CHILDHOOD STROKE – THE UNKINDEST CUT OF ALL:
A HISTORY OF CEREBROVASCULAR DISEASE IN
CHILDHOOD

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For rightly is truth called the daughter of time, not of authority
Francis Bacon, 1620

The course and the result of cerebral paralysis depend upon the extent of injury to the brain, its nature and the age at which it is inflicted – all these being conditions which are beyond the power of the physician to modify or control. The treatment of cerebral palsy is therefore extremely unsatisfactory
L. Emmett Holt, 1899

Perhaps the main social responsibility of physicians is hard thinking in our daily work... Sometimes the doctor finds no cause and goes on to say ”there’s nothing wrong”. He was answering his own question... forgetting to ask why the patient got it, we shall never arrive at prevention.
Ronnie Mac Keith, 1971

Introduction
Depictions and descriptions of children who have had a stroke (or apoplexy or acute hemiplegia) have been around for millennia. The concept of children at any age suffering and even dying from a stroke appears anachronistic, given our own experiences that it is typically a disease of the elderly. It is perhaps this very incongruity that has made the occurrence of stroke in childhood the more striking to medical observers often better known for other contributions. Understanding of aetiology had to await the development of the concepts of the systemic and cerebrovascular circulation in adults from the seventeenth century onwards, the distinction between upper and lower motor lesions and therefore between spinal (usually poliomyelitis) and cerebral paralysis, the emergence of the concept of childhood and the later twentieth century focus on differences between diseases of children and those of adults and therefore their needs in terms of investigation and rehabilitation. The increase in research into childhood health and disease in general has at long last started to redress the deficiency.

Table 1.1

The earliest known reference to a movement disorder and aphasia after childhood convulsions, found in a Mesopotamian library of the 1st millennium BC. It may well be a copy of an earlier Sumerian work (translated by M. Coleman and J. Scurlock)

If an infant of one year, two years, three years, four years writhes in contortion so he is not able to get up and stand, his mouth is ‘seized’ so that he is not able to talk. [It is] ‘spawn of Sulpaea’; he will not straighten up.

DI.LÚ.TUR MÚ1.KÁM MÚ2.KÁM MÚ3, KÁM MÚ.4.KÁM šu-ub-ú-us-ma te-be-a ū ū uz-uz-za la i-le- ’e NINDA a-ka-la la i-le- ’e KA-šu su ub-ú-us-ma da-ba-ba la i-le- ’e re-hu-ut (DIGER) Šúl-pa-e-a NU SÍSÁ
analogy with the formation of breast milk, or of semen in the time to be transformed into psychic or animal pneuma, in an blood and nutrients while the vital pneuma was drawn up dissecting. However, he considered that the veins transported blood and enters both main vessels, or if it enters but one of them, the patient survives but bears the stigmata. Thus the mouth may be distorted, or an eye, a hand or the neck: according to the part of the body in which some blood vessel become filled and obstructed with phlegm and thus rendered inadequate. As a result of this damage to the blood vessel, the corresponding part of the body must necessarily be weakened.

Taking a long view such a happening is generally a good thing because a child is not liable to another attack after an attack which has produced some permanent damage. The reason for this is that the strain of the attack causes injury to and some narrowing of the remaining blood vessels. As a result of this they will no longer admit the entry of phlegm to the same extent, although they will admit air. It is, however only to be expected that such deterioration in the condition of the blood vessels will lead to some weakening of the limbs.

Those who have a very small discharge at a time when the weather is northerly recover without any permanent injury, but there is a danger in such cases that the disease will remain with the child as he grows older.

prognosis for mild as well as severe cases. The term apoplexy was understood by the general public and appeared in the literature until the twentieth century. In adults the distinction between cardiovascular, cerebrovascular and other causes of collapse and coma became clearer during the nineteenth and twentieth centuries, but confusion has remained over how best to separate the aetiologies of the acute neurological presentations of childhood. In The Sacred Disease’, Hippocrates describes the motor outcome for epilepsy in children which we would recognize as hemiparesis (Table 1.2). Confusion about the overlap between the sequelae of acute convulsions (or hemiseizure-hemiplegia-epilepsy) and childhood stroke secondary to cerebrovascular disease remains to this day, at least in part because so many children with a vascular aetiology present with seizures, although access to emergency imaging has improved the distinction between aetiologies in the majority of cases.

