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MENINGITIS AFTER SPINAL ANALGESIA

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The possibility of introducing infection into the subarachnoid space by spinal tap has been recognized from the time that lumbar puncture was first performed, and this possibility must be considerably increased if anything is injected into the theca. Though Babcock (1932), when reviewing the causes of death following spinal analgesia, says meningitis is extremely rare, it is probable that the percentage of infections is higher after this procedure than after any other necessitating lumbar puncture. The literature would appear to support the infrequency claimed by Babcock, for only scattered references can be found, but this may be accounted for by a natural reluctance to report what should be a preventable happening.

Six cases of meningitis after simple lumbar puncture have been described. Siebert (1922), Spiller and Payne (1924), Symonds (1925), and Reynolds and Wilson (1934) gave the details of this group, in which one death occurred.

After spinal analgesia there are more frequent reports. Barrie (1941) describes 11 cases with one death in 96 consecutive spinal analgesias in three months. Livingstone, Wellman, Clark, and Lambros (1943) describe 2 cases which they label "aseptic chemical meningitis," and quote 8 further cases with three deaths from the earlier literature. Evans (1945) gives an account of two deaths from such a meningitis, but does not indicate whether these were the only cases or whether they were the fatalities in a series. The clinical details of all these cases are scanty, and for this reason the group below is reported.

If infection is introduced along a needle track it may obviously lodge anywhere in the course of that track. With lumbar puncture the possible localities are the skin, subcutaneous tissues, vertebrae, epidural space, and subarachnoid space. Each localization gives a fairly typical clinical picture. In this paper are reported seven cases, occurring in the Middle East, of infection of the subarachnoid space after spinal analgesia. One of these patients died, and a post-mortem examination was carried out. Because of its importance in the argument on aetiology and pathogenesis a precisely similar case following diagnostic lumbar puncture is included. The clinical course of this condition is so prolonged that only the first case is given in full detail. The others are briefly summarized. For ease of comparison the C.S.F. findings are collected in the accompanying Table.

Case I: Male aged 22

Jan. 9, 1942.—Herniotomy was performed after the administration of 13 c.cm. of nupercaine. He remained well for seven days and then headache and pyrexia occurred, but it was not until Jan. 29 that he developed clinical meningitis—confirmed by lumbar puncture (Table, L.P.1). Sulphapyridine was given with apparent improvement, but he relapsed very soon. These remissions and relapses continued in spite of treatment, and the patient was transferred to the neurological unit on March 4. He was then fairly well and had a positive Kernig's sign as his only abnormality. On March 18 he relapsed (L.P.5) and was given a course of sulphathiazole. No real improvement occurred (L.P.6), and the next relapse on March 26 was treated with sulphadiazine.

March 29.—Felt very much better. No headache and temperature settled. Neck and back felt easier (L.P.8).

April 1.—He had been very well until the early hours of this morning, when he had a sudden onset of severe renal colic, more marked

on the left, with haematuria. The total dosage of sulphadiazine was 100 g., and no more was given. The patient was put on a glucose-saline intravenous drip and given 1 dr. of sodium citrate by mouth every three hours. As no urine was passed between 10 a.m. and 6 p.m., the ureters were catheterized by Lieut.-Col. Ogier Ward. Small clots protruded from the ureteric orifices, and the renal pelvis were washed out with bicarbonate solution until the return was clear. After this his urine became normal.

April 3.—He now felt fine and had no complaints apart from slight stiffness in the legs (L.P.9).

May 17.—Until this date he continued to improve apart from residual stiffness in the legs. He developed a headache in the night, and temperature rose to 102° F. On examination no physical signs could be made out—certainly nothing to suggest a recrudescence of meningitis. This settled after two days.

May 25.—Blood count: R.B.C., 4,510,000; Hb, 85%; W.B.C., 10,200, differential normal. B.S.R. (Westergren): Fall in one hour, 48 mm.; in two hours, 31 mm.

