Introduction: approach to the patient

It happened on April 13, 1737, as "the whole house vibrated from a dull thud. . .something huge and heavy must have crashed down on the upper floor." The servant of the composer George Frederick Handel ran up the stairs to his master's workroom and found him "lying lifeless on the floor, eyes staring open. . ." Handel had come home from the rehearsal in a furious rage, his face bright red, his temples pulsating. He had slammed the house door and then stamped about, as the servant could hear, on the first floor back and forth so that the ceiling rebounded: it wasn't advisable, on such anger-filled days, to be casual in your service.

From the lower floor Christopher Smith, the master's assistant, went upstairs; he had also been shocked by the thud. He ran to fetch the doctor for the royal composer. "How old is he?" "Fifty-two," answered Smith. "Terrible age, he had worked like an ox." Dr. Jenkins bent deeply over him. "He is, however, strong as an ox. Now we will see what he can do." He noticed that one eye, the right one, stared lifeless and the other one reacted. He tried to lift the right arm. It fell back lifeless. He then lifted the left one. The left one stayed in the new position. Now Dr. Jenkins knew enough. As he left the room, Smith followed him to the stairs, worried. "What is it?" "Apoplexia. The right side is paralysed." "And will. . ." Smith formed the words–"will he recover?" Dr. Jenkins laboriously took a pinch of snuff. He didn't like such questions. "Perhaps. Anything is possible."

This colorful excerpt from the famous story *George Frederick Handel's Resurrection* by Stefan Zweig illustrates a long-lasting dilemma for doctor and patient after an acute stroke: the question of diagnosis and prognosis.

Today, 260 years after George Frederick Handel's stroke, Dr. Jenkins' successors are informed better about the pathomechanisms involved in the acute situation; for example, ischemia versus hemorrhage, cardio- and arterioembolic versus hemodynamic sources of ischemia, or small-vessel versus large-vessel disease. Even less common etiologies can be identified by additional tests (e.g., cerebrospinal fluid [CSF], biomarker and antibody tests). The benefits of acute therapy with a view to the different etiologies have risen, and the prognosis can be estimated more accurately: small cerebral hemorrhages or lacunar ischemic lesions have a good prognosis, both

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being related to chronic, often inadequately treated hypertension in patients with subcortical vascular encephalopathy (SVE); this was most likely the cause of Handel's stroke. In addition, we have begun to elucidate the mechanisms of recovery after stroke. Functional magnetic resonance imaging (fMRI) and studies with positron emission tomography (PET) have shown that, following ischemic damage to either cerebral hemisphere, residual connections to corresponding remote areas can be activated and that even new synapses and neural network transformations are possible. These new findings have updated previous misconceptions regarding lack of plasticity in the adult human brain. Many of these new techniques have limited the application of our nearly outdated traditional tests (e.g., conventional angiography).

Nevertheless, the clinical case still presents a challenge for our colleagues in medicine, whether they are students, residents, or physicians with advanced expertise in stroke care. Like Dr. Jenkins, generations of physicians and neurologists in particular have based their diagnosis on a combination of (a) temporal profiles of illnesses, and (b) the presence or absence of focal, common, or uncommon signs and symptoms of stroke to conclude on the likely pathogenesis and pathobiology. The editors and contributors of this new book have tried to extend the series of common and uncommon stroke cases published in 2007 and to discuss key elements, whether they are clinical, brain and vascular imaging derived, or of other types of individual workup. Beyond traditional concepts and performance, the actual principle "time is brain" or probably "penumbra is brain" for stroke patients is illustrated, and consequently, clinical evaluation as well as technological studies are speeded-up; rather than traditional neurological examinations, a short but sufficient and therapy-related diagnosis-restricted repertoire is essential and includes all aspects of respiratory and cardiovascular function, as well as scores of the level of consciousness (using the Glasgow Coma Scale [GCS]) (Figure 1) and neurological and behavioral deficits (using the National Institutes of Health Stroke Scale [NIHSS]) (Figure 2). Detailed investigation should be avoided, but medical and surgical history from patients and their relatives still are to be carefully considered with regard to previous stroke events, treatments for other cardiovascular diseases, etc.

Standard technical tests include:

(i) electrocardiogram (ECG),
(ii) chest X-ray,
(iii) blood sample studies/blood cell counts (including thrombocytes) glucose, creatinine, creatinine in kinase or troponin and HS-troponin, electrolytes, international normalized ratio (INR), activated partial thromboplastin time (aPTT), and toxic substance quinine.

