THE TERM, ATTACKS IN PROGRESSION, is immediately attractive for clinicians since it implies action, i.e., counter-attacks, that might stop or reverse cerebral disorders. The concept of stroke-in-evolution (synonyms: stroke-in-progression, progressing stroke) is now 30 years old but, judging from the relevant literature, it has generated very few studies (v. infra).

There are, of course, understandable reasons for a discrepancy between a prima facie strong appeal and limited success in achieving the goal. First, it may be presumed that in many places many stroke cases referred to hospitals are admitted only late in the course of the disorder, after the time when a progressing course could have been witnessed. Second, many stroke cases are admitted to non-neurological departments where a careful record of on-going events and appropriate investigations are less likely to take place.

After all, keeping accurate records in a progressing stroke is an exacting task, one which requires a large amount of round-the-clock work from stroke-oriented clinicians. It may be difficult even in Neurological Departments to meet these requirements and Stroke Units where this could be best done are still few in number.

Even taking the foregoing into account, there are yet other reasons for the stagnation of the concept of stroke-in-evolution. To categorize a stroke as one in progression the following questions must be answered: 1) is this stroke a stroke-in-progression (starting diagnosis)? 2) is this stroke no longer a stroke-in-progression (end diagnosis)? Obviously, such answers rest on a definition that provides the clinician with clear and non-ambiguous guidelines for making such categorizations. Unfortunately, it has been widely recognized, even by its proponents, that the definition lacks clarity. It has been imprecisely described. is obscure when compared with transient ischemic attacks and is a subject that should be clearly defined as soon as possible.

Recently, a different and radical blow against stroke-in-evolution has been struck by the proposition to waive the concept entirely. According to this view, stroke-in-evolution (together with RIND, partial non-progressive stroke and completed stroke) is a product of another era, with little if any utility to its continued use.

Thus, prior to examining further the merits and flaws of stroke-in-evolution it must be asked whether it is really an obsolete idea. A simple approach to this question is to ask about its place in clinical practice. Few doubt that such cases exist. Well before the term, progressing stroke, and its synonyms were created, strokes that failed to come to completion abruptly were well-known under other names, including ingravescent apoplexy, fits and starts, stepwise, stuttering attacks. Although the classical hallmark of strokes is a sudden onset, what about events after the onset? Are cases with a progressing course rare or frequent?

Among 443 cases included in the Cooperative Study on Anticoagulant Therapy, fully 128 (28%) were labelled 'progressive' or 'thrombosis-in-evolution'.

Admittedly, in these reports short clinical accounts of 40 cases of thrombosis-in-evolution (28 control, 12 with anticoagulants) indicated that in a good number worsenings occurred several months (up to 15 months) after the onset of the neurological disorders. Such cases would not probably be categorized nowadays as strokes-in-evolution. However, evidence from other sources indicate that strokes with a progressing course are frequent indeed. In 179 cases of acute infarction in the carotid territory, a progressive course has been recorded in 26%.

In 37 cases of acute infarction in the vertebrobasilar territory, they were twice as frequent (54%), an interesting difference if confirmed by further studies. In the Harvard Stroke Registry patients with a progressive onset, i.e., stepwise or stuttering + smooth or gradual + fluctuations, were more frequent than were those with sudden onset in large artery thromboses, lacunes and even hematomas. They still made up 20% of the clinical course in patients with embolism and were encountered even in aneurysms + AVMS.

The 15 instances of progressing stroke reported by Irino et al were highly selected from 510 cases which accounts for this small proportion.

It may thus be concluded that progressing stroke is a frequent type of evolution for all types of strokes, one which is as frequent or even more frequent than the classical abrupt completion for several major causal categories. Consequently, clinicians must be prepared to be confronted with this clinical entity and rather than jettison the concept it may prove worthwhile to look at its present state and to ask why it has not really gained a large place in clinical studies. Such a scrutiny could hopefully boost interest and stimulate further research.

Difficulties arise from 3 sources: 1) the lack of a clear and comprehensive definition; 2) the diversity and complexity of the clinical and pathological conditions that are embraced by the concept; 3) the small number of clinical and pathological studies. Obviously these reasons are reciprocally related. They will be examined separately here only for the sake of clarity.

