The Study of Stroke

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The information gained from any study is only as good as the methods used to obtain it. Some of the information gained from current research into stroke disease is of limited value because of methodological problems.

'Stroke' can be defined as the sudden onset of a focal neurological deficit due to a local disturbance in blood supply to the brain. 'Sudden' may refer to a period ranging from a few seconds to a few days[1]. The recent trend is to describe strokes in terms of their time course rather than pathology. The terms 'transient cerebral ischaemic attack' (TIA), 'continuing stroke' or 'stroke in evolution', and 'completed stroke' are now in common clinical usage. These terms found favour because the clinician could not reliably distinguish between the processes of 'thrombosis', 'embolism' and 'haemorrhage', and because concepts of the pathology of stroke have changed with the discovery of 'lacunar infarcts' and increasing awareness of extra-cranial vascular disease.

Most studies are concerned only with certain types of stroke, e.g. completed stroke resulting in major deficit such as hemiplegia. If such a temporal classification is used, any assumption this makes about underlying pathology must be made clear. Since the vast majority of neurological deficits characterised by rapid onset of loss of function on one side of the body will be of vascular origin, and 80 per cent of them will be 'thrombembolic', any very large series might iron out such problems of definition. But many studies are on relatively small numbers, which makes definition, classification and diagnosis crucial.

Diagnosis

The underlying pathology in stroke has important implications for the natural history of the disease and its treatment. Cerebral thrombosis has a much better prognosis for survival than haemorrhage. In one large series[2], the 30 day survival was 73 per cent for thrombosis, and 17 per cent for haemorrhage. Therefore, it is necessary to ensure that studies of small groups do not include a disproportionate number of haemorrhages. However, clinical differentiation can be difficult[3]; a lumbar puncture can give misleading results and is a hazardous procedure in a patient with increasing drowsiness and gross 'lateralising' signs. Fortunately, computerised axial tomography (CAT) scanning is excellent for distinguishing haemorrhage from infarction, as well as going a long way towards accurate localisation, another common clinical failing[4].

Estimates of the number of strokes in which cerebral tumour is present vary from 7 per cent[5], to 10-15 per cent[6]. While there are difficulties in distinguishing CAT scan appearances of tumour and infarct[7,8], the technique is probably more reliable than clinical judgement. A study by Weisburg and Nice[9] related CAT scan findings to different presentations of 'stroke'. In eight patients with a truly step-wise evolution, CAT scan showed only one neoplasm. In ten patients whose evolution was complete within 12 hours, no neoplasm was found. In 20 patients whose disease progressed for between 12 and 72 hours, a non-vascular cause was found in 13. In 30 patients whose deficit was complete within two hours, and who had a normal cerebrospinal fluid, five had neoplasms and one a subdural haematoma.

However limited in application to general clinical practice in the near future, this technique is an important refinement for research purposes.

Selection

A criticism aimed at many studies is that the patients do not represent an unselected group, usually being hospital in-patients. Latterly, the proportion of strokes entering hospital at some stage in their illness has risen to two-thirds, but this leaves a substantial proportion about whom very little is known, with obvious implications for our knowledge of the natural history of the condition. The decision to admit a patient to hospital is based on a combination of medical and social factors; it is not a random process. The only realistic approach to selection for study lies in the co-operation of researchers and primary care physicians, so that all strokes occurring in an area over a given period are considered.

Measurement

It is in the increasingly important area of measurement that most confusion and inconsistency exists. Almost no aspect of stroke lends itself to easy, accurate, measurement. The 'long road' from basic pathological lesion, to clinical deficit, to a numerical score for an individual, and from there to the score for a group of patients, is fraught with methodological hazard. The crucial question is always whether the methods used accurately measure what they are supposed to measure. A review of the literature shows that no two researchers use the same system in terms of what aspects are to be measured and how such measurement is to be expressed.

The first step is to recognise that a stroke patient passes through several phases, in each of which the emphasis must be different.
The Pre-morbid Phase

In the pre-morbid phase medical factors such as hypertension, ischaemic heart disease and previous stroke, psychiatric factors such as depression and particularly dementia, and previous functional level in terms of mobility and personal independence, are of interest but usually impossible to document fully. The patient can seldom give any account of himself after the stroke and has often been socially isolated. For factors such as hypertension there are well established criteria of severity (i.e. electrocardiographic, fundoscopic, etc.), but most other aspects of the pre-morbid phase do not lend themselves to any retrospective attempt at measurement.