The B.S.R. indicated that some active infection was still present, and three days later he again complained of severe pain in the head which was both retro- and supra-orbital. He also had pain in the neck and lower back, going down the backs of both thighs and legs. He had two further relapses, which appeared to respond to sulphadiazine, but by June 16 (L.P.10-13) the lumbar punctures suggested the infection was sealing itself off in the spinal canal. Every now and again apparently a pocket leaked into the general subarachnoid space and there was a recrudescence of the general manifestations. This loculation could be regarded as a stage of lumbar arachnoiditis, and it might account too for the failure to clear completely with sulphadiazine therapy. The drug appeared capable of dealing with the infection when it was generalized in the spinal theca, because this settled more rapidly with than without treatment. The presence of loculation was supported by the poor response to jugular compression and the rise in C.S.F. protein without a corresponding rise in cells. Support for this theory was also given by the symptoms, which were mainly confined to the back and legs and persisted even when the patient was otherwise fairly well. It was decided that the next time lumbar puncture was carried out a simultaneous cisternal puncture should be done and the fluids compared. Any significant difference would indicate that the theory was possibly correct. This was done on June 19 (C.P.14 and L.P.15). Macroscopically the two fluids were very different and, with the laboratory findings, supported the diagnosis of infection confined mainly to the lumbar subarachnoid space with partial blockage of C.S.F. circulation. It was now suggested that, owing to the block, the sulphadiazine did not reach the infected area in reasonable concentration, and it was decided to put a weak solution of the drug into the lumbar theca. The danger of using sulphonamide derivatives by that route was well known, but it was felt that this was due to the great alkalinity of ordinary solutions, and carefully neutralized 1/4% sulphadiazine was used. The pH of this was just above 8, and 20 c.cm., containing 50 mg., was injected by lumbar puncture. No untoward reaction occurred.

June 29.—There had been no local or general reaction and the patient felt much better, but could not bend his back with ease and the back of both thighs felt stiff (L.P.16).

July 7.—In the past week the patient had been feeling rather better, but on this day had more local pain in the back. There was no tenderness or redness over the lumbar spines. The legs felt stiffer, but there was no neck stiffness (L.P.17). 20 c.cm. of 1/2% (100 mg.) sulphadiazine solution of pH just over 8 was introduced into the lumbar theca. No reaction of any kind occurred.

July 13.—The patient had been very well during the past week. He thought his back and legs were less stiff. Again simultaneous

cisternal (18) and lumbar (19) punctures were carried out. These indicated that, temporarily at any rate, the local introduction of weak sulphadiazine solution had cut down the infection, though the rise in protein was a little disturbing. There was certainly no clinical evidence of gross damage to the spinal cord, nerves, or membranes. No sulphadiazine was present in either fluid.

July 17.—(L.P.20.) The rise of protein indicated either further obstruction by adhesions in the spinal arachnoid space or a reaction locally to the sulphadiazine.

July 24.—He had a sudden onset of headache and his temperature rose to 101°, but there was no neck stiffness or any increase of leg

of six weeks after the initial treatment with sulphadiazine. The generalized meningitis had disappeared, either naturally or as a result of treatment, but the recrudescence proves that pocketing had already occurred. The clearing of the spinal obstruction was also seen in later cases. It is probable that in this spontaneous disappearance of adhesions an occasional pocket of infection is liberated into the general subarachnoid space. The continuation of infection in the pockets suggests that the sealed-off areas cannot be reached by chemotherapy. It is possible, however, that these pockets contain sterile pus and that the clinical manifesta-

Table showing C.S.F. Findings in Case I

	Date	Route	Pressure	Jugular Compression	Appearance	Protein mg./100 c.cm.	Polymorphs per c.mm.	Lymphocytes per c.mm.	Film	Culture
1	29/1/42	L.P.	150	Free rise	Turbid	90	400	1,600	Nil	Sterile
2	5/2/42	L.P.	160	"	Opalescent	80	50	450	"	"
3	26/2/42	L.P.	140	"	Turbid	100	3,200	600	"	"
4	9/3/42	L.P.	190	"	Opalescent	70	750	350	"	"
5	18/3/42	L.P.	200	"	Turbid	90	1,500	500	"	"
6	23/3/42	L.P.	240	"	Opalescent	90	510	220	"	"
7	26/3/42	L.P.	200	"	"	85	460	170	"	"
8	29/3/42	L.P.	160	"	"	60	70	45	"	"
9	3/4/42	L.P.	170	"	Clear	40	—	25	"	"
10	31/5/42	L.P.	200	"	Turbid	120	2,800	480	"	"
11	5/6/42	L.P.	130	"	Clear	50	28	16	"	"
12	13/6/42	L.P.	120	Poor rise	"	85	—	2	"	"
13	15/6/42	L.P.	150	Very poor rise	Opalescent	150	80	320	"	"
14	19/6/42	C.P.	90	Free rise	Clear	65	12	48	"	"
15	19/6/42	L.P.	70	No rise	Opalescent	100	650	600	"	"
16	29/6/42	L.P.	100	"	Clear	100	24	16	"	"
17	7/7/42	L.P.	100	"	Opalescent	120	160	40	"	"
18	13/7/42	C.P.	100	Free rise	Clear	90	—	15	"	"
19	13/7/42	L.P.	80	Slight rise	"	95	5	5	"	"
20	17/7/42	L.P.	140	No rise	"	200	—	—	"	"
21	24/7/42	L.P.	150	Slight rise	Opalescent	85	410	270	"	"
22	31/7/42	L.P.	100	"	Hazy	40	36	24	"	"
23	23/8/42	L.P.	150	Slow rise	"	100	150	100	"	"
24	31/8/42	L.P.	140	"	"	80	77	33	"	"
25	7/9/42	L.P.	120	Moderate rise	Clear	90	—	7	"	"
26	14/9/42	L.P.	130	Free rise	"	70	—	20	"	"

stiffness (L.P.21). After this he was given sulphadiazine by mouth in a three-day course of 10 g. daily. This was to be repeated each week for four weeks.

