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# Introduction

The condition or syndrome to be considered in this monograph has been a clearly recognized clinical entity since the descriptions given by Quincke (1893, 1897) and Nonne (1904, 1914) over 100 years ago. However, reports of cases which were almost certainly examples of the same condition undoubtedly antedated their pioneering accounts by almost four decades. The essential elements of the syndrome are the symptoms and signs of intracranial hypertension without ventricular dilatation and without an intracranial mass lesion. For reasons which will be made clear in the following chapters, we shall call it the pseudotumor cerebri syndrome (PTCS) although quite a variety of terms have been applied to it. It is a particularly intriguing condition for a number of reasons, as follows:

1. Clinically the condition presents an essentially pure picture of raised intracranial pressure (ICP) without focal neurological disturbance and without investigative evidence of structural disturbance, either focal or general. As such, it is a condition which manifests, in isolation, what is a critical component of many neurological and neurosurgical conditions, i.e. intracranial hypertension, thereby creating a situation in which the pathological effects of this component exist in a pure form.
2. Despite much speculation and numerous clinical and laboratory studies (although clinical investigations are constrained by the exigent circumstances of the condition and laboratory studies by lack of a suitable model) there is still no clear consensus on its mechanism, although the predominant view is that the intracranial hypertension is due to a disturbance of cerebrospinal fluid (CSF) dynamics.
3. In the absence of a clear understanding of mechanism, there is no agreement on the nomenclature. Since the condition was first recognized a series of quite distinct names have enjoyed relatively transient popularity, although only pseudotumor cerebri (Nonne's coinage) has endured. The use of the other terms has depended, in part, on which specialty was mainly responsible for management and, in part, on which theory of mechanism was in vogue.

Some of the more tenacious examples, in approximate temporal sequence, are serous meningitis, hypertensive meningeal hydrops, otitic hydrocephalus, benign intracranial hypertension, and, most recently, idiopathic intracranial hypertension.

4. Again related to uncertainty about mechanism, there has been notable variation in methods of treatment. As with nomenclature, different treatments have had a period of popularity only to be discarded or replaced as side-effects and complications became apparent or as ideas of mechanism changed. What can be said is that all the major forms of treatment employed over the past century have been effective to a significant degree. This is to judge, at least, by the relatively crude criteria of ultimate resolution of the condition and patient survival without apparent neurological deficit, although persistent ophthalmological and possibly psychological disturbances may occur.

The evolution of ideas on these four aspects, and other related points, will be examined in the following chapter on the history of the 'pseudotumor cerebri' concept. An attempt will then be made to provide a critical analysis of the different theories of mechanism which will include an examination of the fundamental question as to whether there is, in fact, a single mechanism involved or not. Having come to a conclusion about mechanism, however tentative, the vexed question of nomenclature and the related issue of classification will be addressed. Clearly, if mechanism is securely established, nomenclature may become more logically based. The question of classification will, of course, depend on resolution of the issue of whether there is, indeed, one basic mechanism, or at least one final common pathway, as we shall argue.

These three chapters, on history, on mechanism, and on nosology and nomenclature, comprise the theoretical component of this monograph. At this point a provisional conclusion will be reached that we are dealing with a defined syndrome, the underlying mechanism of which is impairment of CSF absorption at the point of transfer of the fluid from the subarachnoid space into the venous system; that is, at the arachnoid villi. The suggestion is, then, that an increase in the fluid component of the intracranial and spinal spaces due to impaired CSF absorption in the face of continuing production at normal rates is the cause of the increase in intracranial pressure, although precisely where and how this excess of fluid is accommodated remains to be determined. The basic abnormality at the point of absorption may be due to one of three mechanisms:

1. A change in the arachnoid villi themselves
2. A change in the cranial venous outflow adversely affecting the pressure differential across the arachnoid villi on which CSF absorption depends
3. A change in the physical nature of the fluid being absorbed

For each of these three primary causes there exists a number of secondary causes. Despite this multiplicity of causative factors, and the obvious lacunae in our knowledge of how precisely these factors operate, there is a clearly definable clinical entity to which, in the absence of exact delineation of the disease mechanism, a somewhat non-specific but appropriate name should be given. The term 'pseudotumor cerebri syndrome (PTCS)', it will be argued, most satisfactorily serves this purpose, at least at present.

