NTERNATIONAL STROKE TRIAL WORKSHOP

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Problems in stroke trial methodology

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The published trials of drug therapy in acute stroke provide many examples of design failure.[1] Although it is true that 'stroke' presents and develops in a variable manner, making unpredictable therapeutic demands, this is not peculiar to stroke amongst acute medical emergencies. Selection, assessment, compliance and control are all important in acute stroke trials and the problems lie in the methods to deal with them.

There are two broad approaches, which have been labelled 'pragmatic' and 'explanatory',[2] and the trial method depends upon which is adopted at the onset of the trial. Failure to distinguish between the two has invalidated many trials, or caused the wrong question to be answered.

PRAGMATIC

A pragmatic study asks: "Does prescribing treatment A bring more benefit to the patient than prescribing treatment B?" The emphasis is on *intention to treat* in the context of daily clinical practice, without selection, categorization or compliance. The pragmatic approach accepts patients who are misdiagnosed and in whom the disease is not being treated, as well as those who do not comply with the treatment regimen; their inclusion is appropriate because this is what happens in standard clinical practice. All circumstances that affect the patient are relevant to the assessment of outcome; for example, if a patient dies an accidental death that has nothing to do with his stroke or the treatment, it is still a treatment failure, since the patient has not benefited from it.

EXPLANATORY

In the explanatory approach, the question is more specific: "Does treat-

ment A improve recovery after stroke more or less than treatment B?" Here, the trial procedure must demonstrate that the patient has the disease and complies with treatment. Careful selection of patients is necessary, including the avoidance of other illnesses that may interfere with assessment of recovery. This means, however, that the group is not typical of normal clinical practice.

Exact determination of outcome requires frequent assessment and more than routine follow-up demands. Accidental death is irrelevant in this approach, being an 'intercurrent condition' which interferes with assessment; these patients therefore have to be excluded.

Neither approach can be said to be right or wrong, though some illnesses tend naturally to favour one rather than the other. Acute stroke offers opportunities for trials, not only because an effective treatment would modify clinical practice, but also because the current consensus is to do very little.[3] For this reason, acute stroke trials should usually be explanatory, despite various problems: patients are mostly elderly; many have other illnesses which interfere with recovery and assessment; they are forgetful and, in general, comply poorly with treatment; and their response to treatment can be unpredictable because of altered physiology. On the other hand, acute stroke patients often start as hospital inpatients, allowing control at least over their early therapy.

DIAGNOSTIC CONFIRMATION

Diagnostic precision is important because one pathology that may present as stroke – infarction – has a quite different natural history from others (haemorrhage and tumour), and clinical assessment cannot always distinguish them. Furthermore, the natural history of cortical infarction is different from internal capsule, or brainstem, infarction. Diagnostic confirmation, at present, means CT scanning. Since few trials yet published have demanded CT scans on all patients, they could nearly all be considered invalid on this ground alone.

If the course of events in ischaemic, but not yet infarcted, tissue is to be favourably altered, the available time-scale for intervention is hours rather than days,[4] so that stroke appears to require emergency treatment. This means that entry to the trial may have to precede diagnostic confirmation, especially as initial CT scans are commonly negative. Other forms of diagnostic scanning, particularly those of cerebral blood flow (such as SPECT[5]), may prove to be more useful. This suggests that definitive explanatory trials of treatment in acute stroke should be undertaken only at centres where such techniques are available. This may seem unrealistic; however, where diagnostic confirmation *follows* trial entry, patients cannot be separated into diag-

nostic subcategories prior to assignment to a treatment group. Thus, diagnostic confirmation serves the purpose of fulfilling definitive inclusion criteria but not that of treatment group matching.

CONTROL

Matching of treatment groups

Matching of patients still has to be achieved through the application of clinical judgement. This is quite satisfactory provided that the pathological diagnosis (e.g. infarction) and site (e.g. cerebral hemisphere) are later confirmed or, if not, the patient is secondarily excluded. Clinically, the following factors[6] are predictive of poor outcome:

1. Reduced level of consciousness;
2. Failure of conjugate gaze;
3. Dense hemiplegia.

Other factors that affect recovery include severity of neurological deficit, sex, age, side affected and history of previous episodes.

Attempts at *a priori* patient matching are further confounded by the variable course of the disease in its early stages. Even with diagnostic confirmation, it is not usually known what pathophysiological processes are involved (e.g. whether an infarct is embolic and, if so, the nature of the emboli). Two patients who are clinically (and, apparently, prognostically) similar at the time of entry to a trial may, during the next few hours, take different courses, one recovering and the other deteriorating. Although treatment may have been started, this disparity can occur before the treatment has had any effect. Therefore, patients who were matched originally are no longer matched at the relevant time for the trial.