L.P.22 and 23 were done on July 31 and Aug. 23. It was disappointing to find the persistence of infection when the four-weeks course had been completed. The possibility of washing out the lumbar theca as described by Symonds (1925) through high and low lumbar or through cisternal and lumbar needles was discussed, but it was decided to postpone this for the present, and to give another intrathecal dose of sulphadiazine at the next lumbar puncture.

Aug. 31.—(L.P.24.) 20 c.cm. 1/2% sulphadiazine (100 mg.) was given intrathecally. Within half an hour there was a reaction, with severe pain in the back which spread up, and in one hour there were severe headache and neck stiffness. The temperature rose to 102° four hours after the injection and there was definite head retraction. Vomiting began about two hours after the injection and continued for ten hours. The patient said that he had not had so severe a headache or pain in the neck or back since the original onset of meningitis. He required 1/4 gr. morphine and 1/100 gr. hyoscine in the night for the relief of pain and headache.

Sept. 1.—The headache, neck stiffness, and backache had now gone and the temperature was normal. Apart from feeling limp, the patient said he was not too bad. Examination showed no physical signs apart from lower back and thigh stiffness. The sulphadiazine solution was investigated, and it was found that the pH on this occasion had been tested with a colour indicator which had deteriorated and that the pH might actually have been as high as 9. On the previous occasions the pH had been determined with the hydrogen electrode. The reaction produced in the patient was therefore due to the alkalinity of the solution, and was a true irritation of the arachnoid giving a meningitic picture.

Oct. 24.—The last two lumbar punctures were done in September, and during the past month the patient had been very well. There had been no pyrexia for six weeks and, apart from a minor bout of furunculosis, no untoward happenings. He walked well, but his legs tired very rapidly. Examination showed no physical signs in any system beyond a limitation of straight-leg raising to 45°. The other systems were normal. B.P., 130/90. Urine: Sp. gr., 1020; no albumin, sugar, or casts present. Blood urea, 32 mg. per 100 c.cm. Blood count: R.B.C., 4,750,000; Hb, 85%; W.B.C., 9,000, with a normal differential. Sedimentation rate (Westergren) normal.

Eight months later this patient was very well apart from stiffness of the lower back and thighs. He still tired very easily. These were his only symptoms and the only signs of damage to the cauda equina.

There can be little doubt that this man had had a lumbar obstruction to the flow of the C.S.F. which cleared spontaneously. It is difficult to see why there had been a completely free period

tions are due simply to the liberation of this irritant material into the general subarachnoid space.

Case II: Male aged 25

On Sept. 9, 1942, appendicectomy was carried out under spinal analgesia, 13 c.cm. of light percaïne being used. The appendix was acutely inflamed. The patient had a continuous pyrexia after the operation, and three days later complained of some pain in the back, for which no cause was found. It was not until Sept. 21 that there were any clinical signs of meningitis, but the local tenderness prevented any punctures being carried out. He was started on sulphadiazine and began to improve, only to relapse exactly as the previous patient had done. He was transferred to the neurological unit on Oct. 3. He then had an obvious clinical meningitis, but was very tender over the lumbar spine. This suggested a possible osteomyelitis of the spine or a spinal epidural abscess. Skiagrams of the spine were negative, and a cisternal puncture confirmed the meningitis. The back soon settled and lumbar puncture as low as possible showed a free flow of fluid, thus negating a large epidural abscess, which would have caused an obstruction. This patient did not respond to sulphadiazine, having many remissions and relapses. Several transfusions were given because the haemoglobin was falling, but with only temporary improvement. By the middle of November his condition had deteriorated greatly; it was obvious that spinal block had developed, and on Nov. 27 intrathecal sulphadiazine accurately buffered was given. This was repeated on three occasions. In spite of the C.S.F. improvement there was no clinical progress, and early in December he had passed into a state of akinetic mutism with definite papilloedema. As in spite of the spinal block the C.S.F. protein remained relatively low it was felt that this block must be very high up. On Dec. 18 the left lateral ventricle was tapped through a burr-hole. Instillation of methylene blue followed by cisternal and lumbar punctures showed that the block was below the cisternal level. In spite of ventricular tapping his condition deteriorated, and on Jan. 8, 1943, as he was moribund, 2,000 units of calcium penicillin were instilled into the ventricle. This produced no clinical change, but his C.S.F. now gave a profuse growth of *Ps. pyocyanea*. He died on Jan. 11.