The Definition

A brief historical review is relevant here. The categorization of strokes according to their temporal profile was proposed in 1955 by Millikan and Siekert. Speaking on problems of Nomenclature at the Second Princeton Conference (January 1957) Millikan used the term 'slow stroke'. By September 1955 the Advisory Council to the NINDB had established an Ad Hoc committee to elaborate a Classification and Outline of...
Classification only stressed the importance of the temporal profile and acknowledged the existence of some cases of 'thrombotic vascular disease' with a 'saltatory progression' and the 'accretion of neurologic derangement'. In 1960 Millikan, Siekert and Whisnant proposed to categorize strokes in: 1) incipient or impending; 2) advancing; 3) completed. They had found 'a temporal clinical classification an extremely useful procedure in relation to both diagnosis and treatment.' Some general characteristics of advancing or progressing stroke were mentioned together with features pointing to the carotid or vertebral-basilar system. By 1961–62 the term thrombosis-in evolution, meaning patients in whom a neurologic deficit was developing in a stepwise, progressive fashion, was still used.7,8 The Third Princeton Conference was entirely devoted to the 3 temporal categories of strokes.16 Several major aspects of progressing stroke were addressed: pathogenesis,16 anticoagulant therapy,16 thrombolysis17 and surgical therapy.18 There was no clinical study and the definition of progressing stroke was only reiterated: "... progressing stroke refers to the period of time during which the focal neurological deficit is increasing in amount as judged by the clinician in immediate and continuous attendance."19

And:

"Dr. Miller Fisher has used the term stroke-in-evolution and the generally accepted designation is that, regardless of the site of the occlusive process and the subsequent infarction either in the carotid system or the vertebral basilar system, the clinical picture of progressing stroke is represented by the patient whose neurological deficit is gradually or in stuttering fashion progressing over a period of hours, during which time the clinician sees the patient."20

Thus in 1961 simple definitions in broad terms had only been proposed and there was no published clinical study in which patients had been selected along the criteria included in these definitions.

Rather surprisingly, for the ensuing 14 years the concept of stroke-in-evolution disappeared from the mainstream of Neurological literature. It reappeared in 1975 in the Second Classification and Outline of Cerebrovascular Diseases21 under the heading of 'actively changing neurological deficit'. The definition then excluded changing to improvement and stated: "This category represents the common circumstance where focal ischemia is worsening and the process of infarction is beginning or extending. (In unusual instances slow onset bleeding may produce a similar temporal profile) ... as mentioned earlier, because of the evolution of the deficit, it is likely that patients will be in different categories at different times. ..."

One year later (1976) an attempt was made at defining more tightly the conditions of starting diagnosis: "A progressing stroke (stroke-in-evolution) is that temporal category in which there has been progression (increased severity of the neurological signs) within recent minutes (my italics). This value judgment may be made from analysis of the history or from repeated examination of the patient. It may be difficult to be certain from minute to minute or even from hour to hour whether progression will occur. However, if there has been definite worsening of the neurological deficit during the few minutes immediately prior to making a judgement about a particular patient's status, the situation is classified as a progressing cerebral infarction (stroke-in-evolution)."

For the end diagnosis it was stated:

"If the site of focal ischemia is in the carotid system there has been a general impression that 18 to 24 hours without progression is ordinarily sufficient time to mean that further progression is unlikely and that the status of the temporal profile should no longer be categorized as "progressing stroke". If the lesion is in brain supplied by the vertebrobasilar system, a longer period of time (up to 72 hours) should probably elapse before the patient is removed from the progressing stroke category and is designated as a 'completed stroke' since there seems to be a tendency for a period of progression to be separated by many hours when the impaired circulation is in the vertebrobasilar system. These matters are somewhat uncertain: in our experience there have been some instances of late worsening (e.g. worsening occurring after 36 or even 48 hours in carotid system cerebral infarction patients) which were both surprising and catastrophic — leaving the patient dead or permanently disabled".

