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The Swollen Brain

"As the substance of the brain is nearly incompressible, the quantity of blood within the head must be the same at all times—those cases only excepted in which water or other matter is effused or secreted from the blood vessels; for in these a quantity of blood will be pressed out of the cranium."[1]

In accordance with this doctrine, reciprocal changes occur in the volume of the various components of which the intracranial contents is made up. Increased intracranial pressure results when the reciprocal equilibrium breaks down. As the principal variable elements of the intracranial contents were considered to be blood and cerebrospinal fluid, raised intracranial pressure is generally ascribed to an increase in either of these elements. When correlation between normal skull capacity and brain weight was established, it first became possible, early this century, to demonstrate conclusively generalized brain swelling after death.[2]

The technical means whereby generalized brain swelling could be recognized during life became available only in recent years. The ventricles on pneumographic visualization are diminished in size. Brain tissue pressure is increased, and the electrical impedance of the white matter of the brain is decreased.[3 4] Brain swelling, which appears rapidly during craniotomy and causes herniation through the skull opening, is due to inflation of the brain by blood and is immediately relieved by hyperventilation.[5] Another type of swelling is regional and occurs round an intracerebral lesion. The simple concept of generalized brain swelling was thrown into confusion when an attempt was made to distinguish swelling according to whether it is due to intercellular or intracellular oedema.[6]

The problem of the exact distribution of oedema fluid has not been fully resolved even by the advent of electron-microscopy. So far as macroscopic appearances and symptoms are concerned the syndrome of swollen brain is uniform, but its causes are exceedingly diverse. Generalized swelling of the brain must be regarded as a non-specific response to a variety of insults. Among possible causes are the following: ischaemia of the brain;[7] head injury;[8] malignant hypertension;[9] hypercapnia;[10] massive hepatic necrosis;[11] hypoparathyroidism;[12] Addison's disease;[13] Dandy's syndrome of "intracranial pressure without brain tumour";[14] interruption of corticosteroid therapy;[15] iron deficiency;[16] interruption of dominant dural sinus drainage;[17] intoxications by vitamin A,[18] tetracycline,[19] nalidixic acid,[20] and lead.[21]

It has been shown experimentally that a 2·5% increase in brain water can effect a fourfold rise in cerebrospinal fluid pressure.[22] In man, the clinical effects can be related to the rapidity and intensity of the brain swelling. In addition to bilateral papilloedema they comprise—in consequence of tentorial herniation of the brain—headache, abducens nerve palsies, disturbance of consciousness, and eventually Cheyne-Stokes respiration. Papilloedema can be regarded as a direct consequence of the swelling of the vessel-bearing part of the optic nerve.[23 24] It will be seen that this syndrome of pseudotumor cerebri has almost all the clinical stigmata found in association with brain tumours. Such close parallelism between these two conditions is due to the fact that even small tumours may give rise to widespread brain swelling.[25] But in these cases the cerebral ventricles do not conform to the pattern of the pseudotumor cerebri syndrome.

The compensatory redistribution of intracranial contents such as Monro postulated is impeded in the presence of intracranial tumours or of brain swelling. This explains the excessive rise of intracranial pressure shown by patients with brain tumour when they are exposed to the vasodilator effect of halothane anaesthesia.[26] The swollen brain can be dramatically relieved by large doses of dexamethasone.[27] The effects of glucosteroids have recently been re-evaluated experimentally by electronmicroscopy. This has fully confirmed that they effectively reduce the amount of brain oedema produced by a standardized experimental procedure.[28] The favourable clinical effects of dexamethasone in patients with metastatic brain tumours were similarly ascribed to shrinking of the brain and consequent increased cerebral blood flow.[29] A similar march of events occurs when brain swelling is ischaemic, non-tumoral causation. In these cases cerebral swelling may also impede cerebral blood flow and cause transtentorial herniation, with compression of the brain stem.[30] The optic nerve circulation may become critically reduced by the effects of swelling, and loss

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of vision so caused may be wrongly attributed to papilloedema.[24]

Monro's and George Kellie's (1779-1829) concern with the "circulation within the head" was due to a prevailing preoccupation with the congested brain, then considered to be at the root of many cerebral disorders. Kellie's reassuring conclusion that "to whatever extent the one set of vessels is becoming overcharged to the same extent, it seems probable, is the other set voided" had a profound impact upon medical thought of the day.[31] Correctly interpreted, the Monro-Kellie theorem is still a valuable adjunct to a consideration of the swollen brain.