Galen distinguished paralysis, a deficit restricted to part of the body, from epilepsy, stupor, drowsiness and stiffness, and from apoplexy, which implied generalized loss of movement and sensation, but covered a number of non-neurological, as well as catastrophic neurological diagnoses. He considered that apoplexy was caused by at least two mechanisms: an excess of abnormal phlegm in the ventricles and an excess of blood in the vessels. He recognised the potential importance of the cerebral arteries and vessels of the rete mirabile, whose description he attributed to Herophilus, in the animals he was dissecting. However, he considered that the veins transported blood and nutrients while the vital pneuma was drawn up through the arteries to the rete mirabile where it spent enough time to be transformed into psychic or animal pneuma, in an analogy with the formation of breast milk, or of semen in the similar but less complex plexus of the testis. He ascribed higher cerebral functions to the rete mirabile but does not appear to have realized that this vascular structure did not exist in Man. In addition, although he linked haemoptysis to vascular rupture, there is no evidence that he linked apoplexy to the rupture of cerebral sex. Galen commented on the association of apoplexy with lack of exercise, and the different pulse seen in paralysis, suggesting that he may have recognized the link with cardiac dysrhythmia. He mentions the protective effect of female sex, the aetiology of which is still an active issue, attributing it to the loss of blood at menstruation, which remains a potentially important hypothesis, but did not refer directly to childhood stroke.

Within traditional Indian Medicine, ailments that would today be described as the effects of stroke are usually classified as various types of paralysis, convulsion and spasm. The existence of the heart and various ducts was acknowledged, but because it was taboo for high caste individuals to touch the dead, anatomical knowledge could only be gained by observing the decomposition of a body in flowing water, which meant that the anatomy of the bones was better understood than that of the soft tissues. The four humours, including blood, were recognized, and were considered to be carried by a multitude of vessels arising from the navel, while consciousness was considered to reside in the heart, the brain was considered insignificant and the causes of neurological illness were speculative. Diseases specific to children were well recognized and there is a reference in the work of the Ayurvedic canon of Susruta (fifth century AD) to children being a vulnerable group, susceptible (in Sanskrit Ardita) to facial palsy, attributed by some interpreters as indicating apoplexy and by others as Bell’s palsy (Table 1.3). We might recognize this condition now as poliomyelitis or perhaps as posterior reversible encephalopathy syndrome (PRES). The

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**TABLE 1.2**

**Description of acute focal neurology in the Sanskrit Ayurvedic canon of Susrata (SUŚRUTA; 5th century AD; in Wujastyk)**

Infants who suffer from this disease usually die if the phlegm is copious and if the weather is southerly. Their little blood vessels are too narrow to absorb a large quantity of inspissated phlegm and so the blood is at once chilled and frozen, thus causing death. If the amount of phlegm is small and enters both main vessels, or if it enters but one of them, the patient survives but bears the stigmata. Thus the mouth may be distorted, or an eye, a hand or the neck: according to the part of the body in which some blood vessel become filled and obstructed with phlegm and thus rendered inadequate. As a result of this damage to the blood vessel, the corresponding part of the body must necessarily be weakened.

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distinction between upper and lower motor neurone facial palsy is not always easy to make in children even now and facial weakness is well recognized in hypertension, which is probably the most common cause of PRES. The emphasis was on treatment with several medicines to cover all possibilities, with psychological support in addition.

Ibn Sina, known in the West as Avicenna, distilled the previous Egyptian, Greek, Indian and Arab work in the Al-Qanum fi al-Tibb.\textsuperscript{31,32} He published his observations on Laqve previous European work in the transmission of ancient knowledge through the Dark Ages in Europe,\textsuperscript{15} when there was little empirical work but many theories linking apoplexy to the brain or the vessels but not specifically to the cerebral vessels.\textsuperscript{36,37}

There is little clinical material specific to neonatal and childhood stroke in the historical record until the nineteenth century, although parallel developments in anatomy\textsuperscript{38} and the scientific method\textsuperscript{39} laid the groundwork from the Renaissance onwards which led eventually to the concepts of the systemic and cerebrovascular circulation which we recognize today.\textsuperscript{15}-\textsuperscript{17}

In 1605 Francis Bacon (1561–1626) in his Advancement of Learning defined the problem:

In the enquiry which is made by anatomy I find much deficiency: for they enquire of the parts, and the substance, figures and collocations: but they enquire not of the diversities of the parts, the secrecies of the passages, and the seats or nestling of the humours.

\textit{Bacon}\textsuperscript{39}

\textbf{Anatomy}

The return to human dissection with illustration in the universities of Renaissance Italy, particularly Padua, led by the Flemish Andreas Vesalius,\textsuperscript{36} was of fundamental importance in challenging Greek and medieval misconceptions, and soon afterwards, the anastomotic circle at the base of the brain was described by Gabriele Fallopius in the Observationes Anatomica (1561),\textsuperscript{40} published with humility as corrections to Vesalius' work but without illustrations, probably because it was at his own expense. Understanding of the cerebral circulation followed on from the key observation by William Harvey that the blood circulated through the body in response to the pumping of the heart.\textsuperscript{10} Although medicine in Europe remained part of the Aristotelian and Galenic tradition, passed down through Ibn Sina's canon, as well as having a basis in alchemy, the Cartesian split between body and mind, the intellectual challenge to describe the limits of knowledge characteristic of the development of the Enlightenment in Europe and the preference for experiment opened up the possibility of describing new mechanisms for neurological diseases such as apoplexy.\textsuperscript{41-43} Harvey's work spread by way of the printing press to Padua, where Johann Wepfer (1620–1690) was studying\textsuperscript{44} as well as to Thomas Willis (1621–1675); both accepted Harvey's findings, and independently injected dye into the cerebral circulation,\textsuperscript{14,16} documenting the functional anastomoses of the circle which eventually led to further understanding of the vascular territories involved in stroke and the discrepancies between diseased vessels and cerebral pathology.

