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OTOGENOUS MENINGITIS

INTRATHECAL ADMINISTRATION OF A SULPHONAMIDE

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As is only too well known, cases of otogenous meningitis with numerous culturable organisms in the cerebrospinal fluid have been of extremely bad prognosis until comparatively recently. With the introduction of chemotherapy this prognosis has considerably improved, and many cases have been reported in the literature in which satisfactory recovery has followed administration of one or other member of the sulphonamide group of drugs.

Unfortunately, however, the different members of the group exhibit varying degrees of toxicity, the sensitiveness of the individual patient also varies considerably, while certain factors—notably surgical shock—are strongly suspected of enhancing such sensitiveness. In addition to certain blood dyscrasias, gastritis is a prominent sign of intolerance, and, with the object of avoiding it, more or less successful attempts have been made to substitute intramuscular, intravenous or rectal in place of oral administration.

The rationale underlying the use of the sulphonamide group in meningitis is that these drugs alone appear to be able to overcome the chemophobia of the choroid plexus and, being secreted into the cerebrospinal fluid, are brought into immediate contact with the micro-organisms there present.

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It would seem, therefore, only reasonable to conclude that, if a sulphonamide derivative could be found of such low toxicity and low irritant properties that it could be introduced with impunity directly into the cerebrospinal fluid, its immediate availability in full concentration right at the seat of infection would surely enhance its prospects of successfully combating that infection; even though its actual bactericidal properties be less than those of other members of the group, which have to run the gauntlet, so to speak, of the choroid plexus and so only reach the seat of infection in attenuated concentration.

Attempts to introduce sulphonamides intrathecally have hitherto not been very encouraging, mainly owing to the irritant properties of the particular derivatives available such as Dagenan Sodium (the soluble sodium salt of M. & B. 693) resulting in hyper-secretion of cerebrospinal fluid and excessive local production of fibrin coagulum; moreover Messrs. May & Baker, to whom the writer is extremely obliged for their courtesy and helpfulness, strongly advise against the intrathecal administration of Dagenan Sodium as having been followed on occasions by convulsions and death, and recommend the adoption of this procedure only in cases which are practically moribund.

The writer's experience however with Soluseptasine in a bad case of streptococcal meningitis leads him to believe that possibly here is a sulphonamide derivative capable of intrathecal administration. The case is reported in some detail below in the hope of showing the satisfactory toleration of this drug by a patient who was apparently extremely intolerant of both Prontosil Album and M. & B. 693; while it also demonstrates the possibility of introducing it not only by lumbar puncture, but also (believed to be a new route) by direct injection into the cisterna magna—in both cases under careful manometric control of the cerebrospinal pressure.

Soluseptasine (M. & B. 137) is a crystaline powder of formula Disodium —p (γ—phenyl—propyl—amino) benzene sulphonamide—a—γ—disulphonate. It is manufactured by Messrs. May & Baker, of Dagenham, and it is put up in 5 and 10 per cent. solutions. Its use was discussed with some French colleagues during the early months of the war, and it was learnt that they too were favourably impressed by its intrathecal use.

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The obvious criticism is that one case is insufficient to go by and that it is impossible to say whether the patient recovered "*Post hoc vel propter hoc*"; the fact, however, remains that the drug *was* tolerated intrathecally, and therefore there would seem to be justification for recording the procedure.

The writer would welcome reports from colleagues as to results secured by this method and with the particular derivative quoted, to which he himself is certainly going to give further trial.

APPENDICES.

1. Case record.
2. Temperature chart.
3. Bacteriological reports.

CASE I.—G.G., æt. 15½.

27.2.39. Admitted Bath E.N.T. Hospital with history of many years of foul right otorrhœa. o/e Chronic mastoiditis with attic cholesteatoma.

28.2.39. *Modified radical mastoidectomy*. Roof of whole middle-ear cleft found eroded and dura exposed.

3 to 7.3.39. Prontosil Album, 1 tablet t.d.s. by mouth prophylactically, both dates inclusive.

4.3.39. Temperature 101.

7.3.39. Temperature back to normal; first dressing done. Apart from intense cyanosis, no signs of intolerance of Prontosil.

11.3.39. Sudden onset of severe headache in p.m. Temperature 102. Pulse 64. Owing to heavy incidence of influenza in Hospital at the time, treated by salycilates, etc.

