Transient ischemic attack (TIA) as a predictor for cerebral infarction is generally thought to be of recent vintage but, in reality, the concept dates from the dawn of our understanding of the cerebral circulation. Perhaps the first description of heralding episodes preceding stroke was that by Thomas Willis, who recorded:

"The seat of apoplexy seems to be within the same inward portion of the brain. ... Both affects, the imagination and common sense, though in far differing degree affected, viz. in the latter the irradiation of the spirits is wont ... to be interrupted with little clouds, as it were, scattered here and there, but in the former, the same is forthwith wholly darkened and undergoes total eclipse.

The apoplexy, according to the import of the word, denotes a striking, and, by reason of the stupendous nature of the affect, as though it contained something divine; it is called a sideration; those who are seized with it, as though they were planet struck, or smitten by an invisible Deity, fall on the ground on a sudden being deprived of sense and motion. ... Moreover, Willis graphically described blood-borne embolism as one of the pathogenetic mechanisms of TIA.

Its practical causes are like, as in most other affects of the brain, the blood is in fault, that either engendering of itself or taking from elsewhere extraneous particles and such as are very averse to the texture or constitution of the animal spirits and, as it were ... sends them to the brain. If, after the first seizure of a speechlessness being well over, the diseased afterward becomes more drowsy and dull, is affected with a scotoma, and a frequent vertigo, it is a sign that he will be obnoxious to other accesses of the apoplexy.

This knowledge of transient warning episodes persisted into the 19th and 20th centuries in the writings of Wood, Hammond, Gowers, Oppenheim, and Osler but received short shrift from Wechsler, Kinnier-Wilson, and Merritt as well as from the attendees of the first Princeton Conference on Cerebral Vascular Disease, held in 1954 during the era of nihilism regarding prevention and management of stroke. It was Fisher and Millikan who reintroduced, emphasized, and popularized TIA as a marker for excess risk of cerebral infarction. Using careful history-taking and keen observation of individuals along with epidemiologic and biostatistical..."
tools, these authors and their colleagues discovered that almost one third of patients with TIA eventually have cerebral infarction and that approximately 20% of infarctions occur within the month following the first episode.

It is now accepted that most episodes persist for less than 15 minutes and, by general agreement, that the deficit must resolve within 24 hours; beyond this arbitrary limit, another diagnosis must be made. A TIA usually occurs without a precipitant, is sudden in onset, and results in functional disturbance limited to their common denominator is temporary cessation of blood flow to a focal area of neurons and glia.16

For clinicians of the 1960s and 1970s, TIA was diagnosed by appropriate history and normal findings on a neurologic examination and was, therefore, one of the few syndromes without confirmatory laboratory tests, a situation that persisted beyond the first generation of cranial computed tomography (CCT).15,18 To differentiate TIA from cerebral infarction, Buonanno and I19 emphasized that the former can be diagnosed on a neurologic examination and was, therefore, one of the few syndromes without confirmatory laboratory tests, a situation that persisted beyond the first generation of cranial computed tomography (CCT).15,18 To differentiate TIA from cerebral infarction, Buonanno and I19 emphasized that the former can be diagnosed on a neurologic examination, but the underlying silent infarction may convert from ischemic to hemorrhagic if either therapeutic approach is chosen.

To prevent the error of our predecessors who classified disease by symptoms, rejecting data that do not fit preconceptions, the definition of TIA coined in the 1950s must now be reconciled with brain abnormalities persisting long after the 24-hour limit, which have been demonstrated by technology developed in the 1970s. This problem of incomplete information is augmented by patients and families who cannot describe the symptoms and sequence of events as clearly as necessary for accurate classification. Because of our arbitrary definitional and time boundaries, episodes that fall outside these boundaries can be misclassified, particularly if the ictus affects the nondominant hemisphere so that the event is described vaguely or almost ignored by the patient. Wilkinson et al25 administered a questionnaire comprising TIA symptoms to 10,861 elderly

