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# THE LYMPHATIC CONNEXIONS OF THE SUBARACHNOID SPACE

## AN EXPERIMENTAL STUDY OF THE DISPERSION OF PARTICULATE MATTER IN THE CEREBROSPINAL FLUID, WITH SPECIAL REFERENCE TO THE PATHOGENESIS OF POLIOMYELITIS

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There have been suggestions current in the literature from time to time that infective agents (and in particular the virus of poliomyelitis) may extend to the central nervous system along certain ill-defined lymphatic pathways. Yoffey and Drinker (1939) introduced the concept of a combined lymphatic and haematogenous spread, depending on lymphatic absorption from the nasopharynx, and dissemination through the blood stream with the lymphocyte as a virus carrier. However, their experiments were not successful in establishing this mode of spread for poliomyelitis, though it appeared to hold good for the virus of vaccinia (Yoffey and Sullivan, 1939). It is, however, with the elucidation of direct anatomical pathways, particularly those between the spinal subarachnoid space and the abdominal lymphatic system, that the present communication is largely concerned. In the course of this investigation the potentialities of dispersion of fine particulate matter introduced into the cerebrospinal fluid have been observed, and would seem to be not without bearing on the problem of the pathogenesis of poliomyelitis. The principal features of the circulation of the cerebrospinal fluid, as elucidated by the labours of Weed and his co-workers from 1914 onwards, are well known and have been widely accepted. Weed's concept of the formation of the fluid by the choroid plexuses has been broadened to include cortical and spinal blood vessels as formative agencies (Schaltenbrand and Putnam, 1927), and there is now evidence also that a not inconsiderable resorption of fluid takes place into the lymphatic system, not only in the cervical region but also in the lumbosacral zone (Brierley and Field, 1948).

A detailed review of the literature of this problem has been given elsewhere, and only the salient features can be considered here. Schwalbe (1869) and Quincke (1872) both reported the deposition of particulate matter (of unspecified size) in the prevertebral lymph nodes following subarachnoid introduction. The former, moreover, noted in his experiments with dead rabbits that Berlin-blue granules could also pass out from the subarachnoid space extension along the sheath of the optic nerve close behind the eyeball, spread in the episcleral (Tenon's) space, and even pass in along the perivascular spaces of the venae vorticosae to reach the perichoroidal space. Schwalbe was able to demonstrate an excellent filling of lymphatic plexuses in the nasal mucosa from the cranial subarachnoid space, though Quincke (like Weed many years later) was unable to confirm this. These contradictory results were no doubt due to the difference in size of particles employed, for fine particles (0.5 $\mu$) certainly pass with ease from the subarachnoid space into the nasal mucosa. Much of the earlier work on the subarachnoid lymphatic connexions is invalid because of the high injection pressures used, often resulting in obvious tissue damage (cf. Spina, 1900, 1901).

Weed (1914), working with a true solution (iron ammonium citrate and potassium ferrocyanide) as indicator, showed that a small proportion of the cerebrospinal fluid passes into the cervical lymphatic system via the nose, though he did not believe that particulate matter could take this course. He suggested that a similar outflow to the lymphatic system might take place from the spinal subarachnoid space. For this latter suggestion, however, he proffered no experimental evidence, and indeed the technique he used precluded investigation of such an outflow in the lumbosacral region—the very region where it will be shown below to be most marked.

The problem of the spinal subarachnoid connexions was investigated once more by Iwanow (1928), who worked both with living and with dead dogs. He showed that indian ink could make its way from the spinal subarachnoid space to the aortic lymph nodes, but was unable to outline the pathways completely.

### Experimental Methods and Results

The animal used was the rabbit, and all experiments were carried out in the living. Under "nembutal" anaesthesia sterile indian ink was introduced into the cranial subarachnoid space or lateral ventricle, precautions being taken to prevent backflow to the surface along the track of the needle. In all cases the amount of indian ink introduced was less than the volume of cerebrospinal fluid withdrawn as a preliminary, and the pressure under which the ink was allowed to run in never exceeded 120 mm. of ink. In order to introduce as large a quantity of ink as possible, more than one instillation was carried out in several animals. In this way it was possible to introduce as much as 4.5 ml. into one animal as opposed to the 0.8 to 1.2 ml. at the single sitting. With this technique there could be no question of any sudden increase in intracranial pressure as a result of the introduction, and conditions within the cranium remained relatively undisturbed. The ink used was

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made by rubbing down a stick of solid indian ink in physiological saline and filtering the suspension through a No. 5 Whatman filter paper. The size of the particles in the resulting preparation ranged from 0.4 to 1.5 $\mu$, but 90% were about 0.5 $\mu$.