[1] Monro, A. (Secundus), *Observations on the Structure and Functions of the Nervous System*. Edinburgh, Creech and Johnson, 1783.
[2] Reichardt, M., *Deutsche Zeitschrift für Nervenheilkunde*, 1905, **28**, 306.
[3] Brock, M., Winbelmüller, W., Pöll, W., Markakos, E., and Dietz, H., *Lancet*, 1972, **1**, 595.
[4] Fujita, S., Veda, T., and Yagi, M., *Journal of Neurosurgery*, 1972, **37**, 156.
[5] Langfitt, T. W., and Kassell, N. F., *Journal of Neurosurgery*, 1966, **24**, 975.
[6] Spatz, H., *Archiv für Psychiatrie*, 1929, **88**, 789.
[7] Levine, S., and Klein, M., *Archives of Pathology*, 1960, **69**, 544.
[8] White, J. C., Brooks, J. R., Goldthwait, J. C., and Adams, R. D., *Annals of Surgery*, 1943, **118**, 619.
[9] Byrom, F. B., *Lancet*, 1954, **2**, 201.
[10] Miller, A., Bader, R. A., and Bader, E., *American Journal of Medicine*, 1962, **33**, 309.
[11] Ware, A. J., D'Agostino, A. N., and Combes, B., *Gastroenterology*, 1971, **61**, 877.
[12] Grant, D. K., *Quarterly Journal of Medicine*, 1953, **22**, 243.
[13] Jefferson, A., *Journal of Neurology, Neurosurgery, and Psychiatry*, 1956, **19**, 21.
[14] Dandy, W. E., *Annals of Surgery*, 1937, **106**, 492.
[15] Neville, B. G. R., and Wilson, J., *British Medical Journal*, 1970, **3**, 554.
[16] Knizley, H., and Noyes, W., *Archives of Internal Medicine*, 1972, **129**, 483.
[17] Marr, W. G., and Chambers, R. G., *American Journal of Ophthalmology*, 1961, **51**, 605.
[18] Morrice, G., Havener, W. H., and Kapetansky, F., *Journal of the American Medical Association*, 1960, **173**, 1802.
[19] Kock-Weser, J., and Gilmore, E. B., *Journal of the American Medical Association*, 1967, **200**, 345.
[20] Boreus, L. O., Sundstrom, B., *British Medical Journal*, 1967, **2**, 744.
[21] Popoff, N., Weinberg, S., and Feigin, I., *Neurology*, 1963, **13**, 101.
[22] Rosomoff, H. L., and Zugibe, F. T., *Archives of Neurology*, 1963, **9**, 26.
[23] Behrman, S., *Neurology*, 1964, **14**, 236.
[24] Behrman, S., *Brain*, 1966, **89**, 1.
[25] Brain, W. R., *Brain*, 1925, **48**, 105.
[26] Jennett, W. B., *et al.*, *Lancet*, 1969 **1**, 61.
[27] Galicich, J. H., and French, L. A., *American Practitioner and Digest of Treatment*, 1961, **12**, 169.
[28] Long, D. M., Maxwell, R. E., and French, L. A., *Journal of Neuropathology and Experimental Neurology*, 1971, **30**, 680.
[29] Weinstein, J. D., Toy, F. J., Jaffe, M. E., and Goldberg, H. I., *Neurology*, 1973, **23**, 121.
[30] Langfitt, T. W., *et al.*, in *Brain and Blood Flow*, ed. R. W. R. Russell. London, Pitman, 1971.
[31] Kellie, G., *Transactions of the Medico-Chirurgical Society of Edinburgh*, 1824, **1**, 84.