To be sure, such instructions for starting and end diagnosis were expressed in a cautious way ('there has been a general impression,' "these matters are somewhat uncertain") doubtless reflecting the practical difficulties to arrive at an adequate definition. Both for the carotid system and the vertebrobasilar system infarctions they were in a paper reporting the time-course of acute carotid territory infarctions18 in an introductory paragraph ('Definitions') and appeared to be based not upon reported facts but on the experience of the authors. More recently these definitions have been stated again.22 They are more stringent than the former ones since they put time limits for both diagnoses. However the progress of the definition is questionable.

The starting diagnosis is often not easy since during the 24 hours after onset differentiation from TIA's may be difficult or impossible.15,22 A recent worsening is not necessarily a step in the course of a progressing stroke but may be the final aggravation of a case ending in a completed stroke. The proviso that a worsening has occurred "within recent minutes" makes it clear that the worsening has been witnessed by the clinician but many such strokes may have been progressing even during the hours before admission. Why not rely on the history from reliable patient or family? Clinicians only exceptionally are on hand to witness TIAs and in most instances the whole neurological story of TIAs is based on reliable patients and families.
The time limit of the *end diagnosis* seems also questionable for both the carotid and the vertebrobasilar infarctions. In acute carotid infarctions Jones and Millikan\(^1\) mentioned worsenings after 36 and 48 hours and in their series there were 8 patients with a 'late exacerbation' between the third and the seventh days. In the vertebrobasilar system, Jones, Millikan and Sandok stressed that definite changes continued to develop up to 96 hours.\(^9\) Patrick, Ramirez-Lassepas and Snyder concluded that instability and late exacerbations can be expected even for as long a 7 days after the onset of symptoms.\(^23\) In the progressing strokes reported by Irino et al (13 carotid, 2 vertebrobasilar) worsenings occurred from the 3rd to the 16th day. Thus 18 to 24 hours without progression in the carotid system and 72 hours in the vertebrobasilar system are probably not safe margins of time for the end diagnosis. Finally should the (rare) cases of brain infarction with a protracted course of weeks or months\(^24\) be excluded from stroke-in-evolution? The number of reported cases is obviously too small for a definite opinion. For the time being it would appear reasonable to revert to the early 'open' simple definition without stringent time criteria.

### Clinical and Pathological Studies

#### Carotid Territory

Adams, Torvik and Fisher in a clinico-pathological study of the pathogenesis of progressing stroke reported 1 detailed case.\(^15\) Jones and Millikan reported in 1976, 48 retrospective cases examined well before the CT era (from 1967 to 1969). Post-mortem findings were summarized for 8 cases.\(^3\) Irino et al reported 13 clinical cases with serial angiographic and CT examinations.\(^5\)

#### Vertebrobasilar Territory

Adams, Torvik and Fisher reported 3 detailed clinico-pathological cases.\(^15\) Jones, Millikan and Sandok reported 37 cases examined between 1967 and 1969.\(^9\) Patrick, Ramirez-Lassepas and Snyder reported 22 clinical cases collected from 1975 to 1978 with CT.\(^23\) Irino et al reported 2 clinical cases with serial angiography and CT.\(^5\)

Thus at the present time, clinical data can be based on 62 patients with carotid artery infarction, 48 of whom had no CT and on the data from 47 patients with vertebrobasilar infarctions 23 of whom had no CT. Thorough clinico-pathological reports are available for patients with 3 vertebrobasilar and 1 carotid lesion.

#### An Approach to Stroke-in-Evolution

From the small number of reported cases and from data scattered in the literature some observations can be proposed.

#### Different Causes

1. **Occlusions of large arteries** Atherosclerotic thrombosis of large arteries is generally held as the main cause of progressing stroke\(^1, 9, 15, 21\) but the former equation stroke-in-evolution = thrombosis-in-

   evolution is no longer warranted.\(^4\) Cardiac embolism can also cause a stroke-in-progression. A fluctuating or gradual onset of the neurological deficit over 3 to 5 days has been reported.\(^25\) Among the 215 cases of embolism in the Harvard Stroke Registry the onset was stepwise or stuttering in 11\%, smooth or gradual in 5\% and was fluctuating in 5\%.\(^10\) Five of the 25 patients reported by Irino et al had atrial fibrillation.\(^5\)