The animals recovered from operation in two to two and a half hours and showed no disturbances whatsoever. They were sacrificed at intervals ranging from one to 96 hours after operation. Details of experimental technique have been described elsewhere (Brierley and Field, 1948).

Laminectomy showed that ink reached the caudal end of the spinal arachnoid sac in some seven to nine hours. Where relatively large amounts had been introduced and the animal was allowed to survive for an adequate period the extreme caudal segment was often jet-black. Around the dorsal-root ganglia of the lumbosacral region there were conspicuous accumulations of ink which produced the appearance of two columns of black beads in relation to the faintly grey cord. In the cervical region these cuffs of ink around the dorsal-root ganglia were also present, but were not nearly so well marked. In both places ink was also present in relation to the anterior nerve roots. The epidural pads of fat in the lumbosacral region were grey in colour owing to the presence of free indian-ink particles in their interstices (Fig. 1A g). Microscopical

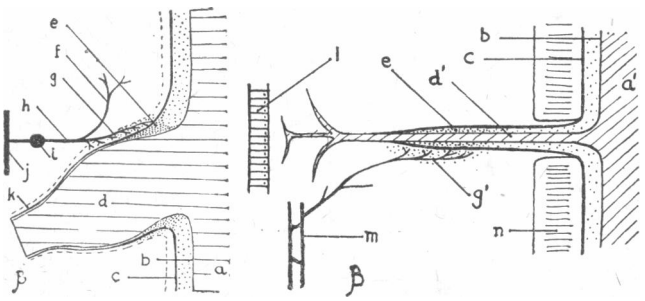


FIG. 1A.—Scheme showing the mode of elimination of indian-ink particles from the subarachnoid cul-de-sac around the dorsal-root ganglion of a spinal nerve. FIG. 1B.—Scheme showing mode of elimination of indian-ink particles from the subarachnoid extensions along the olfactory nerves. Note that in both cases ink particles are eliminated from the subarachnoid space into interstitial tissue and pass secondarily into the lymphatic system. a. Spinal cord. a.[1] Olfactory bulb. b. Pia. c. Fused dura and arachnoid. d. Spinal nerve root. d[1]. Olfactory nerve. e. Accumulation of indian ink in subarachnoid cul-de-sac. f. Lymphatic draining spinal muscles. g. Lymphatic in epidural fat. g[1]. Lymphatic arising in interstitial tissue of nasal mucosa. h. "Segmental" collecting trunk. i. Prevertebral lymph node. j. Longitudinal abdominal lymphatic. k. Epidural connective tissue. l. Nasal mucous membrane. m. Submucous lymphatic plexus. n. Cribiform plate.

examination of the dorsal-root-ganglion region showed that here ink particles were passing through the covering membranes and coming to lie freely on the surface or passing into the superjacent epidural fat. Whilst many particles were intracellular, many on the other hand were free.

Examination of the abdomen showed that the lymph nodes in relation to the spinal column, particularly those around the aortic bifurcation and in the hollow of the sacrum, were filled with ink in degrees varying from pale grey to jet-black. Tiny scattered lymph nodules behind the aorta and inferior vena cava were also filled with ink, and in some favourable cases it was possible to make out under the binocular dissecting microscope fine black lines passing backwards towards the spine. Similar small scattered nodules were also found in a corresponding position in the thorax, though only after good filling of the subarachnoid space. In all cases the cervical lymph nodes, both superficial and deep, contained indian ink. In order to determine more fully the channels by which cervical filling took place, indian ink was introduced continuously into the subarachnoid space through a cannula carefully inserted in the lumbar region after laminectomy in the fresh cadaver. In this way under controlled pressure several millilitres of ink could be introduced. Subsequent dissection showed that the ink-bearing afferent vessels of the cervical nodes originate largely from the mucous membrane of the nose. A certain number, however, were found to emerge from the jugular foramen and enter the upper pole of the highest deep cervical node—a fact noted already by Schwalbe in 1869. As will appear later such vessels deserve consideration in any discussion of possible modes of invasion of the nervous system by an infective agent.

