EXPERIMENTS ON THROMBOSIS OF THE SUPERIOR LONGITUDINAL SINUS

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The experiments to be described were planned to throw light upon the problem of "otic hydrocephalus": a term originally introduced for a syndrome in which raised intracranial pressure and papilloedema are assumed to be due to sinus-thrombosis following otitis media, but are unaccompanied by evidence of leptomeningitis or of cerebral abscess. The cause and mechanism of this increased pressure are still controversial. Symonds (1937)\textsuperscript{13} believes the syndrome to be dependent upon thrombosis: the lumen of the lateral sinus is blocked and the blockage extends across the torcular Herophili, thence ascending in some instances into the superior longitudinal sinus. Alternatively, in those cases where jugular compression proves both lateral sinuses to be patent, he suggests that the endothelium of the sinuses may be plastered with a thin layer of clot by retrograde extension from the lateral sinus to the superior longitudinal sinus, thus obstructing the arachnoid villi.

While the existence of the syndrome is generally accepted, the presence of an accompanying hydrocephalus is debated. According to some (Gardner, 1939\textsuperscript{9}), the ventricles in these cases are of normal size or may even be reduced. Again, raised intracranial pressure with papilloedema may occur without clinical evidence of thrombosis or of antecedent infection either in the middle ear or elsewhere in the body—the so-called "pseudotumor cerebri" (Davidoff and Dyke, 1936;\textsuperscript{7} Dandy, 1937;\textsuperscript{5} McAlpine, 1937\textsuperscript{11}). To such cases the term "toxic hydrocephalus" has also been given (McAlpine). No satisfactory explanation of the increased intracranial pressure has been offered for these. Yet there can be little doubt from certain records (Ellis, 1937;\textsuperscript{5} Bailey and Hass, 1937;\textsuperscript{1} Russell, 1944\textsuperscript{12}) that thrombosis of the longitudinal sinus may be followed clinically by the syndrome and, in the cases quoted, ventriculography or postmortem examination has secured evidence of internal hydrocephalus.

In view of the existence of such cases it was felt that, could a spreading thrombosis from the longitudinal sinus be induced experimentally, the clinical and pathological study of such animals would throw further light upon the syndrome. So far as we are aware, only one attempt has been made in this direction. In one dog, Bize (1931)\textsuperscript{3} occluded the torcular Herophili and hind end of the longitudinal sinus with a tampon of iodoform gauze, and in

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a second dog he injected 1 cc. of quinine urethane solution at the same site; in neither experiment was there any significant consecutive clinical or pathological change.

Since the middle segment of the longitudinal sinus appears to be the site of election in the initiation of spontaneous thrombosis (Welch, 1909; Bailey and Hass, 1937), this region was selected for our experiments. These fall into groups as follows:

A. Rabbits

1. Inducement of Stasis. The exposed sinus was occluded by a silver clip placed just anterior to the torcular Herophili (4 animals), or by two clips placed from 1.0 to 1.8 cm. apart (3 animals). The animals remained in normal health and were killed at periods from 2 days to 3 weeks later. None showed evidence of thrombosis either macroscopically or microscopically. The brains were normal.

2. Stasis with Introduction of Coagulants. The above procedure was combined with the injection of coagulants into the lumen of the sinus. (a) A physiological coagulant, thrombin, was used in 5 animals. When the greater part of the sinus had been exposed an occluding silk ligature was tied immediately anterior to the torcular, and about 0.1 c. cm. of a mixture in equal parts of a 10 per cent dilution of the thrombin solution and thorotrax was slowly (30 sec.) injected into the lumen anterior to the ligature. The mixture used was tested for us by Dr. R. G. MacFarlane and was found to clot rabbit's blood within 30 seconds in vitro. By adding thorotrax we hoped to gain radiographic information concerning the site of the expected thrombosis. The animals, however, remained normal and no trace of thrombosis was found on examination of the tissues from 5 to 22 days later.

