Role of Stroke in Dementia

AS THE AVERAGE life span increases throughout the world, the medical and social problems of the presenile and senile dementias increase apace. Knowledge about these dementing diseases of middle and late life has lagged, however, and in its absence, speculation about their etiology has grown and even perhaps attained the cachet of reliability. The most attractive hypothesis to both physician and lay person alike has been that most dementia results from disease of the cerebral vasculature. So accepted was this theory that in medical terminology dementia became virtually synonymous with “arteriosclerotic cerebral vascular disease,” and in lay terms, with “hardening of the [cerebral] arteries.”

Several factors prompted the rather general acceptance of this theory. First, as everyone knows, strokes can cause severe disintegration of the highest cerebral functions. Further, every physician knows that atherosclerotic changes are unavoidable with age and thus might conceivably be important in causing the dementias of advancing years. Lastly, progress in understanding and treating vascular diseases has advanced spectacularly in the past quarter century, understandably creating hope that these advances might afford relief to patients with dementia.

There is no doubt that cerebral infarction or hemorrhage, single or multiple, can destroy enough brain tissue to impair the higher cerebral functions. The specific question is whether or not it is justifiable to attribute mostly to strokes those disorders marked chiefly by gradual deterioration in the highest (especially the cognitive) functions, i.e., the dementias. The answer is that the facts do not support this ascription. Evidence to the contrary comes from both clinical and pathological studies.

Clinical Studies

Dementia due to cerebral vascular diseases cannot be differentiated by mental status examination from dementia due to the cerebral degenerative diseases (which may, in fact, inaccurately be labeled “degenerative”). The end-stage mental changes are the same, whatever the cause. The clinical processes, however, are different. A significant body of evidence about these processes comes from those clinicians who have closely and critically followed the course of patients with known cerebral vascular disease and those with identified cerebral disorders such as Alzheimer’s disease. The course of cerebral vascular disease is characteristically marked by abrupt onset (which usually can be dated exactly), remissions and exacerbations, a stepwise or stuttering progression, focal neurological symptoms, and focal neurological signs. On the other hand, Alzheimer’s disease and senile dementia Alzheimer type (SDAT), which are pathologically indistinguishable, are usually characterized by insidious onset which usually cannot be dated with exactness, a slow and inexorably progressive course without acute episodes, and the absence of focal neurological symptoms and signs.

With his characteristic close attention to clinical detail, Fisher concluded some years ago that slowly progressive dementia (without acute episodes or focal neurological symptoms and signs) rarely results from cerebral vascular disease except in the patient with prolonged, sustained hypertension. At the same conference, Paulson and Perrine, on the basis of their studies of chronically institutionalized demented patients, emphasized the infrequency with which dementia due to vascular disease lacked the specific clinical features pointing to vascular disease noted above. More recently Birkett, in a careful clinicopathologic study of a small group also chronically hospitalized because of dementia, concluded that although psychological features could not differentiate multi-infarct dementia from that due to degenerative processes, a sudden onset plus focal neurological symptoms or signs strongly favored cerebral vascular disease.

These studies suggested that thorough clinical evaluation could distinguish multi-infarct dementia from dementia due to primary cerebral degenerative diseases, but the relative importance of vascular versus degenerative processes in the causation of dementia remained unclear. Three recently studied series of patients, admitted to major neurological teaching services specifically for investigation of their dementia, have provided the needed data. These patients were selected because dementia was the predominant manifestation of illness, not an epiphenomenon of already recognized systemic diseases. The diagnostic findings from these 3 series were summarized recently (see table I). The most pertinent data were that the dementia could be attributed to cerebral vascular disease in only 17 (8%) of the 222 patients, whereas in 113 (51%) the dementia was ascribed to atrophy of unknown cause. This atrophy is almost certainly largely due to Alzheimer’s disease (vide infra). In patients evaluated primarily for dementia, therefore, cerebral vascular disease affords an acceptable explanation in only a small percentage.

Pathological Studies

The physician should inquire at this point, however, if these atrophies “of unknown cause” might not in fact be due to unrecognized strokes. The best evidence to the contrary is provided by the meticulous clinicopathological studies of Tomlinson, Blessed, and Roth. These workers reported
Possibly traumatic Intracranial masses specifically characterize Alzheimer's disease result that most "atrophy of unknown cause" are due to diseases dementia than did cerebral infarction. Thus in this group, Vascular disease Atrophy of unknown cause Drug toxicity Dementia uncertain (Creutzfeldt-Jakob disease, Post-traumatic, Thyroid disease, Post encephalitic, Psychiatric disease, Neurosyphilis, Amyotrophic lateral sclerosis, Post-subarachnoid hemorrhage, Parkinson's disease, Pernicious anemia, Liver failure, Epilepsy) 

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atrophy of unknown cause</td>
<td>51%</td>
</tr>
<tr>
<td>Vascular disease</td>
<td>8%</td>
</tr>
<tr>
<td>Normal pressure hydrocephalus</td>
<td>6%</td>
</tr>
<tr>
<td>Dementia in alcoholics</td>
<td>6%</td>
</tr>
<tr>
<td>Intracranial masses</td>
<td>5%</td>
</tr>
<tr>
<td>Huntington's chorea</td>
<td>5%</td>
</tr>
<tr>
<td>Depression</td>
<td>4%</td>
</tr>
<tr>
<td>Drug toxicity</td>
<td>3%</td>
</tr>
<tr>
<td>Dementia uncertain</td>
<td>3%</td>
</tr>
</tbody>
</table>