An ECG should always be carried out because of the high incidence of heart conditions in this population. Stroke and myocardial infarction may occur together. Arrhythmias frequently are either the cause or the result of embolic stroke.

Glasgow Coma Scale

Best eye response	Eye opening spontaneously	4
	Eye opening on command	3
	Eye opening to pain	2
	No eye opening	1
Best verbal response	Oriented	5
	Confused	4
	Inappropriate words	3
	Incomprehensible words	2
	No verbal response	1
Best motor response	Obeys commands	6
	Purposeful movement to pain	5
	Withdraws from pain	4
	Abnormal flexion to pain	3
	Extension to pain	2
	No motor response	1

Figure 1. Glasgow Coma Outcome Scale.

Echocardiography should be performed as well in most patients with stroke to document any cardioembolic source (thrombus in the left atrium or atrial septal aneurysm) or an atheroma in the arch of the aorta. Equally, an echocardiogram is necessary to detect a shunt of blood from the right to the left atrium through a patent foramen ovale (PFO) or atrial septal defect (ASD). The accuracy of this ultrasound examination is greatly increased by transesophageal echocardiography (TEE) and transcranial Doppler sonography (TCD) studies as well as vascular computed tomography (CT)/magnetic resonance imaging (MRI) of the aortic arch.

In the acute situation, a separation between transient ischemic attack (TIA) and stroke is impossible and this term should not be accepted any longer, not least as both prognosis and course of the disease are similar – acute cerebrovascular syndrome is an appropriate alternative.

The same diagnostic studies are used for all patients with brain attacks, whether ischemic or hemorrhagic events, are suspected: both groups need CT/MRI of the brain and vessels including full cardiological workup (Figures 3 and 4).

CT is the standard method in both the acute and follow-up evaluation of cerebrovascular diseases, since its introduction in the early 1970s. Advantages of MRI are: excellent tissue contrast, high sensitivity for detecting early ischemic findings including brainstem and cerebellum, and high susceptibility for

NIH Stroke Scale

Assess level of consciousness

Alert	0
Drowsy	1
Stuporous	2
Coma	3

Assess orientation (month, age)

Both correctly	0
One correctly	1
Two incorrect	2

Follow commands

(1. Open and close eyes
2. Make fist and release)

Obeys both correctly	0
Obeys one correctly	1
Two incorrect	2

Follow my finger

Normal	0
Partial gaze palsy	1
Forced deviation	2

Visual field

Normal	0
Partial hemianopia	1
Complete hemianopia	2
Bilateral loss	3

Facial palsy

(Show teeth, raise eyebrows, squeeze eyes shut)

Normal	0
Minor paralysis	1
Partial paralysis	2
Complete paralysis	3

Motor strength for each of four limbs

(Passively move extremity and observe strength)

a. Elevate left arm to 90 degrees
b. Elevate right arm to 90 degrees
c. Elevate left leg to 30 degrees
d. Elevate right leg to 30 degrees

No drift	0
Drift	1
Some effort against gravity	2
No effort against gravity	3
No movement	4
Amputation, joint fusion (untestable)	9

Co-ordination of limb ataxia

Absent	0
Present in upper or lower	1
Present in both	2

Sensory

(1. Pin prick to face, arm, trunk, and legs
2. Compare sides)

Normal	0
Partial loss	1
Dense loss	2

Speech clarity while reading word list

Normal articulation	0
Mild-moderate slurring	1
Nearly unintelligible, mute	2
Intubated or other physical barrier	9

Language (Describe picture, name items, read sentences)

No aphasia	0
Mild-moderate aphasia	1
Severe aphasia	2
Mute	3

Extinction and inattention

No neglect	0
Partial neglect	1
Profound neglect	2

Total

Figure 2. National Institutes of Health Stroke Scale.

demonstration of even very small hemorrhagic findings. Detection of flow parameters are excellent, although delineation of acute and developing penumbra surrounding the ischemic core or infarction are still insufficient as are sometimes developing ischemic territories close to parenchymal hemorrhage. Already approved early, specific stroke treatment with tissue plasminogen activator (tPA) requires CT within a short time frame of 4.5 hours. Beyond this time limit,

