Concerning transient ischemic attacks[1]

C. M. Fisher, M.D.

To investigate some of the controversies concerning transient ischemic attacks (TIAs) recent experience with cerebrovascular disease at the Massachusetts General Hospital is reviewed. For example, TIAs are commonly thought to last up to 24 hours, but TIAs rarely lasted one hour in Massachusetts General cases (135 cases). Recurrent TIAs preceded strokes in 90% of 100 cases, whereas single TIAs usually posed no threat (32 cases). Of 80 patients who had more than one TIA, 88.5% had the second attack within one week. A clinicopathologic study of endarterectomy specimens in 57 cases supported hemodynamic failure rather than embolism as the cause of TIAs. Embolism from a carotid mural thrombus caused longer spells (1 case). Cardiogenic emboli (200 cases) entering a carotid system did not cause ischemic episodes that mimicked carotid TIAs (50 cases), that is, their behavior did not resemble that attributed to fibrin platelet emboli from carotid mural thrombi. The problem of TIAs in the absence of vascular disease is discussed.

Index term: Cerebral ischemia, transient

Cleve Clin J Med 54:3–11, Jan/Feb 1987

Some 35 years ago attention was directed to the occurrence of transient ischemic attacks (TIAs) preceding strokes that result from cerebral thrombosis.[1,2] At that time, researchers proposed that early recognition of prodromal TIAs might allow therapeutic intervention and prevention or attenuation of the threatening stroke. Although much has been learned about TIAs, their symptoms, mechanism, prognosis, and treatment remain controversial on many points.[3–12]

[1] Neurology Service, Massachusetts General Hospital. Submitted for publication April 1986; accepted July 1986.

Presented at the annual Guy Williams Jr. Memorial Lecture, The Cleveland Clinic Foundation, May 21, 1985. This study was supported by a grant from the Freed Foundation, Washington, DC.

0891-1150/87/01/0003/09/$3.25/0

Copyright © 1987, The Cleveland Clinic Foundation

Downloaded from www.ccjm.org on April 25, 2024. For personal use only. All other uses require permission.

Under discussion here are those TIAs that represent transient cerebral ischemia due to vascular disease. TIAs related to conditions such as migraine, postural hypotension, thrombocythemia, polycythemia, lupus anticoagulant, platelet hyperaggregability, hyperviscosity, and subdural hematoma are not included. Of course, other processes, such as akinetic seizure (cerebral or spinal), labyrinthine dizziness, transient global amnesia, transient increase in the deficits of multiple sclerosis, hypoglycemia, hysteria, etc., must also be separated out.

Two aspects of TIAs in which differences of opinion are especially prominent are their duration and the importance of a single TIA versus multiple TIAs.

The duration of TIAs

In 1958 the first ad hoc committee on nomenclature in cerebrovascular disease defined the upper limit of the duration of a TIA as one hour.[13] At the second meeting in 1975 the committee set the duration at two to 30 minutes.[14] Nonetheless, in the past 10 years the majority of papers published define the upper limit as 24 hours. Typical TIAs that herald a stroke, i.e., multiple TIAs of the same type, are relatively brief, as Massachusetts General cases show (*Table 1*). Transient monocular blindness (TMB) spells lasted less than 10 minutes in 90% of cases in which they occurred; for TMB in the absence of carotid disease the figure was 62.5% and for TIAs in the basilar system it was 70%. The longest duration of TMB associated with carotid disease was two hours in one case and one hour in another; in basilar stenosis the longest duration was one hour and was recorded in only one case. Apparently, it is uncommon for TIAs associated with arterial stenosis to last as long as an hour. Occasionally, full clinical recovery from a TIA seemed to have taken place, but CT or MR examination revealed a residual abnormality in a relatively asymptomatic area. There are circumstances, however, when recurrent TIAs last one to five hours, namely when infarction or prolonged or irreversible ischemia is imminent. Fisher and Ojemann[15] concluded that TIAs lasting progressively longer or present on awakening may be ominous and warrant special attention to forestall a stroke. A particularly treacherous situation exists when a prolonged carotid TIA lasting a few hours is due to distal-stump embolism to the stem of the middle cerebral artery, that is, it represents the prodromal transient ischemia associated with nonsudden major embolism. After a few hours, a devastating paralysis recurs.

