each region of the retina will depend upon the density† of the structure of the particular region under consideration.

*We have not been able for the moment to repeat this experiment, for the opportunity of getting a freshly excised *normal* human eye with a length of optic nerve attached does not frequently arise.

†If a rubber tube which consists of alternating thin and thick portions be taken closed at one end, laid on its side and then gradually filled with water, it is obvious that the thinnest portions would bulge most, although all parts are under the same pressure. In exactly the same way all the tissue spaces drained by the central retinal vein must be under the same pressure; with increase of this pressure the amount of swelling must therefore depend entirely on the structure of the part.

Thus, the nerve fibres at the disc have a relatively loose arrangement and much fluid could collect here and produce obvious swelling, whereas the lamina cribrosa, with its dense meshwork of fibrous trabeculae, would, with the same capillary pressure, contain only very little excess of fluid. In papilloedema it has been noted that the swelling extends in the nerve fibre layer for a short distance only beyond the disc. This, we would suggest, is due to the arrangement of the fibres of Müller which hold together the elements of the nerve fibre layer. The Müllerian fibres in the immediate vicinity of the optic nerve head are stretched or torn (Paton and Holmes⁵), whereas those farther from the disc remain intact and limit the amount of fluid exuded. The remainder of the retina also undoubtedly contains excess of fluid, although usually not sufficient to be visible with the ophthalmoscope and, as aforesaid, may to a large extent disappear on microscopic section. The swelling of the disc (as opposed to the rest of the fundus) in cases of papilloedema appears to be parallel with that in the facial subcutaneous tissues in cases of renal disease, in which the lower eyelids swell, not because their capillaries differ in structure from those elsewhere, but because laxness of the tissues of the eyelid allows a greater accumulation of fluid which exudes from the capillaries. It is the structure of a part which determines the amount of fluid which collects in it (for a given capillary pressure) and therefore the amount of swelling which will take place in that part.

Finally we have to seek for a reason why the swelling of the disc in cases of papilloedema should appear at one part of the disc before another. Paton and Holmes⁵ describe a fibrous band which would tend to keep the outer side of the disc strapped down in cases of papilloedema. The present writers have no knowledge of such a band, nor could any other reference be found to it. Schieck,¹⁴ who believed that the subarachnoid space around the optic nerve communicated directly with the retinal lymphatics, and that papilloedema was due to cerebrospinal fluid being forced into the retinal lymphatics, was of the opinion that the swelling started where the large vessels cross the edge of the disc. Our experiments, however, demonstrated that there is no direct communication between the subarachnoid space and the retinal lymph spaces, at any rate in the dog, and thus Schieck's explanation of the special site of commencement of swelling of the disc cannot be upheld. The structure of the disc appears to us to afford a clue to this question. A study of the relative thickness of various parts of the nerve fibre layer at the edge of the disc in the human, shows that it is thinnest directly outwards, *i.e.*, in the region of the papillo-macular bundle. Next in thickness are the upper and outer quadrant and the lower and outer quadrant, then the innermost part of the edge of the disc, and finally the thickest parts are the

upper and inner quadrant and the lower and inner quadrant. The swelling will obviously first be visible in the thicker parts of the edge of the disc, and from the structure of the disc we would deduce that the order of appearance of swelling will be first, the upper and inner quadrant and the lower and inner quadrant, next the inner edge of the disc, then the upper and outer quadrant and the lower and outer quadrant, while the last part of the disc to show visible swelling will be the direct outer part.

In conclusion, our experiments are in accord with the general result of Weed's³⁶ work. This observer maintains that the subarachnoid space is a closed space.

Summary and Conclusions

1. Non-diffusible dyes injected into the cranial subarachnoid space at pressures compatible with life, do not enter the optic nerve.
2. The claims of previous investigators to have produced papilloedema by the injection of fluids into the cranial subarachnoid space at pressures compatible with life, are not upheld by the present study.
3. Anatomical observations are made on the normal structure of the optic nerve head in the dog and in man.
4. Structural reasons are advanced for the special site of commencement of papilloedema in man, and for the extent of distribution of the oedematous fluid associated with papilloedema.

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