These problems, which have no practical answer, have to be solved statistically.

Randomization

Where predictors of outcome are not good enough to allow a rational categorization according to prognosis, or are impossible to apply, the statistical solution depends on randomization, which has implications for patient numbers.

Patient numbers

A study with 95% power to show an effect sufficient to reduce death rate by one-half, or to increase the number of patients returning to independence by one-half, requires 300–400 patients, even if initial

matching for all important prognostic variables is good. If they are not well matched, either the study's predictive power is less or more patients are needed. Matching can be facilitated by restrictive selection criteria; this is acceptable in an explanatory trial, but limits generalization of the result; for example, we cannot safely extrapolate from middle to posterior cerebral artery territory. An immediate effect of rigid selection criteria is to exclude some 90% of all presenting patients, thus necessitating a multicentre trial, or a trial of prohibitively prolonged duration.

Multicentre organization

If there is to be an extrapolation of trial results to other patients, a record must be kept of all those *not* included (the denominator) – which may be 3,000–4,000 patients – so that one group can be related to the other. These figures argue that multicentre organized trials are a necessity, whatever other problems they introduce. Committee decisions account for many of these problems, and they are greater in an explanatory study.

TREATMENT

Rules of treatment

Treatment in stroke can affect one of the following:
1. Acute development (prevention of progression);
2. Sub-acute course (early resolution);
3. Rehabilitation (late resolution);
4. Recurrences (secondary prevention).

The timing, manner and duration of treatment depend upon in which of these phases the treatment is thought to act. An exact regimen is never followed in practice, even in hospital inpatients, but the treatment rules should exclude any arbitrary decision over permissable departures from the prescribed protocol in individual cases. It is just as important not to exclude commonsense, when the rules do not allow for an unexpected circumstance, and it is impossible to make specific provision for every contingency. The necessary balance between flexibility and rigidity in the formulation of treatment rules requires an intimate practical experience of treating the disease.

Blindness

The need to maintain therapeutic 'blindness' will be reflected in treat-

ment rules, as it may be impaired if one treatment is regularly identified with specific side-effects (e.g. hypotension or venous thrombosis). Introduction of a separate, unblinded monitor to control the treatment regimen is a design complication but, since side-effects must be both monitored and recorded, it is sometimes unavoidable.

Period of follow-up

In a trial assessing recovery from acute stroke, the *rate* and *degree* of recovery can be measured, and they correspond approximately to intermediate and eventual outcome, respectively. Not only are these not the same thing, but also one may not reflect the other. Recovery may be protracted, following a largely unpredictable course, with accelerations and plateaux. Progress measured after one month cannot be assumed to indicate final outcome, say at one year, even though there may be a degree of correlation.

The period of follow-up appropriate to the study relates to the initial question asked. The eventual outcome is usually the object of interest, but follow-up in most published trials has been too short. On the other hand, the longer the follow-up, the greater the interference from extraneous influences. These include compliance failure, loss to follow-up, non-stroke death and intercurrent illness, which may have nothing to do with the disease, its treatment, or evaluation, though proof of their irrelevance may be required during statistical analysis. In an explanatory trial, recurrent stroke and drug interactions may be extraneous factors.

Compliance

Compliance may be of limited importance in pragmatic studies; this is not to say that it should not be monitored, only that *special* efforts to promote it can be inappropriate. In explanatory studies, compliance is of greater importance. In trials of recovery from stroke, compliance tends to be good and patients in hospital present little difficulty, though periods of dysphagia will be encountered along with errors in nursing, dispensing, prescriptions and drug supply, as well as capricious refusal of medication by patients or acute failures of bioavailability through gastric upset or other illness.

Findings may be more certain with some parenteral routes, but intravenous infusions needing accurate long-term control create many of the same problems. In addition, a patent venous line has to be continuously maintained in patients who are often elderly, confused, uncomfortable and restless.

Patients who are out of hospital are, by inference, getting better and will probably continue taking their tablets since they attribute their recovery to them. If the patient is told he may be taking placebo tablets, this benefit is lost and long-term compliance becomes a major problem.