Table 1. Duration of recurrent prodromal TIAs in Massachusetts General cases

	Duration (min)		
	½–5	5–10	10+
Transient monocular blindness in carotid stenosis (% of 40 cases)	72.5	17.5	10
Transient monocular blindness in absence of carotid disease (% of 45 cases)	55	7.5	37.5
TIAs in basilar stenosis (% of 40 cases)	35	35	30

Table 2. Number of TIAs preceding strokes due to cerebral thrombosis in Massachusetts General cases

	No. of TIAs		
	1	2–10	>10
Internal carotid artery stenosis (% of 50 cases)	6	60	33
Basilar artery stenosis (% of 50 cases)	12	32	56

Single TIA versus recurrent TIAs

In the interpretation of TIAs, does it matter whether there has been only one TIA or more than one? It is my experience that when two or more TIAs of the same type have occurred, tight stenosis of a cerebral artery will prove to be the underlying pathologic correlate. A review of Massachusetts General cases of stroke due to cerebral thrombosis showed a high incidence of multiple TIAs among prodromal events (*Table 2*). Only 6% of patients with internal carotid disease had a single TIA and only 12% of those with basilar artery disease. A single TIA may be the first of a series of similar spells to come, thus heralding a stroke, or it may prove to be an isolated event not associated with tight stenosis, not the harbinger of an oncoming stroke, and therefore harmless, or relatively so. When there has been only one TIA, it may be difficult or impossible to distinguish between these two possibilities with their widely different connotations.

If two or more similar TIAs are going to occur, what will the interval be between the first and second? An analysis of 80 unselected Massachusetts General cases in which TIAs were either the prodrome of a stroke or were associated with

Downloaded from www.ccjm.org on April 25, 2024. For personal use only. All other uses require permission.

severe arterial stenosis (TMB cases were excluded), the interval between the first and second TIA was as shown in *Table 3*. Judging from these data, TIAs associated with occlusive arterial disease will prove to be multiple within seven days in 88.5% of cases in which multiple attacks occur, that is, approximately 9 of 10 cases. It is unlikely that severe arterial lesions are present if more than two weeks have passed since a single TIA. The analysis also indicated that when two or more TIAs (or TMB) occur in one day, occlusion is imminent.

Table 3. Interval between first and second TIAs of the same type in 80 Massachusetts General cases

Interval	% cases
24 hr or less	55
2, 3, or 4 days	27
5 to 7 days	6
8 to 14 days	5
2 to 3 weeks	3
More than 3 weeks*	4

* 3 cases: 5 weeks, 2 months, 3 months.

The single TIA

What are the characteristics of isolated, single TIAs? Do they differ from recurrent TIAs? What is their prognosis? A review of 32 Massachusetts General cases with a single TIA will help answer these questions. These cases were not selected in retrospect. In these patients, aged 50 to 70 years, a single, isolated TIA lasting less than one hour occurred in a period of three months up to nine years. Almost all cases were seen within three months of the event, usually within a matter of days. The carotid territory was involved in 30 cases, the vertebrobasilar in two; in three-quarters of cases, the left cerebral hemisphere was thought to be affected. TIAs in which dysphasia or dysarthria was combined with a right-sided facial weakness and/or right-hand weakness accounted for 10 cases. For example, one patient had an episode of slurred, gibberish speech and weakness of the right hand lasting two minutes. Angiographic findings were normal. It is likely that a disturbance of speech will attract attention to a spell that might otherwise be disregarded. Other examples of single TIAs included: a two-minute episode of gibberish speech; a 10-minute episode of numbness of the tongue and lips; a 40-minute episode of complete paralysis and sensory loss involving the left arm; an 18-second attack of complete paralysis of the left arm and weakness of the left leg; a two-minute attack of paralysis of the right arm and leg; and a 45-minute episode of numbness, weakness, and lightness of the right leg. Unusual examples were as follows: a three-minute spell of inability to tie shoes or to decide which sleeve to put an arm in; a 10-minute spell of inability to understand what was being read; and a sudden queer feeling that the right hand did not belong to the patient.

Only three of the 32 spells lasted more than 30 minutes. In none of the cases was there an unfavorable course. Features that reliably distinguished single TIAs from multiple ones were not recognized, but simultaneous involvement of the arm and leg on one side occurred in four of the 32 cases, an unusual combination in recurrent carotid TIAs in which the arm is regularly involved while the leg is spared. Also, recurrent carotid TIAs rarely take the form of gibberish speech alone, which should suggest a TIA of embolic origin.

How are single TIAs of this type to be interpreted? Severe arterial stenosis was not evident in any of the cases, but only eight patients underwent angiography. A source of embolus was not obvious. In many cases a lone TIA probably results from the passage of a *small embolic particle* arising in a cardiac chamber, from the mitral or aortic valve, or from a large cerebral artery. But establishing a minor event as embolic is an all-but-impossible task unless the retina is involved. Brief weakness, numbness, and brief speech disturbance may be *migrainous*.[16] Occasionally, young migraineurs under age 25 report paralysis of a limb or limbs lasting 30 seconds to two minutes. The full spectrum of such activity in later life has yet to be described. In a few cases, an *akinetic seizure* may have been responsible for what appeared to be a TIA. It is unclear how transient the symptoms of a *minor lacunar infarct* may be. Very rarely, the final, complete occlusion of a carotid or other cerebral artery may be associated with a transient minimal deficit (*distal-stump embolism*), but this should be suspected only as a last resort.