2. **Distal field infarction** In those cases in which there are neither episodes of hypotension nor sources of microemboli, distal field infarction is said often to have a stepwise or evenly progressive course.\(^26\)

3. **Lacunes** Among 131 patients with lacunes, a sudden onset was reported in only 38\%, a stepwise or stuttering evolution in nearly as many (32\%), a smooth or gradual course in 20\% and fluctuations in 10\%, making a full 60\% with actively changing neurological deficits.\(^10\) Mohr has commented that this 'surprisingly leisurely mode of onset' characterizes many lacunar strokes.\(^27\)

4. **Intracerebral hemorrhage** The Second Classification and Outline of Cerebrovascular Diseases acknowledged the possibility that hemorrhage could determine stroke-in-progression (v. *supra*). It was subsequently stated that the category of progressing stroke was restricted to non-hemorrhagic cerebrovascular disease\(^9\) but this would not correspond to clinical situations. An unexplained gradual worsening not infrequently takes place a few days after the clinical onset of intracerebral hemorrhage.\(^28\) The 115 cases of hematoma collected in the Harvard Stroke Registry were particularly informative on that point: 34\% only had a sudden onset, 63\% had a smooth or gradual course and 3\% had a stepwise or stuttering evolution. After admission 56\% experienced further worsening and 25\% of these deteriorated suddenly.\(^10\)

It may thus be concluded that many different conditions from large infarcts to small deep infarcts, border-zone infarcts to hemorrhage may underlie the clinical events of stroke-in-evolution.

#### Different Worsenings

Different authors recognized different worsenings or at least categorized them differently. Jones et al reported progressive deficits, remissions/relapses and late exacerbations in infarction of the carotid territory.\(^3\) In vertebrobasilar infarction progressive and remitting/relapsing courses only were mentioned.\(^9\) Patrick et al distinguished gradual onset reaching stabilization within 24 hours, gradual onset with progression beyond 24 hours, delayed worsenings after stabilization.\(^23\) Mohr et al reported 3 kinds of progressive onsets: stepwise or stuttering, smooth or gradual, fluctuating.\(^10\) Irino et al did not categorize the worsenings but as these occurred at various times from the 2nd to the 16th day after the onset it is likely that they also belonged to different kind.

Jones and Millikan thought that early worsenings are probably different from late ones\(^3\) and Adams et al clearly stated that:

"This progression may consist of a worsening of a given symptom i.e. weakness of a limb over \(\ldots\)"
an extended period of time, or of the addition of other symptoms referable to a disorder of neighboring structures. It may be added that in a good number of cases progressive symptoms and signs are due to cerebral herniation (v. infra).

The clinical features of progressing stroke are obviously complex. However, variable terminology hampers useful comparisons. Moreover most of the available reports do not mention detailed clinical descriptions. From these however significant pathological and prognostic patterns could emerge.

**Different Mechanisms**

Different causes resulting in progressing strokes different mechanisms may be expected. They have been well summarized by Genton et al:

"It is important to note that stroke-in-evolution does not necessarily indicate thrombus-in-evolution. The variety of pathogenetic mechanisms that can lead to either the slowly progressive or the stepwise development of a stroke are summarized as follows:

1. A progressive thrombus extends from its site of origin in a primary artery and obliterates collateral branches thereby interfering with anastomotic circulation and extending the area of insult.
2. At the side of maximal atherosclerotic involvement with or without ulceration and/or stenosis, initially there is insufficient thrombus to produce occlusion. Continuing accretions to this thrombotic nidus slowly obliterate the lumen of the vessel and either gradually or intermittently add to the area of brain ischemia.
3. Brain edema spreads in concentric fashion and progressively reduces clinical function without extension of the original area of infarction.
4. The general condition of the patient, including his cardiorespiratory, altered water and electrolyte regulation and/or acid-base balance, or the acquisition of systemic infection, interferes with cerebral metabolism sufficiency to increase the extent of the neurological dysfunction. The event that cardiorespiratory function is altered the area of infarction actually may be extending."

Irino et al considered that possible causes of progressing strokes were brain edema, recurrent stroke, visceral complications and changes in arterial pathology.