The Acute Phase

The acute phase of high early mortality is usually thought of as the first three or four weeks. In this phase the problems are those of accurate medical and neurological diagnosis. Treatment is concerned more with life support and prevention of complications than with other considerations. The approach to the acute phase usually consists of some assessment of consciousness, orientation, communication, motor and sensory function, vision and continence. This is then translated into a numerical scoring system such as 5 = normal, down to 0 = dead. This numerical representation is a helpful shorthand when studying an individual, and an absolute requirement when studying and comparing groups. Its validity depends on how carefully one moves the two steps from pathological lesion to clinical deficit to measurement of deficit.

How much of any clinical deficit is due to, say, infarction, and how much due to surrounding underperfusion or oedema, and how these change in the first few days, is only partly understood. The use of stereotyped lesions in experimental animals has illuminated some of the basic processes, but the site, size and severity of an individual patient’s stroke is a very different matter, even allowing for the degree of stereotype recognised in the much quoted ‘syndromes’ of the individual cerebral arteries.

From clinical studies certain factors are known to be important for short-term survival: for example, haemorrhagic strokes fare much less well than thrombotic ones. Within this latter group, Oxbury et al. [10] showed that three variables—unconsciousness, any combination of impaired consciousness with dense hemiplegia, failure to conjugate gaze towards the weak side—all bode ill for survival. Other items on Oxbury et al.’s 52-item proforma for examination did not reliably or accurately predict events. Therefore, only these three variables are worth recording in a clinical study of the acute phase and are of use in measuring the effects of treatment. It has to be conceded that many of the elaborate schemata aimed at the finer points of neurological examination cannot be usefully applied to the drowsy patient. It could certainly be argued that these items should be more heavily weighted in any scoring system than the other variables which have been shown to be less important for survival.

Postmortem evidence in this study [10] also showed that a particular pathological process underlies such a clinical presentation of unconsciousness, dense hemiplegia and impaired conjugate gaze, namely infarction of at least the territory of one middle cerebral artery and severe cerebral oedema.

Similar deficits can, of course, be produced by lesions at different sites, e.g., hemianopia by posterior or middle cerebral lesions, and hemisensory loss by cortical or brain stem lesions. Even if the overall prognosis for hemisphere and brain stem strokes is similar, the predictive value for survival (or recovery) of a given deficit, such as hemisensory loss, may be different for the two territories. Therefore, hemisphere and brain stem strokes should be considered as separate groups until suitable studies show that they can be safely combined. Longitudinal studies correlating clinical findings with precise knowledge of the nature, site and extent of the lesion (using serial CAT scans) may provide the information by which scoring systems could more accurately represent actual brain damage.

The Steady State Phase

The steady state phase is that in which the survivors must be assessed and treated, with the emphasis on rehabilitation. This period is usually considered to last up to six months, though some useful rehabilitation can still be achieved after 12 months [11]. Rehabilitation presents similar complex problems of assessment. In acute studies, outcome can at least be measured in terms of life or death. The outcome of rehabilitation has been assessed in terms of (a) neurological deficit, (b) functional deficit (c) length of stay, or (d) final placement. Examples and combinations of each abound in the literature.

Neurological Deficit. The fact that the patient is probably fully awake does help some aspects of the neurological examination that are difficult in the acute phase. Even a relatively straightforward item such as motor weakness still poses its share of questions. In order to arrive at a numerical score, one must decide on (i) a scale of severity from normal power down to zero; (ii) which movements at which joint will be assessed, and (iii) whether certain movements should be more heavily weighted in the light of the already known patterns of recovery, or their functional relevance. The number of different published systems for doing so suggests that no one is really sure of the best systems. If this is a vexed question, then even worse is the measurement of deficits that have come to be called the ‘mental barriers to recovery’, after the work of Hurwitz and Adams [12,13]. They outlined the importance of conditions such as dementia, communication disorders, perceptive and cognitive disorders, and depression, and their tendency to impede recovery. The approach to the assessment of these disorders, especially the cognitive disturbances, has been outlined by Isaacs [14] and many others subsequently. In such expert hands, the presence or absence of such deficits, and some idea of their severity, can be deter-
mined. The difficulties are, nevertheless, considerable. First, there is a general lack of expertise in this field. Confusion, fluctuations in concentration, and mood problems all affect outcome to a degree that is difficult to measure. Stroke deficits such as dysphasia and non-stroke deficits such as blindness, deafness, illiteracy and innumercy all disqualify the patient from certain groups of tests. For an individual, these can all be added as riders to the final score, even though it makes the procedure cumbersome. But in a group, all with different riders, expression of a single total or average score may be either meaningless or impracticable.