*Nasal Outflow.*—Histological examination of the whole decalcified nose region showed that ink passed down the sheaths of the olfactory nerves to reach the connective tissue stroma and lymphatic plexus of the nasal mucosa (Fig. 1B). Ink was also present in the endoneurial septa of the nerve filaments. These findings are quite analogous to those of Faber (1938).

*Orbital Outflow.*—Enucleation of the eyeball revealed the anticipated accumulation of ink in the subarachnoid sleeve of the optic nerve. In addition, however, a diffuse greyness of the retrobulbar fat in the vicinity of the nerve was apparent. In order to obviate difficulties arising from the normal occurrence of pigment in this region a series of experiments were undertaken in pure albino animals. Histological examination showed ink particles making their way through the optic-nerve sheath immediately behind the eyeball, spreading out in the episcleral space and extending between the fibres of the retractor bulbi muscle. Details of these findings will be published elsewhere.

*Passage into the Brain Substance.*—In those cases in which ink was instilled directly into the ventricle subsequent examination revealed particles in the depths of the brain substance. Some ependymal cells were seen to be finely stippled with very small granules, and these were also to be found at some depth from the ventricle. Many of these deeper particles had been ingested by phagocytic elements, especially if the animal had been allowed to survive for some time. Some evidence was also found to suggest that ink-laden ependymal cells might become detached and move into the subjacent nervous substance. Such passage of indian ink occurred particularly at the inner "angle" of the lateral ventricle as seen in coronal section. To a smaller extent ink particles were also found to have penetrated the wall of the third ventricle. Unfortunately the fourth ventricle was not examined, but there is evidence in the literature that this is a site at which penetration of particulate matter from the cerebrospinal fluid may take place with relative ease (Hurst, 1930; Hamperl and Heller, 1934).

## Discussion

The interpretation of the microscopical appearances in the nerve-root region presents some difficulty and has been discussed fully elsewhere (Brierley and Field, 1948). Briefly it may be stated that transport by phagocytes cannot account entirely for the passage of ink out of the subarachnoid space, a process which must be, in part at least, a passive one dependent upon an actual outflow of cerebrospinal fluid. The arachnoid culs-de-sac around the nerve roots may thus be looked upon as definite points of exit of cerebrospinal fluid into the lymphatic system and the prevertebral nodes regarded as the regional nodes of the spinal subarachnoid space.

The rapidity with which indian ink introduced into the cranial division of the subarachnoid space makes its way down to the lumbosacral region is striking. It would seem that particulate matter introduced into any region of the subarachnoid space accumulates in relation to the lumbosacral root ganglia (and to a lesser extent also the cervical) within some six to twelve hours. In the cranial region the most important outflow to the lymphatic system is along the sheaths of the olfactory filaments, though outflow also takes place by lymphatics which emerge through the jugular foramen and possibly also through other nerve foramina. In the spinal region outflow occurs along lymphatic vessels which arise in relation to the dorsal-root ganglia, more especially in the lumbosacral and cervical regions. By the mechanisms indicated the subarachnoid space may be largely cleared of fine particulate matter within some 24 hours or so of introduction. Of course, a certain amount of foreign material is taken up by arachnoid cells which may become phagocytic (Goldmann, 1913; Woollard, 1924), but this process is not under consideration here. In some

cases, in addition, fixation by the nervous tissues themselves may play a part in clearing the cerebrospinal fluid.

It is of interest to see how far the results outlined above may facilitate the interpretation of the clinical and experimental findings in poliomyelitis. Furthermore, the possibility of retrograde spread from the periphery to the central nervous system along a lymphatic pathway has been shown to rest on a definite anatomical basis. The experimental accomplishment of such spread by indian-ink particles will be described below.

Two aspects of the poliomyelitis problem may be considered: (1) How far are these findings consonant with the belief that the virus is spread by the cerebrospinal fluid? (2) What pathways are available as channels of access to the cerebrospinal fluid in the first place?

