Senile Dementia - A Report on the Anticoagulant Treatment of Thirteen Patients

This study indicates that this form of therapy can be a practical procedure in a large hospital if a minimum of extra facilities is supplied.

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Thirteen patients with senile dementia were treated by anticoagulant therapy in a large state hospital over a two and one-half month period. Although this was a pilot study, preparatory to treating a larger group with controls, the results were so favorable (TABLE I) that they are worth reporting at this time. In addition, the outlining of the problems encountered in anticoagulant therapy in this setting might be of value to other physicians wishing to try this form of treatment in patients suffering from a disease which carries a hopeless prognosis and heretofore had no specific therapy.

The rationale for the use of an anticoagulant in patients with senile dementia is fully discussed in a recent article in which I proposed that senile dementia (using the term to include chronic brain syndrome due to arteriosclerosis, senile dementia, presenile dementia, and Pick's disease) was due to arterial insufficiency of the brain which resulted from sludging or clotting of the blood in stenosed intracranial or extracranial arteries. This hypothesis was based on previous successful experiences with anticoagulant therapy in patients having recurrent strokes and transient ischemic attacks and on the fact that 40 percent of the people over fifty years of age have significant narrowing of the main arteries to the brain. It was postulated that we might expect anticoagulant therapy to be helpful in senile dementia. To test this theory a large group of patients would have to be treated and compared to untreated controls.

Before embarking on such a program it was felt that a pilot study should be done to answer two questions:

1. Can we demonstrate any beneficial effect on patients with senile dementia by treating them with anticoagulants? If not, there would be no purpose in treating a large group with controls, which would involve considerable time and expense as well as risk to the patients.

2. What are the practical problems of anticoagulant therapy in this group of senile patients in a large mental hospital?

With these two goals in mind, thirteen patients were selected from the New Admissions Building of Woodville State Hospital, Carnegie, Pennsylvania. They were chosen from the two male and female wards which admitted mostly patients over sixty-five years of age and hence were populated almost entirely by patients diagnosed as having "chronic brain syndrome due to arteriosclerosis." Such wards were ideal for the project now to be described, since the patients were localized and easily treated.

A satisfactory answer to both questions was found.

Selection of Patients

Each patient was interviewed; his chart, including the physical examination, was reviewed; a relative was interviewed to discuss the treatment and obtain the detailed history of the illness; the records of previous hospitalization with pneumoencephalograms, consultant reports, etc. were studied when available. All this I did personally to insure as standard a selection of patients as possible.

Indications for Admission to the Treatment Group

I chose patients who were most likely to show noticeable improvement in the short period of six weeks allotted to their therapeutic trial. This involved using various criteria not yet clearly defined, such as:

Younger age group with more hope of recovery of useful function: Seven patients had their onset of illness before age sixty. Six were under age sixty-five at the time of this study.

Recent deterioration: Many of these patients we would expect to continue deteriorating relatively rapidly so that the effectiveness of the anticoagulant treatment in stopping this deterioration should be more readily observable. In addition, some of these patients will show improvement back to their condition prior to their most recent episodes of deterioration. In a way most of the thirteen patients were in this category since they all had been able to carry on at home or in another institution until further deterioration in their behavior necessitated admission to a mental hospital. Some, however, had been waiting a long time for admission.
and three had been in Woodville for over ninety days. But the fact that during the three month period of observation death occurred in three patients in the group and in two other patients on the ward shows that we were dealing with a group of patients with a progressive condition. In the chronic wards of the hospital it might be different: most of the patients might show no deterioration over a three month period and there could well be no deaths.

Delirious type of behavior: These patients were rather seriously confused so that they did not know how to dress, how to use the bathroom or feed themselves. It was felt that this was a reversible state compared to the delusional patient who thinks he is still at work or living in a club, but can still tend well to his personal hygiene, finding the bathroom and feeding himself, even though he never remembers the nurse’s or doctor’s name. Five patients were in this category.

Contraindications for Admission to the Treatment Group

There were other factors in the selection of patients, such as omitting those with medical contraindications to anticoagulant therapy, especially those with bleeding tendencies. Patient # 3 was taken off therapy after thirteen days because he was so frail, so unsteady and apt to fall, and had a hemoglobin of only ten grams; injury probably would have been fatal for him. In retrospect he should not have been included in this study; but, as it turned out, after the therapy had been discontinued for six days he died, so perhaps we should have taken a risk and kept him under treatment longer—his hemoglobin actually increased during therapy.

In addition to the above medical contraindications we had to omit any patient whose relatives would not consent to a trial of treatment and sign the necessary permission form indicating that they were aware of the risk of hemorrhage involved in the use of the anticoagulant. Only two patients considered for the study were omitted on this account. One because the wife did not want any “experiments” on her husband. He was a severely ill old man, falling many times on the ward because he was so confused and weak. He died within one week of admission. The relatives of the second patient were so fuzzy about the danger that I felt dealing with them would be too strenuous and represent too much of a legal hazard. Patient # 13 should have been rejected for the same reason; her husband’s fearful attitude resulted in the patient’s receiving too little anticoagulant to constitute a genuine trial of therapy. She showed no improvement.

Method of Proceeding with the Study

Two and one-half months were to be devoted to the selection and treatment of patients. After selection, anticoagulant therapy was to be started and continued to the middle of June, a period of about two months of treatment. Therapy in some patients was stopped earlier, some new patients were included later in the series, and a few patients were continued on anticoagulant therapy beyond the proposed cut-off date.

The patients were observed during and at the end of therapy for the assessment of any changes in their condition. Two weeks after treatment was terminated they were again checked and thereafter at weekly intervals to note any changes.

Anticoagulant Medication

Dicumarol® * was used because it is a drug with which I am familiar, because it may have a better effect than other anticoagulants in relieving platelet adhesiveness 4 and because it is the anticoagulant used successfully in the initial study. 5 Only the 50 mg strength was used, patients who could not swallow the capsule were given the powder from the capsule suspended in fruit juice. The dose was regulated to keep the prothrombin at two to two and one-half times the control time.