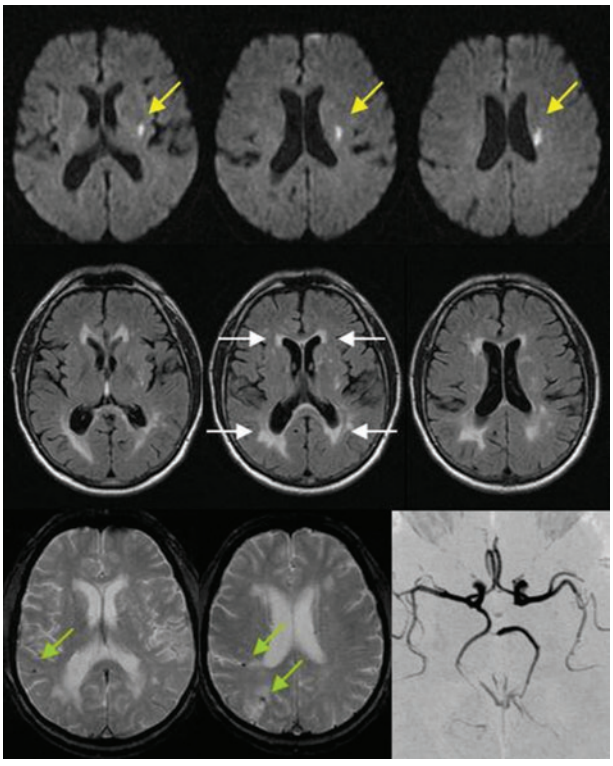


Figure 3. Typical MRI findings in a 78-year-old stroke patient with cerebral microangiopathy. DWI (upper row) shows a single hyperintense acute ischemic lesion in the territory of a perforating artery (arrow). The T2-weighted FLAIR technique (middle row) demonstrates quite extensive chronic white matter lesions in a pattern typical for SVE with hyperintense lesions in the para- and periventricular white matter. T2* susceptibility-weighted sequences (bottom left and middle) show several small cortical/subcortical microbleeds, while the MRA (bottom right) demonstrates irregular contrast of intracranial vessels–a finding suggestive of arteriosclerosis.

successful treatment can be established only if MRI or specific CT methodologies are used, facilitating separation of perfusion deficits surrounding the core of already developing tissue necrosis (i.e., an equivalent of the ischemic penumbra) or if "bridging techniques" are used experimentally.

Conventional angiography, first performed in 1927, is selectively used only in very few acute stroke patients today for diagnostic purposes, but is still considered for early interventional treatment. Despite encouraging and evidence-based results of intra-arterial thrombolysis (IAT) in the carotid system and the basilar artery in randomized clinical trials (RCTs), current indications for angiography are left to patients with suspected vascular malformations or bleeding aneurysms. They

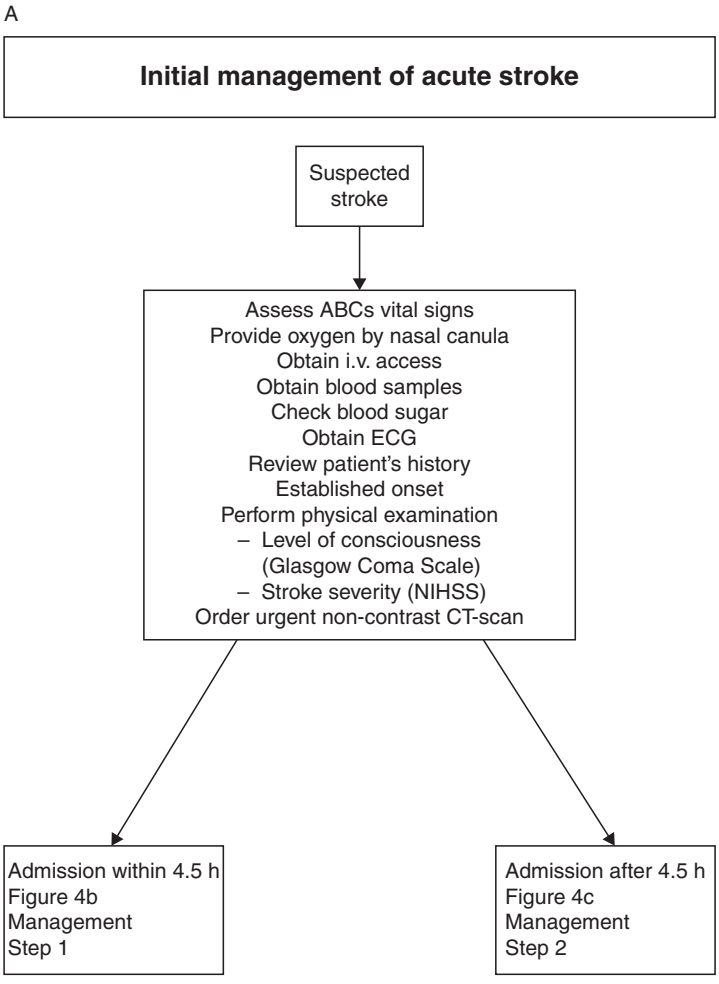


Figure 4(A). Initial management of acute stroke.