#### Presence of Virus in the Cerebrospinal Fluid

There are many reports in the literature claiming that the cerebrospinal fluid in human poliomyelitis is not infective. However, it is known that in the experimental animal, following intrathecal introduction of virus, the cerebrospinal fluid remains infective forty-eight hours after inoculation but is no longer so at the sixth day—the time of development of symptoms (Clark and Amoss, 1914). Apparently virus may be eliminated from the cerebrospinal fluid rapidly. Assuming that virus did enter the cerebrospinal fluid from outside the nervous system, its detection would be likely only in the first twenty-four hours or so. With these considerations in view the reports on infectivity of the cerebrospinal fluid were scrutinized with particular reference to the times at which the tests were carried out. Many of the human reports deal with the paralytic stage of the disease—when, presumably, any virus which may have been in the cerebrospinal fluid has long since been eliminated or fixed. Abramson (1917) tested the sediment obtained by spinning fluid from forty cases—"many in the pre-paralytic stage"—with negative results. However, in the absence of more precise information as to time after infection—information which it may be very difficult if at all possible to obtain—the significance of this result is equivocal. So far as the human disease is concerned, therefore, no certain evidence is available as to the infectivity of the fluid at the time when it might be expected to be at its height.

Unfortunately the position is little better for experimental poliomyelitis. The scanty reports available are at variance, and adequate testing of cerebrospinal fluid at the crucial times following par-neural inoculation does not appear to have been carried out. Flexner and Amoss (1914) reported the presence of virus in the cerebrospinal fluid before the onset of the disease. However, they were using the intravenous route, for which the minimum infective dose and the incubation period are greatly increased. On the other hand, Fairbrother and Hurst (1930) made examinations of the cerebrospinal fluid at daily intervals following intracerebral inoculation of virus, and failed to find it in the fluid. These authors are of the opinion that axonic transmission far outweighs cerebrospinal fluid dissemination in importance. There are, however, so many factors which may influence the result of cerebrospinal fluid testing (e.g., time, dose of fluid, strain of virus, susceptibility of test monkey), and the point is of such importance that confirmation of their results is needed. Incidentally it should be noted, as the authors themselves point out, that any intracerebral inoculation is in no small measure also a subarachnoid introduction, since leakage along the needle track cannot be prevented. This fact throws the differences between the results of Clark and Amoss (1914) on the one hand and Fairbrother and Hurst (1930) on the other into still sharper relief.

Leiner and v. Wiesner (1910), in a small series of experiments, found that virus introduced intracerebrally could be readily detected in the cervical, prevertebral, and mesenteric lymph nodes but not in the inguinal group. This suggests that elimination takes place from the subarachnoid space along the same channels as serve for the elimination of particles of indian ink. However, Yoffey and Drinker (1939) found that the virus of poliomyelitis did not pass readily into the cervical lymphatic system following introduction into the nose, and concluded that the particular strain of virus used (Toomey "T") "did not spread by way of lymphatic vessels and nodes." Nevertheless, vaccinia virus, the particles of which are of the same order of magnitude as the smallest ink particles in our own experiments, readily utilizes lymphatic channels of spread (Yoffey and Sullivan, 1939). This difference is all the more remarkable since the virus of poliomyelitis is so much smaller (0.008–0.012 $\mu$ up to 0.058 $\mu$—Elford, Galloway, and Perdrau, 1935; Levaditi, Kling, Païc, and Haber, 1936) than is that of vaccinia (0.125–0.175 $\mu$—Elford and Andrewes, 1942).

#### Lesions of the Dorsal-root Ganglia

These lesions are a constant feature of poliomyelitis in human beings (Peabody, Draper, and Dochez, 1912), and may account for the severe pain of root type which is often a feature of the pre-paralytic stage (Russell, 1947). Experimental work suggests that whatever the route by which infection of the nervous system is brought about, such lesions are an early—sometimes the earliest—finding (Flexner and Amoss, 1914). This is what one would expect if the virus were in the cerebrospinal fluid and accumulated at the same outflow points round the nerve roots as does indian ink. Moreover, ink particles may be found in the depths of the dorsal-root ganglia, where many are taken up by the satellite cells. Flexner and Amoss (1914), using carmine particles "smaller than many bacteria," found the pigment to penetrate the ganglia only with difficulty. The fine ink particles employed by us do so readily, however, and no doubt virus may penetrate with even greater facility.