Problems Encountered and Their Solution

Laboratory Problems

The patients were grouped for the taking of blood to reduce the work of the technicians and to reduce the time lost between the taking of blood and performing of the test. We recorded the control time, prothrombin time, the percentage of prothrombin activity and the dose of Dicumarol on one sheet for each patient so that the data was available at a glance. Ideally the test results should be back by 10:00 or 11:00 A.M.; we received them by noon or 1:00 P.M., because of the extra work load thrown upon the laboratory. This problem could be solved by extra personnel and better transportation between buildings. Some days the patients would not receive their medication until 2:30 or 3:00 P.M., which meant that they did not reflect the full activity of the Dicumarol in the next day’s prothrombin time. This may have been one of the reasons it took so long to stabilize the dose of anticoagulant and space the blood tests to once a week. Not being able to obtain prothrombin times on Saturday and Sunday also made it more difficult to obtain quick and adequate control of the prothrombin time but did not basically interfere with the treatment. Ordinarily by the end of two or three weeks the prothrombin time would be needed only once a week. Later it would be needed only once every three or four weeks. This would considerably reduce the work load of the laboratory and the needle punctures for the patients. There was a breakdown of laboratory equipment towards the end of June so that control was lost and treatment terminated in four patients in whom it had been decided to continue treatment beyond the prearranged cut-off date. Such an event could be forestalled by having extra equipment available or by having an arrangement whereby the test could be done by another laboratory. In the early weeks of treatment daily prothrombin times are essential to the safe and adequate control of anticoagulant therapy.

Ward Problems

Standing orders for the nurse to follow in case of hemorrhage were posted

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* Eli Lilly & Co.
on the ward. The antidote, Vitamin K-1 tablets and ampules, was readily available on the ward but was never needed: there were no hemorrhagic complications though several patients had open ulcerations and one had some bleeding from an anal fissure.

Swallowing the medication was difficult at first for many patients, necessitating emptying the powder from the capsule into fruit juice. Some of the powder stuck to the sides of the cup so that the patient would sometimes not receive the exact dosage, especially when 25 mg had to be estimated. This also may have contributed to our inability to achieve rapidly a level dose of Dicumarol.

Despite the fact that some of these patients were very weak and appeared as if they might fall any minute, no accident occurred. This may indicate that I was more apprehensive than necessary or simply that we were lucky, for even with the careful watchfulness of our attendants it was impossible for them to be with each patient every minute of the day. It should be noted that when the patient has had the full influence of the anticoagulant he often becomes much steadier on his feet so that the chances of falling actually become less as treatment progresses; but the danger from falling increases.

Assessment of the Mental Function of the Patient

This was a difficult and crucial problem. It was done in several ways:

1. Psychological Tests: The Grade Assessment Questionnaire (GAQ) as described by Whitman was administered to all patients by a psychologist at the beginning of the study and after the effects of anticoagulant therapy had worn off. These were rather simple questions such as: What is your name?, What is your address?, Who is President of the United States?, etc. The patients ranged from those who could answer all questions to several who could answer none of the questions. This type of test is not likely to be of much value over the short term that these patients were treated but over a period of a year it could prove to be a very useful and easily administered test.

2. Nursing Staff Observations: The opinions of the ward personnel in close contact with the patients were obtained from personal conversation as well as from notes on the chart. Some changes were especially noteworthy: lessening or cessation of incontinence, regaining the ability to feed oneself, increased ability to follow directions and a lessening in the degree of restlessness.

3. Physician's Clinical Impression of the Mental Status: This I did myself by checking the patient's ability to reason, to converse, and to do simple tests such as the finger-nose test, the counting of fingers and naming of objects.

4. Relatives' Opinions: These were solicited by myself on visiting days or by telephone. When the relatives noticed improvement, it was usually after we had detected it ourselves but sometimes they would notice subtle changes such as the patient's ability to use friends' names which he had not used for a long time or to perform some small task, such as peeling a banana, which he had not been able to do for a long time. Sometimes the relatives noticed no improvement, but we observed that the patient was less restless and able to co-operate better on the ward, even though his tranquilizer had been reduced or stopped entirely.

5. Social Workers' Observations: Social service workers assessed some of the patients before, during and after treatment by interviewing patients on the ward or by talking with their relatives. This information was not available on all patients, but was sometimes valuable as corroboration of other information.

6. The Amount of Major Tranquilizer Required to Keep the Patient's Behavior Manageable: As the patient seemed less confused, less disoriented and more co-operative his medication was reduced. One finding here was that the patients were all on a tranquilizer on admission and no one had tried reducing the dose to see if it was still needed. Nevertheless, most of them really did need it and some indeed had been on a larger dose before admission. Some patients in whom I reduced the dose had to have it increased again.

7. The Effects of Other Medications Taken by the Patient: This could only be assessed by the clinical judgment of a physician. Tranquilizers, hora somni sedation, digitalis, and anti-diabetic medications were among those encountered. Judging the effect of an intercurrent infection, the onset of atrial fibrillation or a high blood sugar could only be made in the light of medical experience, but these decisions were not commonly crucial to the project and were well enough controlled and assessed so as not to affect the statistical findings here reported. It is a very important area of study, though, and could be a source of considerable error in assessing the results of treatment.

Comments on Problems Encountered

We had no problem that could not be overcome with ingenuity and extra effort. There were no bleeding problems but this was a small, short series and in a larger series over a long period of time, there would likely be some serious hemorrhages.

Perhaps more patients who are weak and in danger of falling should be given the benefit of a trial of therapy anyway, for it is likely that this type of patient will very soon become bedridden and die without it and may be much more comfortable and more easily cared for while taking an anticoagulant.

The Results of Treatment

TABLE I summarizes the results in thirteen patients with senile dementia treated at Woodville State Hospital with anticoagulant therapy. It is noteworthy that no patient deteriorated while under treatment and that three patients who had been improving died shortly after therapy was discontinued. It is possible that these patients would have died anyway, but the fact is they improved on anticoagulant therapy and probably would have remained alive under treatment. Tending to confirm this impression was an accidental control which was introduced into the series in the form of a patient who was admitted to the ward while the study was under progress but whose wife refused permission for anticoagulant treatment. He was dead within a week of admission. Judging from previous experience, this patient would have responded to anticoagulants by ceasing to deteriorate, would have resumed his deterioration after the anticoagulant had been discontinued and have died within a week after discontinuation of therapy. It would appear, even in this small, short study, that Dicumarol does indeed prevent mental and physical deterioration in patients with senile dementia.

