PREVENTION OF SENILE AND PRESENILE DEMENTIA BY BISHYDROXYCOUMARIN (DICUMAROL) THERAPY*

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ABSTRACT: Research data from many sources appear to confirm the theory that circulatory insufficiency of the brain plays a major role in the development of senile and presenile dementia. This insufficiency is probably caused most frequently by sclerotic narrowing of the arteries supplying the brain combined with blood sludging or thrombosis in the arteries, capillaries or veins. Experience gained thus far from therapeutic trials in a small number of patients indicates that progression of the dementia can usually be arrested at once by the use of bishydroxycoumarin (Dicumarol). In some patients there has been worthwhile improvement in mental status. These findings suggest that for many patients, early treatment with Dicumarol may prevent progressive mental deterioration, and thus put senile dementia in the category of a preventable disease.

Research conducted over a period of more than five years has thus far confirmed an earlier hypothesis that senile and presenile dementia result primarily from an insufficient supply of blood to certain parts of the brain. From the data obtained it would appear that bishydroxycoumarin (Dicumarol) can prevent further reduction of this diminished blood supply and thereby arrest the dementia process. In some cases the effects on cerebral blood flow of administering and then withdrawing Dicumarol resemble the effects of turning on and off a water faucet, except that several days are required to see the results. In most cases, however, the effect is not so dramatic; it is merely a matter of maintaining the blood flow by preventing further clogging of the "pipes."

It is the purpose of this paper to explain the theories and factors involved and to present supporting evidence. Most of this evidence is in the form of references carefully chosen from the large number in the medical literature. Each reference provides observations and facts to support the ideas being discussed. Included are my own observations on patients with senile and

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presenile dementia in studies in which these principles were put to the therapeutic test.

The use of an anticoagulant drug to arrest the progress of senile dementia evolved from the successful use of bishydroxycoumarin in preventing strokes. In 1955, Millikan et al. (1) of the Mayo Clinic first reported the value of Dicumarol in cerebrovascular disease. This was a logical approach to the problem since, according to Boyd (2), the pathologist, 85 per cent of strokes are due to coagulation of the blood. The practicality of this approach was illustrated in my general practice when it became apparent that my patients who were prone to recurrent strokes stopped having them while being treated with Dicumarol (3).

It then occurred to me that this blood clotting might also cause the mental deterioration that often accompanies repeated strokes. And since such mental deterioration sometimes precedes the motor symptoms, it seemed logical to assume that mental deterioration alone—that is, dementia—could also be caused by blood clotting. In other words, dementia could be thought of as a "mental stroke." It should follow that if anticoagulant therapy prevents motor strokes, it should also prevent the mental equivalent—dementia. The hypothesis was as follows: senile and presenile dementia are due to clotting of the blood in the vessels supplying the mental areas of the brain, and prevention of further clotting by use of an anticoagulant drug should arrest progression of the dementia (4).

This hypothesis was borne out by the very first patient with progressive senile dementia to be treated with Dicumarol. In January 1963, a 66-year-old woman was brought to see me by her daughter, who was a registered nurse and the wife of a surgeon and hence aware of the implications of anticoagulant therapy. The patient's illness began in 1960 with very minor spells of confusion. Over the next few years her memory and reasoning power gradually became worse. At the time I saw her she was unable to use the bathroom, to dress herself or to light her own cigarette. A pneumoencephalogram had shown brain atrophy, and the neurological consultant predicted progressive deterioration. The daughter was starting to make arrangements to place her mother in an institution. In an attempt to avoid this I suggested a trial of treatment with Dicumarol to see if further deterioration could be prevented. Much to our surprise Mrs. N. improved. In two months she was able not only to perform her own personal hygiene but also to resume her meticulous needlepoint work. The anticoagulant was continued for the remaining one and a half years of her life, during which time she was able to live at her own home, by herself most of the time, and even do some of her own interior decorating. She died in August 1964 within twenty-four hours of the onset of myocardial infarction.

Several interesting details about Mrs. N's background are worth noting: she was an intelligent and fastidious woman, a school teacher and the daughter of a former United States senator. Her mother suffered from simi-
lar brain deterioration relatively early in life, and died at age 62 after a fracture of the hip.