How transient can minor embolism be? Almost all embolic insults last hours or days, but on rare occasions, I believe, they last only a few minutes. Because a lone TIA due to embolism may last from minutes to hours, gradually merging with minor persistent ischemia, attempting to classify such events as TIAs or not according to their duration becomes unrewarding.

Downloaded from www.ccjm.org on April 25, 2024. For personal use only. All other uses require permission.

When TIAs are recurrent but with different clinical patterns, or arise in opposite hemispheres or in both the carotid and vertebrobasilar territories, embolism must be held responsible—or at least a process other than tight arterial stenosis.

On the premise that the lone TIA has a quite different connotation than multiple TIAs of the same type, what clinical procedure is recommended when only one TIA has occurred? Evidence of severe arterial stenosis must be sought clinically and by noninvasive technology. Obviously, this is more effective in cases of carotid artery disease than in cases of vertebrobasilar disease. If more than two weeks have passed and there is no evidence of tight stenosis, the odds against serious disease increase. It is possible that when arterial stenosis is not obviously present, it may be permissible to delay consideration of angiography and surgical or anticoagulant therapy until a second spell of the same pattern occurs. In support of this is the finding that when there has been only one TIA before a stroke, the next event is usually a minor deficit that still allows timely intervention. However, if cardiac embolism associated with paroxysmal atrial fibrillation or acute myocardial infarction is suspected, anticoagulant therapy should be considered immediately to prevent a major embolic insult.

Several investigations of the prognosis in TIA cases have been undertaken, with widely varying results. In only three studies was a distinction made between cases with a single TIA and those with multiple TIAs.[4,17,18] For example, in one study of 314 cases, 274 (85%) had only one TIA.[19] The lack of uniformity of results probably reflects the variability of the TIA cases selected for observation. When studying TIA cases, not only should those with single TIAs be separated from multiple TIAs, but the information should also include the number of spells, their duration, the interval since the last spell, the patient's age, the details of the symptoms, the nature of any speech disturbance, the circumstances of the onset, and the vascular basis. TIAs associated with stenosis or occlusion of the large arteries in the neck, except for the internal carotid artery, have a benign prognosis. For accuracy, it is important that angiography of the involved arterial territory be undertaken, but this is tempered by the fact that TIA patients are now more apt to be elderly. An exact diagnosis must be sought. The view that vaguely defined or undifferentiated TIAs can be placed together in one large group for analysis is untenable. TIAs are too heterogeneous for such an approach.

The mechanism of TIAs

Another source of controversy concerning TIAs is their mechanism, especially of recurrent TIAs of the same type, which may herald a thrombotic stroke. Is their origin embolic or hemodynamic? A survey of the current literature indicates that, almost without exception, TIAs are considered to be the result of microembolism. According to this hypothesis, platelet or fibrin-platelet particles are dislodged from the surface of an atherosclerotic plaque and swept distally, where they give rise to transient symptoms.

Before examining this theory, it is necessary to point out some pathoanatomical differences between the internal carotid, middle cerebral, anterior cerebral, and posterior cerebral arteries on the one hand and the vertebrobasilar artery on the other. In the former, the atherosclerotic stenosis occurs at a distance from the locus of symptoms, whereas in the vertebrobasilar trunk, the atherothrombosis may be so situated that the orifices of penetrating branches may be compromised, that is, the vascular process may be close to the locus of symptoms. This anatomical difference, although it may prove not to be a factor, should be considered when TIAs in the two systems are the basis for speculation. It is interesting that TIAs associated with penetrating branch disease are relatively few compared with those in large artery disease.

Evidence for the embolic theory of TIAs

Early evidence favoring the embolic theory was provided by observations of the retinal arteries during a spell of TMB.[20] In that case, the patient, with arteriographically proven tight carotid stenosis, had had at least 500 spells of TMB in one and one-half years. In the hospital, he had five attacks of TMB lasting 20 minutes, 1 hour, 1 minute, 30 minutes, and 75 minutes. While he was receiving warfarin sodium therapy in the next five years, he had no spells. The retina was examined 20 minutes after the onset of blindness in the left eye. White material lay in the central retinal artery, and the column of blood in the veins was interrupted and moving slowly. During the following 55 minutes (75 minutes from the onset), the white material was seen moving peripherally in the retinal arteries. At 35 minutes blindness was still present in the lower half of the

Downloaded from www.ccjm.org on April 25, 2024. For personal use only. All other uses require permission.

visual field. It was postulated that thrombotic material in the carotid artery was a source of microemboli reaching the retina. In retrospect, it might be asked if the findings were representative of TMB spells in general. The episodes were atypical in their unusually long duration, and the general conclusions may not be justified.