A point that may be even more impressive than the prevention of deterioration is that eleven patients improved on therapy and that eight of the eleven lost much of this improvement when treatment was stopped. It is true that some of the improvement was minor and required close examination to detect, but it was rather objec-
tively demonstrated in the reduction of the need for major tranquilizers in nine out of the thirteen patients. In fact, in seven patients the tranquilizer was discontinued entirely. Details of this are included in TABLE II. Dramatic and quite objective improvement was seen in several patients: three (patients #8, #10, #11) became able to feed themselves, and one (patient #10) became continent.

Detailed Histories of the Thirteen Patients and Their Assessment Five Months after the Investigation Was Begun

TABLE II was drawn up July 5, 1967 after all patients had been off anticoagulant therapy and their condition reassessed. The latter was done by personal interview with the patient, interview or telephone conversation with a close relative and discussions with ward personnel who had been in close contact with the patient.

There were nine men and four women and their ages ranged from fifty-three to eighty-one. In seven the illness had begun before age sixty. The longest period of treatment was sixty-two days and the shortest fourteen days. Two patients (#3 and #11), in whom the anticoagulant had been discontinued, died before this preplanned assessment date. For them the number of days after treatment was stopped is related to their date of death, not to July 5.

The number of days after treatment was stopped was recorded so that we would know how long after the action of the anticoagulant ceased that deterioration took place. Patient #3 died six days after and patient #11 seven days after the anticoagulant was stopped—that is, shortly after the effect of the anticoagulant was lost. In patient #2, who did not die until five weeks after anticoagulant was stopped, deterioration began in one week.

A short description of each patient and his response to treatment follows. The reader will see from these histories, and should fully consider this fact, that these are severely ill patients. They are in the terminal stages of a long illness in which deterioration, not improvement, is to be expected. The objective of the anticoagulant treatment is not to cure them—it was not expected that they would walk out of the hospital as well persons. Rather the hope was that in all patients the deterioration would be stopped and in a few some improvement would take place: the patient would be more comfortable and more easily cared for. This proved to be the case.

An unexpected and unpredictable phenomenon occurred—some patients continued to improve after the anticoagulant had been discontinued. This I shall refer to as the "coasting effect:" a car parked on a gravel road with a slight downhill slope refuses to start, several people push it and once rolling the car continues to coast down the hill. In a similar way the anticoagulant may stop the sludging of the blood, break up the clumps of red blood cells and re-establish a free, faster flow of blood through the arteries and this regained momentum keeps the blood from resludging despite the discontinuance of the anticoagulant. Whether the blood will sludge again will to a great extent depend upon the presence or absence of the original cause of the sludging. The factors involved in this process have been thoroughly investigated by Knisely. They are rather complex and unpredictable as we shall find from the histories of these patients.

1. J.C.: The patient is a seventy-three year old white male who retired as a professor of metallurgy three years prior to admission and had written textbooks on the subject. His illness started two years ago with confusion and memory impairment following surgery for a hernia. Because of increasing forgetfullness and loss of weight from 185 to 150 pounds his wife took him to a physician on November 29, 1966 for an examination and he was treated with hormones and a vasodilator. In October, 1966 he could still drive his car but by November he did not always recognize his wife and had deteriorated markedly, with delusions that his home was a house of prostitution. He went into a general hospital for tests in November and was transferred to the Western Psychiatric Institute November 30 because he had become unmanageable. On February 8, 1967 he was transferred to Woodville with a diagnosis of "chronic brain syndrome, due to cerebral deterioration (Alzheimer's Disease) and cerebral arteriosclerosis." His prognosis was "very poor." While in Western Psychiatric Institute and Clinic he had to be secluded four times for agitation and confusion, and on one occasion he attempted to break a window and a lamp.

It was planned to include this patient in the series in the beginning but he was inadvertently transferred to another building so he was not begun on anticoagulant therapy till May 3, 1967. At this time he was usually very pleasant, very well spoken but not always making good sense. He could not name the watch hands but could count fingers and remember that I was "Doctor" but not my name. During the interview he became angry about having an identifying wrist band and tore it off later that day. By May 22 he was less restless, slept in the afternoons, and we were able to reduce his Thorazine®* from 75 to 25 mg four times a day. On June 14, he could tell the time and name the minute, hour, and second hands but was still confused as to where he was and why, but he did try to sort things out in his