Functional Deficit. Assessment of functional deficit is common and usually carried out by physiotherapists and occupational therapists. Areas studied are mobility (in bed, chair, walking on stairs), dressing, toilet activities, feeding, and so on. Account is taken of aids used, and verbal or physical assistance required. Scores are usually expressed on a numerical scale such as: 1 = independent; 2 = independent but with some aid, e.g., walking stick; 3 = needs verbal or minimal physical help; 4 = needs a lot of physical assistance, and 5 = total inability. The theoretical and practical limitations of such assessments of the activities of daily living have been reviewed by Nichols[15]. Whatever their limitations, their importance is simply that it is functional deficit that largely decides whether the patient will go home or will need to stay in hospital, other factors such as family and domestic circumstances being equal. The success of rehabilitation programmes in reducing handicap does not depend on their reducing neurological deficit or disability.

Length of Stay and Final Placement. Length of stay is becoming a much-used measurement. The significance of length of stay in relation to the natural history of certain types of neurological or functional deficit, or to the effectiveness of a form of treatment, requires careful interpretation. There must be a clear statement of the social background and family support of the patient; the basis for the decision to discharge or transfer him, e.g., following weekly assessments and then discharge after a set period of 'no change'; (this means that length of stay can only be stated in terms of the same units as the intervals between assessments, and not in terms of a number of days, unless assessments are done daily); and any premature or delayed discharges for non-medical reasons. Furthermore, the system applies only to a specific type of health service, the USA and UK not being strictly comparable.

It is clear that if enough riders were added in each case, the expression of length of stay for a whole group would be difficult, unless the group was so large as to average out most of these variations. This is not often the case. Unless a similar approach is adopted for the expression of 'final placement' as a measure of outcome, it, too, is of limited value.

Other Problems of Method. When a given variable is being discussed, it should be noted whether it is being assessed in relation to final neurological or functional status, or length of stay. A factor affecting one may not necessarily affect the other; for example, Feigenson et al.[16] found that hemisensory loss increased length of stay but did not influence ultimate functional status. A recent study of naftidofuryl in acute stroke disease showed that the treated group and controls reached similar levels of neurological recovery, but the treated group spent only half as long in hospital[17].

One or two other methodological problems apply to the study of the rehabilitation phase. When the effects of a drug are being studied, the control side of the study is relatively simple, the patients being given appropriate placebo tablets or injections. But in studying the effectiveness of, for example, speech therapy, what constitutes a control can be problematical. Would the speech therapist have to attend the control patients and do something other than communicate with them? That may sound ridiculous, but simply to have speech therapy versus nothing whatsoever is not controlling enough variables, as it may simply be one-to-one regular social contact rather than formal therapy that is responsible for any improvement. This argument applies equally to the benefits of physiotherapy and occupational therapy, there being no equivalent of 'placebo' therapy.

Observer variation is a major source of error in measurement. Garraway et al.[18] illustrated the point. Four consultants each examined the same group of stroke patients. Assessments were made on four occasions. On the first occasion assessment was left to each consultant’s individual technique and judgement, and total agreement occurred in only 35 per cent of the evaluations. The second assessment was made after a standard examination technique had been imposed, and agreement was reached on 55 per cent of the assessments. The third assessment was a repeat of the standard technique ten days later, and the level of agreement was 50 per cent. Final assessments were made after extensive discussion and revision of the techniques, and total agreement improved to 70 per cent. The authors showed several factors to be operating and, despite increased agreement in assessment, they considered that the figures left no room for complacency. This sentiment could be reasonably applied to all other aspects of stroke analysis.