\textbf{Connecting Apoplexy to the Brain and Cerebral Vessels in Adults and Children}

Despite the improved understanding of anatomy, progress on the pathology of disease was relatively slow as there were relatively few autopsies correlated to the clinical symptoms of the patient in life. The earliest unambiguous case descriptions of vascular causes of apoplexy (i.e. strokes) in adults and children, with confirmation that there was vascular pathology in the brain, were published in the seventeenth century. Jakob Wepfer described cases of cerebral haemorrhage in adults with apoplexy.\textsuperscript{11,12,44} Thomas Willis invented the term neurology and also cared for children.\textsuperscript{14,45} He described intracranial haemorrhage in an infant at post mortem but there is a good case for considering that this was subdural haemorrhage secondary to child abuse rather than a stroke.\textsuperscript{47} The earliest childhood case of venous sinus thrombosis was described by Willis in \textit{De anima brutorum} in 1672 (Table 1.4).

Recent comments on this case felt the history and post-mortem findings were in keeping with a venous infarction of the brain following a septic thrombosis of the vein of Galen or the straight sinus.\textsuperscript{46,49} However, Willis's own reasoning was that ‘without doubt in this case the headaches and subsequent delirium were caused by the incursion of the effervescent blood into the meninges and its accumulation there which caused a phlegmon’, another in a long list of hypotheses for this condition.

Many of these cases were collected together with appropriate attribution in the Swiss Théophile Bonet's \textit{Sepulchretum sive Anatomia Practica} (1679),\textsuperscript{36,51} which was widely used by physicians during the seventeenth and eighteenth centuries. Morgagni, working in Padua in the Anatomical tradition of his predecessors, published his magnum opus \textit{De Sedibus et causis morborum per anomen indagatis} as letters to a younger disciple at the end of his life in 1761, which was widely read in Latin and translated into English 8 years later.\textsuperscript{52} Morgagni recognized subarachnoid haemorrhage as a cause of death in a 14-year-old boy but although he considered that cerebral aneurysms might be relevant, he did not report any in his cases and as a ‘solidist’ rather than a ‘humourist’ considered that the sudden onset of apoplexy was related to brain compression.\textsuperscript{53} Whereas Bonet had included a number of patients who had sustained head injury prior to their apoplexy, Morgagni’s series is mainly of spontaneous cases; whether or not to include post-traumatic cases of stroke, for example secondary to arterial dissection, remains a problem in the twenty-first century.
Stroke and Cerebrovascular Disease in Childhood

The first unambiguous description of childhood stroke by Thomas Willis in 1672 (translated by the late Professor Alfred Moritz). Contemporary sources (Aubrey*) relate to boys attending Oxford and Cambridge from their early teens

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Occasionally, survivors of acute paralysis in childhood were also reported; for example, Wepfer described a stroke in a child with hemiplegic migraine published posthumously in 1727. The next 200 years continued in this vein with parallel descriptions of surviving cases with putative clinical triggers including infection and more convincing pathology in case series of those who died.

**SPECULATION ON AETIOLOGY: CASE SERIES OF CHILDHOOD HEMIPLEGIA**

The first case series of ischaemic stroke presenting in infancy was published by Cazauvieilh in 1827, which was acknowledged as being an important landmark.

L’espèce de paralysie décrite dans ce mémoire, survenue chez le foetus ou dans la première enfance, dépend de deux états différents de l’encéphale. Le premier est un défaut de développement sans altération de tissu: le second est une altération de tissu, accompagnée d’un défaut de développement de la partie affectée et des parties environnantes.

*Cazauvieilh, 1827*

Cerebral palsy as presented in this thesis and originating in fetal life or infancy is associated with two distinct forms of brain defect: firstly a primary developmental defect – i.e. without any focal damage – and secondly an acquired focal brain insult with secondary developmental effects.

*Cazauvieilh, 1827*

In Cazauvieilh’s footsteps, many of the giants of nineteenth century medicine followed. Jules Cotard induced cerebral atrophy by the experimental embolization of cerebral arteries in animals and suggested that this might be a mechanism in children as well as in adults, although he also noted some differences, for example in the likelihood of aphasia following apoplexy. The work of Virchow shed considerable light on the pathology of thrombosis and embolus in vessels and was recognized to be of importance in adult stroke, although its relevance to infantile hemiplegia continued to be an area of controversy.