14.3.39. Temperature has gradually returned to normal; headache subsided.

15.3.39. Temperature rose suddenly to 101·6. Pulse 82. Frontal headache reappeared. Antipyretics again brought the Temperature back to normal; but

16.3.39. Headache become rather worse. By p.m. temperature 102·6. Pulse 74.

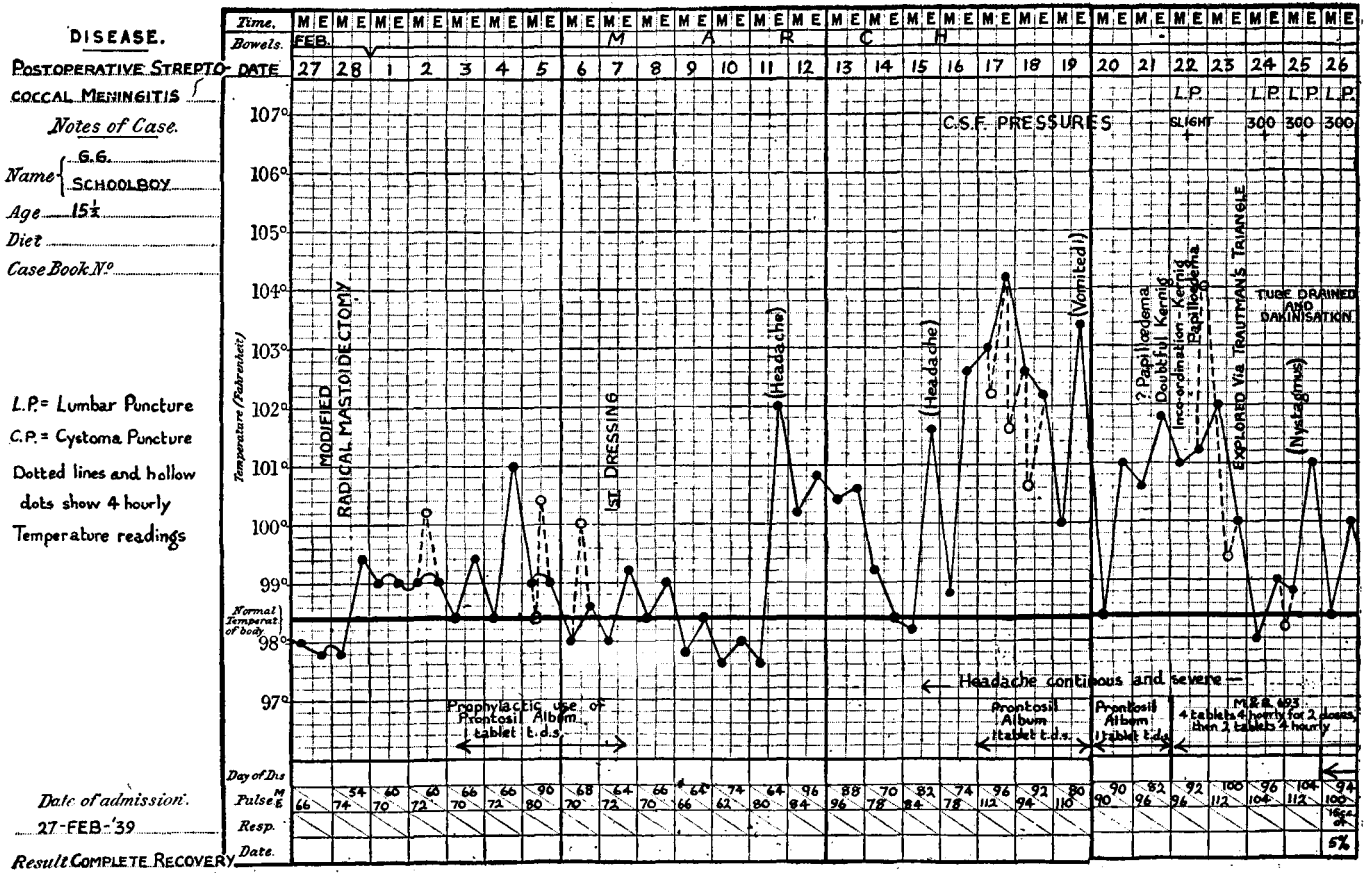
17.3.39. Temperature 103 and now assuming a definitely "swinging" character. Kernig absent. Fundi apparently normal. Prontosil Album resumed in dosage as before.

19.3.39. Temperature 100 in a.m. Pulse 110. Headache persisting and severe. In p.m. he suddenly vomited. Temperature rose to 103·4. Pulse 80. Cyanosis very intense. Headache most acute. Fundi still apparently normal.