MEASUREMENT OF OUTCOME

Evaluation of response in each patient and comparative assessment of group outcome are two distinct measurements, and the same method cannot be applied to both. Confusing these two issues is another major contributor to trial invalidity. A summed neurological score, to which points awarded for the presence of various neurological deficits or disabilities contribute (with or without weighting), is only of value in monitoring progress in a particular patient. It is a basis neither for determination of group outcome, nor for statistical comparison between patients or groups of patients, because the score for each does not represent the same variables. Such use of neurological scores would imply a belief that the course towards recovery in a patient who speaks but cannot walk is the same as in one who walks but cannot speak. The two situations have only a slight mutual relevance, which is not altered by a scoring system that makes them equal or that weights one more heavily than the other, a system for which there can be no logical basis.

If trial entry is restricted to patients disabled by hemiparesis through recent middle cerebral artery territory infarction,[7] neurological recovery (but not necessarily rehabilitation) may be identified and plotted against time simply by separate measurements of arm and leg *function.* Other measurements may be more appropriate to other stroke syndromes, but whichever ones are selected require separate analysis.

Attempts to use the same assessment procedure for trial admission and follow-up introduce another major problem, since the purposes of the two are different, i.e. prognostic matching in the first and determination of change towards a preconceived goal in the second. An alternative to the latter could be a simple comparison of final state in the two groups, which presupposes good initial matching. However, it is impossible for the ingredients of initial and subsequent assessments to be the same; the first attempts to measure, from clinical markers of acute loss of function, the degree of damage expected to contribute to long-term functional loss, while the second estimates actual functional status in terms directly measurable at the time.

Analysis

Adequate and reliable analysis of a major study requires better acquaintance with statistical methods than is achieved by most clinicians, and statisticians argue convincingly that they should be consulted in advance of protocol planning. What to measure is still a clinical decision. Interim analyses and multiple analyses are wisely avoided, or both beta and alpha risks are increased. However, the former are sometimes ethically necessary; preliminary analysis, followed by continuation of the trial to a definitive conclusion only if results are promising, is an extremely unsound procedure. There is a good argument for conducting the final analysis before treatment codes are identified (the so-called 'triple-blind' study), since the choice of statistical method is not without influence on what is determined to be the result.

SUMMARY

Stroke is an emergency in the sense that effective treatment should start within hours rather than days. Admission to a trial of treatment may therefore precede diagnostic confirmation. Yet the latter is important because the natural history of the disease depends upon pathology (haemorrhage or ischaemia) and site (cortical, capsular or brainstem) in a way that clinical presentation may not. The several recognized predictors of outcome do not establish a sufficiently rational discriminant factor, and matching of groups prognostically depends upon randomization. This has implications for numbers. Recovery is protracted, with accelerations and plateaux, and may not take a predictable course, so that outcome judged too early can misrepresent eventual outcome, the usual object of interest. Long-term follow-up of many patients imposes constraints upon organization and manner of follow-up. Within that period, extraneous factors intervene.

These considerations may be particular for stroke. Others arise on a conceptual basis and apply more generally. Organization is quite different for explanatory and pragmatic approaches. Failure to realize the distinction between the two has invalidated many trials, or caused the wrong question to be answered.

It is true that acute stroke trials pose a number of methodological difficulties, but these can be identified in advance and, in a centre with adequate facilities, it should be possible to prepare for them. If not, the fault is due to a failure of design, not the illness.

Problematic areas that have not been discussed include: the practicalities of obtaining consent, whether informed or not, and the ethics of acute stroke trials in general; particular difficulties that arise with

the in-hospital use of new (unmarketed) drugs on restricted licence, especially those for prolonged intravenous infusion; practical organization of outpatient follow-up and patients who move away or emigrate; compliance checking; inter- and intra-observer error during multiple follow-up assessments; involvement of primary care general practitioners with outpatients participating in hospital-organized trials, and its impact on conformity; and the influences of social environment. These are essentially local issues; that is, though general principles clearly apply, these may be subordinate to regional peculiarities of opinion and practice. It is hoped that others will be encouraged to contribute to the solution of these problems.

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Pathology of stroke
Recent research

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According to United Nations population statistics, the percentage of the population aged over 65 years will continue to increase up to the year 2034, leading to a dramatic increase in the incidence of strokes in the next few decades (Table 1). As the percentage of people over 65 years increases, the worldwide incidence of stroke is expected to rise by about 50% by the year 2000.

Between the ages of 45 and 65, stroke is the third most common cause of death. After the age of 65, stroke is the second most common cause of death, after heart disease. World statistics indicate that the incidence of stroke is three times greater in people aged 70–79 years than in those aged 60–69 years, rising from 3,300 to 9,900 per million. Above the age of 80, the figure rises to 20,000 per million (Fig. 1).