In the latter half of the nineteenth century, debates raged about the apparently better outcome for apoplexy sustained in childhood and about the aetiology of congenital and acquired hemiplegia in the quest to find a single universal cause. Charles West (1816–1898), who founded Great Ormond Street Hospital in London in the middle of the nineteenth century, noted in 1852 that:

> Disturbance of the nervous system shows itself in children as well by loss of the motor power as by the occurrence of involuntary movements; and such an accident as the palsy of a limb naturally occasions parents the greatest anxiety. In the adult, a paralytic seizure is generally the result of a very serious disease either in the brain or spinal cord, and the sign of the commencement of a series of morbid processes which issue sooner or later in the destruction of the patient’s life. Non-professional persons are aware of this fact, and suppose that the same rule holds good in the case of a child as in that of the adult; but you may in most instances quiet their fears with the assurance that paralysis in infancy and childhood seldom betokens any peril to life, though the affection is often very slow in disappearing, and sometime is quite incurable.

West, 1852

Interest in the subject during the late nineteenth century was stimulated by similar observations on outcome and the interest in cerebral localization in adults alongside the further addition to the pathological literature of cases with porencephaly by Richard Heschl and Hans Kundrat, the suggestion by Joseph Parrott, a pioneering paediatrician in Paris, that venous congestion was important and Ernst Von Strümpell’s (Fig. 1.1) unifying theory invoking a post polioencephalitic cause. Several physicians in Europe and North America, including Thomas Barlow, Aletta Jacobs, Ernest Gaudard, Otto Huebner, Pierre Marie, L. Emmett Holt (Fig. 1.1), Sarah McNutt, William Osler, Bernard Sachs and Frederick Peterson (Fig. 1.2), published their experience with congenital, infantile and childhood hemiplegias between 1875 and 1900.

Osler, who had trained with Virchow and had conducted large numbers of autopsies as part of his research at McGill University, wrote his monograph after moving to Philadelphia, where his interest turned to clinical follow-up of various
conditions including the cerebral palsies, a term that he coined. Both before and after he was President of the Clinical Section of the Royal Society of Medicine in London, cases were presented in various sections in the era when the majority of children were cared for by general physicians and neurologists before paediatrics became a separate specialty.

Sigmund Freud, who had described hemianopia in association with childhood hemiplegia, in *Infantile Cerebral Paralysis,* undertook an extensive literature review and produced what can be regarded as a definitive nineteenth century opinion on childhood stroke. Reading this mighty work today, although we may have a greater understanding of the pathophysiology leading to a stroke in terms of practical effective management for the majority of cases, there has been little real progress beyond supportive care.

Lack of therapy does not mean there is no chance for improvement or therapy. We know it is typical for many forms of infantile cerebral paralyses to tend to improvement, that there are light cases of the disease, and that even a complete recovery has occurred in a number of cases. An active interference on the part of the physician that can affect the process appears to be possible . . . . yet even under such conditions one must consider successful treatment as questionable.

Freud, 1897

It was clear to most authors that there were multiple risk factors for infantile hemiplegia, rather than a single cause. Sarah McNutt, whose work was recognized by Osler and Gowers as being important and was the first female member of the American Association for Neurology, described hemiplegia after traumatic delivery with meningeal haemorrhage. Osler mentions trauma as a trigger in older children in addition. There was general agreement that infection was an important association but skepticism about the relationship with the flaccid paralysis of poliomyelitis. In 1860, Jacob von Heine had described hemiplegia after scarlet fever and after vaccination. Gibotteau, who reported milder cases with improvement as well as those left with a residual hemiparesis, considered that all cases had an infectious aetiology. Osler mentions measles, scarlet fever, diptheria and whooping cough while Freud discusses congenital syphilis and smallpox (but not chickenpox) and these infectious aetiologies were noted as triggers throughout the twentieth century. Interestingly, poliovirus was documented in the motor cortex of patients dying of the paralytic form of the disease but the protagonists lost interest in the controversy once the disease was eradicated by the same author and his rival in the development of a safe vaccine. Most of these diseases have either been eradicated or considerably reduced in prevalence at least in Western medicine through public health measures, immunization and antibiotics but children have continued to develop acute hemiplegia after infections. Ford and Schaffer in 1927 cited previously reported cases of focal encephalitis and monoplegia post-chickenpox and reported a case of their own. The development of ventilation for patients with paralytic poliomyelitis has had benefits for the management of children presenting acutely with other neurological disorders including convulsions, coma and hemiplegia which, although it is difficult to prove, has probably improved outcome alongside emergency protocols for status epilepticus of any cause.