In the chapters subsequent to these theoretical deliberations, the practical clinical aspects of the syndrome are considered in chapters following the conventional sequence, i.e. aetiology, clinical features, investigative findings, treatment and outcome. In each of these five chapters a similar format will be followed, beginning with a summary of our own clinical experience based on two substantial series of cases comprising 260 patients investigated and treated in two large centres (the Institute of Neurological Sciences in Glasgow and the Royal Prince Alfred Hospital and Royal Alexandra Hospital for Children in Sydney) over a period of almost 60 years. This will be followed by a detailed review of the literature and conclude with a brief general summary of each section.

With respect to aetiology, one of the more remarkable aspects of PTCS is the large number of putative aetiological agents that have been identified. In many instances, however, the question of whether a particular agent has a true causal relationship to PTCS, rather than being merely a chance association, is not satisfactorily elucidated. Moreover, many of the inculpated agents, whether drugs or other medical conditions, are used or occur very widely, whilst only very few instances of a conjunction with PTCS are recorded. All the supposed aetiological agents will be tabulated and considered, as will the presumed nature of the often somewhat tenuous connection between the particular agent and PTCS in each case. We shall also consider from a practical point of view the issue which bears particularly on the question of nomenclature; that is, whether there are forms of the condition that do arise *sui generis* and might properly lay claim to the title 'idiopathic intracranial hypertension', setting aside etymological questions about the term 'idiopathic'.

In considering the clinical features of PTCS, initial consideration will be given to the rather striking epidemiology of the condition. What is the significance of the uniformly observed preponderance of young obese women in any large series of cases and, in particular, does this have any bearing on the issue of mechanism? In relation to the presenting symptoms and signs, details will be given of their relative frequency and range of severity. Attention will also be directed at two 'minority' groups: patients who are diagnosed as having PTCS despite lacking either symptoms or signs of intracranial hypertension, and patients who have symptoms or signs other than those directly attributable to intracranial hypertension.

This latter group bears on the issue of the applicability of the so-called 'Dandy criteria', considered in detail in Chapter 4.

In considering the investigation of patients with possible PTCS, the history of the changing pattern of investigative strategies is outlined before considering in turn each of the methods that have been used or are currently in use. Despite this changing pattern, the two key components of investigation have remained the same. The first is the demonstration of raised CSF pressure, whether by direct puncture and simple manometry or by more elaborate monitoring techniques. The second is exclusion of some other cause of raised CSF pressure, now most satisfactorily achieved by magnetic resonance imaging (MRI). As with clinical features, there are issues relating to how rigidly diagnostic criteria should be applied with respect to CSF pressure measurements, CSF composition, and the normality or otherwise of imaging studies which will be considered here. Attention will also be given to another important practical aspect of investigation – how far investigations should be pursued. Specifically, should the role of clinical investigations be simply to exclude conditions other than PTCS, or should they also be directed towards the identification of some causative factor for the PTCS?