either need immediate treatment during the diagnostic procedure itself or after previous magnetic resonance angiography (MRA)/computed tomography angiography (CTA)/ultrasound studies have suggested interventional rather than surgical or conservative therapy planning. MRA and modern ultrasonography have overtaken large domains of conventional angiography and further technical and software development for refined analysis and online investigation will demonstrate preferential use and utility of such techniques in early ischemic stroke monitoring.

However, in patients with hemorrhagic strokes and subarachnoid hemorrhage (SAH) that form 15%–20% of all stroke cases, conventional angiography continues to represent the gold standard for diagnosis, and is increasingly used for

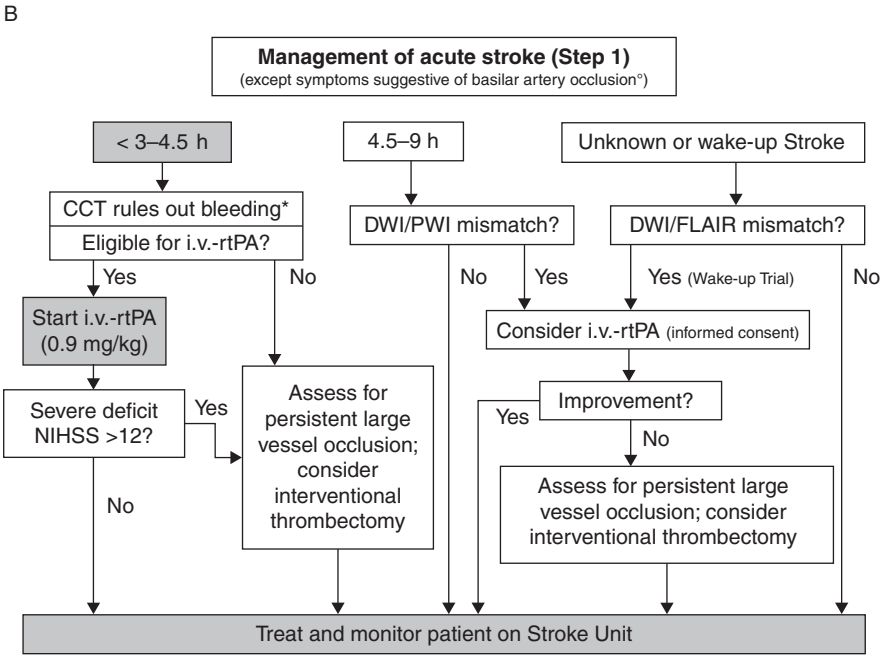
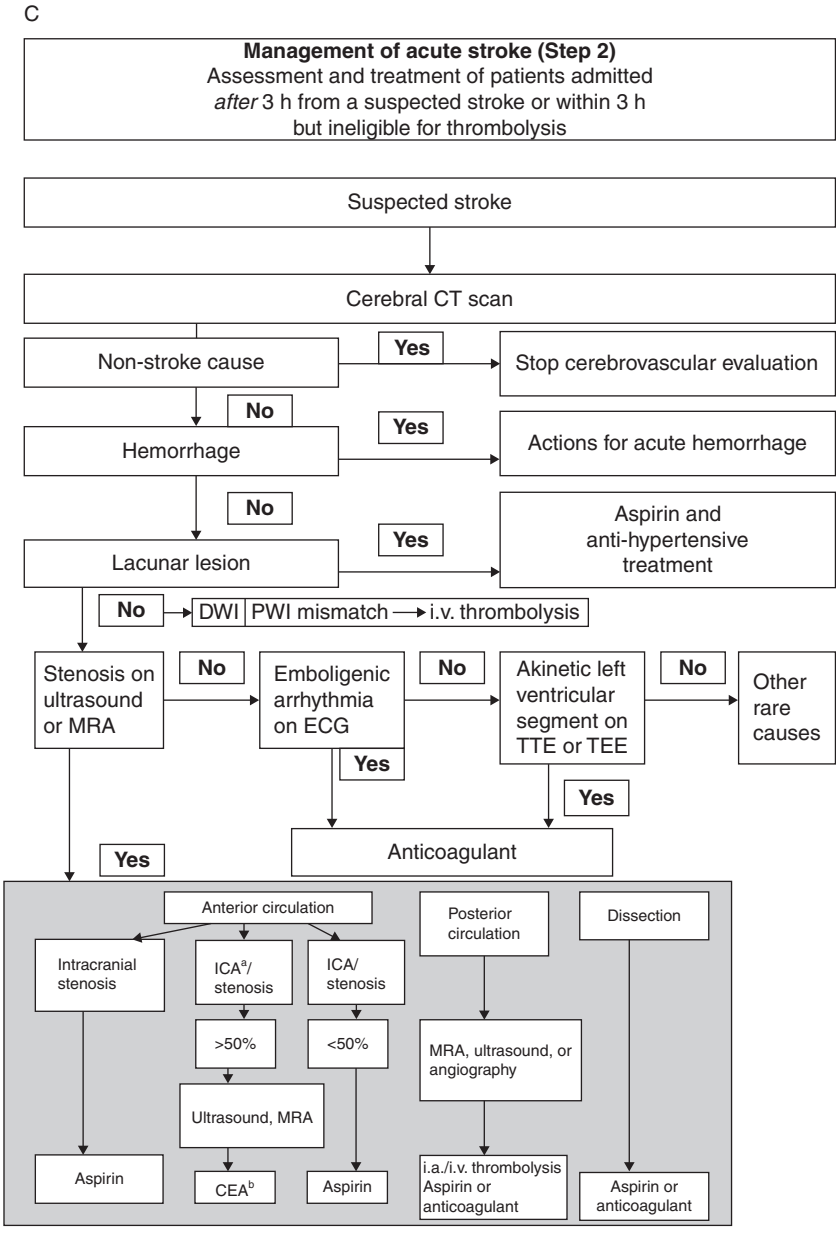