#### Distribution of Lesions

Hurst (1932) was of the opinion that the distribution of lesions in experimental poliomyelitis did not follow the pattern in which indian ink or trypan-blue was distributed after introduction in the monkey. Nevertheless, many of Fairbrother and Hurst's (1930) results would seem to be best interpreted on the basis of a cerebrospinal fluid spread of virus. Hurst himself envisages the early involvement of the globus pallidus, hypothalamus, and occasionally the thalamus as possibly due to infection along the perivascular spaces of the anterior perforated substance. Further evidence of invasion from the cerebrospinal fluid was met with in the midbrain and pons. Moreover, the distribution of lesions after infection by intrathecal, intraneural, or intracerebral routes "is essentially the same" (Hurst, 1932). The common factor in distribution would seem to be the cerebrospinal fluid, more especially as neither virus nor lesions are to be found in the areas intervening between widely scattered foci. Furthermore, the various levels of the cord become involved almost simultaneously; and Fairbrother and Hurst (1930), having postulated axonic transmission as the chief mechanism of spread, are forced to the conclusion that "there is an initial delay in the infection of fibres at the site of inoculation, after which the virus travels so rapidly as to reach distant regions of the nervous system as quickly as closely adjacent areas" (p. 40). A simpler working hypothesis would be that of cerebrospinal fluid spread, especially as it is entirely consonant with the observed phenomena. Indeed, the weight of evidence is such that Hurst (1930) himself feels impelled

to allow that "infection of the cerebrospinal fluid contributes to the final picture of fully developed poliomyelitis" (p. 1141).

The experimental results obtained with fine indian-ink particles (in rabbits) suggest that such material in the cerebrospinal fluid has widespread access to the nervous substance. Undoubtedly virus could disseminate in a similar manner, and this together with invasion from the superficial subarachnoid space along perivascular channels may account for the early lesions of poliomyelitis in loci accessible to cerebrospinal fluid.

The interesting results of Jungeblut and Spring (1930) require consideration. They found that intracerebral inoculation of virus in a monkey whose cord had been previously transected resulted in an attack of poliomyelitis, and although the distal segment of cord was freely bathed in cerebrospinal fluid neither virus nor lesions could be found in it. Howe and Bodian (1941) repeated and extended the work of Jungeblut and Spring, and found that even after careful section of the spinal cord and obliteration of the subarachnoid space (checked by indian ink and methylene-blue injection at necropsy) virus could pass down to the isolated lumbar cord in one case out of four after intranasal or intracerebral inoculation. (The technique in this one positive case, however, was such as to render the significance of the result equivocal.) On the other hand, inoculation of the sciatic nerve in animals with completely divided cord and subarachnoid space resulted in progression of virus into the upper-cord segment in two out of four cases—"possibly along the paravertebral sympathetic chains." However, further experiments showed that even after bilateral sympathectomy of two or three ganglia at the level of cord section had been carried out, inoculation direct into the lumbar cord resulted in progression of virus to the upper segment of nervous system in every case. The authors suggest that virus passed from the spinal cord to the wall of the gut via sympathetic-nerve fibres and thence to the brain-stem along the vagus nerve. An alternative and simpler interpretation will be considered below after further experimental results of our own have been described.

### Channels of Access of Virus to the Cerebrospinal Fluid

The nasopharynx, tonsil, and upper respiratory tract have all been implicated from time to time as portals of entry for virus both in the human and in the experimental animal. Our own results have substantiated the existence of a definite anatomical pathway (in the rabbit) between the cranial subarachnoid space and the deep cervical lymph nodes by means of lymphatics which emerge through the jugular foramen. Since the tonsil, too, is connected with these nodes, the anatomical basis exists for lymphatic extension of virus from tonsil to cranial subarachnoid space. This connexion is in addition to the well-known and more readily demonstrable paths from the nasal mucosa.

In recent years much attention has been given to the gut as a portal of entry, largely from the standpoint of axonic transit of virus. Although there is a wealth of pathological evidence to suggest that the lymphoid tissue of the bowel is the site of early and often severe lesions (Wickman, 1913; Burrows, 1931; and many others), no serious attempt seems to have been made to examine systematically the possibility of a retrograde lymphatic spread of virus to the spinal cord from the bowel. In view of the definite connexions which have been shown to exist between the spinal subarachnoid space and the abdominal lymphatic system the possibility of bringing about experimentally retrograde spread of ink particles from the mesenteric and prevertebral lymph nodes to the cord was explored.