TABLE II

<table>
<thead>
<tr>
<th>Patient</th>
<th>Diagnosis</th>
<th># Days on Drug Before</th>
<th># Days on Drug After</th>
<th>Time # Days Under or Over</th>
<th>Unable to Feed Self</th>
<th>Incontinent</th>
<th>行走</th>
<th>Active</th>
<th>Unable to Lift</th>
<th>Improved</th>
<th>Deteriorated</th>
<th>New Condition</th>
<th>No Change</th>
<th>Slight</th>
<th>Moderate</th>
<th>Marked</th>
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<tbody>
<tr>
<td>3. J.C.</td>
<td>Senile Dementia</td>
<td>85</td>
<td>53</td>
<td></td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Slight</td>
<td></td>
<td></td>
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<td>4. D.B.</td>
<td>Recurrent Strokes + Senile Dementia</td>
<td>8</td>
<td>39</td>
<td></td>
<td>?</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td>Moderate</td>
<td></td>
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<tr>
<td>5. M.G.</td>
<td>Senile Dementia</td>
<td>14</td>
<td>6</td>
<td></td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Slight</td>
<td></td>
<td></td>
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<tr>
<td>6. W.K.</td>
<td>Presenile Dementia + Reactive Depression</td>
<td>111</td>
<td>42</td>
<td></td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Marked</td>
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<td>7. M.L.</td>
<td>Presenile Dementia</td>
<td>50</td>
<td>46</td>
<td></td>
<td>x</td>
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<td></td>
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<td></td>
<td></td>
<td>Slight</td>
<td></td>
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<tr>
<td>8. M.M.</td>
<td>Presenile Dementia</td>
<td>44</td>
<td>47</td>
<td></td>
<td>x</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td>Little Improvement</td>
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<td>9. G.S.</td>
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<td>24</td>
<td>45</td>
<td></td>
<td>x</td>
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<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td>Slight</td>
<td></td>
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<tr>
<td>10. W.S.</td>
<td>Presenile Dementia</td>
<td>24</td>
<td>52</td>
<td></td>
<td>x</td>
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<td></td>
<td></td>
<td>Slight</td>
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<tr>
<td>11. J.Z.</td>
<td>Senile (Chronic B.S.) Dementia</td>
<td>16</td>
<td>61</td>
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<td>x</td>
<td></td>
<td></td>
<td></td>
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<td>12. F.C.</td>
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<td>47</td>
<td></td>
<td>x</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>Anosmia</td>
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<td>13. S.C.</td>
<td>Chronic Brain Syndrome</td>
<td>27</td>
<td>42</td>
<td></td>
<td>x</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td>Same</td>
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<tr>
<td>14. M.D.</td>
<td>Presenile Dementia</td>
<td>230</td>
<td>18</td>
<td></td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Unimproved</td>
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<td>15. M.H.</td>
<td>Obsessive Compulsive Rejection, Early Onset</td>
<td>215</td>
<td>39</td>
<td></td>
<td>0</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>No Change</td>
<td></td>
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</table>

* Slight    ** Moderate    *** Marked

* Smith Kline & French
mind. He thought he had two wives. The Dicumarol was stopped June 26.

On July 5 he could not tell the time nor name the hands of the watch. He was more restless, spilt some milk, was upset over things and wanted to go to bed at the time of the interview.

July 17 he was started on warfarin sodium when it was decided to continue anticoagulant treatment. September 8 he was quiet, polite, but still disoriented. He incorrectly told the time as "thirteen minutes after seven" whereas it was twenty minutes to three. He persevered with professorial detail when trying to name the watch hands, but co-operated well during the tests and did try to reason things out. His wife reports the visits as improved, that the patient could now "walk as fast as I could." She was pleased that he was improved, having expected more deterioration.

#2, D.B.: The patient was a seventy-four year old former brick layer of Italian birth, in good health until his first stroke in 1961 while on a visit to Italy. He was in the hospital there for two weeks and his speech returned, but he had some slight weakness in his arm. He had repeated "little strokes," especially in the past two or three years but none since he has been bedfast recently. He has been paralyzed in the left arm and leg for the past one and one-half years. His wife died three months ago and he has had no one to care for him. He gradually became too depressed and confused and agitated for the nursing home to handle him. Prior to this, on October 29, 1964 he had an unsuccessful thrombendarterectomy of the right internal carotid artery following a bilateral arteriogram, which showed slight narrowing of the left and great narrowing of the right internal carotid artery. He was admitted to Woodville April 17, 1967 from Suburban General Hospital where he was reported as being "very confused, memory severely impaired, disoriented as to time and place, loud and noisy at times with considerable senile agitation and confusion at times approaching senile psychosis."

He spoke little English but I saw him with his daughter April 19 and she stated that he recognized his family but was confused, thinking his wife was still living, and that he was still in the First World War. He remembered things twenty years ago but not yesterday. He could not name the thumb but he knew the President was Lyndon B. Johnson.

He was given the first dose of Dicumarol on April 25, 1967 and was rather sensitive to the medication, maintaining a low prothrombin time for five or six days without more medicine. May 22 his daughter said his mind was much clearer. He did sit much more quietly in his wheelchair on the ward, drooled less though he still had a vacant look on his face. He was able to identify the thumb as "pollicis" and to count fingers though he appeared dull and apathetic. June 1 he counted fingers well, was less noisy and more alert. June 3 he received his last dose of Dicumarol and on June 9 his prothrombin time was still over two times the normal. June 13 he became bedridden and developed a temperature of 101 and had to be transferred to the infirmary. July 5 he was bedridden in the infirmary with an intermittent fever and had to be fed. Despite the physical deterioration his daughter said his mind remained clearer, he realized his wife was dead and he no longer saw rats or mice on the bed or felt "ants in his legs" as he had for the previous few months. He died July 10.

This patient improved on anticoagulant therapy—both mentally and physically. When it was stopped, he deteriorated rapidly physically, less so mentally. It is likely that he would have continued to improve had we continued anticoagulant therapy.

At the autopsy the right frontoparietal region of the brain was atrophic, the left side was normal, and the ventricles were not enlarged. The basilar artery was moderately atherosclerotic with irregular narrowing of the lumen. The internal carotid arteries were not removed but their sigmoidal portions showed a fairly marked degree of arteriosclerosis; the lumens were patent.

#3, M.G.: The patient was a seventy-three year old white male who, according to his daughter, began to deteriorate in November, 1966 when he sometimes did not recognize her and kept thinking he had to go to work. Once he ran away at 1:00 a.m. and almost got lost. He was admitted to Woodville April 17, 1967. He was very confused, often picking at the window of the nurses station and unable to touch my finger on request. He was taking Thorazine Spansules 25 mg two times a day, had a hemoglobin of 10 grams and was on iron medication. He was very unsteady on his feet and had difficulty getting seated in a chair.

He was given his first dose of Dicumarol April 21, 1967. By May 1 his prothrombin time was over twice the normal, he was less confused and quiet and co-operative. By May 5 he no longer was picking at the window, required no sedation, but was incontinent and still unstable on the chair. Because of the danger of falling and the fact that he had slight rectal bleeding the previous night it was decided to discontinue the anticoagulant for fear that bleeding might bring on a dangerous anemia. The last dose of anticoagulant was given May 3 and by May 8 his prothrombin time was well outside the therapeutic range. When seen May 7 he was bedridden, barely conscious and able to say only a few words. The hemoglobin on May 8 was 14.6 gm but he had developed pneumonia May 5 and despite penicillin, he died May 9, 1967.