Acquired was clearly separated from congenital hemiplegia in the early nineteenth century French literature and in the writings of Osler, Sachs and Freud. In the field of neonatal stroke, clinical descriptions were typically included as ‘congenital hemiplegia’ as part of works on the outcome for birth asphyxia or the aetiology of cerebral palsies. Many conditions presenting as acquired hemiplegia now known to have separate aetiologies, such as unilateral status epilepticus, were published in the same series until the 1970s as were patients who presented in coma. Nevertheless, some of those presenting with convulsions or coma almost certainly had a vascular aetiology, reminding us of the importance of broad nosological terms unless we really understand the pathology.

Otitis media as a cause of cerebral venous thrombosis with ‘the infection being carried by the blood vessels’ was previously well recognized as a cause of childhood and adolescent stroke. Interestingly, the debate as to the relative importance of arterial disease and venous thrombosis as a cause of childhood stroke is equally longstanding. In 1887 Abercrombie was disputing Gowers’ opinion that ‘thrombosis in arteries is a very rare lesion in childhood, far more rare than combined thrombosis in sinuses and veins’, feeling instead that arterial...
obstruction ‘will hold good in the great majority in the other cases’. Although cerebral venous sinus thrombosis continues to be underdiagnosed in the twenty-first century, unless transient thrombosis in the venous circulation turns out to be common when sensitive imaging becomes available for all neurological emergencies in childhood, the passage of time has probably vindicated Abercrombie’s judgement for the present day but it is impossible to obtain a clear answer for his own time or for the twentieth century.100 Otitis media is frequently cited as the most common cause of cerebral venous thrombosis in the pre-antibiotic era, but as late as the 1960s venous occlusive disease made up 60% of cases in some autopsy series.101 As antibiotics are prescribed less in the twenty-first than in the twentieth century, we need to maintain vigilance for this important and treatable cause of childhood death and disability. These series of cases presenting to adult or paediatric neurologists rarely included children with underlying conditions that we consider common aetiologies now, such as sickle cell disease or cardiac disease. The importance of sickle cell disease102 as an aetiological factor for childhood stroke went largely unrecognized for decades.103-107 MacKenzie in the first volume of Brain108 reported a case of cerebral embolus in a girl who appears to have endocarditis, probably secondary to rheumatic heart disease. He mentions the work of Kossuchin, a Russian pathologist who published on the pathology of cerebral embolus in Virchow’s Archives in 1874.109 In addition to the recognition of the association of cerebral aneurysm with coarctation,110 reports of stroke in congenital heart disease appeared,76,82,111-113 although whether the mechanism was embolic remained controversial even when pathological studies were available. Interestingly Wood’s case of a child with pulmonary stenosis and an atrial septal defect with severe cyanosis mentions venous congestion and the occipital softening may well have been secondary to venous thrombosis,112 anticipating the current interest in the wide range of stroke syndromes in children with pre-existing problems.

**Epidemiology**

Over the last century, the epidemiology of childhood stroke appears to have changed with a decline in childhood stroke mortality being seen during the latter half of the twentieth century. Children less than 1-year old consistently have the highest mortality rate, the majority of deaths being due to haemorrhagic stroke.114,115 This understanding has come about because there has been increased recognition of cerebral haemorrhage, at least in part because population-based studies have been undertaken and have included children who died.116-121 Sachs74 emphasized the relative rarity of intracerebral haemorrhage as a
cause of stroke, whilst Broderick\textsuperscript{121} demonstrated that it made up to 50\% of cases seen. The fall in childhood stroke mortality seen during the late twentieth century has been mainly due to a fall in haemorrhagic stroke as opposed to other stroke subtypes. It could well be a reflection of changing aetiological factors that have been sustained now through several generations. On the other hand, the aggressive management of seizures has led to a marked reduction in cases of postictal hemiplegia and the severe and irreversible brain damage seen as a result.\textsuperscript{24} However, iatrogenic causes have become more important as a consequence of medical advances allowing management to extend beyond supportive care.