Almost identical funduscopic events were observed in a case of polycythemia rubra vera with hyperaggregable platelets.[21] A platelet count was not made in the aforementioned case, but platelets were reported to be normal in the blood smear. It is surprising that there have been almost no observations corroborating the original retinal findings, despite the frequency of TMB. Negative observations, and they are not uncommon, are probably not reported. It should also be mentioned that a branch of the central retinal artery is only 90 μ in diameter, one-fifteenth or less the diameter of a branch of the middle cerebral artery, and, in this respect, the size of symptomatic embolic particles at the two sites must be quite different. TMB is only one aspect of TIAs, but retinal examination during TMB appears to offer the most rewarding approach to understanding the mechanism of TIAs.

A study by Gunning et al[22] supports the embolic theory of TIAs. They examined carotid endarterectomy specimens grossly and microscopically and found that, when there had been TIAs within seven weeks before surgery, the plaque showed fibrin-platelet mural thrombi, which presumably acted as a source of emboli. When there had been no TIA activity in the previous seven weeks, the plaque surface was devoid of mural thrombus. In only one of their 12 cases were the symptoms limited to TIAs. In the other 11, infarctions had occurred in either the brain or the retina, so any inferences concerning TIAs are clearly limited.

Evidence against the embolic theory of TIAs

At odds with the embolic hypothesis are the conclusions drawn by Fisher and Ojemann[15] from their pathologic study of carotid plaques removed at surgical endarterectomy. The plaques were dissected out in one piece (*Fig. 1*), placed unsectioned in formalin fixative, and later embedded in paraffin. Serial sections were prepared and stained with various stains. Each specimen provided 1,000–3,000 sections, permitting detailed study of the plaque, residual lumen, mural thrombus, ulceration, and intraplaque hemorrhage. In all, 141 cases were studied, divided into two large groups as follows: TIAs, TMB, and asymptomatic cases; and cases with a permanent or prolonged deficit lasting more than 24 hours.

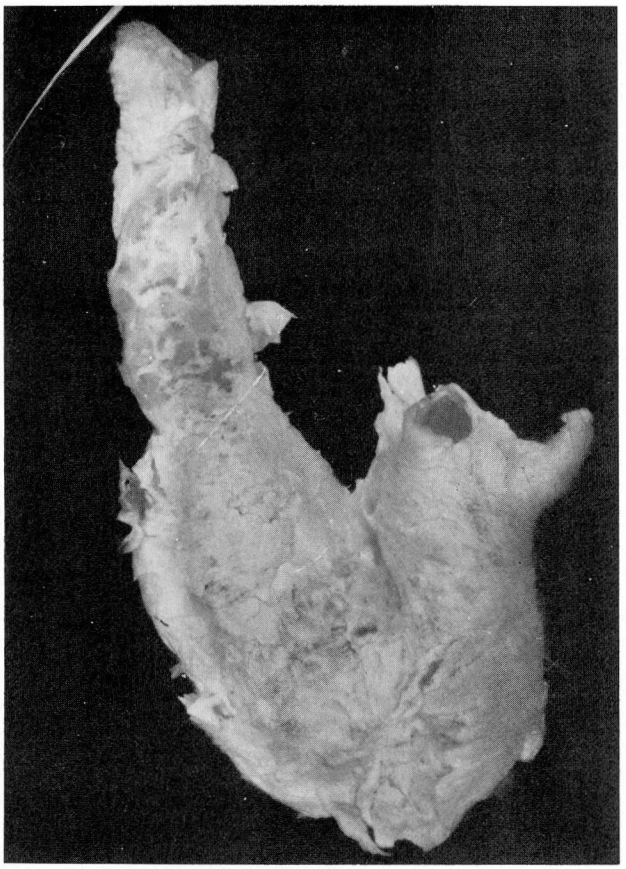

Fig. 1. Surgical carotid endarterectomy specimen.

Group 1 comprised 34 cases of hemispheric TIAs, 23 cases of TMB, and 33 asymptomatic cases. For each case, observations were made of the residual lumen and the presence or absence of mural thrombus, ulceration, and intraplaque hemorrhage. The results are shown in *Table 4*. The diameter of the *residual lumen* was 1 mm or less in 98% of the cases with hemispheric TIAs and 90% of cases with TMB, giving a combined figure of 94%. In one hemispheric TIA case, the residual lumen was crescentic and measured 2 × 0.5 mm. The hemispheric TIA cases were analyzed separately from those with TMB because some 50% of typical TMB spells occur in the absence of discernible vascular disease.[23] It was therefore possible that a relationship between TMB and some degree of carotid disease could be inferred when no relationship existed. One of

Downloaded from www.ccjm.org on April 25, 2024. For personal use only. All other uses require permission.