(b) A chemical coagulant, ethamolin (an aqueous solution of 5 per cent ethanalamine oleate with 2 per cent benzyl alcohol), which is used clinically for the injection of varicose veins, was tried in 9 animals. In these experiments the ligature was omitted, and the lumen of the sinus was compressed in two places with artery-forceps while the injection was made into the segment between them. Both the forceps and the needle of the syringe were held in situ for 2 minutes after the injection had been completed. Most of the animals in this group appeared unduly excitable on the following day but, with two exceptions, they returned to normal and remained so until killed from 7 to 40 days later. The latter then showed neither thrombosis nor any other abnormality of the brain. Of the two exceptions one animal was found dead on the following day with extensive intraventricular haemorrhage, apparently due to accidental operative trauma. The other showed retraction of the head and convulsions following operation, and was killed on the second day, as it appeared moribund. The sinus at the site of injection and the great vein of Galen were greatly engorged, and there was moderate congestion of the superficial cerebral veins. The middle lobe of the cerebellum was swollen and protruded for a distance of about 0.6 cm. through the foramen magnum. On section the cortex forming the postero-medial angles of the occipital poles appeared softened and the occipital horns were dilated. On microscopic examination the torcular was partly occluded by recent thrombus but none was found in the longitudinal sinus. There was slight diffuse subarachnoid haemorrhage, more marked at the base of the brain than elsewhere. The occipital poles showed gross oedema of both grey and white matter, with occasional perivascular haemorrhages about the subependymal blood-vessels. The ependyma of the tips of the horns, which normally are not patent in the rabbit, was interrupted in many places by the blowing out of the cavity.

Comment. It was not expected that the degree of stasis induced by ligatures alone would effect thrombosis. But it seemed desirable to perform these initial experiments in view of the suggestion that the longitudinal sinus is particularly susceptible to thrombosis. But our failure when this measure
was combined with the use of coagulants was disappointing. Thrombin is a potent coagulant in vitro, and it had been anticipated that widespread thrombosis might preclude the survival of our animals. Ethamolin is an effective coagulant in vivo when used in the treatment of varicose veins but produced a limited thrombosis in one animal only, adjacent to, but not at the site of the injection.

To gain further information concerning the action of these two agents a series of experiments was then carried out upon the marginal vein of the rabbit’s ear. In these it was found that, in parallel circumstances, the marginal vein was quite unaffected by the injection of undiluted samples of rabbit, bovine or human thrombin, but was invariably thrombosed, within two minutes of the injection, by ethamolin. The thrombosis occurred throughout the length of the compressed segment of the vein and proceeded to organisation during the succeeding 2 to 3 weeks.

The damaging effect of ethamolin upon the tissues was further demonstrated in 3 rabbits, by the application of the solution upon a pledget of lintine to the exposed cortex and leptomeninges. In two of the animals, killed 2 and 4 days later respectively, a wedge of haemorrhagic necrosis occupied the brain at the site of exposure. In the third animal, killed after 8 days, the cortex however appeared normal.

Since ethamolin appeared to be the most potent coagulating agent available, and since we had experienced some success in one of the nine rabbits in which it had been used, we decided to try it on the dog, where the sinus is of such dimensions that operative procedures can be better controlled than in the rabbit.

B. Dogs

1. Injection of Ethamolin into Sinus (Dogs 1, 2, 3). Under nembutal anaesthesia, supplemented when necessary with ether, the sinus was exposed over a length of 2 to 3 cm. Ligatures were tied to compress the lumen at either end of the exposed area and were released 2 minutes after 0.1 cc. of ethamolin had been injected into the intervening segment. Two of the animals were killed at the conclusion of the experiment (20 and 45 minutes after injection, respectively) and the third 2 months later. This last dog remained in normal health and activity during survival. None showed any abnormality in the dural sinuses or in the brain, either macroscopically or microscopically.