Scientific Contributions from Anatomy and Pathology

Scientific advance was largely dominated by post-mortem studies until the middle of the twentieth century (Fig. 1.3), with increasingly accurate descriptions of the arterial and venous anatomy by meticulous neuropathologists and embryologists including Helena Riggs, Charles Rupp and Dorcas Padget.\textsuperscript{122–127} Dorcas Padget’s career is of particular interest as she originally trained as an illustrator and worked for many years with Walter Dandy, a pioneer of paediatric neurosurgery.\textsuperscript{125,126} There were also steady advances in the understanding of cryptogenic and symptomatic arterial and venous stroke, periventricular leukomalacia, central pontine myelinolysis, hypertensive encephalopathy, Sturge–Weber syndrome and vein of Galen anomaly from the use of histopathological techniques and their detailed illustration or photography by Wilfred Le Gros Clark and Dorothy Russell, Morgan Berthrong, Betty Banker, Jeanne-Claudie Larroche, Dorcas Padget, Lucy Balian Rorke, Gilles Lyon and Ronald Norman amongst others.\textsuperscript{23,101,128–152} Betty Banker pointed out the importance of cerebrovascular pathology as a cause of death in childhood as this was present in nearly 9\% of 555 consecutive autopsies at the Children’s Hospital of Philadelphia.\textsuperscript{101} She re-emphasized the importance of cerebral venous pathology, particularly in those with congenital heart disease,\textsuperscript{101} and separated out those with periventricular leukomalacia,\textsuperscript{101,133} who only occasionally had demonstrable venous pathology, although she pointed out that the distribution of lesions suggested that these vessels were involved in aetiology, a subject of interest in the twenty-first century. When pathology could only be confirmed at autopsy, either in the acute phase or many years after the event, the timing of focal injury in infancy could only be guessed at, and many conditions, including cerebral venous sinus thrombosis\textsuperscript{142,153} and arterial dissection,\textsuperscript{141} were considered to have a poor prognosis because they may leave little trace after recovery so autopsy descriptions were considered representative. Even now we may not have the tools to exclude these conditions in settings in which its diagnosis and appropriate management might reduce childhood disability.

Outcome: Relation to Age at Injury

There have been relatively few long-term prospective follow-up studies of motor or cognitive outcome after childhood stroke before the twenty-first century (see chapter 17) and some potentially important material is not currently available in English.\textsuperscript{154} As part of a series looking at aetiology and outcome of 334 children with spastic hemiplegia, Philip Hood undertook statistical analyses for his doctorate under the supervision of Harold Westlake of the School of Speech at Northwestern University in Chicago and published the findings with Meyer Perlstein, who had a longstanding interest in cerebral palsy.\textsuperscript{9} They looked at motor and language development\textsuperscript{156} and at intelligence,\textsuperscript{155} finding no difference in mean intelligence quotient between left and right hemiparesis or between congenital and postnatally acquired hemiparesis, although the developmental milestones were achieved a little earlier in the latter group. When computed tomography (CT) became available, several series were published linking presence, size and site of lesion to motor and cognitive outcome for congenital and acquired hemiplegia.\textsuperscript{50,157–161}

Interest in the effect of age on outcome for focal damage to the hemisphere dates back to the nineteenth century when,
soon after the description of cerebral lateralization in adults, Felix Vulpian described experiments in young animals that appeared to move on both sides despite focal decortication.\textsuperscript{162,163} Otto Soltmann hypothesized that motor function in the neonatal period was not reliant on the cerebral cortex and undertook experiments in dogs which showed that electrical stimulation in the cortex in the neonate did not lead to movement in the limbs and that unilateral lesions lead to late walking but not spasticity.\textsuperscript{164,165} It became established that aphasia in adults typically resulted from lesions in the left hemisphere,\textsuperscript{59,60} but the publication of an apparently transient case of aphasia from Great Ormond Street in a child with a right and then a left hemiplegia\textsuperscript{62,63} led to the development of theories about equipotentiality and the development of specialization (see Chapter 17) which continue to be influential today.

Margaret Kennard worked at Yale during the 1930s and was undertaking experiments to look at the effects of cortical ablation in primates when she developed a collaboration with her obstetric colleagues which allowed her to study neonatal animals in addition. She and her colleagues were very surprised to realize that neonatal animals with focal cortical lesions did not develop spasticity and that this age effect persisted when lesions were performed in one- and two-year-old animals, although those operated on at later ages did worse than the neonates but less badly than the animals operated on as adults. Kennard’s work was very influential\textsuperscript{163,166–168} and was interpreted rather overenthusiastically to mean that outcome after focal lesions was generally better in the young. However, permanent aphasia may follow focal lesions sustained at a young age\textsuperscript{169} and many children grow into their cognitive deficits even if language and motor function are relatively spared. The effect of age on motor and neuropsychological function after focal injury continues to be an area of controversy to the present day.

The advent of imaging

The twentieth century marked a decisive change in the visualization of cerebrovascular disease and its consequences in terms of haemorrhage or infarction. When previously only clinical acumen and craniotomy or trephination for extradural or subdural haematoma could reveal the cause of apoplexy in the living child,\textsuperscript{170} imaging the living brain marked a decisive step,\textsuperscript{149} even if this was initially only gross pathology.\textsuperscript{171} Some of these techniques, such as pneumoencephalography,\textsuperscript{172} although groundbreaking in their day, have become redundant and are now forgotten outside an historical review.\textsuperscript{98} A limited understanding of ventricular size could be obtained from a skiagram\textsuperscript{173} or pneumoencephalogram\textsuperscript{24} (Fig. 1.4) and occasional series of unselected cases of acute hemiplegia in childhood were published, although the results were not necessarily illuminating except in showing atrophy independent of any vascular territory after status epilepticus\textsuperscript{24} and unilateral brain swelling in the acute phase of hemiplegia.\textsuperscript{90,95,174–176}