20.3.39. Morning temperature normal. Headache persisting. Evening temperature 101. Pulse 90. Slight cervical rigidity.

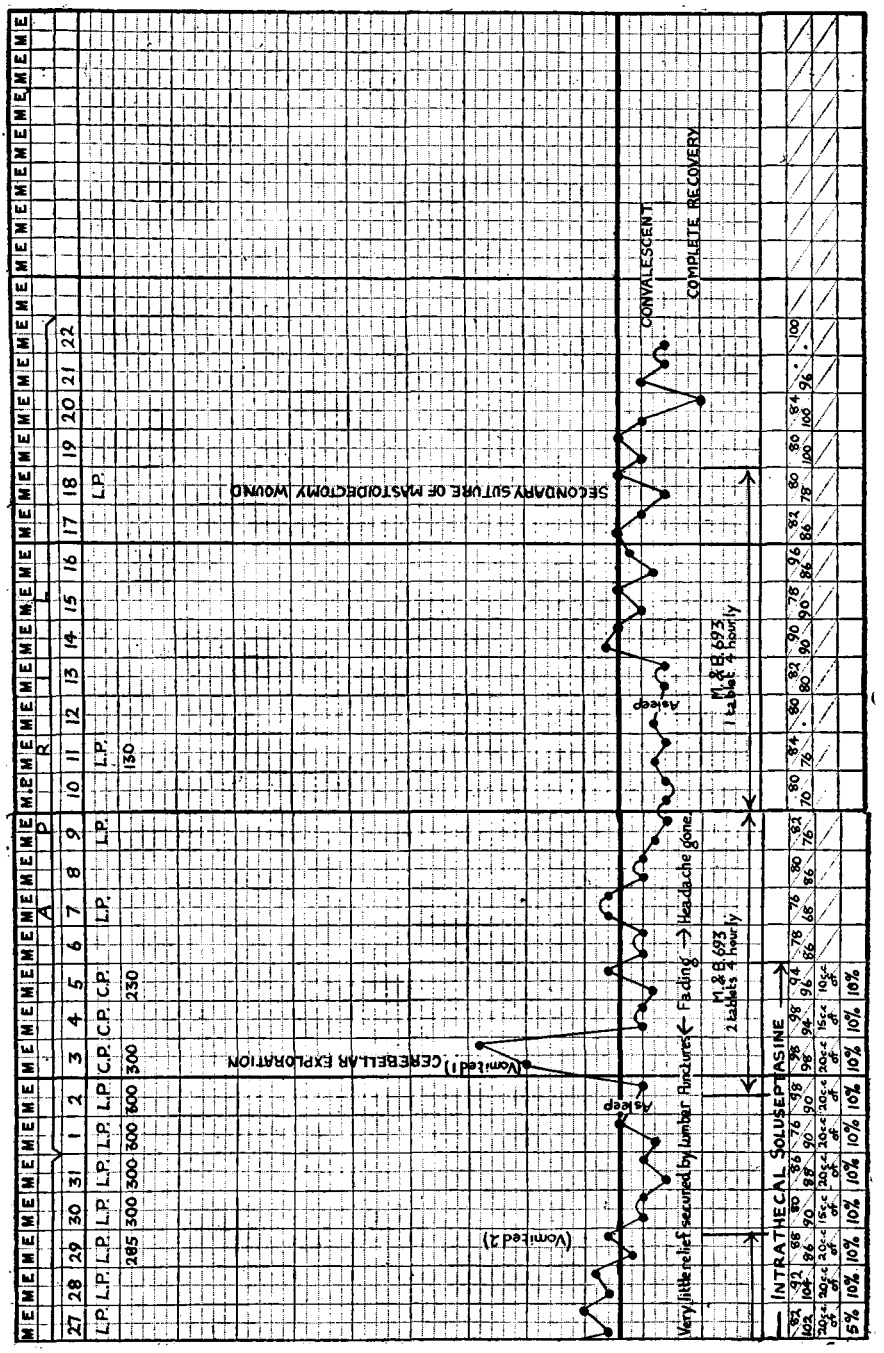
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In spite of extreme cyanosis Prontosil persisted with in same dosage.

21.3.39. Condition slowly deteriorated. Indefinite early Kernig and papillœdema.

22.3.39. Seen with Dr. H. Extremely restless; markedly cyanosed; marked photophobia; early papillœdema and small retinal hæmorrhage in right fundus. Nystagmus on looking to right. Inco-ordination of right arm and leg; well-marked Kernig. Temperature 101. Pulse 96.

Lumbar puncture yielded turbid bloodstained fluid under slight pressure, with fibrin coagulum.

Hæmolytic streptococci grown in pure culture both from C.S.F. and from mastoid swabbings (same strain). (See Pathological Report 1.)