2. Coagulation by Heat (Dogs 4, 5). The sinus was exposed as before and the dorsal wall was cauterised, over segments measuring 0.4 and 1.5 cm. respectively, with a diathermy-point at a temperature just sufficient to coagulate muscle. In addition a ligature was tied at the posterior end of the exposed sinus in Dog 5. The animals showed no postoperative disturbance and were killed after 4 and 6 days respectively. Though no thrombosis was visible to the naked eye microscopic examination revealed a small mass of clot showing early organisation in the lateral angle of the sinus in the cauterised area in Dog 5. In both animals the wall of the sinus showed coagulative necrosis with diffuse extravasations of red corpuscles down to the intima, which was raised by oedema, the subendothelial spaces so formed being infiltrated with polymorphonuclear leucocytes. In both animals the brain was unaltered.

3. Mechanical Blockage of the Lumen. (a) By muscle (Dogs 6, 7). Portions of muscle, beaten out into small stamps such as are used by neurosurgeons to check haemorrhage, were introduced into the lumen of the sinus with the idea that the haemostatic action of the tissue
combined with mechanical obstruction might produce the desired effect. It was also anticipated that the necessary manipulations would cause some damage to the sinus endothelium. Therefore a small stamp, measuring 0.4 by 0.1 to 0.2 cm. thick in the case of Dog 6 and somewhat larger in Dog 7, was attached to a thread on a curved needle and was drawn after the needle into the lumen. Its entry was effected by enlarging the hole made by the needle with a sharp hook at the appropriate moment. Although ligatures had been temporarily placed on the sinus at either end of the exposed area the manoeuvre was accompanied by considerable haemorrhage which, however, instantly stopped when the muscle slipped into the lumen. The dogs remained well and active after operation and were killed after 4 and 10 weeks respectively.

**Macroscopic examination.** In both animals the sinus appeared normal except where the muscle had been inserted. This was converted into firm greyish-white tissue which was firmly adherent to the dura, and at one level completely filled the lumen except for a narrow crescentic slit (Dog 6), or a pin-point lumen near one border (Dog 7). In both the brain appeared normal.

**Microscopic examination.** Transverse sections through the sinus showed replacement of the muscle by a circumscribed mass of fibrous granulation tissue, rich in young collagen fibres, enclosing islands of large mononuclear cells, many of which had formed foreign-body giant-cells about degenerated and atrophied muscle fibres. Throughout the tissue there were occasional spaces lined with endothelial cells and these, near the periphery, contained blood. Larger spaces, present between the sinus wall and the granulation tissue, appeared in part to be continuations of the lumen proper, and in part distended lacunae laterales.

**Comment.** Although the muscle had doubtless effectively blocked the lumen in early stages, it had become organised with considerable rapidity. Moreover there was no evidence that any thrombosis had been promoted by the muscle. The operation was therefore repeated using muscle that had previously been steeped in ethamolin.

(b) **Muscle steeped in ethamolin** (Dogs 8, 9, 10, 11). The procedure was similar to that in
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(a) except that the muscle was steeped in ethamolin for about one hour before being introduced into the sinus. Increasingly large bits of muscle were used in successive experiments, up to 0.8 by 0.3 cm. in Dog 10 while, in Dog 11, three portions were separately introduced at different points into a segment of sinus about 3 cm. long. In Dog 9 the ligatures on the sinus were tied off for a period of 11 minutes, including 5 minutes after the muscle had been inserted. In Dog 10 (killed after 7 weeks) an attempt was also made to occlude the lateral sinuses by exposing them through a drill-hole made in the skull about 0.7 cm. lateral to the mid-line, and filling the hole firmly with bone-wax.

All the animals appeared in normal health until killed and showed no evidence of pапilloedema. In Dog 8, however, the wound opened after 9 days, following removal of the stitches, and discharged slightly; it was therefore killed on the 16th day. The remaining three were killed after 4, 6 and 8 weeks respectively.