Understanding of the relative importance of various cerebrovascular pathologies improved with the advent of contrast
cerebral arteriography during the 1920s and 1930s. Moniz included an 11-year-old girl with a tumour in an early series but for stroke, the technique was used mainly in adults and only occasionally in children unless surgery, for example for intractable epilepsy or to prevent recurrence, was considered, because of the perceived risk of the procedures after the experience with pneumoencephalography and the perception that childhood stroke had a good prognosis and rarely recurred. However, the series of Charles Poser and Juan Taveras in New York, Kenneth Till and Dick Hoare in London and Edwin Bickerstaff in Birmingham, UK, John Shillito in Boston, Mark Dyken in Indianapolis and Derek Harwood Nash in Toronto, amongst others, made it clear that the test was commonly abnormal when haemorrhagic or ischaemic stroke was suspected clinically and that the benefit of making an ante-mortem diagnosis probably outweighed the relatively small risk for arteriography in their experienced hands. Werner Isler in his series, published as a book, acknowledged his debt to his predecessors and particularly to the participants at the Spastics Society meetings on Congenital Hemiplegia in Bristol (Fig. 1.5) and on Acquired Hemiplegia in Clevelon in 1961, which brought together clinicians and pathologists as well as the renowned anatomist Alf Brodal. Arteriography was felt to be safer and more useful in establishing a diagnosis than pneumoencephalography, so that even before cross-sectional imaging was available, case series including the systematic use of vascular imaging in ischaemic stroke in childhood with clinical and laboratory information began to appear with the series of Hugh Greer and Arthur Waltz from the Mayo Clinic, Jean Aicardi, Françoise Goutières and Jean-Jacques Chevrier in Paris, Gail Solomon and Sadek Hilal from Arnold Gold’s department at Columbia Presbyterian in New York, Tibbles and Brown from Canada, Janaki and Malik from India, and Gösta Blennow and Orvar Eeg-Olofsson from Scandinavia. Systematic use of conventional angiography also allowed the distinction of cases with acute hemiplegia without cerebrovascular disease, facilitating the diagnosis in life of venous sinus thrombosis, which had been deduced previously, the distinction of alternative diagnoses such as alternating hemiplegia and the exclusion of hemiconvulsion-hemiplegia-epilepsy, which had been previously included in many case series of acute hemiplegia in childhood. These remain important issues as there is an important proportion of childhood stroke cases without vascular occlusion who must be excluded from any treatment trials to be conducted, for example of clot-busting drugs.

The advent of less invasive ultrasound, CT and magnetic resonance imaging (MRI) has led to a renaissance of interest in the subject. Our perspective on childhood stroke has been revolutionized, allowing new perspectives including accurate identification of high risk groups with sickle cell disease, the diagnosis of silent or covert infarction and

Fig. 1.5. Participants at the National Spastics Society Study group meeting on hemiplegic cerebral palsy in children and adults, held at the Wills Hall, University of Bristol, 1961. Ronnie Mac Keith is in the front row on the extreme right.
comparisons with adults as well as giving us a greater understanding of the whole realm of cerebrovascular disease.

The Dawn of Physiology and Pathophysiology

Once investigation of the cerebrovascular circulation in life became possible, some workers began to explore the physiology as well as the anatomy associated with cerebrovascular disease in childhood. Cerebral blood flow was found to be much higher in normal children than in adults, using the nitrous oxide clearance method of Kety and Schmidt and these data have proved useful in understanding the pathophysiology of sickle cell anaemia. Using the Kety-Schmidt technique, Dyken found evidence that the least damaged hemisphere received blood from the contralateral carotid system in people who were long-term inpatients because they had sustained infantile hemiplegia, but these data are unlikely to be representative as most patients who have had a childhood stroke live independently as adults. Chronic focal perfusion deficits have been shown using other techniques, but the relevance of these studies to outcome awaits less invasive methodologies which can be used in all children in the acute and chronic phases of stroke.

Although electroencephalography (EEG) was a breakthrough for the management of epilepsy, it was not a particularly sensitive technique for demonstrating the effect of focal infarction. Attempts to use it for the diagnosis of paediatric neurological problems, including congenital and acute hemiplegia, did not bear fruit as it did not distinguish aetiology or predict prognosis. However, monitoring EEG during cardiopulmonary bypass using single channel devices such as the cerebral function monitor did lead to understanding of the role of intra-operative microembolization in the aetiology of poor neurological outcome in children as well as adults and thus to the introduction of filters which reduced the incidence.