### Table 1. Frequency of Infarction in Patients With Transient Ischemic Attacks

<table>
<thead>
<tr>
<th>Author(s)</th>
<th>Year</th>
<th>Number of patients</th>
<th>Examined territory</th>
<th>Patients with focal lesion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kinkel and Jacobs20</td>
<td>1976</td>
<td>32</td>
<td>CA</td>
<td>0%</td>
</tr>
<tr>
<td>Perrone et al21</td>
<td>1979</td>
<td>35</td>
<td>CA+VB</td>
<td>12%</td>
</tr>
<tr>
<td>Ladurner et al27</td>
<td>1979</td>
<td>44</td>
<td>NS</td>
<td>8%</td>
</tr>
<tr>
<td>Houser et al22</td>
<td>1981</td>
<td>21</td>
<td>NS</td>
<td>6%</td>
</tr>
<tr>
<td>Biller et al24</td>
<td>1982</td>
<td>45</td>
<td>CA</td>
<td>2%</td>
</tr>
<tr>
<td>Araki et al23</td>
<td>1983</td>
<td>26</td>
<td>CA</td>
<td>12%</td>
</tr>
<tr>
<td>Calandre et al24</td>
<td>1984</td>
<td>88</td>
<td>CA+VB</td>
<td>22%</td>
</tr>
<tr>
<td>Bogousslavsky and Regli22</td>
<td>1985</td>
<td>57</td>
<td>CA</td>
<td>16%</td>
</tr>
<tr>
<td>Turnbull and Bannister26</td>
<td>1986</td>
<td>261</td>
<td>CA</td>
<td>101%</td>
</tr>
<tr>
<td>Awad et al27</td>
<td>1986</td>
<td>22</td>
<td>CA+VB</td>
<td>7%</td>
</tr>
<tr>
<td>Weisberg28</td>
<td>1986</td>
<td>100</td>
<td>CA</td>
<td>17%</td>
</tr>
<tr>
<td>Grigg et al29</td>
<td>1988</td>
<td>104</td>
<td>CA</td>
<td>50%</td>
</tr>
<tr>
<td>Davalos et al30</td>
<td>1988</td>
<td>122</td>
<td>CA+VB</td>
<td>25%</td>
</tr>
<tr>
<td>Murros et al31</td>
<td>1989</td>
<td>284</td>
<td>CA+VB</td>
<td>34%</td>
</tr>
</tbody>
</table>

CA, carotid; VB, vertebrobasilar; NS, not stated. From Nicolaides et al.27

without CCT changes, there were often prolonged focal physiologic and metabolic disturbances. What these disturbances represent is still unresolved because clinicopathologic correlations have yet to be made (C.M. Fisher, personal communication, 1990).

In 1983, Waxman and I33 pointed out that some patients with transient symptoms and signs typical of TIA have fresh infarction that can be demonstrated by CCT. We described several patients, one of whom was a 50-year-old professor who suddenly developed aphasia and weakness of his right hand. His wife and a friend, who had been conversing with him at the initiation of the event, observed that his sense of time was distorted. For example, he believed that only 1 or 2 minutes had elapsed when the emergency squad arrived 15 minutes later. When examined by a neurologist within an hour of onset, the patient had Broca's aphasia and right hemiparesis, both of which resolved within 20 hours. However, CCT performed at 24 hours was compatible with evolving infarction in the left posterior frontal region. Twenty-four hours thereafter, regional cerebral blood flow studies demonstrated a focal area of luxury perfusion in the same region. Serial CCT showed evolving infarction, and the patient had focally abnormal regional cerebral blood flow for 6 weeks.

Despite evolving anatomic and pathophysiologic changes, this patient's neurologic deficit resolved within the 24-hour limit. Should he be classified as having a TIA on the basis of history and examination or as having an infarction on the basis of imaging? We decided to call this cerebral infarction with transient symptoms (CITS), a term that has become generally accepted.25,31,34 Identifying this category is important because its prognosis differs from that of TIA (unpublished observations), and CITS should be a consideration in the selection of medical or surgical management. For example, TIA patients may seem to be at minimal risk from endarterectomy or anticoagulant treatment because of a normal neurologic examination, but the underlying silent infarction may convert from ischemic to hemorrhagic if either therapy is chosen.
persons and found positive responses in 57%. Not surprisingly, when a neurologist interviewed and examined the positive responders, only 12.8% had events that fit the definition of TIA. What is most disturbing is that those rejected as not having had a TIA because of vague or indefinite symptoms had exactly the same prognosis for stroke as those with phenomena accepted as being TIA. From this one must conclude that the accepted criteria for TIA are too rigid.

Whether a patient has residual neurologic abnormality is also an inexact determination. Transitory cognitive changes have not usually been accepted as a TIA because we have no ready means for characterizing and quantifying them. However, there are patients who by their own accounts and by neurologic examination are normal, but whose spouses report permanent behavioral changes following ictus. What the patient and physician regard as transient may, in truth, be permanent (unpublished observations).