On macroscopic and microscopic examination the appearances were similar to those obtained with the untreated muscle. In the dog killed after 16 days the sinus was blocked for a length of 1 cm. and the muscle was coated with a small amount of ante-mortem thrombus. But there was no further extension of the thrombus. In the remaining three animals a variable length of sinus, up to 2.5 cm. in Dog 9, appeared to be blocked by granulation tissue which, microscopically, was similar to that seen in (a). In spite of the addition of ethamolin the wall of the sinus appeared healthy. In Dog 10, in which the lateral sinuses were also attacked, the lumen of the right lateral sinus at the site of operation was compressed into a crescentic slit but was patent. Though the left lateral sinus had not been occluded by the bone-wax it was filled with recent thrombus which, however, on microscopic examination showed no evidence of organisation. The brains in all save Dog 9 appeared normal; in Dog 9 there was slight dilatation of the left lateral ventricle, most marked in the posterior horn (Fig. 1).

Comment. Obstruction of the lumen of the superior longitudinal sinus by fragments of fresh muscle, or by similar muscle steeped in ethamolin, was ineffective in promoting a spreading thrombosis. By the end of 16 days the muscle was replaced by granulation tissue and, at later stages, showed microscopic and sometimes macroscopic evidence of recanalisation (Fig. 2). The brain was unaffected with the doubtful exception of Dog 9, in which a maximal length of the sinus had been occluded, and the animals showed no clinical disturbance.

(c) Cotton-wool (Dogs 12, 13). Cotton-wool was substituted for muscle with the idea that this foreign substance might effectively occlude the sinus for a longer period of time. The wool was fashioned into an elongated sausage-shaped mass of suitable calibre and was intro-
duced into the sinus as before, after steeping it in ethamolin. Both animals remained healthy, with no evidence of papilloedema, and were killed after 10 and 7½ weeks respectively.

Macrosopic examination. In Dog 12 the sinus appeared to be completely obliterated throughout a segment, 2.2 cm. long, by tough grey fibrous tissue; the lumen elsewhere was patent and normal. The left lateral ventricle was slightly more capacious than the right anterior to the level of the occlusion but this inequality disappeared at more posterior levels (Fig. 3). In Dog 13 a length of 1.1 cm. was similarly obliterated. The sinus elsewhere was normal and the brain unaltered.

Microscopic examination. The appearances in transverse sections through the occluded part of the sinus, were similar in both animals. The lumen was distended with fibrous granulation tissue which everywhere was closely applied to the wall of the sinus and separated the wool-fibres (Fig. 4). The fibres were frequently surrounded, wholly or in part, by foreign-body giant-cells. Numerous blood-vessels, mostly of small calibre and containing red corpuscles, were present in the granulation tissue (Fig. 5). The wall of the sinus was unaltered and the adjacent brain, apart from slight deformity caused by the pressure of the distended sinus, appeared normal.

Comment. The substitution of cotton-wool for muscle as a blocking agent made no difference to the results. It was observed, however, that in groups (b) and (c) a slight unilateral hydrocephalus had coincided with a maximal blockage of the sinus (Dog. 9, 2.5 cm.; Dog. 12, 2.2 cm.). In the experiments described an attempt was made to carry this observation further by blocking as great a length of the sinus as possible.

C. Puppies and Kittens

A litter of four puppies aged 6 to 7 weeks, and of four kittens aged 6 to 8 weeks were used because of the known high incidence of spontaneous sinus-thrombosis in young subjects, the advantageous dome-shaped skull of these young animals and the fact that the sutures of the vault were unlosed. The procedure was the same as in 3 (c) above. By using two elongated pledgets
of ethamolinised wool, and passing these both forwards and backwards from a central point of entry on the fully exposed sinus, it was possible to obliterate lengths varying from 0.5 to 0.8 of the whole sinus (Fig. 6). With the exception of one puppy (3) all recovered well from this operation and remained perfectly normal until killed from 5 to 7 weeks later. There was no evidence of papilloedema. Puppy 3 did not regain consciousness and died after 36 hours, apparently from loss of blood combined perhaps with an excess of nembutal.