Figure 4(B). Management of acute stroke (Step 1).
Gray = Highlighted, are the only evidence-based treatment options of acute ischemic stroke.
° = Patients with clinical signs of basilar artery occlusion should be treated with i.v. r-tPA as soon as possible, and in individual cases, up to 12 h after onset. In case of subsequent acute worsening, additional intra-arterial thrombolysis/thrombectomy can be considered.
* = Some institutions perform vascular and/or perfusion imaging using CT or MRI in patients presenting within the 3–4.5 h time window (according to national approval), and in selected patients before thrombolysis to identify potential candidates for bridging therapy early on. This approach may lead to a delay of i.v. r-tPA administration; the benefit from thrombolysis, however, has been shown to be greater if started within 90 min after onset. Assessing for large vessel occlusion should be done preferably after the start of thrombolytic therapy.

therapeutic interventions (e.g., coiling of aneurysms) along with neurosurgical approaches.

Cardiovascular investigations on site and in close cooperation within the stroke team taking care of acute stroke patients are important for three major reasons: first, cerebral injury may force cardiac damage, even in patients without pre-existing cardiac disease; second, brain attacks may be cardioembolic in about 20%–30% of the cases; and third, more than half of vascular patients may have coexisting coronary artery disease, and the risk of coronary events with long-term follow-up exceeds the risk of cerebrovascular recurrences. While the last two



[a]ICA, internal carotid artery; [b]CEA, carotid endarterectomy

Figure 4(C). Management of acute stroke (Step 2).

reasons are well considered commonly, the first is debated still; knowledge of the pathophysiology of the autonomic system and the increasing number of patients with cerebral death as a possible donor for heart transplantations suggest that the cardiac consequences of cerebral damage is underestimated by far. ECG

monitoring has identified numbers of life-threatening ventricular arrhythmias in stroke patients treated on stroke units with continuous ECG monitoring, and consequent treatment has rescued many of them from acute, formerly suspected "stroke death." Acute cerebral injury may cause myocardial damage, which can be documented by two-dimensional echocardiography, serum markers, and myocardial necrosis; the clinical relevance of this is uncertain at present. Possible triggers of ventricular arrhythmia are hypoglycemia, hypoxia, autonomic nervous system imbalance, and Q–T prolongation; some of them can be identified promptly and treated adequately.

Sources of cardioembolic stroke, whether from coexisting cardiovascular or cardiac diseases, need to be diagnosed early and treated immediately to improve late prognosis, because of the coexistence of cerebrovascular and cardiovascular diseases in almost every second patient. A brain attack can be considered a "warning sign" for future coronary events, and therefore, should be of utmost importance in the network of secondary prevention.