A second patient, on whom there was autopsy proof of Alzheimer's disease, also responded to anticoagulant therapy. He was a 56-year-old lawyer, engineer and successful executive. His first symptoms were the forgetting of his secretary's name and an inability to sign checks without practicing his signature ten times. For several years he deteriorated progressively, until he became unmanageable at home and was admitted to our hospital preparatory to going to a State institution. While being treated with Dicumarol he was cooperative, able to go to the cafeteria, had no spells of confusion or collapse, and did not need a constant attendant. However, on four occasions the Dicumarol was stopped, and each time his mind deteriorated noticeably; as soon as the prothrombin time returned to normal he became more confused, uncooperative, combative and subject to spells of collapsing on the floor. Each time Dicumarol therapy was resumed, he improved. After it was discontinued for the last time, upon admission to the State hospital, he soon became bedridden and died within two months. This man had so much permanent brain damage before treatment was begun that even in his best state of improvement he was never well enough to be cared for at home.

This repeated improvement with anticoagulant medication and relapse without it is the counter-proof method of testing a hypothesis, as discussed by the famous French physiologist, Claude Bernard (5). It should be emphasized that because deterioration does not always follow withdrawal of anticoagulant therapy, this does not necessarily mean that the anticoagulant was not the cause of the improvement; sometimes there seems to be a "coasting effect" whereby the improved flow of blood resulting from therapy creates a momentum which prevents the blood from clotting or resludging even after treatment is stopped. The increased activity of some of the patients during therapy, also likely contributes to a better flow of blood with less chance of thrombosis.

STATISTICAL RESULTS

These two illustrative cases, reported in detail elsewhere (6), are from a total of 30 treated since 1959. The first group of 17 cases were of mixed diagnoses—some showing motor, some psychological, and some both types of deficits. In none of these patients was there serious progression of the symptoms during Dicumarol therapy, and some were treated for eight years. Significantly, some patients deteriorated severely after treatment was stopped, and improved when it was resumed.

The second group consisted of 13 mental-hospital cases of senile and presenile dementia treated with Dicumarol during the period April to July, 1967, and reported elsewhere in detail (7). Once again no patient deteriorated during treatment. In fact, 10 of the 13 showed improvement: 1 became well enough to be discharged, 1 became continent and able to feed
herself, 2 others also became able to feed themselves, and 7 no longer needed
the major tranquilizer. It is noteworthy that after the Dicumarol was dis-
continued 8 patients deteriorated—3 to the point of death.

RELATIONSHIP OF DEMENTIA TO ORGANIC BRAIN DAMAGE

To understand better why anticoagulant treatment can be effective, it is
pertinent to consider how dementia might develop following damage to brain
tissue. The normal person appears to perform any task by the orderly asso-
ciation of impulses from multiple areas of his brain. Each area supplies an
element necessary to that particular mental process, as discussed by Freud
(8) in his book on aphasia. Thus the simple act of writing a thought on
paper involves the use of many different areas of the brain: 1) to perceive
the pen as an object; 2) to recognize it as a pen by memory association;
3) to initiate and develop the thought to be written; 4) to change this
thought into words; and 5) to perform the motor action necessary to put
the words on the paper with the pen. Hence damage to any one of many
areas of the brain will upset the essential orderliness of these multiple
associations. This damage may involve only as insignificant detail such as
inability to remember a specific word, for which the mind may easily sub-
stitute a synonym or neologism. However, an essential function may be de-
stroyed, such as the ability to recognize the pen, and this will frustrate all
the subsequent associations needed to write the word on the paper. The
anticoagulant acts by preventing the tissue damage—the villain that inter-
rupts the association pathways.

This concept could explain the frequent finding of a puzzling discrepancy
between the degree of brain atrophy and the degree of dementia, as noted
by Corsellis (9). He suggests that this discrepancy may be due to some un-
known morphological change, but more likely it is due to functional changes
which are not manifest at autopsy. There are three main possibilities:
(a) the site of the damage rather than its extent may be more important;
(b) the patient's emotional reaction to the damage, e.g., severe anxiety,
depression or paranoia, as discussed by Brosin (10), may overshadow other
symptoms; and (c) sludging of the blood, which also is not visible at autopsy,
may reduce the blood supply to key areas of the brain, destroying their
function but not their cells.