The risk of stroke is greater in hypertensive individuals (who account for 50% of all cases of stroke), patients with heart failure, diabetics and patients who have had a myocardial infarction (Table 2).

Primary brain death is most frequent in patients who suffer a massive cerebral haemorrhage, which occurs in 70% of cases. In patients with ischaemic cerebral infarction, the primary brain death rate is relatively low (9%), mainly as a result of embolism affecting the left middle cerebral artery (Tables 3 and 4).

A greater insight into the pathophysiology of cerebral infarction is an important precondition for development of more effective therapies.[1,2] In recent years, computer tomography and several experimental investigations have contributed greatly to our understanding of how cerebral infarctions develop, leading to new approaches to their treatment.[3–8]

PATHOPHYSIOLOGY OF ISCHAEMIC BRAIN INFARCT

Ischaemic brain infarct develops as a result of arterial occlusion due to

thrombosis, embolism or arterial compression. Compared with myocardial infarctions, which become apparent within about half an hour, ischaemic brain infarctions develop very slowly. Even after embolic occlusion of the artery supplying the territory in question, the collateral blood supply is adequate to maintain basal vital processes for up to four hours, so that normal function may be restored by embolectomy, shunt operation or fibrinolytic therapy (pro-urokinase, plasmin activating factor) (Fig. 2).

Approximately half of all infarcts are due to a thrombus and initially

TABLE 1

Population in millions (1980–2000)

	Total population			Population aged 60 + years		
	1980	2000	Increase %	1980	2000	Increase %
Australia	14.5	17.8	23	1.9	2.7	38.7
Brazil	122.3	187.5	53	7.5	14.0	86.7
Egypt	42.0	64.4	53	2.4	4.6	91.7
Germany (FRG)	60.9	58.8	−3	11.4	13.3	16.9
France	53.5	56.3	5	9.1	10.8	19.4
India	684.5	960.6	40	33.9	65.7	93.8
Israel	3.9	5.6	44	0.4	0.6	38.2
Italy	56.9	59.1	4	10.0	13.5	34.6
Japan	116.6	129.3	11	14.8	26.4	78.4
Kenya	16.5	30.4	84	0.7	1.3	85.7
Nigeria	77.1	150.0	95	3.1	6.4	106.5
Philippines	49.2	77.0	57	2.2	4.6	109.1
United Kingdom	55.9	55.2	−1	11.1	11.3	1.3
USA	223.2	263.8	18	33.9	40.1	18.3
World	4,432.1	6,118.8	38	375.8	590.4	57.1

Source: Provisional projections of the United Nations Population Division, New York, 1980.

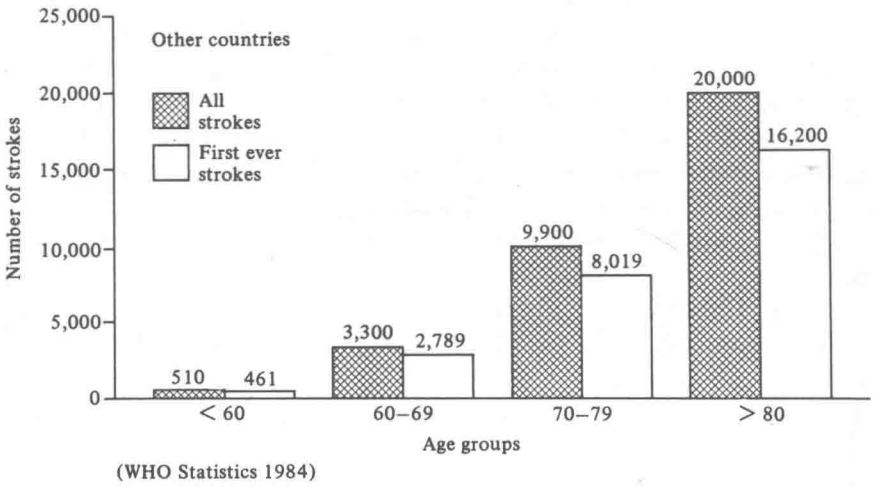

Fig. 1. Annual strokes per million population (age adjusted).

the arterial occlusion is only partial (75–90%). Hence, provided the collateral blood supply is adequate, the basal vital processes may be maintained for up to 12 hours or more (Table 3). Symptomatology of stroke starts if blood flow in the brain drops below 18 ml 100 g^{-1}