Table 4. Pathologic findings in endarterectomy specimens from 90 patients[15] (number of cases)

	Hemispheric TIAs (34 cases)	TMB (23 cases)	Asymptomatic (33 cases)
Residual lumen (diameter)			
1 mm	33 (98%)	19 (90%)	5 (15%)
1–2 mm	1 (2 × 0.5 mm)	0	8
2–3 mm	0	1 (3 × 0.5 mm)	15
3 mm	0	1	5
Mural thrombus	26 (77%)	22 (96%)	7 (21%)
Ulceration	8 (24%)	13 (57%)	9 (27%)
Internal carotid artery	6	11	8
Common carotid artery	2	3	1
Intraplaque hemorrhage	13 (39%)	15 (65%)	6 (19%)
Cul de sacs	5	2	5

the TMB cases showed a residual lumen diameter of more than 3 mm, which may have represented idiopathic TMB. It is probably more reliable to base conclusions on the experience with hemispheric TIAs. It should be pointed out that in 52 of the 57 cases in the TIA and TMB categories (91%), there had been two or more transient spells of the same pattern lasting 30 seconds to 60 minutes. Angiography was performed in 55 of the 57 cases.

Fibrin or *fibrin-platelet mural thrombus* was present on the plaque in 26 of 34 cases with hemispheric TIAs (77%) and in 22 of 23 TMB cases (96%), giving a combined figure of 84%. In the asymptomatic group, mural thrombus was present in seven of 33 cases (21%). *Ulceration* of the plaque was present in 24% of hemispheric TIA cases, 57% of TMB cases, and 27% of asymptomatic cases. Ulceration can be ruled out as a factor in TIAs because it occurred with the same frequency in the TIA cases as in the asymptomatic cases.

The occurrence of TIAs correlated strongly with both a residual lumen diameter of 1 mm or less and the presence of mural thrombus. The correlation was slightly better with the residual lumen of 1 mm or less, and eight hemispheric TIA cases showed no mural thrombus. In five of the TIA cases, the mural thrombus was 1 mm or less in diameter, a size that would not block a main division of the middle cerebral artery if the entire thrombus was dislodged. In other instances, the mural thrombus was only slightly raised and appeared to merge indistinguishably with the underlying wall, a position from which it might not be easily dislodged. On the other hand, two of the mural thrombi in the asymptomatic group were large and pedunculated. In the TMB cases, the incidence of tight stenosis and mural thrombi was the same. A tight residual lumen correlated better with the occurrence of TIAs than did the presence of mural thrombus. Deposition of mural thrombus may be the mechanism by which tight stenosis is eventually produced, but mural thrombus may not be the source of recurrent embolic particles. This formulation is consistent with our 25-year experience that slightly elevated carotid plaques causing only minor stenosis are not associated with recurrent TIAs or TMB of the same pattern.

According to these findings, TIAs and TMB are related to tight stenosis and are not the result of recurrent minor embolism, i.e., they may be hemodynamic in origin. Indeed, evidence supporting this is now being provided by reports of the correlation between clinical manifestations and the findings on noninvasive carotid imaging.[24,25]

Further evidence against the embolic theory of TIAs is the general experience that when emboli cause brief spells, the spells are likely to last longer than one hour. In this regard, the following case may be unusually instructive. In one endarterectomy specimen, the large plaque in the proximal internal carotid artery consisted almost entirely of fibrin mural thrombus (*Fig. 2*). The patient, age 70, who had a prosthetic aortic valve and had undergone a coronary bypass procedure, suddenly lost vision in the upper nasal quadrant of the right eye. Pale yellow material lay at the first bifurcation of the inferior temporal branch of the central retinal artery. The material disappeared in approximately 31 days, and the patient thought his vision at that time had returned to normal. Warfarin sodium therapy was begun. About three and one-half years later numbness and complete paralysis of the left arm suddenly developed. The patient wondered what was striking him on the left thigh as he walked along. It was his flail left arm. Power was almost normal

Downloaded from www.ccjm.org on April 25, 2024. For personal use only. All other uses require permission.