### Retrograde Lymphatic Flow to the Cord: Experimental Methods and Results

In order to produce a stasis of the abdominal lymphatic drainage, a condition favourable to the retrograde flow of ink, ligation of the thoracic duct was performed. Because of the multiple lymphatico-venous communications met with in the lumbar region of many lower animals, the stasis resulting from such an operation is incomplete. The ligation was performed in the mid-chest region by a right transpleural approach, respiration being maintained mechanically throughout the experiment. Laparotomy was then performed and indian ink, made up in reconstituted plasma, injected into the aortic and mesenteric lymph nodes. By repetition of this procedure at two- to three-hourly intervals up to 4 or 5 ml. of ink could be introduced. Animals have survived these formidable operative procedures for periods up to twelve hours, during which time the pulse has been good and repeated doses of nembutal have been needed to prevent recovery of consciousness.

By this technique it has been possible to trace fine lymphatic channels backwards from the region of the cisterna chyli, usually through one or more tiny prevertebral nodes, round the side of the vertebral column. To such vessels come tributaries which collect lymph from the dorsal-root-ganglion region, and in particularly successful fillings of these minute vessels ink is to be found right on the dorsal-root ganglion itself and the adjacent cord membranes. Ink may even spread further back in the main lymphatic vessel and pass into the substance of the erector spinae musculature. A detailed account of these anatomical pathways (Field and Brierley, 1948) is not necessary here, but they may be summed up as follows. Lymphatic vessels in the substance of the erector spinae muscle unite to form one or more vessels which accompany the nerve and blood supply of the muscle towards the intervertebral foramen. Here lymph-vessel branches come in from the dorsal-root ganglion and its related epidural fat, and the main vessel then continues ventrally round the side of the spine, to reach the cisterna chyli or one of the many subsidiary longitudinal ducts which empty into it. As a rule a small lymphatic nodule is interposed in the course of the vessel on the anterolateral aspect of the spine (Fig. 2).

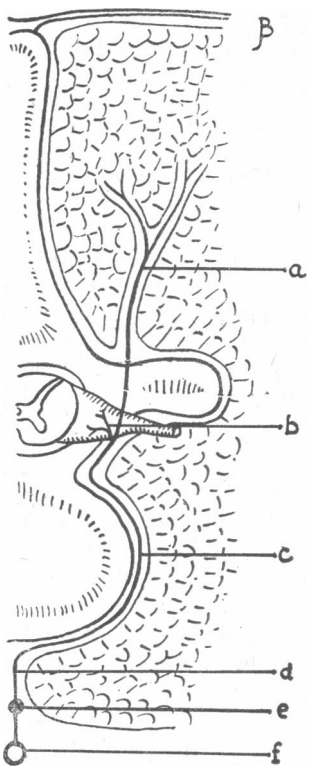


FIG. 2.—Scheme indicating the disposition of the lymphatic drainage of the nerve roots. a. Lymphatic arising in the posterior spinal musculature. b. Small lymphatic tributaries from dorsal-root-ganglion region. c. Lymphatic channel passing ventrally round vertebral body under cover of psoas muscle. d. "Segmental" vessel visible from the abdomen. e. Small prevertebral lymph node. f. Longitudinal collecting channel on front of spine.

It would seem, then, that under certain experimental (and admittedly highly artificial) conditions there is the possibility of a retrograde flow of fine particulate matter from the mesenteric and prevertebral nodes to the spinal cord. Conditions approximating those of the experiments out-

lined above might come about in man or monkey should a temporary functional occlusion of the thoracic duct leading to lymphatic stasis take place.

Unfortunately, little is known of the responses of the thoracic duct to physio-pathological stimuli, though the presence of plain muscle fibres and nerves in its wall suggests that variations in calibre do take place. Spasm of larger lymphatic channels is a phenomenon well recognized by experimental workers, and often arises, it is said, as the result of drying or unnecessary handling. This problem is receiving further attention.