Post-mortem Examination.—This was carried out by Capt. A. D. Morgan, R.A.M.C. External appearances:—The body was that of a pale and extremely emaciated young man. The right pupil was dilated. In the right iliac fossa was a healed surgical wound. Spine:—The muscles in the lumbar region were rather juicy, but there was no evidence of extradural abscess or osteomyelitis. The C.S.F. in the lumbar theca was yellow, turbid, and under pressure. The dura mater was slightly thickened and the pia-arachnoid inflamed throughout. Over the thoracic segments of the cord was a thick yellow exudate causing fairly firm adhesions between dura and cord.

In the meshes of these adhesions lay pools of turbid C.S.F. Over the posterior aspect of the lower medulla were numerous small subpial haemorrhages. **Head and contents:**—High in the left parietal bone was an exploratory burr-hole. The dura and its venous sinuses were healthy. The brain surface was dry and the gyri were flattened. A thick fibrino-purulent exudate was observed over the base of the brain; elsewhere the meninges were congested. A moderate degree of internal hydrocephalus was present, the ventricles containing air and a little turbid cerebrospinal fluid, their ependyma being coated with a thick glairy tenacious exudate, most marked in the right lateral and third ventricles. On removing this the ventricular wall showed mottled red foci of inflammation. There was no evidence of abscess formation. **Abdomen:**—The appendix scar was healthy. The liver, spleen, and kidneys were normal in size and appearance; the adrenals somewhat atrophic. The stomach and alimentary tract were normal.

Histology.—Spinal cord:—The grey and white matter appeared normal. The pia-arachnoid immediately surrounding the cord was infiltrated with polymorphs. The nerve roots were surrounded by a similar fibrino-cellular mesh-work. Deep-blue staining, circumscribed patches of concentrated polymorphs, and fibrin indicated cross-sections of elongated strands of fibrino-purulent material which had become inspissated in the larger interstices. Outside this zone the cellular reaction became more lymphocytic, and, further out, a very chronic arachnoiditis was represented by a thick layer of fairly dense, avascular, and relatively acellular fibrous tissue, intimately adherent to the inner aspect of the dura mater. This picture was that of a very chronic infection of the pia-arachnoid membrane, with a peripheral deposition of fibrous tissue. **Brain:**—The ventricles were lined by a thick layer of pus. The vessels just deep to the ependyma showed marked lymphocytic cuffing. The appearances indicated that infection at this level was more recent than in the cord.

This is a most instructive case because the necropsy findings prove what had been suspected on clinical grounds. The patient had had a very chronic, relatively mild inflammation of the sub-arachnoid space, which had resulted in fibrin deposition with subsequent organization. Some of this may perhaps have been due to the intrathecal sulphadiazine, but there is good clinical evidence that obstruction in the spinal subarachnoid space had begun some four or five weeks earlier. In this process of organization pools of infected C.S.F. had become shut off, and if the unorganized or even organized fibrin should break down then this infected C.S.F. would be liberated into the general sub-arachnoid circulation. It is possible, too, that these loculi may not develop the same concentration of any therapeutic substances as is present in the free-flowing C.S.F., so that even if the causal organism is sensitive to sulphonamides it is cleared only from the general C.S.F. circulation and not from these loculi. Any dilution of sulphonamide can be obtained, and endless possibilities of rendering a sensitive organism sulphonamide-fast arise. It is impossible to say how these loculi are liberated, but that this does occur can be seen from the relative rapidity with which a spinal block may disappear. This would seem to be a reasonable explanation for the relapses which form the most striking clinical feature of the condition.