1. **Extension of thrombus** Except for embolization, the consequences of accretions of thrombotic material on a thrombus in situ short of occlusion of the arterial lumen are poorly documented. However it may be presumed that reduction of the arterial lumen by 80–90% decreases blood flow thereby possibly aggravating brain ischemia. On the other hand the development of antero a/o retrograde thrombus (secondary thrombus, stagnation thrombus) has been found nearly always to follow arterial occlusion due either to atherosclerotic thrombosis or cardiac embolism. In a few cases there were both a progressive course and post-mortem evidence of thrombus extension. However, such are the difficulties of ascribing a precise age to a thrombus or to the different parts of it that it is often impossible to draw firm relationships between clinical events and arterial pathology. In this respect the angiographic study of Irino et al is of particular interest: in 15 patients with a progressing stroke an angiogram was performed on admission and was repeated after neurological worsening. In only 1 case the second angiography showed no change. In 12 of the 14 remaining cases it showed progression of arterial occlusion: propagation of occlusion in 3; stenosis to occlusion in 3; nonvisible lesion to stenosis in 2; occlusion of collaterals in 4. This obviously lends support to thrombus extension as a basic mechanism of progressing stroke. In cases with recurrence of stroke resort would be had to the same principle, i.e., additional occlusion. However, in 2 cases of Irino et al, the second angiogram showed recanalization (in 1 of these cases the second CT suggested an hemorrhagic infarct). These findings indicate that one angiogram performed before worsening(s) does not provide an adequate basis to account for a progressive course and that changes in the arterial pathology other than thrombus must be considered.

2. **Brain edema** There are very few reports on progressing stroke allowing an analysis of the neurological symptoms and signs, that should suggest brain edema with herniation. However, it is likely that these account for some of the worsenings. Among 19 patients who died in the carotid series, autopsy was performed in 11. In 7 of 8 cases with progressive deficit there were midline shift, temporal herniation and brain stem hemorrhages. In 1 case of stroke in progression due to internal carotid artery occlusion with a large cerebral infarct there were pronounced tentorial herniation and cerebellar pressure cone. Yet it is likely that brain edema does not account for worsening in which there are successive accretions of a focal neurological deficit. A progressive course has been reported in brain stem infarction, including lateral medullary infarction in which edema would appear to have played but a minor role.

3. **Metabolic and infective disorders** Some, but probably not all, of the late worsenings result from heart, lung, kidney, or digestive tract complications. Cerebral focal damage could possibly be aggravated by these complications or the whole brain may suffer from metabolic, acid/base, water-electrolyte disorders which may in addition aggravate brain edema.

**Treatment**

Previous reports on treatment and the general lines of therapeutic decisions have been recently reviewed. From the evidence gathered in the present paper it appears that no general rules can be set for a condition (stroke-in-progression) that is really a mosaic of conditions with a pathological span large enough to include lacunes, distal field infarctions, thrombotic and embolic infarcts and cerebral hemorrhages. CT is obviously mandatory. Recognition of this complexity is at least a warning against the emergency use of heparin which...
was formerly advocated. What is urgent is to try to understand the causes and the mechanisms in each case which, hopefully, will lead to reasonable therapeutic attitudes.

Summary and Conclusions

Stroke-in-progression or stroke-in-evolution or progressing stroke is a clinical entity which is frequently encountered in several major types of stroke possibly even more frequently than the classical abruptly progressing stroke. Stroke-in-evolution is in fact a mosaic or condition and one which has been in fact imperfectly understood clinical cases in the literature is surprisingly small. Many of the proposed definitions are not adequate.

Although it has been advised that the concept of of progressing stroke be discarded, this advice seems premature considering that it is a common and critical condition and one which has been in fact imperfectly and incompletely investigated. Instead, it would appear better to organize a prospective study with detailed clinical reports, serial CT, angiography, and when possible NMR PET or SPECT and detailed pathological examination of brain and extra-intracranial cerebral arteries. The magnitude of the task is such that a multicenter study would probably be required.

Acknowledgments

I wish to thank Mrs. M. T. Guirand for secretarial assistance.

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doi: 10.1161/01.STR.16.4.729

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/16/4/729