Another problem is the minimum array of symptoms and signs that can be accepted as a TIA. For example, if a patient loses motion in one finger or suffers numbness in one toe for a few seconds, it is unlikely that the physician would diagnose a TIA because the occurrence was too brief and trivial. However, the physician might well do so if the occurrence persisted for minutes or hours or if it involved several fingers or toes.

It is curious that physicians have never considered that TIAs occur during sleep. Surely events identical to those of which we are aware take place when we are not; for example, if one does not talk during an episode, one cannot determine whether speech is normal. This may help to explain the frequency with which lesions that provoked no clinical event—silent infarctions identified years ago by pathologists—before the opportunities for clinicopathologic correlation that we now have—are being discovered by neuroimaging.

Thus, our accepted TIA criteria of evanescence of event and absence of residual findings are at least partly obsolete and help to explain the unacceptable frequency of interobserver, and even intraobserver, disagreement regarding classification. These inexactitudes were vividly demonstrated by the Cooperative Group for the Study of TIA, who reported that fully one third of patients hospitalized for TIA were misclassified. Although neurologists with special training independently agreed in 88–93% of the cases, in other series there was disagreement in almost one third of the cases. In the Italian Multicenter Study on Reversible Cerebral Ischemia, agreement between examiners varied from 42% to 76% for history and from 21% to 92% for neurologic signs. Such findings have been verified repeatedly.

In an effort to improve agreement, Koudstaal and colleagues devised a questionnaire using patient language rather than medical terms. With a standardized checklist to obtain data, their questionnaire increased agreement between neurologists on classification from 65% to 77% and on vascular distribution from 31% to 65%. Yet even this is not sufficiently exact given the means now available for categorizing patients precisely by ultrasound imaging of the extracranial and intracranial arteries and CCT and MRI of the brain. Reggia et al constructed a computerized algorithm that agreed with physician diagnosis of TIA in 71% and with localization in 73% of 103 randomly selected TIA patients. The greatest disagreement involved patients with clinical deficits that resolved within 24 hours but who had CCT evidence of evolving infarction. In 65 patients in whom both the neurologist and the algorithm agreed that a TIA had occurred, there was agreement on localization in 50 and disagreement in 12; the algorithm was unable to localize the event in the remaining three patients. The 12 disagreements were reviewed by another physician, who agreed with the algorithm in 11.

These imperfections in history-taking and examination—the bedrock of TIA classification—are much greater when patients consult a physician weeks or months following the event. By then, recall is sketchy and deficits that may have lasted beyond the 24-hour limit have probably disappeared. Both could be major problems for ongoing randomized trials designed to assess the efficacy of medical and surgical intervention for preventing cerebral infarction, some of which access patients as long as 6 months after the event.

This vexing problem of uniform and validated criteria for the diagnosis of TIA is epitomized by the seven multicenter prospective randomized carotid endarterectomy trials and by the Atherosclerosis Risk in Communities Study and the Cardiovascular Health Study. All use event-detection questionnaires modified from the one originally developed by the Study Group on TIA Criteria and Detection of the Joint Committee for Stroke Facilities. As described previously, this original questionnaire was administered to 10,861 elderly individuals and validated against one neurologist’s judgment. Individuals having vague, nonspecific, or unclassified cerebrovascular events had the same incidence of stroke during follow-up as those classified as having TIAs. To resolve these inconsistencies, it is vital that a single standardized, validated, and universally accepted instrument for eliciting the symptoms and signs by which we classify TIA be developed and adopted. Only then can we screen large populations to identify persons at excess risk and compare the effects of different interventions.

It is current practice for patients to consult a physician regarding stroke risk only if they have TIAs. I do not agree with this view because 1) half of the persons at excess risk will have no warning event before a major infarction, 2) others will progress to occlusion before any heralding event, after which surgical remediation cannot be done, 3) occlusion causes a sudden, permanent deficit without a preceding TIA in nearly half of cases, 4) the herald TIA is often ignored or misdiag-
nosed until after infarction, 5) many persons have silent infarctions, and 6) ultrasound has provided reliable, inexpensive, and safe detection of extracranial atherosclerosis and its longitudinal reassessment as a means of identifying many of those at excess risk. Almost half of the annual 180,000-plus strokes in the United States are associated with, if not caused by, lesions located ≤2 cm from the origin of the internal carotid artery. Therefore, it is only logical to identify these persons during the presymptomatic phase (using validated screening methods) to intervene appropriately to inhibit or reverse disease progression. On the other hand, there is not yet the corresponding capacity to prescribe validated therapeutic interventions, which is precisely why the ongoing prospective randomized trial for asymptomatic carotid stenosis is so important.