Interest in the physiology of sleep in the young dates back at least to the work of the Russian Maria Mikhailovna Manasseina-Korkunov, also known as Marie von Manassein and Marie de Manacéine, one of the first women doctors in Europe. In a paper presented at a meeting in Italy, she reported that depriving puppies of sleep led to reduced red cell counts and to death, with the youngest animals dying earliest, typically with localized intracerebral haemorrhage and abnormal blood vessels. Her findings were followed up and largely replicated by Italian scientists, but although links between sleep physiology and stroke have been reported in adults and children, particularly those with sickle cell anaemia, relatively little attention has been paid to the effects of duration since then, although this might be important in the preterm neonates vulnerable to intraventricular haemorrhage, in addition to the effect of nocturnal hypoxia on endothelial function. Interaction with haematologists and other laboratory scientists has been increasingly important in understanding the pathophysiology of childhood stroke, particularly as Maureen Andrew showed very clearly that haemostasis is affected by a number of factors, including age and hypoxia. Like many of the pioneers, she also trained up a number of distinguished clinical academics who continue to try to understand these complex problems.

Conclusion

The change in attitude is reflected in the increased medical literature devoted to this topic. Additionally there have been important changes in nomenclature. Osler’s book gives a useful list of terms previously used in the nineteenth century, while works from the mid-twentieth century tended to use his term ‘cerebral palsy’ or, following Freud, ‘hemiplegia’, as did the early volumes of the Clinics in Developmental Medicine series supported by the Medical Advisory Committee of the National Spastics Society. The different titles to the volumes published by key players based in Toronto, San Francisco, Chicago, Dallas and Paris in the 1980s and 1990s reflect a more recent and wider understanding of the vascular nature of the majority of these conditions, as well as changing public attitudes. The definition of what we are including in clinical research has both hardened and widened in this period from that first suggested 40 years ago, when hemiplegia lasting less than one week was not included at Ronnie MacKeith’s insistence. In contrast, most contemporary authors include not only patients with clinical stroke on the World Health Organization (WHO) criteria of a focal event lasting >24 hours with no cause other than vascular, but also those with transient ischaemic attacks lasting <24 hours (WHO) if there is a new lesion on cross-sectional imaging, and carefully clinically defined episodes lasting any length with reversible neuroimaging changes.

Arnold Gold and his colleagues attempted to examine the implications for treatment 50 years ago but it is only now that the challenges of running interventional studies are at last being met. The first large case controlled studies are now being published, examining the role of aetiological factors, often genetically controlled, which may not be obvious clinically at initial presentation, for example prothrombotic states. In preparation for, and subsequent to, the first international symposium on childhood stroke in 1998, attempts have been made to develop a consensus, create a critical mass for research and to set a future research agenda. The conference on childhood cerebrovascular disease at the National Institutes of Health (NIH) in 2000 reviewed the available evidence on aetiology, risk factors for recurrence and outcome, and in 2005 this was followed by an NIH-funded international meeting ‘Towards the Establishment of Pediatric Stroke Trials’. The development of guidelines and an international registry are stepping stones towards the trials needed for an evidence base for management. Re-inventing the wheel is not an option.

A historical review merely provides pointers, restates unsolved questions and cautions against simplistic thinking. Historians are sometimes asked from their understanding of the past to predict future developments. This we would hesitate to do, but would add that an examination of the changing management of other previously incurable conditions, for...
example childhood leukaemia, illustrates future possibilities as well as the difficulties, both in the short and long term, which have to be overcome. Already for stroke, authors have started to consider future therapeutic possibilities including neuronal regeneration and its limitations.

Childhood cerebrovascular disease has been described, if not recognized, since the dawn of medical literature and we can recognize its stigmata in art and literature. We are clearly seeing a sea change in attitudes to the investigation and management of childhood stroke and cerebrovascular disease on a background to changing attitudes to disability in childhood. For childhood cerebrovascular disease we appear at long last to be finally crossing from an era of ‘one long hypothesis’ through to an era of action based on sound theory.

We should not be complacent. At the beginning of the twenty-first century, we are still at an early stage in the medical evolution of the management of this condition. Single case reports and relatively small case series still inappropriately dominate the present day literature. Studies with matched controls have now been published which lay the groundwork for the future. The Stroke Prevention in Sickle Cell Anaemia (STOP) trial demonstrates the effectiveness of targeted intervention.237 At the time of writing large international interventional studies are actively being considered. One hundred years after Freud’s comprehensive review of this field the majority of cases still have little beyond general supportive care, but L. Emmett Holt’s then contemporary gloomy thesis can no longer be supported. Our greater understanding and the new will of international cooperation raise the possibility that within our working lifetime, evidence-based acute and rehabilitative treatments for the acute stages of childhood cerebrovascular disease will become a realistic prospect for the majority.

Dedication
We would like to dedicate this chapter to the memory of Dr Stuart H. Green, MA (Cantab) MRCS, FRCP, FRCPCH consultant paediatric neurologist, children’s physician, inspirational teacher and friend.

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