It seemed that his decreased confusion and discontinuance of picking at the window indicated some improvement from anticoagulant therapy but not enough to warrant the risks of continuing it. The onset of pneumonia may well have been related to the discontinuance of the anticoagulant two days previously—in fact he might have had microthrombin in the lungs rather than infection. Or his lungs may have been infected and his resistance lowered because the anticoagulant was stopped, predisposing him to thrombosis. We have no way of knowing whether or not he would have lived had the anticoagulant been continued but he did improve while under treatment and he did follow the pattern of other patients who have been treated longer but died soon after discontinuance of therapy.

#4 W.K.: The patient was a 53 year old, white, married, father of four grown children, unemployed dairy manager whose first symptoms began about ten years ago when he woke up with vague symptoms such as dizziness and weakness. The doctor was called and the patient was off work a short time. About nine years ago he suffered from dizziness and did not dare use a ladder; at this time he was investigated at Johns Hopkins Hospital but no organic problem was found. His main symptoms were anxiety, depression and lack of self-confidence. In 1957 he was dissatisfied because he did not get an expected promotion so he quit the company and went to work for a small dairy in Uniontown. At this time he started to drink rather large amounts of wine although he never became "staggering
drunk". He went to visit his son in California for five months, returned to his old job, but six months later lost this job and became very depressed. He joined Alcoholics Anonymous and stopped drinking but continued to be very depressed and complained of lack of energy. He was then under the care of a psychiatrist and was hospitalized at St. Francis in January 1965 for a month and again in February 1966 for several weeks and had some ECT treatments. Psychology tests at that time showed no organicity. Following discharge he did not improve so he was admitted to the Western Psychiatric Institute in 1966 as a voluntary patient, rather than going to a State hospital which had been considered at that time because the patient was becoming belligerent at home. He threatened suicide on one occasion at least and intended to over-dose himself with medication. A diagnosis of "severe neurotic depression with passive dependent character disorder" was made and the patient was transferred to Woodville State Hospital January 24, 1967.

I saw the patient at Woodville April 5, 1967 because the staff knew of my project and thought this patient might have some organic brain damage. He was a slim, short, bald man who appeared alert and intelligent but complained of his memory being poor at that time—"I block out" frequently by which he meant when trying to express himself he couldn't think of the proper word. He was able to tell the time with little difficulty and was able to name the second hand but got the hour and minute hands mixed up until I coached him. He would not even attempt to interpret proverbs—"1ike a bifocal line". This was surprising in view of our adequate conversation until that point. He complained of visual trouble—a line across—"like a bifocal line". He was poor at copying designs and his signature was shaggy. A tentative diagnosis was early organic brain damage with reactive depression and anxiety and it was decided to include him in the therapy group since he had not responded to any other form of therapy but the chances of organicity being an important factor appeared to be slim.

The dicumarol was begun May 15, 1967 and by May 19, his prothrombin was in the therapeutic range (control time 15 seconds, prothrombin time 30 seconds). May 22 his wife reported that he was very good when he was home on Sunday—worked in the yard—the best for a year. May 31 he reported a good three day home visit on the weekend but on June 6 he was angry and anxious again so I thought his main problem may be the depression. He continued to ask if there was any hope and why couldn't we cure him. Nevertheless he wanted to carry on the medication and he had a good visit from July 1 to July 5 although his wife said that near the end of this he was restless. The dicumarol was inadvertently discontinued June 26 when I was on vacation. July 17 a bad weekend was reported—he dropped cigarettes and was "like a baby," not letting his wife leave him alone. He was started on coumadin on this date with the hope that we could revive his previous improvement. He never did regain the improvement he had on July 4. But most of his home visits were satisfying and on September 8 he reported a good weekend with his son out-of-town and was able to tell the time, knew the "sweep", the minute and the hour hand. It appeared that he had less organicity but he still had many symptoms of anxiety and depression. October 25 his tofaril, compazine and mempronabe were discontinued and he was changed to mefloil 50 mg tid which made him more depressed so he was changed to other medication.

December 15 despite his prothrombin time being in the therapeutic range most of the time he was more confused and said he cannot go on like this, "you've got to do something," and appeared very depressed. He said he could not see well enough to count fingers and he would not even try. During the finger touching test he touched the knuckles on my hand instead of the finger tips. It was decided to discontinue the anticoagulant therapy because most of his problem was depression and anxiety. December 22 his prothrombin time was down to normal, he was more confused and on the finger nose test touched my thumb instead of the finger tips. I decided to give him one more try on dicumarol therapy but no great improvement was noticed and on February 22, 1968 he had a temperature of 104 and the anticoagulant had to be discontinued. On February 17 he was apathetic, dull, complained of blurred vision, remembered my name with difficulty. When he got up rapidly, he had to sit back down and get up slowly. He told time incorrectly and could not name the hands except for the "sweep" hand, called the hospital "Millville" and then corrected it to Woodville.

Because the patient's outlook was hopeless otherwise it was decided to do an aortic arch study to see if there might be a surgically correctable lesion. He was admitted to Western Psychiatric Institute and Clinic March 6, 1968 from Woodville and these studies were done and showed no lesion of the carotid or vertebral arteries. While in the hospital anticoagulant treatment was given a trial once more and the patient seemed a little better physically but still remained depressed and anxious. Psychology tests at this time showed gross organicity. It was interesting that although he had significant loss of abstract thinking this was not severely deteriorated and the main "deficits in conceptualization and abstract reasoning result more from his inability to attend to complex stimuli, his inability to 'hold in his mind' more than a few stimuli at once, and a tremendous anxiety blocking which is evoked when he attempted to conceptualize." For example in arithmetic he could not remember the original numbers or the problem long enough to arrive at an answer.

He was discharged back to Woodville and while there he began to develop small strokes observed by the staff and had to be transferred to the infirmary. His mind deteriorated so that he did not even remember his wife's name most of the time and did not remember my name or the name of the hospital he was in.