Our group increasingly suspects that stenosis per se is the abnormality that increases the risk for infarction and that a TIA resulting from infarction is only the marker that identifies stenosis. In other words, TIA is not the risk factor, but the symptom that identifies the risk factor. If this is true, we will eventually classify arterial lesions by their degree of stenosis rather than by the presence or absence of TIA, and the existence of the lesion, not the presence or absence of symptoms, will be the critical factor in making decisions regarding therapy.

Lastly, one must never forget that even though patients with carotid stenosis are at excess risk for
cerebral infarction, they will probably die of coronary atherosclerosis. Therefore, this population must be evaluated for both cardiac and cerebrovascular disease.

Conclusion

I see similarity between what has recently happened in the field of cerebrovascular disease and what happened during Thomas Willis’ lifetime, in which new technology opened vistas and caused reexamination of the validity of previously accepted clinical concepts. Our current decade of the brain is also comparable to previous decades of the heart, in which programs to identify asymptomatic segments of health care providers. With time, the wisdom of this application of large-scale screening became evident in the dramatic reduction in the occurrence of cerebral hemorrhage. We now have the tools to produce an equally dramatic effect on the ravages of atherosclerosis in the brain.

Appendix 1. Thomas Willis

Thomas Willis was born on January 27, 1621, in Great Bedwyn, UK (Figure 1); he died in 1675 and is entombed in Westminster Abbey. In 1644, Willis’ family moved closer to Oxford, where he began studies for the clergy. Because of the Civil War, he trained instead for medicine, an exercise that in those days required 1 year after collegiate matriculation. Soon thereafter, the social structure and medical dogmas of a thousand years were abandoned when Cromwell’s forces defeated the Royalists in the Civil War. This was the beginning of the age of the scientific method, which required proof for beliefs that had previously been accepted on authority. It was also the time for clinicopathologic correlations, the invention of new instruments and techniques, and, most importantly, the substitution of English for Latin as the language of education. However, it remained the time for superstitions, when witches and religious heretics were burned at the stake, not only in England, but also in colonies such as Salem, Massachusetts.

Eventually, Willis became a popular practitioner of physic and a clinical researcher performing collaborative, multidisciplinary experiments with Richard Lower, Christopher Wren, Robert Hooke, Robert Boyle, Sir Isaac Newton, and William Harvey. Willis’ landmark work was Cerebri Anatomie, which was published in Latin from Geneva, Switzerland, in 1664. It was in Pordage’s English translation of this work that the term “neurology” was first used.

Willis’ birthplace in Great Bedwyn, his abode during his years of practice and clinical research in Oxford (Beam Hall, 3 Merton Street), and his crypt in Westminster Abbey are all worthwhile visits for those interested in the history of medicine and the cerebral circulation.

Acknowledgments

A great many have molded my ideas over the years and hence helped me formulate these concepts. Those who have been outstanding in this are C.M. Fisher, Clark Millikan, Irving S. Wright, and Carlo Loeb, to whom I dedicate this contribution even though I suspect they will not agree with some of its contents.

References

1. Willis T: Instructions and precepts for curing the apoplexy, in Fordase S (ed): The London Practice of Physic or the Whole Practical Part of Physic. Dring T, Harper C, Leigh J, Martyn S, 1679
3. Hammond WA: Disease of the Nervous System, New York, D Appleton Co, 1881, p 133
23. Araki G, Mihara H, Shizuka M, Yunoki K, Nagata K, Yamauchi K, Mizukami M, Kawase T, Tazawa T: CT and arteriographic comparison of patients with transient ischemic...
attacks—Correlation with small infarction of basal ganglia. Stroke 1983;14:276–280
46. Hatano S, on behalf of the participants in the WHO Collaborative Study on the Control of Stroke in the Community: Variability of the diagnosis of stroke by clinical judgement and by a scoring method. Bull WHO 1976;54:533–538

KEY WORDS • carotid artery diseases • cerebral ischemia, transient
The Willis lecture: transient ischemic attacks, scientific method, and new realities.

J F Toole

doi: 10.1161/01.STR.22.1.99

*Stroke* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1991 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

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/22/1/99

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in *Stroke* can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to *Stroke* is online at:
http://stroke.ahajournals.org//subscriptions/