Case III: Male aged 27

Herniotomy was performed on Jan. 26, 1942, in a general hospital under spinal percaine analgesia, 13 c.cm. being used. The patient developed clinical meningitis the next day and was treated with sulphapyridine. He improved and relapsed several times and was transferred to the neurosurgical unit on March 4. At first *Ps. pyocyanea* had been found in the C.S.F., but after arrival a short-chain non-haemolytic streptococcus, allied to *Str. faecalis*, and *B. coli* were found. The C.S.F. soon became sterile. Shortly after admission the meningitis increased in severity and he developed papilloedema followed by a right flaccid hemiplegia which became complete. He went on to develop a pseudo-bulbar palsy with increased jaw-jerk and an explosive dysarthria. He did not respond to sulphathiazole in large doses, and on March 23 it was certain that he was developing an obstructive hydrocephalus. He was almost moribund and certainly too ill to stand a posterior fossa decompression. He was started on sulphadiazine. From this time he began to improve and became less drowsy. The sulphadiazine was stopped after 100 g. had been given in seven days. He could now answer questions and respond to commands. The paralysis began to improve, and it became evident that he had a marked cerebellar ataxia on the right. He also had nystagmus on lateral gaze and a cerebellar dysarthria. He continued to improve physically, but as he did so it became obvious that he was badly hit mentally. He complained that he felt in a daze and that his brain worked very slowly. His memory and concentration were very poor, and he could not carry on a conversation for more than a few minutes because he seemed to fall into a dream state. By the time he left for the United Kingdom, at the beginning of June, he was able to walk alone and use his right arm for feeding himself and for writing.

I heard from his wife at the end of November, and he had then been invalided from the Service. He was still hazy and unable to concentrate, and, compared with his state before this illness, seemed like a different man. His right arm and leg had almost recovered and he had had no relapse of the meningitis.

This case almost went the way of Case IV, and we were certain that the patient was beginning an obstructive hydrocephalus. It would appear that, whatever infecting organism was present, it was sensitive to sulphadiazine and that the formation of adhesions around the brain-stem did not continue to extend once this compound was given.

Whether the paralysis, which was pyramidal in type, and the cerebellar manifestations, which this paralysis masked, were due to brain-stem adhesions or whether they were due to a toxic vascular accident such as thrombophlebitis is uncertain. In addition to these local happenings there can be no doubt that the higher functions of the whole cerebral mechanism were impaired. The apathetic appearance, the continual complaint of being in a mental haze, and the marked inability to sustain any effort are remarkably reminiscent of the after-effects of a severe closed head injury. No formal intelligence tests were carried out in this case, but ordinary conversation was enough to suggest a falling off from the level indicated by his previous personal history. His wife describes an undoubted change of personality. These are certainly an indication of generalized hemisphere damage. It is unlikely that such damage could be due to the hydrocephalus alone, as this was of relatively short duration. It is more probably a direct result of cortical damage, though whether toxic or directly inflammatory, as has been suggested in meningococcal meningitis (Banks and McCartney, 1942), it is impossible to say.

Case IV: Male aged 24

On Dec. 27, 1941, this patient had a radical cure of a left inguinal hernia performed under spinal analgesia, 12.5 c.cm. of light percaine being used. The next day he developed meningitis. The C.S.F. and ampoules of percaine from the same batch were sterile. He appeared to respond to sulphapyridine, but, as with the other cases in this group, he relapsed frequently. By Jan. 30, 1942, he had developed papilloedema and was transferred to the neurosurgical unit. It was felt that he had an obstructive hydrocephalus, and the right lateral ventricle was tapped and methylene blue instilled. This failed to pass into the cisterna magna, thus demonstrating an internal hydrocephalus. He continued to have acute hydrocephalic attacks, which could be relieved by tapping the ventricles, but this relief was only temporary. On Feb. 20 a right subtemporal decompression was performed and, after this, lumbar puncture gave as much relief as ventricular puncture. This indicated that the hydrocephalus which was still present was no longer internal but external. As daily lumbar punctures did not help, a posterior fossa decompression was performed on March 9 by Major P. B. Ascroft, R.A.M.C. A fistula was made between the cisterna magna and the posterior cervical muscles, and the papilloedema slowly subsided. He improved very slowly. On June 17 an air encephalogram showed considerable dilatation of the ventricles. There was no obstruction at the fourth ventricle foramina, but there was obstruction round the brain-stem—no air passing on to the cortex.

In this case natural cure resulted. In the early stages the patient undoubtedly had a ventriculitis and a blocking of the outflow from the fourth ventricle. By the time this cleared he had developed an obstruction to the passage through the tentorium. He did not respond to any form of chemotherapy.

Case V: Male aged 25

On Dec. 23, 1941, appendicectomy was carried out under spinal analgesia, 12 c.cm. of nupercaine being used. Both the operation and the puncture were uneventful. The appendix was thickened and contained many concretions. Four days later he developed clinical signs of meningitis and was immediately lumbar-punctured. His C.S.F. was sterile at first, but later specimens grew an anaerobic *Staph. aureus*. He had several remissions and relapses, and was transferred to the neurosurgical unit on March 4, 1942. A control period without any form of therapy showed that a remission could occur spontaneously. He made no lasting response to sulphapyridine or sulphathiazole, but after a course of sulphadiazine he improved and no further remissions occurred. He was the only patient in whom no clinical evidence of spinal block occurred during the course of the illness. This lasted for 14 weeks, and a follow-up a year later showed that he had remained free from symptoms. It is impossible to say whether the cure in this case was due to sulphadiazine or to a spontaneous remission. In only one other patient (Case III) did cure follow so dramatically on a first administration of sulphadiazine. In the next three cases it obviously had no permanent effect whatsoever.