Fig. 4. Same as in Fig. 3, showing the sinus with occluding cotton-wool. (Phosphotungstic-acid haematoxylin, X11.)

Fig. 5. Same as in Fig. 4, showing cotton-wool fibres (pale oval structures), foreign-body giant-cells, and a blood-vessel to left of centre. (Haematoxylin and eosin, X270.)
In none of these animals was there thrombosis of the sinus either in front of or behind the blockage, which appeared complete throughout the greater part of the lumen. No abnormality was found in the brain in any of the kittens. In Puppy 3 the brain appeared full and soft and the convolutions were slightly flattened. There was uneven engorgement of the superficial veins. The wool filling the sinus was soaked with blood, and postmortem clot filled the residual parts of the sinus and the lateral sinuses. On section the cerebral tissue appeared soft and oedematous; the ventricles were small, their walls being in apposition. Of the remaining three puppies two (1 and 4) showed slight dilatation of both lateral ventricles, most marked in the body. In Puppy 2 the left ventricle was slightly more capacious than on the right.

Comment. Although it is possible, especially in puppies and kittens, to occlude the greater part of the longitudinal sinus, this operation is not followed by any unequivocal clinical or pathological evidence either of increased intracranial pressure or of hydrocephalus. The slight degree of dilatation observed in the puppies may have been significant; if so it is perhaps to be accounted for by the more numerous venous tributaries to the sinus found in dogs as compared with cats. But the dog has fewer tributaries than man and these experiments should be repeated on the monkey before any final decision is reached concerning the implications of extensive blockage of this sinus in man.

The absence of any gross effects upon the brain in our experiments indicates that the collateral circulation is fully adequate to deal with the degree of disturbance that we were able to induce. It should however be noted that the anastomoses between the cerebral and diploic veins, demonstrated by Cushing (1902) to be of great abundance and importance in the dog, were necessarily sacrificed in the operative exposure of the sinus in our animals.

It is possible that a condition analogous to that of "otitic hydrocephalus" in man can be produced experimentally only by inducing a thrombosis that will spread from the main sinus into the adjacent lacunae and the mouths of the venous tributaries. Reviewing the published reports of human cases of this kind one is struck by the frequency with which an infective process is present in some part of the body although the thrombosis of the intracranial sinuses is essentially aseptic. It may be—and the idea is not new—that tissue-immunity is a factor deserving of more attention in this connection. With this in mind we attempted to reproduce the Shwartzmann phenomenon in the walls of the longitudinal sinus in rabbits as follows:
D. Schwartmann Phenomenon in Rabbits

1. In two rabbits the centre of the sinus was exposed over a length of about 1 cm., and its dorsal wall was well scarified with the point of a needle. A pledget of cotton-wool soaked in a tested potent filtrate of B. coli, kindly prepared for us by Dr. E. S. Duthie, was laid over the area for 10 minutes and the wound was then closed. Twenty-four hours later a precipitating dose of 4 c. cm. of the filtrate was injected into the marginal vein of the ear. An hour later both rabbits appeared prostrated; respiration was rapid and they had passed a large quantity of fluid faeces. On the following day they appeared more lively and, two days after the injection, their behaviour was normal. They were killed 3 and 9 days respectively after the operation.

Microscopic examination. In the animal killed after 3 days there was haemorrhage and necrosis of the soft tissues bordering the operation area. The dura however appeared normal and showed no thrombosis of the sinus. The brain also was normal. In the animal killed after 9 days there was no haemorrhage in the tissues and the gap in the skull was occupied by yellowish-grey granulation tissue. Beneath this the dura and brain appeared normal; there was no thrombosis.