Because of his unsteadiness on his feet he fell August 18, 1968 and fractured his hip and had to be transferred to St. Francis Hospital for surgery. I was contacted and postoperatively the patient was put on coumadin to improve his mental functioning and this was continued on his return to Woodville. He continued to improve until he was able to recognize his wife but about November 1, 1968 he was injured by another patient and the anticoagulant had to be discontinued as he was transferred to St. Francis where he had to have a prosthesis placed in the right hip because of aseptic and necrosis of the femoral head. Again the patient became unable to recognize his wife. When I saw him he was very thin and did not recognize me let alone
know my name. He could not count fingers or talk sense. He was completely disoriented as to time and place.

This patient's course is most interesting in that he began as what appeared to be severe anxiety and depression and eventually turned out to be very organic. In retrospect the very first attack was probably a small stroke which affected his higher intellectual powers reducing his working ability but not noticeable in general conversation. His psychological reaction to this loss was one of depression and apparently he used alcohol to combat this. The alcohol would tend to lead to further brain damage. Eventually the organic damage became grossly observable and then he developed obvious little strokes observed by the mental hospital medical staff.

He did appear to respond at first to anticoagulant therapy but we were never able to relieve his depression, anxiety and organicity all at the same time. This type of patient represents some of the most difficult to diagnose and treat—the psychological reaction overshadows the underlying organic process.

#5, W.L.: The patient is an eighty-one year old widower admitted to Woodville March 1, 1967 with a diagnosis of chronic brain syndrome associated with arteriosclerosis. The first symptom of illness occurred in October, 1953 when returning by himself from a Florida vacation he had "a little stroke" on the train and got off at the wrong place. His daughter and her husband moved in with the patient when his wife died in 1952 and the daughter says the patient gradually gave up more and more interests and changed from a very outgoing, unselﬁsh man to a selfish man. In 1964-65 the decline was more rapid with increased memory loss and "little strokes" according to the family doctor. At times his eyes were glassy and stary and he would have wild ideas such as "he knew where a young boy was who got a girl pregnant and he was going to get him." The daughter talked him out of this just as he was going out to drive the car in pursuit. He had already voluntarily turned in his driver's license in 1961 following a car accident and court hearing—he was having little spells of confusion and the daughter felt he should not drive the car. In September, 1966, having been up at night for weeks, he fell at 5:00 a.m., and was taken to Mercy Hospital where he remained for two weeks. October 9 he was placed in a nursing home but had to be transferred January 24, 1967 to the mental ward of St. Francis General Hospital because he had become too combative, confused and uncooperative. While there he remained confused, talked to imaginary people, was restless and required spoon-feeding. He was transferred to Woodville March 1, 1967 for long term care.

When examined April 19, 1967, the patient was confused, did not know where he was, was indigent at times, was careless at counting fingers but did recognize the thumb. He was superficially pleasant and able to make some simple jokes. He had his first dose of Dicumarol April 21, 1967. On May 12 the Thorazine was reduced to a 75 mg Spansule once daily and by June 1, he was on no tranquilizer at all. He was still careless at counting fingers but seemed more pleasant, quieter and had no angry spells. He sat quietly by himself most of the time, not realizing he was in a mental hospital. He had his last dose of Dicumarol June 5. When examined July 5 he had the delusion that he was at a "sick benefit meeting," he was able to count fingers, name the thumb and little finger but could not name the Hospital, "Woodville," and was very poor at interpreting proverbs.

There was no dramatic improvement with this patient on Dicumarol but he seemed to reason a little better, was calmer and was able to be taken off tranquilizers entirely and he was a little less incontinent though not completely continent. Following discontinuance of Dicumarol, he was a little quieter and less inclined to reason things out. He remained quiet on the ward, answering with his usual pleasant and the usual polite joke. I felt there was some definite improvement in his mental status while on the anticoagulant and some of this was maintained even after treatment was discontinued and he did not have to be restarted on a tranquilizer.

#6, M.M.: The patient is a fifty-eight year old, single, laborer who lived at home with his family until admitted to Woodville March 6, 1967. His illness started eight years ago with inability to reason and remember recent events. Six years ago he had "a nervous breakdown" and was slowly becoming worse until November 1, 1966 when he had, according to the family doctor, a mild stroke. He was admitted to Western Psychiatric Institute where a note was made December 9, 1966 that his mental condition had "become worse over the past several years but in the last four or five weeks had deteriorated 50 percent. He needed hospitalization for two years but had refused to go." He was in the local Veterans Administration Hospital in February, 1967 and the following note was made by the psychiatrist, "Marked disorientation to time and loss of recent memory. Periodically confused. No localized lesion, brain scan normal, EEG diffusely abnormal, pneumoencephalogram showed hydrocephalus in the lateral and third ventricles. Impression: chronic brain syndrome (dementia) probably secondary to cortical atrophy." The patient had been in good physical condition but at age three had suffered carbon monoxide poisoning and required efforts to revive him, so he may have had some brain damage then.

The patient was seen April 14, 1967. He had a rather vacant expression to his face, smiled rather automatically, was able to count fingers and name the thumb; he recognized the name of Shafer as Governor of Pennsylvania, named a pencil and a tie clasp and did very simple arithmetic such as 4 x 4 = 16. He was poor in the differentiation of fruit and could not interpret the simplest proverb such as "no use crying over spilt milk." He was very poor on the finger-nose test—sometimes touching my nose instead of his own. He was given his first dose of Dicumarol April 20, 1967. On May 1 Thorazine had been discontinued, he was still poor at touching his nose and showed no improvement in his behavior on the ward. June 5 the Dicumarol was discontinued. His relatives noticed no improvement when he was home on Sundays; the staff noticed little improvement though one nurse thought he could follow directions better. I could see little change in his condition apart from slight indications that he was making more effort to understand his environment.

On July 5 he was about the same with a very poor memory, being unable to tell what he did on his day home; but he did wonder why he was here in the hospital which may indicate some attempt at reasoning things out.

In summary, there was little if any effect from anticoagulant therapy and it might have been possible to discontinue Thorazine without putting him on Dicumarol since he had shown no signs of agitation for some time.