Case VI : Male aged 26

This patient had a radical cure of a right inguinal hernia after receiving 12 c.cm. of nupercaine. Two days later he developed clinical meningitis, which was confirmed by lumbar puncture. His fluid grew coliform bacilli and *Ps. pyocyanea*, but soon became sterile. In spite of this and continued chemotherapy with sulphadiazine he continued to relapse for three to four days at a time. During a prolonged remission his sedimentation rate (Westergren) was 39 mm. in one hour. He developed clinical spinal block about two months after the onset, and following this his relapses were characterized by severe pain in the back and a decrease of straight-leg raising with relatively little headache or neck stiffness. He improved slowly and did not relapse again after four months from the onset. His sedimentation rate was now 5 mm. in one hour, and his straight-leg raising 70° on each side.

Case VII : Male aged 19

On Sept. 3, 1942, this patient was operated upon for a low-grade pelvic peritonitis after receiving 13 c.cm. of light percaïne. The appendix was involved, but it was thought unlikely that this was the cause. Three days later he developed clinical meningitis, confirmed by lumbar puncture, and a pneumococcus was grown from the fluid. The ampoules of percaïne from the same batch as used in this case were sterile, but the local analgesic used for the skin grew *B. coli*. He appeared to respond to chemotherapy with sulphadiazine, but soon relapsed, and he continued relapsing and improving for five months before the infection fully cleared up. Like the preceding case, he developed spinal block about two months after the onset, and this disappeared slowly as the condition improved.

Case VIII : Male aged 29

In this patient the meningitis followed lumbar puncture. He is included because the course of the disease was precisely similar to that in the previous cases though no foreign substance had been injected into the subarachnoid space. In July, 1942, he had a pyrexial illness, in the course of which a lumbar puncture was performed. C.S.F. was perfectly normal. As his symptoms continued he was lumbar-punctured again, and on this occasion the puncture was reported as being difficult and a heavily blood-stained fluid was obtained. Six days after this second puncture he developed meningitis, which was confirmed by lumbar puncture. No organisms were grown. He was transferred to the neurosurgical unit and found not to respond to chemotherapy. He developed spinal block in five weeks, and lumbar punctures were given up. He did not improve, and five months later he was given calcium penicillin 2,000 units by lumbar tap. Unfortunately this was from the same infected batch as used in Case II, and there was a recrudescence of symptoms with a frank *Ps. pyocyanea* infection. This slowly cleared, and a month later he was almost cured. No further relapses occurred after this. The spinal block diminished as the condition improved. Until infected with *Ps. pyocyanea* in Jan., 1943, the case had differed in no essential feature from the previous three recorded. This case is of great importance, for it demonstrates that such a meningitis can occur without the deliberate injection of a foreign substance and cannot be due to chemical irritation alone.

These cases are similar enough to be considered as one group. The condition is a low-grade meningitis which, if it is not stamped out almost at once, causes the deposition of fibrin and the formation of adhesions, in the meshes of which infected C.S.F. may remain for a long time. Periodically this infected C.S.F. may be liberated into the general subarachnoid space and so cause a relapse. This illness is not as a rule immediately serious because the infecting organisms are rarely of high pathogenicity and, unlike the pyococcal infections, life is not at once threatened. So long as the condition is confined mainly to the spinal canal the arachnoiditis, whether it produces spinal obstruction or not, can cause no serious complications and, given time, will eventually resolve. When the infection spreads into the cranium, then adhesions may cause an obstruction to the flow of C.S.F. through either the fourth ventricular foramina or the tentorial hiatus. This results in hydrocephalus with its characteristic signs and symptoms. A ventriculitis may occur, but the general symptomatology and the post-mortem findings suggest that it is rare and if it occurs is late.

At some stage during the course of the illness the stiffness of the back becomes and remains more pronounced than the neck stiffness. This back rigidity usually continues for some time after the infection has died out and recovery is apparently well established. It is probable that the stiffness is due to spinal-root irritation. In the necropsy on Case II it was seen that the nerve roots were surrounded by a fibrino-polymorph cuff, and it is probable that until this undergoes resolution the irritation and consequent stiffness are maintained.

Aetiology

Three possible explanations have been advanced to account for the production of this form of meningitis.