The treatment of PTCS remains problematical, and there are still no methodologically satisfactory studies establishing the efficacy of a particular treatment, or properly comparing one treatment against others. There is also the important issue of how vigorously treatment should be pursued in the individual case, weighing up the risks to the patient of continuing intracranial hypertension against those of the treatment in question. The treatments considered are the medical options of serial lumbar punctures, acetazolamide (Diamox®), other diuretics, steroids, weight loss, and a miscellaneous group of other agents used in small numbers of cases, and the surgical options of subtemporal decompression (STD), optic nerve sheath decompression (ONSD), CSF shunting and various direct approaches to cranial venous outflow tract occlusion. It is a striking fact that almost all the treatment methods employed to any extent over the past hundred years, since the disease was first recognized, are still in use. One aspect of the treatment issue, touched on above, is the question of whether therapy can be 'tailored' to the individual case, based for example on the degree of severity. Another, and related aspect is what to regard as the 'end-point' of treatment, i.e. how important is it to attempt to return the patient's ophthalmological status and/or CSF pressure to normal, or as close to normal as possible, and as soon as possible? This issue is obviously linked to the natural history of the condition and studies of outcome in treated cases.

Outcome will be the subject of Chapter 9 in which three aspects in particular will be brought into focus. The first is the time course of resolution of PTCS and the relationship of this to its initial severity and method(s) of treatment.

The second is the likelihood of sequelae, especially ophthalmological and psychological sequelae, and how these relate to the severity and duration of the condition. The third is the possibility of error in the initial diagnosis, with some other cause of the intracranial hypertension subsequently coming to light that invalidates the initial diagnosis of PTCS.

The penultimate chapter will consider the various experimental studies that relate particularly to PTCS, and will include a discussion of some of the theoretical issues raised by these studies. Broadly, two groups of experimental studies will be considered. The first group consists of studies of three factors with a well-established aetiological relationship to PTCS – cranial venous outflow impairment, hyper- and hypo-vitaminosis A, and steroids, both prolonged use and withdrawal. All these are factors that have been shown to have the capacity to alter CSF dynamics. Moreover, all of them, and possibly other agents such as tetracycline and its derivatives, offer possibilities as far as establishing an experimental model of PTCS is concerned. The second group consists of various agents which have been shown to have a marked effect on CSF formation, an action which has been assumed to be relevant to the treatment of PTCS.

In the concluding remarks (Chapter 11) the aim will be to summarize the findings and conclusions of the preceding chapters *seriatim* and, in so doing, to come up with a defensible working hypothesis on disease mechanism, to make a logical recommendation on nomenclature, to bring some clarity to the murky waters of aetiology, to define the basic clinical picture and its acceptable variations, to recommend practical strategies for investigation and treatment, to document the range of outcomes in PTCS, and how these relate to severity on presentation and vigour of treatment, and, finally, to make some suggestions as to how further experimental studies might shed some light on the still obscure aspects of this remarkable condition.

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# History of the pseudotumor cerebri concept

## Introduction

The evolution of the pseudotumor cerebri concept has depended on a combination of precise clinical description and continuing technological advances in the methods used for investigation. Tracing the history of the concept is not only of intrinsic interest but also helps to clarify how our present ideas on disease mechanism, nomenclature, classification, and treatment, all areas of on-going contention, have been arrived at. It must be said, however, that while discussion of the history of ideas on the condition does undoubtedly provide insights into some of its fundamental aspects, it also has the somewhat sobering effect of bringing into focus how little progress has actually been made. For example, on mechanism, the idea of a disturbance of CSF circulation as being at the root of the condition was originally canvassed in the very early years before being discarded, but is now returning to favour. On aetiology, cranial venous outflow impairment, which featured so strongly in early accounts, has now re-surfaced as a major consideration. In treatment, optic nerve sheath decompression, which was initially advocated over 100 years ago before quickly being abandoned, has now returned to a position of prominence. In these three aspects the wheel has turned full circle.