#7, G.S.: The patient is a sixty-two year old white male admitted to Wood-
This document is a medical case study. It describes the medical history of a patient named W.S. who was admitted to Woodville Hospital on March 30, 1967, with a diagnosis of Presbyterian-University Hospital of Alzheimer's disease: "The pneumoencephalogram showed severe cerebral cortical atrophy. He has an organic psychosis and periodically is severely confused and agitated." The patient was given Dicumarol and other treatments. The patient's mental functioning improved while on Dicumarol, but he did lose some of this improvement when the treatment was stopped. The patient's speech became more stuttering and un-
worker in the mill and in the tavern he had owned. Having to quit work and doing nothing to do depressed him, especially in the winter. His memory had been failing a little and in the past year he would complain about forgetting names. He voluntarily gave up driving one year ago. He had emergency surgery for a hernia under spinal anesthesia two months before his present illness started and, though he was bright before his release from the hospital, he was worse after that. Six weeks before admission he went for a walk at 3:00 a.m., then tried to set rags on fire in the kitchen, broke up a table, punched the glass out of a window and required fourteen stitches after being taken to the VA Hospital in an ambulance by the police. After his admission there his mind "was not right—he raved and had to be strapped down." He knows his relatives now but feels they have "false faces on" and feels bad about being in a state hospital and, unnecessarily, according to his son, worries about owing hospital bills.

When examined April 14, this thin wiry man was strapped in a wheelchair, would not or could not count fingers, was able to name a pen but called a cigar a pen. He was given his first dose of Dicumarol April 21, 1967 at which time he was able to name my thumb, knew the name "Woodville," was able to touch my fingers but with a moderate tremor. By April 28 the nurses said he was very good, the patient said he felt well too, he looked well and was very clear mentally. While he had been improving since his admission to the hospital this improvement seems to have been more rapid, since the anticoagulant had been started. By May 3 he was very alert, helpful with the other patients, and the Thorazine was discontinued the preceding day. He had attended Vocational Therapy, remembered all he had eaten for lunch, but could not remember my name, thinking I was "a social worker." His improvement continued and he was allowed home for weekend visits which were satisfactory. May 19, because of slight hyperactivity, he was put on meprobamate 400 mg three times a day which calmed him satisfactorily. On that day also, he showed atrial fibrillation with a pulse of 120 per second and a blood pressure of 160/90, which was controlled by digitalization.

The Dicumarol was gradually discontinued so that he was free of the effect of it by June 26. He knew my name, was well oriented and had all the appearances of being "normal." He has since been discharged from the hospital maintaining his improvement without the use of anticoagulant and under the care of his own physician. September 3 he was reported as doing well at home.

This patient showed the most dramatic improvement. While he was slowly improving prior to treatment, the anticoagulant seemed at least to speed up the process and make it more complete. In fact, judging from the relatives' description, the patient improved beyond his condition before his acute illness occurred, so that he was actually better than he had been a year ago. Like patient #7, he continued to benefit from the "coasting effect" of the anticoagulant, improving after the treatment had been discontinued. The patient had taken Digitalis by mouth for some chronic brain syndrome, varicose veins, arteriosclerotic heart disease, diabetes mellitus and some deafness. Her daughter told me the patient began to deteriorate three or four years ago but the patient's husband kept her going by dressing her, taking her out for walks and doing the cooking. This past year she was much worse; she was
hard to control, and had to be locked in to keep her from running away. Three years ago she had a hysterectomy and was worse after discharge from the hospital. She did not agree it was her house, was confused, relived her childhood and did not acknowledge her children as her own. She was "essentially dead to us for two years." The last year she scratched her head to the point of bleeding, ran away and so had to be taken to St. Francis Hospital. While there she developed pneumonia and became bedridden and thus ended the almost continuous walking which was a habit before hospitalization.

When examined May 4, 1967 she was sitting tied in a chair, did not respond to my taking her pulse and was incontinent all the time. She was a frail, gray-haired lady with a vague, confused look on her face, conversing not at all. The first dose of Dicumarol was given May 4, 1967. On May 7 she was brighter, smiled a little and talked to me a little. By May 16 she was able to feed herself with little help, tried to be pleasant and converse, but was extremely confused. The Thorazine was reduced to 25 mg four times a day on May 9 as she had not been shouting as much. At the same time her tolbutamide was increased to give better control of her diabetes, which was difficult because it was of the high renal threshold type and had to be controlled by blood sugars rather than urinalyses. On May 26 the daughter reported her mother as being "tremendously better—the same as last summer." While in St. Francis she said her mother had said no words.

The last dose of Dicumarol was given June 14 when it was thought the patient had gained the maximum benefit from therapy. She became drowsy, developed pneumonia and was transferred to the infirmary where she died June 22, 1967. This patient improved considerably while on Dicumarol and rapidly deteriorated when it was discontinued. Doubtless some of the improvement was due to improved control of the diabetes but she had improved greatly even before such effort was made and she deteriorated despite maintenance of diabetic control. She probably would have continued to improve on therapy but not to the point of making rehabilitation possible. The improvement in her mental condition resulting from the administration of Dicumarol probably helped to control the diabetes, for she ate better, moved about better and was able to get out of bed into a chair a good part of the day.

#12, M.D.: The patient is a fifty-eight year old, white, married mother of two grown children admitted September 22, 1966 with a diagnosis of presenile dementia. She was considered for treatment in the series at that time but it was not possible to begin the study then. She was transferred June 6, 1967 from the chronic building to our ward to undergo treatment. Her husband said the illness took two to three years to develop and that even one and one-half years ago she was well enough to walk about the farm but would get up at midnight and say, "Let's get out of this place," whereupon he would take her for a ride in the car; also she put her dress on backwards and was incompetent in many other ways. At the time of admission she was unable to do simple, familiar tasks such as preparing meals, was delusional and could not care for her personal hygiene. She had no mental trouble before the present illness and had raised her two children, taught Sunday School and "raised half the kids in town," according to her husband.

Her transfer to our ward was delayed until June 6 because she had been sick with a fever for one week and was under treatment with an antibiotic. Her daughter said she had been unable to walk for three weeks before the transfer, hadn't known any of the family since Christmas and said not one word.