1. The Chemical Theory

This theory suggests that the condition is entirely due to the irritant action of the spinal analgesic and that infection plays no part. This explanation is used by Livingstone, Wellman, Clark, and Lambros (1943) for two cases occurring in 4,006 nupercaine instillations. The clinical picture they describe is that of a mild meningitis occurring after special aseptic precautions which, on paper, seem almost fool-proof. The meningitis lasted four and five days respectively and then cleared up completely. No relapses occurred. The cellular outflow was almost entirely lymphocytic, with a rise in protein content in a sterile C.S.F. It is possible that these two cases may have been chemical in origin. There can be no doubt that the spinal analgesics are irritants and, like all irritants put into the theca, produce a protective reaction.

There have been several investigations into the changes in the C.S.F. following analgesia. Barker (1909) found that 24 hours after intrathecal stavaine there was an increase in leucocytes of various kinds. Iason, Lederer, and Steiner (1930), 12 hours after novocain spinal analgesia, found a pleocytosis, mainly lymphocytic, in 14 out of 31 cases. There was an increase of sugar but not of protein, and no correlation was observed between C.S.F. changes and post-spinal reactions. Konwaler (1943) investigated a series of patients one, two, and three weeks after spinal analgesia and found no changes of any kind. Experimental work has been done by Davis, Haven, Givens, and Emmett (1931). After the intrathecal injection of nupercaine in dogs, admittedly in larger doses weight for weight than are used in man, meningitic changes were present in the arachnoid. These consisted of a thickening of the membrane and collections of proliferated arachnoid cells and plasma cells in the interstices of the membrane. The exudates were mainly lymphocytic. If the animals were killed later, then organization and scarring was seen. This was most marked in the lumbar and sacral region and diminished steadily up the cord. There were some inflammatory changes in the ganglion cells and axis cylinders, but these were less definite and seemed less permanent.

There is therefore good evidence of the irritant effects of the spinal analgesics, but it would appear that with ordinary clinical dosage this irritation comes on at once, is short-lived, and settles down without relapse as the irritant is got rid of. A very good illustration of this occurred in Case I when sulphadiazine solution of too alkaline a reaction was put into the C.S.F. There was an immediate accentuation of meningitis, beginning in the lumbo-sacral region and travelling up the spine to the head accompanied by an increasing pyrexia. The reaction, though violent, lasted less than 24 hours, and there was certainly no tendency to relapse, as this was the beginning of complete recovery from the existing relapsing meningitis. Similar chemical "meningitis" has been seen after the use of impure or deteriorated iodized oils for opaque myelography. This clinical picture is quite different from that occurring in true infective meningitis.

The infrequency with which the infecting organism has been isolated is used to support the chemical theory, but, as has been shown by Smith and Smith (1941), it may have no significance. This is discussed more fully later. This theory cannot explain meningitis which follows simple lumbar puncture, as in Case VIII of this series and the similar cases quoted from the literature, for in these no irritants had been put into the theca. Yet the natural history of this meningitis is identical with that following the spinal. This would suggest that, whatever part the irritant may play, it is not the direct cause of the condition. It is also difficult to see why only one ampoule of a batch of percaïne should be irritant.

2. Secondary Meningitis Theory

The next possibility is that the meningitis is secondary to infection elsewhere in the body. Weed, Wegforth, Ayer, and Felton (1920) suggested on experimental grounds that lumbar puncture in the presence of bacteraemia may produce meningitis, and their findings were confirmed by Remson (1936). This work is open to criticism because a heavy bacteraemia was necessary before positive results were obtained. Pray (1941), from an

analysis of pneumococcal meningitis in children on whom lumbar puncture had been performed before the onset of the meningitis, was not able to confirm the experimental results.

In the present series, Cases I, III, IV, and VI were "clean" hernia operations, and there was no reason to suspect the prior existence of a bacteraemia. In Case V a subacute mildly involved appendix was removed, in Case II an acute appendix was removed, and in Case VII a low-grade obscure peritonitis was found. In none of these patients was there a suggestion of bacteraemia in the pre-operative phase. The clinical features of all the cases recorded were so similar as to suggest the same aetiology and pathogenesis in all. As secondary meningitis is not possible in the "clean" cases, one may argue that it is an unlikely explanation in the others.

3. Infective Theory

The third possibility is that the meningitis is due to the introduction of infected material along the lumbar puncture needle. It is true that in a number of cases it has not been possible to isolate the organism as might be expected in an infective condition. This may have a variety of explanations. In five of the cases described above the C.S.F. was sterile throughout the course of the disease if the known contamination with infected penicillin be excepted. In the three cases in which an organism was found it very soon became so attenuated that it could no longer be cultured. In spite of this the clinical state did not improve, thus indicating that the infection was still alive. If attenuation is the cause of the failure to isolate an organism then it may be that in the cases in which the C.S.F. was sterile from the first this attenuation was present early. Whatever the cause the only point that is made here is that failure to cultivate an organism is compatible with an infective origin. This is not infrequently seen in the meningitis which follows open wounds of the brain—an infective condition by all other standards. Smith and Smith (1941) have shown that special techniques are necessary to cultivate the organisms which may be found in this type of case, thus explaining some of the failures.