The Final Outcome Phase

The final outcome phase, after any improvement and most serious attempts to bring it about have ceased, may find the patient back at home, independent, even back at work; or bedfast and incontinent in a long-stay environment. Little more can be said of this phase, mainly because very little is known about it. Lawrence and Christie[19] emphasise the need for further study.

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A Gift that was Paid For

By any standards George Edwards was a remarkable man. He was Beadle and Library Keeper at the College, a Fellow of the Royal Society and of the Society of Antiquaries, and he wrote and illustrated A Natural History of Uncommon Birds and Gleanings of Natural History, comprising in all seven volumes. As each volume was completed he gave a copy to the College, suitably inscribed, and received in return a payment of five guineas. Edwards owed his appointment at the College in 1733 to Sir Hans Sloane, President of the College and of the Royal Society. Sloane had given his casting vote in favour of Edwards when a ballot for two out of twelve applicants had resulted in a tie, and in doing so may well have had his own and Edwards' interest in natural history in mind, as much as the well-being of the College.

An Essex man, George Edwards, born in 1694, went to school first in Leytonstone and then in Brentwood. Intended for a career in business, he spent seven years with 'the son of a levite, one John Dod, a man in trade, and a finished scholar in the Greek and Latin languages.' He was probably the father of Peirce Dod, a Fellow of the College, and related to Denton Nicholas, another Fellow. When Dr Nicholas died, his books were stowed away in the room next to George Edwards' bedroom. Access to a 'confused mixture of books on astronomy, natural history, experimental philosophy, travel and painting' stimulated in Edwards a desire to visit foreign parts. So, possessing a small patrimony, and to satisfy his curiosity, he put business aside and set out on a voyage to Europe in 1716. On his return three years later he settled in or near London and occupied himself in teaching drawing and in making drawings of rare foreign birds in private collections, and at the same time made copies for himself with the permission of the owners.

From time to time Edwards showed his illustrations to various visitors who commented that some had never been described by any author and urged him to publish. He was reluctant to do so because he felt he knew insufficient about such birds and the country from which they came. In addition, he knew how expensive engraving, printing and other things were. Part of his objections at least were removed when he learned from Mark Catesby (c. 1679-1749), another naturalist, how to etch the plates himself.

He tells us that he took ten years over the preparation of the first volumes, which were published in parts. This means that the decision to publish was made about 1740, with the first three volumes being completed in 1750, as far as can be seen. The first volume has two title-pages; one presumably relates to the first part and is dated 1743; the title-page for the complete volume has no date but has an engraving of the obverse and reverse of the Copley medal of the Royal Society, which was awarded to Edwards on St Andrew's Day (30 November) 1750. This was an unusual honour since it related to the publication of a book and not to philosophical research, and happened seven years before he was made a Fellow of the Royal Society. The dedication of the first volume to the Royal Society is to be expected, as are those of the next two to Sir Hans Sloane and to the College. After Sloane had retired to Chelsea in 1740 or earlier, Edwards tells us that he seldom missed drinking coffee with him and carrying news of the scientific world and especially of what was happening at the Royal Society's meetings. The dedication of the fourth volume to God may reflect an odd idea of priorities; while that of the first volume of the Gleanings (1758) to the Trustees of the British Museum is interesting, as is the date on one of the several hundred illustrations. The British Museum was established partly as a result of the purchase of Sloane's Collections. The Trustees were appointed in 1753, but the Museum was not open to the public until 1759. This same volume includes an illustration of the yellow water wagtail, with the upper and under side of the insect called the walking leaf, and dated 1756, taken from a specimen now preserved in the British Museum. It is not a perfect specimen; 'the hinder legs are perfect; the others are broken off. I did not care to supply them by conjecture.'

Another illustration is of the Dodo, drawn in Holland from the living bird, brought from St Maurice's Island in the East Indies. Edwards was jealous of his reputation when it came to the accuracy of the colouring. He not only determined to part with no uncoloured prints while he lived, lest they should be coloured by unskilful people; but, having given a set 'carefully and exactly coloured from the original drawings' to the College, he also

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