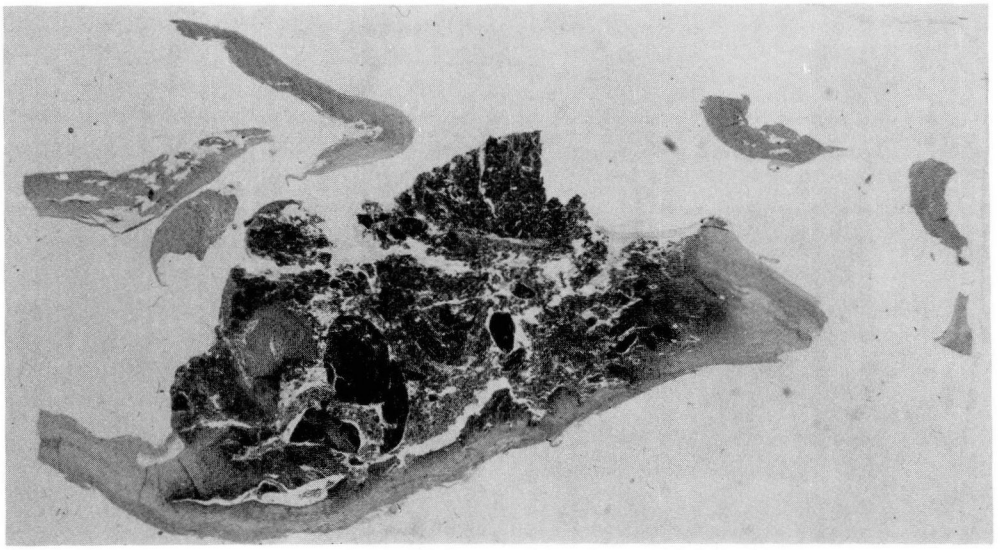

Fig. 2. Large fibrin mural thrombus producing carotid stenosis (hematoxylin-eosin, ×1½).

again in two hours, but some deficit was still present at three days. There was no carotid bruit. Angiography showed a nonstenosing carotid plaque with a residual lumen of 3 mm. Acetylsalicylic acid was added to the warfarin sodium.

Eight months later another scotoma suddenly developed in the patient's right eye. The scotoma improved markedly in 25 minutes and left only a slight residuum at three days. A right carotid endarterectomy was performed, revealing the large fibrin mural thrombus. In four and one-half years the patient had had no TIAs (spells lasting less than one hour), but he did have three minor, largely reversible embolic events lasting 31 days, three days, and three days, respectively.

For such single minor embolic episodes we have adopted the acronym, *ACME*, "acceptable minor embolism."[26] It is a more specific term than *RIND*, "reversible ischemic neurologic deficit," in that a diagnosis of embolism and a duration of more than one hour are implied. An ACME can be more easily defined for a hemispheric insult than for the retina, where a tiny embolic particle may permanently impair vision.

The embolic theory of TIAs holds that a fragment of mural thrombus breaks away into a turbulent stream and is carried repeatedly to the same arterial site by laminar flow. The particles would have to break off repeatedly at the same size unless the patient had both TIAs and TMB, in which case the particles would have to break off systematically at two different sizes.

One way of investigating the behavior of emboli would be to study the distribution of cardiogenic emboli entering a carotid system. To what extent do they duplicate carotid TIAs? To address this question a review was undertaken of 200 Massachusetts General cases of cerebral embolism from the heart associated with atrial fibrillation or acute myocardial infarction. It soon became apparent that such a comparison presupposed precise knowledge of the characteristics of hemispheric TIAs associated with carotid stenosis, and that this information was not available. Therefore, as an initial step, 50 cases of carotid hemispheric TIAs were analyzed as shown in *Table 5*. Numbness and/or weakness of the hand or fingers were part of the TIA in 44 of the 50 cases. Motor speech was involved alone in four cases, face and speech in one, and numbness of the leg in one. Fluent jargon aphasia was not recognized. The theater of TIA action in the middle cerebral artery territory is the superior division in the region of the central sulcus. The involved area is relatively restricted, and the symptoms are focal rather than wide-ranging.

Do cardiogenic emboli in atrial fibrillation or myocardial infarction mimic this picture? Are embolic particles that enter the carotid stream distributed in the same pattern as is claimed for them in TIAs? First of all, emboli from the heart tend to go to either hemisphere, even in the same patient. In none of the aforementioned 200 cases was there a typical hemispheric TIA lasting 10 minutes or less. Deficits resulting from emboli that appeared to involve the superior division of the middle cerebral artery lasted a matter of hours or days. Next to be scrutinized were cases

Downloaded from www.ccjm.org on April 25, 2024. For personal use only. All other uses require permission.

Table 5. Neurologic symptoms in 50 carotid TIA cases at Massachusetts General

Symptoms	No. cases	
	With symptoms alone	With speech also impaired
Numbness of hand (fingers, arm)	16	2
Weakness of hand	8	1
Weakness of arm	2	—
Numbness and weakness of hand	2	2
Numbness of hand and face	2	2
Weakness of hand and face	1	2
Numbness of arm and leg	1	—
Numbness of leg	1	—
Numbness and weakness of hand, numbness of face	0	3
Weakness of face	0	1
(Speech alone)	—	5
TOTAL	33	17

in which infarcts of restricted size involved at least the face, arm, and speech areas, as in TIAs. In 39 of 52 such cases the symptoms were wide-ranging, extending outside the TIA zone, as indicated by the presence of jargon aphasia, hemianopia, paresis of a leg, parietal neglect, constructional apraxia, conjugate deviation of the eyes, or confusion. These data suggested that cardiogenic emboli do not preferentially enter the rolandic branches of the middle cerebral artery with the regularity that fibrin-platelet material from a carotid plaque is alleged to do, according to the embolic theory. The facts do not support the concept that emboli leaving the heart, for example, from a prolapsed mitral valve, are carried repeatedly to the same cerebral territory. It is of interest that in the 200 cases no retinal embolism was recorded.