In presenting this outline of history, the papers of Quincke (1893, 1897 (Figure 2.1)) and Nonne (1904, 1914 (Figure 2.2)) are taken as pivotal, signalling the start of attempts to define a specific clinical syndrome. These papers will be given relatively detailed consideration. It is clear, however, that a number of reports of what would appear to be the same condition antedated those of Quincke and Nonne. A general survey of these will be given. Two particular developments of far-reaching significance that were also critical for the recognition of PTCS were first, the invention of the ophthalmoscope by von Helmholtz in 1851 and its application to neurology pioneered by von Graefe, Albutt, Hughlings Jackson and others, and second, the introduction of the

Figure 2.1 Heinrich Quincke (1842–1922) who studied under such notables as von Kölliker, Helmholtz and Virchow. For many years he held a chair in medicine but later moved to Frankfurt-am-Main to continue his neurological work. Apart from his pioneering studies of PTCS, which he called meningitis serosa, important contributions included his description of angioneurotic oedema and his studies on the mechanism of body temperature. Particularly notable was his introduction of lumbar puncture as a technique.

technique of lumbar puncture by Quincke around the start of the twentieth century, which allowed for the first time objective measurement of the CSF pressure and analysis of its content. The century from Nonne's first paper in 1904 to the present will be somewhat arbitrarily divided into three periods. The divisions are marked most notably by major radiological advances; in the first instance, the development of ventriculography/encephalography and angiography, and in the second, by the development of computed tomography and subsequently magnetic resonance (MR) scanning. The periods, then, are 1904–1936, 1937–1970, and 1971 to the present. The first transition was of major importance in that it marked the abandonment of the idea of a CSF circulation problem as causative, at least for the time being; and the second, because it marked the introduction of very sophisticated technology, not only the scanning methods mentioned but also radionuclide and infusion methods of investigating CSF dynamics, which might reasonably have been expected to clarify the disease mechanism. Unfortunately, the hoped-for elucidation has not altogether eventuated, as will be made particularly apparent in the

Figure 2.2 Max Nonne (1861–1959) who studied in Heidelberg, Freiburg and Berlin before receiving his doctorate in Hamburg in 1884 where he worked as a neurologist from 1889. His teachers included Erb and von Esmarch. In 1889 he became chief physician in the department of internal medicine at the Red Cross Hospital, and in 1896, chief physician in the neurology department at the Eppendorf Hospital. In 1919 he received the teaching appointment in neurology at the newly founded University of Hamburg where he worked with Jakob. Nonne was one of the four physicians asked to consult on V.I. Lenin during his final illness.

following chapter on mechanism. The five epochs identified are, in summary, as follows.

1. The period prior to Quincke and Nonne, i.e. 1860–1897 marked by the first reports of cases which appear to be cases of PTCS without their being identified as a specific syndrome.
2. The period distinguished by the reports by Quincke (1893, 1897) and Nonne (1904, 1914).
3. The period following these reports and prior to the development of neuro-radiological techniques, i.e. 1912–1936. Notable during this period were the writings of Passot (1913), Warrington (1914), Frazier (1930), and Symonds (1931, 1932).
4. The period of neuroradiological investigation, i.e. 1937–1970 during which the demonstration of normal ventricular size led to the abandonment of the idea of PTCS as a disorder of CSF dynamics. Important studies in this period were those of Dandy (1937), Davidoff (1956), Foley (1955), and Sahs and Joynt (1956).

5. The period from 1971 to the present, notable for major technological developments, the return of the concept of PTCS as a disorder of CSF circulation, and the re-emergence of cranial venous outflow obstruction as an important aetiological factor, and of optic nerve sheath decompression as a treatment option.

## Period 1: The first descriptions (1866–1896)

Possibly the first description of a case of PTCS was that of Bouchat in 1866 (reported by Passot, 1913) who, interestingly, introduced the 'pseudo' concept, speaking of 'pseudo-meningitis'. In reviewing these early descriptions, not all of which will be specifically referred to, two particular points emerge. The first is the association of the, as yet, unnamed syndrome with a number of the factors still recognized today as having a close, and possibly aetiological, association with the condition, and the second is the use of several of the treatment methods that are now enjoying something of a renaissance.