N = 222.

to prove the negative, but there is little to support this idea. As early as 1954, Arabo reported a lack of correlation between the distribution and density of senile plaques and the distribution of arteriosclerotic plaques in the cerebral vasculature. Because fully developed senile plaques have an amyloid core, it has been suggested that intracerebral depositions of amyloid might provide nuclei for plaque formation. Amyloid deposition in the brain is not a feature of systemic amyloidosis, however, and electron microscopy has demonstrated that nerve terminal abnormalities precede the appearance of amyloid in the development of the senile plaque. Mandybur has described a type of congophilic angiopathy not infrequently present to some extent in Alzheimer's disease, but Alzheimer's disease may be severe in the absence of these congophilic vascular changes. Most authorities agree that vascular disease should not be indicted in the etiology of Alzheimer's disease.

Implications

Granted that the pathological changes of Alzheimer's disease play a more important role than those of cerebral vascular disease in the etiology of dementia, is the distinction between these disorders important at this time? For several reasons, I believe that it is important both to differentiate these disorders clinically and to acknowledge publicly the statistical importance of Alzheimer's disease in the causation of dementia.

First, it is no longer tenable for the physician to diagnose dementia as such but then to forego a diligent search for the causative disease. Thorough diagnostic evaluation of patients with dementia leads to the recognition of potentially correctable disorders in 15% and of disorders which though not correctable nevertheless require specific therapeutic intervention in 20 to 25. Correctable disorders include depression, drug toxicity, normal pressure hydrocephalus, benign intracranial masses, mania, thyroid disease, pernicious anemia, epilepsy, hepatic failure and other chronic metabolic disturbances. Non-correctable disorders include multi-infarct dementia due to hypertension, malignant brain tumors, alcoholism, normal pressure hydrocephalus, neurosyphilis, and Huntington's chorea. Metabolic diagnostic study is required, therefore, to uncover disorders that call for specific therapeutic intervention.

For the remainder, the wastebasket diagnosis of "arteriosclerotic cerebral vascular disease" no longer suffices. Dementia due to vascular disease can usually be recognized on clinical grounds. Hachinski and coworkers proposed an ischemia score derived from clinical evaluation which they used to separate "multi-infarct dementia" from "primary degenerative dementia." Although their ischemia score requires study in a larger number of patients (and perhaps further refinement), it exemplifies the sort of attention to detail which now should be afforded all patients with dementia. Patients with "primary degenerative dementia" should be diagnosed provisionally as Alzheimer's disease, because the vast majority of such patients will be shown to have Alzheimer's disease on pathological examination.

From a research standpoint, it is also important that the significance of Alzheimer's disease be recognized. Katzman and Karasu estimated, for example, that senile dementia Alzheimer type is the fourth or fifth most common cause of

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Number</th>
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<tbody>
<tr>
<td>Senile dementia Alzheimer type (SDAT)</td>
<td>25</td>
</tr>
<tr>
<td>Arteriosclerotic dementia (AS)</td>
<td>6</td>
</tr>
<tr>
<td>Mixed SDAT and AS</td>
<td>4</td>
</tr>
<tr>
<td>Probably AS</td>
<td>3</td>
</tr>
<tr>
<td>Probably mixed SDAT and AS</td>
<td>5</td>
</tr>
<tr>
<td>Unclassified</td>
<td>5</td>
</tr>
<tr>
<td>Wernicke's encephalopathy</td>
<td>3</td>
</tr>
<tr>
<td>Possibly traumatic</td>
<td>1</td>
</tr>
</tbody>
</table>
death in the United States, yet there is virtually no acknowledgment of its importance or even mention of it in vital statistics. When a patient dies with SDAT, the immediate cause of death (pneumonia, sepsis, etc.) rather than the underlying disease is usually recorded — and when the underlying cause is recorded, it is likely to be recorded incorrectly. Thus there is no widespread recognition of the role of Alzheimer's disease among the dementing diseases afflicting our population, and consequently research in its cause and treatment has lagged.

There is little cause to hope that a fuller understanding of cerebral vascular disorders, as important as that is, will elucidate the nature of Alzheimer's disease. The specific microscopic pathologic changes — senile plaques, neurofibrillary tangles, granulovascular degeneration — bear no predictable relationship to vascular changes. To the contrary, much accumulated evidence suggests that the study of genetic, toxic, biochemical, and possibly infectious factors offers more hope of unravelling the mysteries of the primary dementias than does the study of strokes and their causes. Recognition of the costs of these primary dementias both in terms of human suffering and in economic resources should lead to the allocation of a significant proportion of our research energies to their investigation.

Everything leads, therefore, to the conclusion that cerebral vascular disease is not the major cause of the commonly encountered dementias of middle and late life. Alzheimer's disease, whether senile or presenile, is the major culprit, and it must be recognized and studied sui generis. This does not, on the other hand, imply that cerebral vascular disease is not the major cause of the commonest dementias than does the study of strokes and their causes. Recognition of the costs of these primary dementias both in terms of human suffering and in economic resources should lead to the allocation of a significant proportion of our research energies to their investigation.

References

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