PRESENIILE DEMENTIA

The preceding discussion of the role of inadequate blood circulation to
the brain may seem quite logical in regard to senile dementia, but the ap-
lication to presenile dementia is more obscure. In presenile dementia there
is not enough cerebral arteriosclerosis to account for the atrophy of the
cortex. To help in clarification, it may be useful to regard the brain as a
fifth extremity—the two hands, the two feet and the brain. The hand has
the brachial artery and the foot has the femoral artery, but the brain has
four arteries—two vertebral and two internal carotid. Not only that, but these
four arteries join at their distal ends in the Circle of Willis, forming an "irrigation pool." Thus if one of these four arteries is blocked, the "pool" usually is still supplied with enough blood from the remaining three vessels. Research has proved, however, that often a thrombosis in an internal carotid artery can cause hemiplegia by producing ischemia of the motor areas supplied by the middle cerebral artery. If, in addition to the carotid obstruction, there is an anomaly of the collateral circulation which results in ischemia of the prefrontal lobe, then mental symptoms will result. Similarly, ischemia of other nonmotor areas—such as the occipital or temporal lobes—could easily interfere with the complicated association pathways necessary for normal thought processes and thereby cause dementia.

That such mental disturbances can occur as a result of thrombosis is well documented in the literature. One of the most instructive examples is the case reported by Palmer (11): A 62-year-old salesman suddenly became confused and unable to read the menu or find the bread on the table. Despite personality changes he recovered enough to continue his work, but eighteen days later he suddenly became confused again, with a jargon type of aphasia. That same night, a right hemiplegia developed. The patient died two weeks later. At autopsy an old infarction on the right side of the cerebrum and a more recent one on the left side corresponded in developmental age with the onsets of the two separate sets of symptoms.

**STENOSIS OF THE CAROTID AND VERTEBRAL ARTERIES**

It is important to realize that stenoses of the vertebral and internal carotid arteries are very common occurrences. In 40 per cent of people over 50 years of age there is severe narrowing of one or more of these vessels, according to Chusid (12). Further evidence is supplied by Hutchinson and Yates (13), who performed autopsies on 83 patients with cerebrovascular disease and found such extensive narrowing of the vertebral and internal carotid arteries that they considered these four arteries to be a physiological unit and labeled the pathological condition "carotico-vertebral stenosis." The occurrence of thrombosis or blood sludging beyond a stenosed area will reduce the flow of blood into the Circle of Willis, and could thereby cause serious ischemia of various areas upon the brain. The exact site of this ischemia would depend upon the collateral circulation beyond the stenosis. In a certain number of people, only the mental areas of the brain would be affected—giving rise to dementia.

The connection between arterial stenosis and brain atrophy has been overlooked because sometimes there is no brain atrophy despite the presence of gross arterial stenosis. The explanation for this seemingly paradoxical situation appears to lie in the sparing of the brain in such patients by an adequate collateral circulation. This is dramatically demonstrated in the case recently reported by Hardesty (14). In this 56-year-old carpenter an arteriogram showed that all four neck arteries were occluded, yet he suffered only a minimal neurological deficit. Most people cannot be so fortunate and will
incur various degrees of brain damage, some of which will become manifest as dementia.

The occurrence of presenile dementia, then, depends upon the chance combination of several factors: arterial stenosis, thrombosis, blood sludging, anomalies in the collateral circulation, and the emotional reaction of the patient to his brain dysfunction. The predisposing factor appears to be arterial stenosis, and the precipitating factor is vascular blockage.

The relationship of the dementias to arterial obstruction is no longer mere conjecture. There is now much evidence of the close association between cerebral arterial insufficiency and senile or presenile dementia. Miller Fisher (15) in 1951 reported on the frequent association of thrombosis of the internal carotid artery with senile dementia. Many other reports—Hutchinson and Yates (13), Williams and Breutsch (16), Humphrey and Newton (17), Shapiro (18), Clarke and Harrison (19) to name only a few—make the total evidence in favor of arterial insufficiency as a cause of dementia almost overwhelming. Two Scandinavian investigators, Ask-Upmark and Fajers (20), in their study of the unusual arterial stenosis in young people called Takayashu's syndrome, discovered brain damage similar to that found in Alzheimer's disease, and suggested that this relationship be explored further. Thus, when all the factual evidence is considered, there seems to be little reason to doubt that thrombosis in the extracranial arteries can cause dementia.