TABLE 2

Risk factors to develop stroke

1. Inborn abnormalities of brain vessels
2. Vascular diseases
   (e.g. stenosing atherosclerosis, etc.)
3. Heart diseases
   (e.g. chronic vestibular fibrillation, etc.)
4. Circulatory disease
   (e.g. chronic hypertension, etc.)
5. Haematological disease
   (e.g. increased blood viscosity, etc.)
6. Metabolic diseases
   (e.g. diabetes mellitus, etc.)
7. Impairment of health by injurious way of living

brain hour^{-1}.[9] Accordingly, the first 12 hours after onset of the signs and symptoms of infarction are of the utmost importance from the point of view of therapeutic intervention. During this period, it may be possible to limit the size of the infarct, or even prevent an infarct from developing, by reducing blood viscosity and inhibiting platelet aggregation (Table 5). The longer complete occlusion can be prevented, the greater the chances of a collateral blood supply being established. If the ischaemia – which is always partial initially, inducing a hypoxic hypoxia – can be prevented from worsening, the patient may fully recover.

After an embolism, the period in which basal vital activities are maintained is appreciably shorter (2–4 hours), since no adequate collateral circulation can develop.

The risk of triggering a haemorrhagic cerebral infarct and fatal

TABLE 3

Characteristics and course of acute stroke

Characteristic	Thrombotic infarct	Embolic infarct	Cerebral haemorrhage
Incidence	55 ± 5%	17 ± 4%	15 ± 2%
Time of onset of symptoms	During the night, especially in the early hours (2–5 a.m.)	During the day	During the day
Nature of onset	Gradual (over several hours)	Sudden	Sudden (with rapid progression)
Association with heart failure, with chronic atrial fibrillation and arrhythmia	Rare	Common	Supervenes as the patient's condition progessively worsens
Blood pressure	Mostly low or normal	Function of extent of cardiac insufficiency	High
Pathological reflexes and spasticity	After 24–48 hours	After 12–24 hours	Immediately
Consciousness	Slightly to moderately impaired in most cases	Severely impaired	Severely impaired with rapid deterioration in most cases

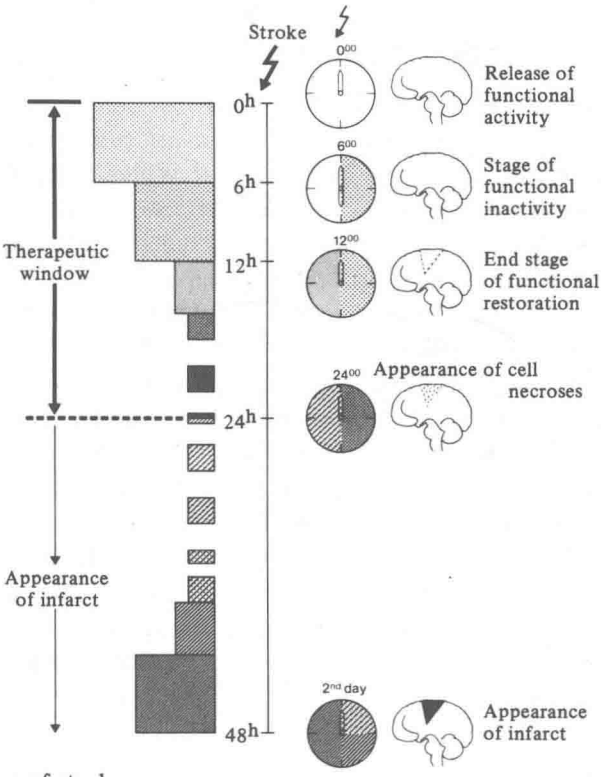

Fig. 2. Phases of stroke.

cerebral oedema by overzealous treatment (e.g. thrombolysis and massive raising of the blood pressure in hypotensive brain ischaemia) increases exponentially from the sixth hour after the first signs and symptoms of stroke. Therapeutic measures of choice involving no risk of haemorrhage are: reduction of blood viscosity, inhibition of platelet aggregation and cardiovascular stabilization (Table 5).

The earlier specific therapy is instituted after a stroke, the lower the likelihood of irreversible brain damage (Table 6). Once an infarct has developed, the scope for therapy is drastically reduced. After rehabilitation, a patient who has suffered a complete cerebral infarction will be left with permanent motor and sensory deficits of greater or lesser severity.

It is important to note that the signs and symptoms of stroke do not parallel the development of infarction.

Systematic therapy in the first six hours after the onset of the signs and symptoms of a stroke may prevent incipient cerebral infarction, especially if the cause is an arterial thrombosis. With appropriate early therapy, a full-blown infarction can often be 'commuted' to a transient ischaemic attack (TIA), prolonged ischaemic neurological deficit (PRIND) or incomplete ischaemia.[4, 6, 7, 10, 11]