It is of interest to recall that severe muscular exercise or bowel contraction results in a considerable increase in lymph flow from the parts concerned and a steep rise in pressure in the larger collecting channels (Drinker and Yoffey, 1941). These circumstances, together with a partial obstruction of the thoracic duct—perhaps at the aortic opening in the diaphragm—might succeed in creating a temporary diversion of lymph towards the spinal cord. It should be recalled in this connexion that the small "segmental" vessels which pass ventrally round the sides of the spine are not valved. Such a retrograde lymphatic invasion of the nervous system would also account for the early presence of lesions in the dorsal-root ganglia of the lumbar region. However, it must be realized that virus which gained access to the subarachnoid space by whatever route would also accumulate in this region (see above). Probably the same route of access does not hold for all cases.

The lymphatic vascular system related to the dorsal-root ganglia must be taken into account in evaluating the important results obtained by Howe and Bodian (1941) referred to above. These authors mention the possibility of lymphatic spread of virus but pass it over in favour of axonic dissemination along "some unusual nervous connexions." Our own results would seem to furnish a relatively simple lymphatic anatomical pathway by which virus might spread from an isolated lumbar segment of cord to the rest of the nervous system. Injection into the lumbar cord is virtually a lymphatic injection, assuming that virus may take a path readily available to fine indian-ink particles. The virus which leaves the lumbar sac by lymphatics from the dorsal-root ganglia may then readily pass upwards (the normal direction of flow) and subsequently in a retrograde manner to dorsal-root ganglia above the site of section. To us—unwedded as we are to the concept of axonic transmission—this seems a simpler explanation and one deserving of experimental testing. Furthermore, experiments by one of us (J.B.B.) have shown that injection of indian ink "into" the sciatic nerve will often lead to a beautiful filling of the lymph nodes around the bifurcation of the aorta. From these the injection mass may pass to the paravertebral lymphatic channels. It is not, therefore, surprising that infection of the upper segment of cord should have occurred in Howe and Bodian's elegant experiments following inoculation of the sciatic nerve with virus.

## Summary of Conclusions

1. Particulate matter in the cerebrospinal fluid is rapidly removed and tends to accumulate at outflow points round the lumbar and cervical nerve roots.

2. The prevertebral lymph nodes are the "regional" nodes of the spinal subarachnoid space.

3. The presence of virus in the cerebrospinal fluid in both human and experimental poliomyelitis would seem to be uncommon. However, in view of the rapidity with which particulate matter has been shown to be eliminated from the subarachnoid space, it is probable that reports in the literature are concerned with stages when any virus which may have been present earlier has already been eliminated.

4. The distribution of fine particulate matter in the cerebrospinal fluid has been compared with that of the early lesions of poliomyelitis, and certain similarities have been noted suggesting that the fluid may play a more important part in the pathogenesis of the condition than that usually accorded it by the adherents of the theory of neuronic transmission.

5. The anatomical basis for invasion of the nervous system along direct lymphatic communications has been described. Lymphatics emerging through the jugular foramen end in deep cervical lymph nodes which also drain the tonsil and nasopharyngeal region. The lymphatic connexions of the cranial subarachnoid space via the neurovascular foramina are in addition to the well-known connexion via the sheaths of the olfactory nerves and the nasal mucosa.

In relation to the spinal subarachnoid space a system of valveless lymphatic channels has been described. They are summarized in Fig. 2. Lymphatic vessels start in the substance of the post-spinal musculature, and pass ventrally in company with the nerve and blood supply of the muscle towards the neighbourhood of the intervertebral foramen. Here fine tributaries reach the lymphatic from the neighbourhood of the dorsal-root ganglia and arachnoid sac around the nerve roots. Having received these, the lymphatic continues around the side of the vertebral body to end in one of the several valveless longitudinal trunks on the front of the spine.

This lymphatic pathway has been filled experimentally with indian ink in a retrograde manner from the mesenteric and prevertebral lymph nodes, after preliminary ligation of the thoracic duct in the thorax. Whilst great caution must, of course, be exercised in carrying over results obtained in the rabbit to man and monkey, the possibility of a similar retrograde passage of virus to the lumbar region of the cord must be maintained.

6. Certain recent results in experimental poliomyelitis have been discussed in the light of the lymphatic connexions set out in this communication.

It is a pleasure to record our indebtedness to Professor J. M. Yoffey for his never-failing interest and encouragement, and for his expert advice on general problems of technical procedure appertaining to lymphatics.

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