VEINS OF THE BRAIN

In some patients, no lesions can be found in the arteries which supply blood to the brain. What can be the role of thrombosis or blood sludging in such patients? Three hundred years ago William Henry observed that "no part of the body is so full of veins as the brain" (21). Nature must have a reason for supplying the brain with such an abundance of veins; they must contribute to the free flow of blood so vital to the full function of the billions of nerve cells. What happens when these brain veins become blocked? In other parts of the body we often consider vein blockage to be unimportant; veins are cut and tied with impunity during most surgical procedures because we are confident that there are other channels for the blood flow. Have we perhaps uncritically transferred this knowledge to the area of the brain, hence neglecting the importance of vein patency to the maximal efficiency of all those brain cells?

This relationship between brain function and the patency of the venous channels of the brain might profitably be re-examined with an open mind. A good way to begin would be to examine carefully the symptoms and pathological changes that occur when the veins are blocked. This is done in a recent book on cerebral venous thrombosis by Kalbag and Woolf (22); they also furnish many references to reports in the literature on the subject. It is evident how important normal venous blood flow is for full function of the brain. Moreover, sometimes the symptoms we consider due to arterial
obstruction are really due to venous obstruction. Obstruction of the main intracranial venous sinuses and cerebral veins can cause severe brain damage. The implications are extremely important:

1. Veins often are subject to thrombosis under many different conditions.
2. Anticoagulant drugs may be effective in preventing such venous thrombosis.

Consequently we now can explain some hitherto inexplicable diseases of the brain, and also often can prevent such lesions from occurring or at least from progressing, by means of anticoagulant therapy. Indeed, Kalbag and Woolf (22) stress the importance of early diagnosis and anticoagulant treatment for patients with intracranial venous thrombosis. Apparently senile and presenile dementia sometimes may result from venous thrombosis inside the skull.

BLOOD SLUDGING

The preceding evidence explains the mechanism by which anticoagulant therapy (Dicumarol) may prevent the progression of dementia—by arresting the thrombotic process in the arteries and in the veins supplying the brain. But how can we explain the improvement in some patients? The phenomenon of blood sludging appears to provide the answer: the arterial lumen at the site of stenosis may be only a few millimeters in diameter; beyond this point the blood flow is sluggish and turbulent, with a tendency for the cells to form clumps. The importance of such cellular aggregation has been emphasized for over twenty years by Knisely (23) who descriptively called it "blood sludging." This thickened blood cannot flow freely through the distal capillaries, with the result that some of the brain cells are prevented from functioning normally because of inadequate blood supply. This is the probable cause of delirium, which may be considered as a temporary interruption of association pathways. Anticoagulants, as shown by Knisely et al. (24), Meyer (25) and others, can break up this sludging. Thus it is reasonable to expect these drugs to improve the circulation, and hence brain function; this would result in relief of the delirium.

My theory is that dementia patients who improve with anticoagulant therapy do so because some of the brain damage is reversible, is due to blood sludging and is relieved by the treatment. That anticoagulants can have a significant effect on the circulation to the brain in some patients is well documented by the report of Baker et al. (26) on the excellent National Cooperative Study of the Anticoagulant Therapy of Cerebral Infarction. Among 44 patients with transient attacks of cerebral ischemia, the untreated controls had 547 attacks of ischemia whereas those treated by Dicumarol had only 25 attacks! That the physical qualities of the blood can affect the functioning of the brain is well illustrated in 3 case reports by Gelin (27). One of his patients is of particular interest: A 61-year-old
worker suddenly became blind in his right eye and had paresis of his left hand and arm. Intravenous infusion of low-molecular-weight dextran\(^1\), a desludging agent, brought immediate improvement. The symptoms recurred after six hours but were relieved by a second infusion. An angiogram then showed an occlusion of the internal carotid artery. Thromboendarterectomy was performed eighteen hours after onset and resulted in full restitution of vision and hand power. Besides being strong evidence that blood sludging can affect brain function, Gelin's experiences indicate that other agents besides anticoagulants may be therapeutic.

ANTICOAGULANT THERAPY

The selection of patients for anticoagulant therapy and their subsequent supervision should be done very carefully. The dangers of treatment have to be weighed against the prognosis without treatment. In senile dementia this prognosis usually is very poor. In Alzheimer's disease it is even worse—according to Busse (28), the life expectancy is two to five years, during which time deterioration is progressive. The incidence of hemorrhagic complications in patients receiving long-term anticoagulant therapy for cerebrovascular disease is 3 per cent per year, according to Toole and Patel's (29) recently published textbook. In view of these findings, we should not be overly fearful of a trial of anticoagulant therapy. Rather, we should keep in mind the thought expressed by Vigran (30) in the preface to his book on anticoagulant therapy: as much responsibility may be involved in withholding as in administering anticoagulant therapy.