The clinical details in cases of cerebral thrombosis support many objections to the embolic theory. Thirty-three illustrative cases were reported in 1976.[27] A few additional examples can be cited, and the list is by no means exhaustive. When carotid stenosis recurs after endarterectomy, the recurring TIAs take the same pattern as they did originally, even though the stenosis is of quite another form.[28] Recently, a patient with a third recurrence of carotid stenosis after three endarterectomies again experienced TIAs in the form of numbness of the fingers, just as she had before her first surgery. Such a course of events points to characteristics of the cerebral circulation specific to the individual. A review of 12 Massachusetts General cases with carotid disease in which TIAs selectively involved one leg showed the presence of bilateral carotid disease in all. Since isolated involvement of the leg is unusual in unilateral carotid stenosis, its occurrence under these circumstances suggested that a flow phenomenon was operative. In a case in which weakness of the right arm developed during angiography, another injection of contrast medium showed an embolic particle in the distal segment of the rolandic branch of the middle cerebral artery. The weakness lasted three hours, demonstrating that a very small particle could cause a prolonged episode. Giant fusiform and saccular aneurysms of the vertebrobasilar system containing masses of thrombus, which might be a source of emboli, are not associated with recurrent TIAs.

What alternatives are there to the embolic theory of TIAs? Although the mechanism remains unexplained, the main candidate is the hemodynamic theory, for which Fisher and Ojemann[15] provided pathological evidence. It is my speculation that recurrent carotid TIAs associated with arterial stenosis are a function of an "unstable" circulatory state in which hemodynamic failure occurs in watershed regions. This would imply that the functional watershed area in carotid stenosis cases is in the hand, face, and speech areas of the middle cerebral territory and not necessarily in the classical location along the anterior cerebral–middle cerebral border zone. Testing this tenet will be difficult in the cerebral circulation, and further efforts to observe the retina during TMB are more likely to be informative. What triggers the failure of flow remains unknown. An important inconsistency in the hemodynamic theory is the absence of TIAs in symptomatic vasospasm associated with subarachnoid hemorrhage in ruptured aneurysm. Also puzzling is the sparing of the retina when a stroke occurs in carotid stenosis cases with prodromal TMB.

Recurrent TIAs with normal angiography

Recurrent TIAs with normal angiography are not rare, and several papers have addressed the subject. Marshall and Wilkinson[29] and Toole and Yuson[30] found the prognosis poor in such cases, whereas Al-Mefty et al[31] and Mendelowitz et al[32] reported just the opposite—their patients did not have strokes. Rather than trying to reconcile these widely disparate results, I shall briefly describe the procedure used by our Stroke Service in this situation. First, the characteristics of the TIAs are reviewed, certifying their ischemic nature, that is, that they are truly TIAs and not related to any of the conditions mentioned in the introduction to this paper. A further attempt is made to localize the symptoms and confirm that

Downloaded from www.ccjm.org on April 25, 2024. For personal use only. All other uses require permission.

the suspected cerebral site, including the extracranial arteries, has been adequately visualized angiographically. The stem of the middle cerebral artery may not be well demonstrated, and this is also true of the anterior cerebral artery. Basilar artery stenosis can be overlooked. When the symptoms are of lacunar origin, the small penetrating arteries in which they arise will not be visualized by conventional angiography—as in pure motor hemiparesis, pure sensory TIAs, ataxic hemiparesis, or midline lower pontine syndrome. When all the facts are affirmed, the possibility of late-life migrainous accompaniments is explored. Many puzzling cases find a niche under this interpretation, although the concept remains controversial. Since no diagnostic tests exist for migraine, conclusions must be drawn with caution. Some 50% of cases with recurrent TMB occur in the absence of vascular disease[23] and are ascribed, rather readily, to migraine. A similar mechanism may operate intracranially. The approach just outlined has proved satisfactory when recurrent TIAs occur in patients with normal angiograms as well as in those in whom the arterial disease demonstrated does not adequately explain events.

Finally, I would like to emphasize that, in my experience, TIAs (and TMB) follow predictable rules that can be understood by the clinician and used in a rational way to interpret and manage strokes and cerebrovascular disease.