M. & B. 693 substituted for Prontosil by mouth because of (1) intolerance and (2) its wider range of usefulness should the bacteriological report (as yet not received) show organisms other than streptococci.

Four tablets four-hourly for two doses, then two tablets four-hourly. P.m. Temperature 104. Pulse 96. It was considered that either there was a petrositis (in spite of absence of retro-ocular pain) or that a cerebellar abscess had leaked into the sub-arachnoid space.

23.3.39. *Exploration through Trautmann's triangle.* Dura bulged considerably. On incising it about 2 oz. of turbid, blood-stained fluid escaped from a shut off area between cerebellum and posterior surface of petrous, extending as far as the internal auditory meatus towards the petrous tip. (This fluid proved to be sterile on culture. See Pathological Report 2.) Cavity thoroughly eusol lavaged and tube drained, the wound being packed open.

Two glucose saline enemas, each containing two tablets M. & B. 693 were given three-hours apart. On recovery from the anæsthetic two doses of one tablet each M. & B. 693 were given one hour apart by mouth, followed by two tablets four-hourly.

24 and 25.3.39. Wound dakinised and tube drain shortened daily. *Daily lumbar puncture,* pressure being reduced each time from 300 odd to about 160 mm. On the latter date nystagmus was marked. Headache still severe. Kernig still present.

The C.S.F. was opalescent on 24.3.39, but very turbid on 25.3.39, yet sterile on culture. (See Pathological Report 3 and 4.)

Temperature round about normal both days, but 101 in p.m. 25.3.39.

26.3.39. Temperature still showing slight tendency to "swing" between normal and 100. *Lumbar puncture.* C.S.F. slightly turbid.

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Scanty nonhæmolytic streptococci grown on culture. (See Pathological Report 5.) Pressure reduced from 300 to 100 mm. and 15 c.c. 5% Soluseptasine introduced intrathecally, in addition to M. & B. 693 by mouth as before. Drain discontinued, dry.

27.3.39. Lumbar puncture and 20 c.c. 5% Soluseptasine intrathecally; rest of treatment as before. C.S.F. clear and sterile on culture. (See Pathological Report 6.)

28.3.39. Lumbar puncture and 20 c.c. 10% Soluseptasine intrathecally, etc. C.S.F. again clear and sterile on culture. Temperature now remains down, but headache persists.

29.3.39. Became extremely cyanosed and suddenly vomited twice in p.m. Temperature normal. Pulse 86. M. & B. 693 discontinued by mouth, but lumbar puncture performed, pressure reduced from 285 to 90 mm. and Soluseptasine repeated as before.

30.3.39. Lumbar puncture, pressure reduced from 300 to 90 mm. and 15 c.c. 10% introduced.

31.3.39, 1.4.39 and 2.4.39. Daily lumbar puncture. Pressure reduced from 300 to 90 mm. and 20 c.c. 10% Soluseptasine introduced. On the latter date his general condition was somewhat improved, but much trouble was experienced at lumbar puncture from fibrin plugs obstructing the needle. In p.m. M. & B. 693 was resumed by mouth, in doses of two tablets four-hourly.

3.4.39. Temperature rose steeply to 100. Pulse 98 and he vomited suddenly once in the a.m.

On my colleague's insisting, the *cerebellum was thoroughly explored* for abscess, but no trace of one could be found. At the same time the cisterna magna was punctured, pressure reduced from 300 to 90 mm. and 20 c.c. of Soluseptasine introduced into the cisterna direct. Unfortunately absence of the pathologist prevented a report on the cisternal C.S.F. M. & B. 693, two tablets four-hourly were resumed on coming round from the anæsthetic.

4.4.39. Very marked improvement. Temperature normal. Headache much less distressing. Cisterna puncture repeated under "local" and 15 c.c. of 10% Soluseptasine introduced intracisternally. M. & B. 693 continued.

5.4.39. Improvement maintained. Headache nearly absent. Inco-ordination much less marked. Kernig barely recognizable. Cisterna puncture under "local" for the third and last time. Pressure reduced from 230 to 100 mm. and 10 c.c. 10% Soluseptasine introduced. M. & B. 693 continued.

6.4.39. Temperature normal. M. & B. 693, two tablets four-hourly.

7 to 9.4.39. (Inclusive.) Found possible to resume lumbar puncture, which was done on alternate days. Soluseptasine discontinued. M. & B. 693 as before. C.S.F. steadily clearing.

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Temperature normal. Headache gone. Inco-ordination barely noticeable.

10.4.39. M. & B. 693 reduced to one tablet four-hourly.

11.4.39. Lumbar puncture. C.S.F. practically clear with a small fibrin coagulum. Sterile on culture. Pressure reduced from only 130 to 110 mm. (See Pathological Report 7.)