Thus far, the anticoagulant I have used in the treatment of senile dementia has been Dicumarol. Baronofsky and Quick (31) showed it to be more effective in vitro than heparin in preventing platelet aggregation. This may mean that in clinical practice different anticoagulants will vary in their effectiveness. Such a possibility is reinforced by the findings, of Spooner and Meyer (32) that Dicumarol does reduce platelet adhesiveness, which may be the most important precursor to vessel plugging (33). The dosage of Dicumarol is that required to keep the prothrombin time at two to two and a half times the control value—the same level as generally used for heart patients. This dosage usually averages 25 to 50 milligrams daily. Lifetime treatment may be necessary in most patients. Only further experience will answer that question.

SELECTION OF PATIENTS FOR THERAPY

The number of patients thus far treated has been relatively small but some guidelines are emerging to help in predicting the results of treatment, as noted in a previous paper (7). Patients with long-standing and severe brain damage are not suitable candidates for anticoagulant treatment because the risks would outweigh the possible benefits. For example, the first

\(^1\) Rheomacrodex, Pharmacia Laboratories, Piscataway, N.J.
patient shown to me at one State hospital was a 90-year-old woman who had been there for twenty years; she was cachectic, bedridden in the fetal position, and had said only the word "sweet" for five years. We cannot hope to revive brain cells that are dead, and prevention of further deterioration in this patient would have been of little benefit to her. In fact anticoagulant treatment would only expose her to the danger of a hemorrhage, which might make her suffer more disability or even death.

The longer the deterioration has been present the more likely are the cells to be dead. Nevertheless many patients with symptoms dating back five or six years may still benefit from long-term anticoagulant treatment. Some of their brain cells, although recently subjected to diminished circulation, may be viable; revival of these cells could produce some improvement in the clinical picture. For the patients, this could mean return of recently lost control of the bowel and bladder and the ability to feed themselves, which would make their lives more pleasant and their care easier. Also in this group will be patients deteriorated almost to the point of incontinence and loss of self-care ability, for whom anticoagulant treatment would be beneficial by preventing the future loss of these important functions.

The most benefit from treatment would be expected to occur in those patients who show a minimum of brain dysfunction, of very recent onset. This is a logical expectation in view of the pathological, physiological and therapeutic principles involved. The problem is: How do we know which patient will not deteriorate further even if left untreated. An example is Hardesty's (14) patient who lived fifteen years after his first symptom before requiring arterial surgery. Blood clotting in live vessels is an unpredictable phenomenon—it may happen tomorrow, in five years, in ten years, or never. But it does happen to thousands of patients, few of whom are as lucky as Hardesty's patient who survived almost unharmed the thrombotic occlusion of both internal carotid arteries and both vertebral arteries. Even this man, however, would likely have been disabled at last, at age 56, had not arterial surgery been performed by Dr. Hardesty on a stenosed external carotid artery.

Several of our patients with diabetes and recent mental deterioration have shown the most rapid improvement. This may be because diabetes is associated with blood sludging as well as with excessive arterial degeneration. One patient (A.M., reference 3) responded rapidly and was discharged from our psychiatric institute after three weeks of Dicumarol therapy; there was no relapse upon discontinuance of treatment.

Satisfactory results also may be expected in the type of patient who has repeated bouts of confusion, like "little strokes." These attacks disappear as long as the prothrombin time is kept within the therapeutic range.

Important as it is, the prevention of deterioration unaccompanied by improvement is not dramatic. Both the physician and the patient would rather see a total cure. We ought, nevertheless, to train ourselves to visualize each patient from one to five years in the future. In what condition will
he be then? Alert, active and self-dependent or incontinent, disoriented and helpless? We might call this the "Rip Van Winkle test," as in our minds we condense several years to one day, thereby exaggerating the changes which otherwise occur too gradually to be noticeable. Or it might be called the "Alumni Dinner Test"; side by side are the older, grayer, slower doctors presenting prizes to the dark-haired eager, agile brand-new M.D.'s, and thus we can see dramatized the changes which pass unheeded year by year. It is imperative to realize that changes are going to occur, and we must decide, with the patient or his relatives, whether or not these changes are sufficiently threatening to warrant the risk of anticoagulant therapy.

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REFERENCES