Penicillamine in the Treatment of Rheumatoid Arthritis

Used initially in the treatment of Wilson's disease,[1 2] penicillamine was later found to be effective in the treatment of lead poisoning, gold poisoning, cystinuria, and some other conditions. But it was its use in the treatment of rheumatoid arthritis[3 4] that brought it into prominence. This year a British double-blind, multicentre controlled trial[5] showed that it undoubtedly benefited patients with acute, severe rheumatoid arthritis.

Thirty of 52 patients on D-penicillamine and 38 of 53 controls completed 12 months' treatment. In the penicillamine-treatment group 30% of the losses were the result of drug intolerance, while none were lost from progression of the disease. In the control group 17% of the losses were because of deterioration in the patient's clinical condition. All measurements except radiographic changes in the small joints showed greater improvement in the penicillamine-treated patients, and the improvement was usually statistically significant. Penicillamine emerged as an effective form of treatment of active rheumatoid disease.

In the treatment of rheumatoid arthritis penicillamine has many points of similarity with gold. It takes several weeks to produce its therapeutic effect, and when treatment has to be stopped prematurely the arthritic condition tends to return gradually to its previous active state.

Which cases should one treat with this drug? And what are its disadvantages? The patients who would be considered suitable for gold therapy are those who should respond to penicillamine. They are the patients with much inflammatory swelling and tenderness of the joints, a high sedimentation rate, but little or no irreversible change. The advanced, largely burnt-out crippled cases with advanced radiological changes would be unsuitable. Early rather than late advanced cases should be chosen, when physical treatment, adequate rest, and analgesic and anti-inflammatory drugs have proved to be unsatisfactory, so that the disease remains active and advances despite these measures.

A further parallel with chrysotherapy lies in the nature of the side effects penicillamine may produce. Regular blood counts and platelet counts must be done, since neutropenia, thrombocytopenia, and aplastic anaemia may occur. The urine should be checked frequently for proteinuria, for the penicillamine molecule readily combines with substances in blood and tissues to give rise to complexes which may be antigenic. Acute hypersensitivity reactions with rash and fever may appear early in treatment, and nausea, anorexia, and vomiting may be troublesome. Proteinuria may be heavy and persist for months, but like the other toxic effects of penicillamine it nearly always disappears completely on discontinuing the drug and leaves no permanent effects.

The drug is tolerated better and side effects are fewer if dosage is initially low and only slowly increased. The usual practice is to give one tablet (250 mg of D-penicillamine *B.P.*) or two capsules (each 150 mg of D-penicillamine hydrochloride *B.P.*) by mouth daily, dosage being increased by the same amount at intervals of two to three weeks or longer, until a total daily dose of 1,000 to 1,500 mg has been reached. Treatment is then continued for 12 months or considerably longer according to tolerance and therapeutic effect. Higher dosage is needed to achieve control in some cases, lower in others. D-penicillamine is used in preference to L or DL-penicillamine, which is more toxic. Its mode of action is still unknown.

Highly effective drugs have sometimes been prescribed with insufficient caution for patients with rheumatoid arthritis. Cortisone and phenylbutazone are two examples. Bad therapeutic results followed their misuse and side effects were unnecessarily frequent, usually as the result of overdosage. W. H. Lyle[6] has recently drawn attention to the possibility of the same thing occurring with misuse of penicillamine. The drug seems likely to be most often used when gold salts are disliked or have proved toxic or ineffective. It would be unfortunate if this drug, which can benefit some patients, were to fail to do so through faulty prescribing.

[1] Walshe, J. M., *Lancet*, 1956, **1**, 25.
[2] Walshe, J. M., *Lancet*, 1960, **1**, 189.
[3] Jaffe, I. A., *Annals of Internal Medicine*, 1964, **61**, 556.
[4] Jaffe, I. A., *Arthritis and Rheumatism*, 1970, **13**, 436.
[5] Multicentre Trial Group, Andrews, F. M., *et al.*, *Lancet*, 1973, **1**, 275.
[6] Lyle, W. H., *British Medical Journal*, 1973, **3**, 235.

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