2. On the supposition that the application of the filtrate to the sinus had been inadequate we repeated the experiments on 4 rabbits. The dura over the sinus was scarified more vigorously and, after applying the filtrate on cotton-wool as before, the bony defect was filled with a layer of stiff agar mixed with the filtrate in equal parts. The wound was closed leaving this mixture in situ. In one animal the dura to one side of the sinus was accidentally torn during the manipulations.

The behaviour of these animals after the precipitating dose was much as in (1) but the scalp, in a broad zone about the wound, became haemorrhagic and proceeded to dry gangrene in two examples. When sacrificed 2, 6, 9 and 17 days respectively after the operation the macroscopic changes at the site of operation were more intense than in (1), especially in those with necrosis of the scalp. In these (killed after 6 and 9 days) the dura was overlaid with opaque yellow fibrinoid material without evidence of granulation tissue. Nevertheless the dura itself was unaltered and the sinus was patent. In the animal in which the dura had been torn a triangular area of haemorrhage, 0.9 by 0.4 cm. and 0.4 cm. deep, occupied the subjacent cerebrum.

Microscopic examination. Residual portions of agar embedded in purulent necrotic debris overlaid the dura. Occasionally the whole thickness of the dura was infiltrated with polymorphonuclear leucocytes. Yet the lining of the sinus was in all instances unaltered and the lumen was empty. The haemorrhagic area found in the cerebrum in one rabbit, beneath a tear in the dura, showed ill-defined necrosis of the cortex and white matter. Many vessels in both the leptomeninges and brain were necrotic and were surrounded by haemorrhage. The meninges were moderately infiltrated with leucocytes. There was no definite thrombosis in the cerebral veins.

DISCUSSION AND SUMMARY

Though we failed in our objective in these experiments the results are instructive in various respects. The idea that thrombosis may readily be induced in the superior longitudinal sinus evidently needs revision. Though the blood-flow may be sluggish, and the walls rigid, thrombosis will not follow occlusion even when combined with the use of irritant coagulants such as ethamolin. But ethamolin with temporary compression will invariably induce thrombosis in the peripheral vein of the rabbit. The physiological coagulant, thrombin, proved another disappointment: although the samples used were potent in vitro they exercised no perceptible effect in vivo. We can offer no explanation of this anomaly.
It was remarkable to find that, in the dog and cat, the greater part of the sinus could be suddenly obliterated without any obvious impairment of normal function on recovery from the anaesthetic. Evidently the collateral circulation can at once compensate for such a disturbance. And reparative processes, ending in organisation and recanalisation of the occluding material, whether this be muscle or cotton-wool, proved surprisingly effective. It is possible that a condition analogous to the "otic hydrocephalus" of man can only be achieved experimentally by inducing a thrombosis that will extend from the main sinus into the adjacent lacunae and the mouths of the venous tributaries. We did not succeed in this in any type of experiment. In support of this theory are the published reports (Dandy, 1940; Jaeger, 1942\textsuperscript{10}) of resection of considerable lengths of the longitudinal sinus in the course of operation for the removal of tumours without subsequent clinical disturbances referable to this measure.

A spreading thrombosis such as we visualise may be impossible without the presence of infection providing a humoral factor such as we invoked in our experiments with the Shwartzmann reaction. In these experiments we obtained necrosis of all tissues that were exposed to the filtrate with the exception of the dural walls of the sinus. A conspicuous reaction was evoked in the brain in one animal in which the dura was torn. The remarkable immunity of the dura is doubtless correlated with its relative avascularity, for the Shwartzmann phenomenon appears to be essentially a vascular mechanism. We believe that the problem of producing the syndrome of "otic hydrocephalus" experimentally lies along these lines, and it is hoped that our records may provide some guide in the planning of any future attempts in the direction.

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REFERENCES