In the cases described by Barrie (1941) no causal organisms were found. The clinical picture and the necropsy findings, however, suggested an infective cause. Because of this negative bacteriology it was suggested that the condition was due to a virus, though the C.S.F. findings were unlike any meningitic reaction to known virus diseases. This carries the significance of the "sterile" C.S.F. too far. If an epidural abscess, osteomyelitis, or a subcutaneous abscess follows a lumbar puncture, it is regarded as infective whatever the bacteriology of the purulent material, and there is no logical reason why this should not be extended to the subarachnoid space.

The delay which usually occurs between the operation and the onset of meningitis is very suggestive of a phase of multiplication of an organism as a preliminary to the phase of clinical activity. The cases described all occurred in small groups—three in one hospital and two in each of two other hospitals. This may indicate that the conditions necessary for infection to take place were present in one institution for a short time and then were no longer found. Probably the most convincing evidence in favour of the infective theory is the cessation of fresh cases with the tightening up of aseptic technique.

4. Mode of Infection

From the evidence presented it is reasonable to conclude that these cases of meningitis are due to the introduction of organisms into the C.S.F. There can be little doubt that the spinal analgesics are mild irritants, and it is possible that the reaction to this irritation with the outpouring of protein-rich fluid gives reasonable conditions for an organism to gain a foothold. In no case has the spinal analgesic itself been infected. Bacteria have been found, however, in every other fluid used during the lumbar puncture. These include the local analgesic used for anaesthetizing the skin at the site of puncture, the spirit used for sterilizing needles and syringes, and the water used for rinsing these needles and syringes. There is no need to give here the details of the asepsis necessary for lumbar puncture and spinal analgesia, as every aspect has been fully considered in papers by Carnegie Dickson (1944), and Evans (1945), and in the *Lancet* (1944). That there is need for an absolutely rigid technique is shown by Smith and Smith (1941), who found bacterial contami-

nation in 89 of 223 specimens of C.S.F. It is true that the contaminants were mainly non-pathogenic, but they suggest that these might be activated under suitable conditions. They thought that the contamination was mainly due to the "sterile" water used for rinsing needles and syringes, but it is possible that the sterilization of needles and syringes by means other than dry heat may be faulty.

Treatment

The only satisfactory treatment is prophylaxis. It should be possible to avoid these unhappy cases completely. If, owing to an emergency, a rigid technique is not possible, then spinal analgesics should not be used.

If the condition does occur it is essential to stamp out the infection as soon as possible, otherwise it may go on for months and even prove fatal. Unfortunately the causal organism is often not susceptible to present-day chemotherapy—i.e., sulphonamides and penicillin—but this should not prevent these substances being given an early and adequate trial. Once it has been established that they are ineffective, not only in preventing relapses but in clearing up each relapse, they should be discontinued. The commonest infecting organisms are probably *Ps. pyocyanea* and atypical *B. coli*. Botterell and Magner (1945) have suggested intravenous iodides for the former, whereas Ecker (1945) has found a combination of urea and sulphadiazine useful for the latter.

The formation of adhesions causing spinal block is common and calls for no special treatment, but if hydrocephalus occurs, then surgical relief may be necessary. In none of our cases was an attempt made to wash through the spinal subarachnoid space as suggested by Symonds (1925). In retrospect it appears that this may be a useful manoeuvre if not put off for too long, as it might break up strands of fibrin and so wash away the foci of infection which cause relapses later on.

Apart from the specific attack on the meningitis all measures used in a long-continued septic illness must be tried, and of these whole-blood transfusion would appear most valuable.

Summary

Seven cases of meningitis following spinal analgesia and one following diagnostic lumbar puncture are described.

The condition is a low-grade meningitis caused by a variety of organisms introduced at the time of lumbar puncture.

The main clinical features are the chronic nature of the illness and the tendency to relapse.

It is suggested that this is due to the formation of adhesions containing infected C.S.F., which is liberated from time to time.

These adhesions may cause spinal block or hydrocephalus.

The cause of the condition is discussed, and on the evidence available it is decided that the likeliest cause is infection due to faulty aseptic technique. The irritation produced by the analgesic may enable an organism to gain a foothold.

Treatment is mainly prophylactic.

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