A lumbar puncture for CSF analysis is not necessary in the regular patient who presents with cerebrovascular disease; however, it may be indicated if intracranial hemorrhages are suspected (parenchymal and SAHs as well as cerebral venous thrombosis [CVT]), or if forms of isolated angiitis or systemic vasculitis with central nervous system (CNS) involvement are considered. Biomarkers indicating neuronal damage, inflammatory reactions, apoptosis, or poststroke reorganization tissue-associated activities (e.g., superoxide dismutase) increasingly are targets of scientific interest; however, whether taken from the CSF or from the blood, so far they have failed to influence diagnosis (ischemia vs. hemorrhage separation) and therapeutic decisions (staging of acute stroke development within 72 h) directly. Only a small number of laboratory tests (Figure 5) belong to the routine workup of stroke patients; a second group of tests is available to detect rare conditions, such as coagulation abnormalities, antiphospholipid syndromes, vasculitis, and hyperviscosity syndromes in selected patients. A third, very heterogeneous group of laboratory tests still awaits validation for its clinical usefulness, but at present, is considered as experimental.

The history of George Frederick Handel's stroke may guide us on rehabilitation after stroke, reminding us about the enormous capacity of brain plasticity. Once acute stroke treatment and monitoring on the stroke unit is terminated, continuous physical therapy to improve functional reorganization may be necessary, at least in some patients with good prognosis according to very recent but few fMRI and clinical studies, and often for reintegration in family and local social environments. This issue has not been investigated adequately scientifically, despite huge amounts of money spent on rehabilitation compared to acute stroke treatment costs and secondary prevention measures.

Biological System	Test	Compartment	Method	Significance	Current clinical value
Glucose metabolism	Glucose (fasting, tolerance) HbA1c	Blood, urine, plasma	Hexokinase method chromatography	Vascular risk factor, diagnostic	Routine
Lipid metabolism	Cholesterol, triglycerides HDL/LDL-cholesterol	Blood	Enzymatic and precipitation techniques	Vascular risk factor	Routine
	Lp(a)	Blood	ELISA	Vascular risk factor	Routine
Methionine metabolism	Homocyst(e)ine	Blood, urine	HPLC	Diagnostic	Selected conditions
Antithrombotic systems	AT III, protein C, protein S	Plasma	Chromogenic assays, coagulometry	Diagnostic	Selected conditions
Coagulation and fibrinolysis	Prothrombin time, aPTT	Blood	Coagulometry, photometry	Therapy monitoring	Routine
	FM, FpA, TAT, F1+2 D-dimer, B-β-peptide	Plasma	ELISA	Pathogenic	Selected conditions
Systemic host defense	ESR, WBC, CRP	Blood serum	Westergren, impedance counter method, nephelometry	Investigation of acute phase reaction	Routine
	IL-6, IL-1β, TNF-α sICAM-1, sELAM-1, sL-selectin	Serum Plasma	Nephelometry, ELISA ELISA	Endothelial activation	Selected conditions
Viscosity of blood	Hematocrit, fibrinogen	Blood	Microhematocrit technique, coagulometry	Risk factor, pathophysiological	Routine
	Whole blood, plasma viscosity, cell aggregability	Plasma	Filtration technique, shear-viscosimeter, aggregometer		Experimental
HPA system	Cortisol, ACTH	Plasma	RIA	Pathophysiological Prognostic	Experimental
Immune system	ANA, anti-dsDNA Sm-Ag, Scl-70, ANCA	Serum	Immunofluorescence, RIA	Diagnosis of vasculitis (e.g., SLE)	Selected conditions
	Lupus anticoagulant/ anticardiolipin Abs	Plasma	Coagulometry ELISA	Pathogenetic	Selected conditions
Brain tissue integrity	NSE, S-100 protein	Serum, CSF	RIA	Prognostic	Selected conditions

Figure 5. Synopsis of biological and immunological tests on cerebrovascular diseases.

Convalescence at the hot baths of Aachen brought George Frederick Handel a considerable improvement.

> After a week he could drag himself along, after a second week he could move his arm and with enormous "will power" and confidence, he tore himself out of the paralysis of death, for life to be much more fervent than before with every unutterable happiness, as only the recovered know. As "Hallelujah" boomed out for the first time, there was a great cheer. . .and this was raised again with the last "Amen,". . .the jubilation had scarcely filled the room with applause, he simply slipped away, not to thank the people who wanted to thank him, but rather the grace that had endowed this work.