C. M. Fisher, M.D.
Neurology Service
Massachusetts General Hospital
Fruit Street
Boston, MA 02114

References

1. Fisher CM. Occlusion of the internal carotid artery. Arch Neurol Psychiatr 1951; **65:**346–377.
2. Fisher CM, Cameron DC. Concerning cerebral vasospasm. Neurology 1953; **3:**468–473.
3. Fisher CM. Concerning recurrent transient cerebral ischemic attacks. Can Med Assoc J 1962; **86:**1091–1099.
4. Acheson J, Hutchinson EC. Observations on the natural history of transient cerebral ischaemia. Lancet 1964; **2:**871–876.
5. Millikan CH. The pathogenesis of transient focal cerebral ischemia. Circulation 1965; **32:**438–450.
6. Barnett HJM. Transient cerebral ischemia—pathogenesis, prognosis and management. Ann R Coll Phys Surg Can 1974; **7:**153–173.
7. Barnett HJM. Pathogenesis of transient ischemic attacks. [In] Scheinberg P, ed. Cerebrovascular Diseases. New York, Raven Press, 1976, pp 1–21.
8. Brust JCM. Transient ischemic attacks: natural history and anticoagulation. Neurology 1977; **27:**701–707.
9. Millikan CH, McDowell FH. Treatment of transient ischemic attacks. Stroke 1978; **9:**299–308.
10. Millikan CH. Transient cerebral ischemia: definition and natural history. Prog Cardiovasc Dis 1980; **22:**303–308.
11. Russell RWR. Pathogenesis of transient ischemic attacks. Neurol Clin 1983; **1:**279–290.
12. Furlan AJ. Transient ischemic attacks: strategies for minimizing stroke risk. Postgraduate Med 1984; **75(6):**183–189.
13. Committee of the National Institute of Neurological Diseases and Blindness, Public Health Service. A classification and outline of cerebrovascular diseases. Neurology 1958; **8:**405–434.
14. NINCDS Ad Hoc Committee on Cerebrovascular Diseases. A classification and outline of cerebrovascular diseases. II. Stroke 1975; **6:**564–612.
15. Fisher CM, Ojemann RG. A clinico-pathologic study of carotid endarterectomy plaques. Keynote address, 10th International Stroke Conference, New Orleans, February 21, 1985.
16. Fisher CM. Late-life migraine accompaniments as a cause of unexplained transient ischemic attacks. Can J Neurol Sci 1980; **7:**9–17.
17. The Canadian Cooperative Study Group. A randomized trial of aspirin and sulfinpyrazone in threatened stroke. New Eng J Med 1978; **299:**53–59.
18. Fields WS, Lemak NA, Frankowski RF, Hardy RJ. Controlled trial of aspirin in cerebral ischemia. Stroke 1977; **8:**301–316.
19. Muuronen A, Kaste M. Outcome of 314 patients with transient ischemic attacks. Stroke 1982; **13:**24–31.
20. Fisher CM. Observations of the fundus oculi in transient monocular blindness. Neurology 1959; **9:**333–347.
21. Kuriyama M, Ishii N, Umezaki H, Kano M. Polycythemia vera and transient monocular blindness. Eur Neurol 1977; **16:**127–135.
22. Gunning AJ, Pickering GW, Robb-Smith AHT, Russell RR. Mural thrombosis of the internal carotid artery and subsequent embolism. Q J Med 1964; **33:**155–195.
23. Ackerman RH. Noninvasive diagnosis of carotid disease in the era of digital subtraction angiography. Neurol Clin 1983; **1:**263–278.
24. Roederer GO, Langlois YE, Jager KA, Primozich, JF, Beach KW, Phillips DJ, Strandness DE Jr. The natural history of carotid arterial disease in asymptomatic patients with cervical bruits. Stroke 1984; **15:**605–613.
25. Chambers BR, Norris JW. The case against surgery for asymptomatic carotid stenosis. Stroke 1984; **15:**964–967.
26. Fisher CM. TIAs and ACMEs. Paper presented at Celebration of 50th Anniversary, The Sir Mortimer B. Davis Jewish General Hospital, Montreal, May 28, 1984.
27. Fisher CM. Transient ischemic attacks—an update—in discussion. [In] Scheinberg P, ed. Cerebrovascular Diseases. New York, Raven Press, 1976, pp 51–53.
28. Fisher CM, Ojemann RG. Reduplication of transient symptoms with recurrences of carotid stenosis (abstract P9). Ann Neurol 1982; **12:**85.
29. Marshall J, Wilkinson IMS. The prognosis of carotid transient ischaemic attacks in patients with normal angiograms. Brain 1971; **94:**395–402.
30. Toole JF, Yuson CP. Transient ischemic attacks with normal arteriograms: serious or benign prognosis? Ann Neurol 1977; **1:**100–102.
31. Al-Mefty O, Marano G, Rajaraman S, Nugent GR, Rodman N. Transient ischemic attacks due to increased platelet aggregation and adhesiveness. J Neurosurg 1979; **50:**449–453.
32. Mendelowitz DS, Kimmins S, Evans WE. Prognosis of patients with transient ischemic attacks and normal angiograms. Arch Surg 1981; **116:**1587–1591.

Downloaded from www.ccjm.org on April 25, 2024. For personal use only. All other uses require permission.