On the issue of the association with other conditions, the period from 1880 to 1900 saw several reports linking the clinical presentation of a spontaneously resolving raised ICP picture with amenorrhoea, ear disease, anaemia, head injury, and intracranial venous occlusion. One of the earliest articles in English is a long section on diseases of the optic nerve in the *Transactions of the Ophthalmological Society* of the UK for 1880–1. Three descriptions within this report stand out. The first is Hughlings Jackson's reference to reports by several ophthalmic surgeons of '. . . a recoverable optic neuritis in young women suffering from uterine derangement'. Apropos this, there is the earlier observation by Foerster, quoted in several papers, that all that is known about the connection between optic nerve disease and menstruation is that it exists. The second is W.R. Gowers' report of a 16-year-old girl with relatively transient bilateral 'optic neuritis' and a VIth nerve palsy, and the third is the description by Broadbent of a young girl with a 2-year history of headache and vomiting with 'double optic neuritis' associated with amenorrhoea whose symptoms and signs resolved, and in whom menstrual regularity was restored. Although her presenting symptoms resolved, she remained blind from the effects of the papilloedema.

Elsewhere, also in 1881, Lawford described a 12-year-old girl with a history of purpura, who developed bilateral papilloedema with reduced visual acuity but without other signs, and who later improved progressively over 9 months. Gowers reported two sisters, both of whom developed the characteristic clinical picture in association with anaemia, in relation to whom he wrote that the clinical progress did '. . . not afford the slightest ground for suspicion of intracranial disease.' He also referred to another case described in his book,

*Medical Ophthalmoscopy*. In relation to ear disease, Taylor wrote in the 1890 edition of *The Practice of Medicine*:

> It is important to remember what has now been verified in numerous cases that in mastoid suppuration there is often double optic neuritis with an entire absence of meningitis or of abscesses proved by post-mortem examination, or by recovery after simple trephining of the mastoid cells.

He described a typical case in his 1894 review of optic nerve disorders (case 6). In an interesting article analysing 57 patients who died from complications of otitis media, Newton Pitt, in 1890, described three other patients, all of whom had ear disease with papilloedema but no other neurological signs, and who recovered, one having had the lateral sinus explored, clot removed and the internal jugular vein ligated. On the matter of treatment, Carter, in two papers in 1887 and 1889, respectively, described the use of optic nerve sheath decompression to alleviate the ophthalmological effects of raised ICP, referring to the initial description of the technique by de Wecker (1872), with whose surgical approach he disagreed. In the first article, Carter described the case of a 26-year-old lady's maid who, 10 days after a minor head injury, developed headache and lost her vision, and had marked bilateral papilloedema but no other findings. Despite treatment (iodide of sodium and mercurials), her eye signs worsened and she had a left optic nerve sheath decompression. There was subsequent improvement with resolution of her papilloedema. Victor Horsley, who had for a brief period advocated de Wecker's operation, became a proponent of cranial decompression for optic neuritis due to raised ICP in general, and spoke of the benefits in the discussion following Taylor's article referred to above. One other report that deserves mention is that of Jacobi who, in 1896, wrote of 'rhachitical hydrocephalus' in children with bulging anterior fontanelle and/or choked discs, and remarks that the outlook is 'by no means unpromising'.

Finally, mention must be made of the rather remarkable article by Williamson and Roberts which appeared in 1900, after Quincke's two articles. In this, the authors analyse 100 cases of 'double optic neuritis'. The article is brief but their groups IX and X probably constitute the first good description of PTCS within the diagnostic limitations of the time. There are, in these groups, 21 cases comprising 13 females of average age 16.8 years (range 10–22 years) and 8 males of average age 17.1 years (range 10–40 years). Of particular importance is that the follow-up for 20 of the cases averages 4.4 years. On the question of incidence, they mention that: 'Most medical men who have paid much attention to cerebral diseases will have met with a case or cases of this kind.' Other salient features in this article include recognition of the importance of looking for an association with ear disease and haematological disorders, and the exclusion of Bright's disease and