12 to 17.4.39 (Inclusive). Convalescence satisfactory. No treatment except M. & B. 693, one tablet four-hourly.

18.4.39. Secondary suture of posterior wound. Temperature normal. No headache. Inco-ordination has cleared up.

Lumbar puncture. C.S.F. clear, colourless, no coagulum. Sterile. Last day of M. & B. 693. (See Pathological Report 8.)

From this time onward the patient never looked back and made a complete recovery. He now plays games, can ride a bicycle and is apparently normal in every respect except for a slight loss of hearing in the right ear.

LABORATORY REPORT (Dr. H. J. GIBSON)

No. 1. G.G. Specimen 22.3.39.

Nature and source of specimen. C.S.F. and pus.

Report. 23.3.39. Serial No. 3305.

C.S.F. Turbid, blood-stained, with fibrin coagulum.

Cells. R.B.C. 2000 cu.mm. Pus cells 370 cu.mm. mainly polymorphs.

Stained films. Gram positive cocei in pairs and short chains + + +. Pus cells + + +.

Cultures. Hæmolytic streptococci + + + in pure culture.

These findings indicate active meningeal inflammation.

Pus from mastoid region. Pus cells and streptococci + + +.

Cultures. Streptococci hæmolyticus + + + in pure culture.

The strain is identical with that of the C.S.F.

No. 2. G.G. Specimen 23.3.39.

Nature and source of specimen. ? C.S.F. Turbid blood-stained fluid withdrawn *viâ* Trautmann's triangle.

Report. 24.3.39. Serial No. 3312.

Cells. A large amount of blood was present rendering cell count impossible. From stained films the leucocytes seen appeared to be in number and proportions corresponding to the blood present.

There was no gross pus.

Protein. 300 mgr. %. This is high and probably more than the blood would account for.

Sugar. 67 mgr. % (not reduced).

Chlorides. 702 mgr. % (N 700—760). No bacteria were found in stained films and cultures have remained sterile.

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The fluid appears to be derived from a closed area to which infection has not penetrated.

No. 3. G.G. Specimen 24.3.39.

Nature and source of specimen. C.S.F.

Report. 25.3.39. Serial no. 3321.

The fluid was slightly opalescent with fibrin flakes.

Cells. 267 cu. mm. (approx. equally polymorph and lymphocytes).

No organisms seen in films.

Sugar. 67 mgr. (normal).

Chlorides. 790 mgr. % (increased).

Protein. 100 mgr. % (increased).

Chlorides are increased in nephritis. In this case the urine is free from albumin. A toxic nephritis is almost to be expected.

No. 4. G.G. Specimen 25.3.39.

Nature and source of specimen. C.S.F.

Report. 26.3.39. Serial No. 3323.

Fluid colourless, very turbid with cells.

Cells. 5,910 cu.mm. mainly polymorph pus cells.

In stained films of deposit no bacteria were seen.

Cultures. Sterile.

The cultures of the specimen received on the night of 24.3.39 have also remained sterile.

No. 5. G.G. Specimen 26.3.39.

Nature and source of specimen. C.S.F.

Report. 27.3.39. Serial No. 3324.

The fluid was very slightly turbid with a considerable fibrin coagulum.

No organisms seen in films.

On culture a few colonies of streptococci were found. They were *completely inert* (*non-hæmolytic*) on blood, and the colonies were mucoid.

This is most likely a variant of the original strain under the influence of M. & B. 693. Although the possibility of a secondary infection cannot be completely overlooked.

No. 6. G.G. Specimen 27.3.39 and 28.3.39.

Nature and source of specimen. C.S.F.

Report. 29.3.39. Serial No. 3338.

Both specimens have proved sterile on culture. A small web of fibrin was present in the last specimen but otherwise the fluid was clear.

No. 7. G.G. Specimen 11.4.39.

Nature and source of specimen. C.S.F.

Report. 13.4.39. Serial No. 3338.

The fluid was clear with a small fibrin coagulum.

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Cells. 77 cu.mm. (polymorph and large mononuclear).
Protein. 120 mgr. %.
Globulin. Faint trace.
Sugar. 63 mgr. %.
Chlorides. 795 mgr. %.
Culture. Sterile.

No. 8. G.G. Specimen 18.4.39.
Nature and source of specimen. C.S.F.
Report. 18.4.39. Serial No. 3338.
Clear colourless, no coagulum.
Cells. 37 cu.mm.
Protein. 100 mgr. %.
Globulin test. Negative.
Films. No bacteria seen.
Cultures. All sterile.

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