When examined June 7, 1967 the patient, a thin gray-haired woman, could not put her tongue out on request, did not talk and was very unsteady on her feet when she was out of bed, appearing about to fall at any minute. The first dose of Dicumarol was given June 7, 1967. June 13 she was walking better, more steady on her feet, fed herself but was incontinent at times. Thorazine 50 mg three times a day was stopped as she had become quieter. She then became more restless and had to be given Mellaril® three times a day. The last dose of Dicumarol was given June 25. July 5, 1967 she was trying to say a few words, tried to get out of the door, being very fast on her feet now and steady. She was still incontinent.

It was decided to include her in a trial with a few other patients who were to be restarted on anticoagulant and on July 17 she had her first dose of warfarin sodium.** The prothrombin time was not in the therapeutic range until August 2. When seen September 8, she was no longer combative (she had started pushing other patients around in August), was feeding herself, was able to say a few words, and behaved very well when she went to the hairdresser, but she would urinate in the middle of the ward floor at times. She walked with me down the corridor and would scarcely let go of my arm when I had to leave. She still could not talk to me except for occasional words. August 21 her husband told me he thought his wife was improving: "She looks better than when she was admitted a year ago and could open a can of soft drink and peel a banana."

Although this patient is severely deteriorated she did seem to respond to anticoagulant therapy by improving, whereas in the ordinary course of events she would have deteriorated even more. The anticoagulant will be discontinued shortly and her condition will be followed.

#13, M.H.: The patient, a sixty-one year old mother of one married son whose husband is twelve years her junior, was admitted to Woodville October 18, 1966, because of "depression." She complained of confusion and inability to organize enough to prepare a meal. An x-ray revealed an enlarged heart and arthritis of the spine with "moderate encroachment on the intervertebral foramen;" physical examination showed an aortic systolic murmur and bruits over the carotid arteries in the neck. She had been a capable person until August, 1965 when she was in a car accident, striking her head against the glass. She was not unconscious and was in the hospital only for x-rays and not overnight.

In September she was depressed, had no appetite, and felt the phone was tapped and people were watching her. By November, 1965 she was worse and could not make up her mind while shopping and could not decide on a guest list for her son's wedding. She was in the psychiatric ward of St. Francis Hospital from January 21 to February 26, 1966 and readmitted April 9, 1966 for six electro-shock treatments. Her personal hygiene became worse; she did not clean her spectacles nor keep her undergarments clean. She attended a chiropractor in between the St. Francis Hospital admissions and intermittently on her

*Sandoz Pharmaceuticals
**Coumarin, Endo Laboratories
visits out from Woodville with no improvement from the neck manipulations. She has shown little improvement since admission to Woodville, still being unable to do the housework on her home visit days.

When examined May 3, 1967 this gray-haired, pleasant lady, appearing more seventy than sixty-one, was well spoken and cooperative, complaining only of some confusion of thoughts and inability to prepare meals more complicated than the simple "soup and hamburger" type. She repeatedly complained of this disability and wondered if she would ever get better. She was poor at proverb interpretation and at comparisons: "I just can't explain it." She could not describe the pills that she took each morning, but she was good at serial seven addition though slow in subtractions; design copying was rather poor. Although her diagnosis seemed mainly to be reactive depression, the staff conference also included chronic brain syndrome secondary to arteriosclerosis and her Rorschack test suggested early organic changes, so it was decided to give her a trial on Dicumarol. The first dose was given May 23, 1967. I was overly cautious due to the patient's and her husband's expressed fear of hemorrhage so that when treatment was ended June 14, the patient's prothrombin time had been in the therapeutic range (over twice the control time) on only four days, hence I do not consider this a fair trial of therapy. There was no change in her condition. She still remained depressed and unable to improve in her thinking or in her performance of her household tasks.

September 8 the social worker reported that the patient had been transferred to the chronic building and although she showed little change her husband was thinking in terms of discharge with someone to help at home.

The organicity appears to play a minor part in her symptoms and was unaffected by the Dicumarol although this could not be considered an adequate trial of therapy. Such a patient would not normally be chosen for a test of effectiveness of anticoagulant therapy because of the degree of functional as opposed to organic symptoms. She was included because part of the purpose of the study was to determine the problems of therapy in different types of patients and to see if elimination of minor organicity would help the functional aspects of the patient's illness.

The clinical course of the thirteen patients can be summarized as follows:

#1, J.C.: Some improvement while on anticoagulant therapy, some deterioration when therapy was discontinued, improvement again when therapy was re instituted, deterioration often when therapy was discontinued September 9, 1967.

#2, D.B.: This patient's mental and physical condition improved on anticoagulant therapy. He deteriorated within one week of discontinuance of the anticoagulant and died five weeks after the last dose of Dicumarol, but some of the improvement in his mental status was maintained until shortly before his death.

#3, M.G.: This patient improved slightly on anticoagulant therapy and died shortly after discontinuance of treatment.

#4, W.K.: This patient improved on therapy, deteriorated when therapy was discontinued, improved again when therapy was restarted.

#5, W.L.: This patient improved slightly on therapy, lost some but not all of his improvement when therapy was discontinued.

#6, M.M.: This patient possibly improved slightly in his reasoning ability while on anticoagulant therapy but this was not very definite and there were no grossly noticeable differences while on or off anticoagulant therapy.

#7, G.S.: This patient improved on anticoagulant therapy, but deteriorated on discontinuance of treatment with gradual return almost to pretreatment status.

#8, W.S.: This patient improved moderately with anticoagulant therapy, showed no gross deterioration for the first month after it was discontinued and continued to improve slightly in the second and third months after discontinuance of therapy.

#9, J.Z.: This patient made remarkable improvement while on anticoagulant therapy, maintained this improvement when the medication was discontinued and was able to be discharged from the hospital.

#10, F.G.: Remarkable improvement. She regained the ability when on anticoagulant therapy to control her bladder and to feed herself and to follow directions. She very noticeably deteriorated when the anticoagulant was discontinued.

#11, S.C.: This patient showed noticeable improvement in her mental status while on anticoagulant therapy and rapidly deteriorated and died after the medication was discontinued.

#12, M.D.: This severely deteriorated patient improved moderately on anticoagulant therapy, continued to improve after it was discontinued and showed slow but continuous improvement when the anticoagulant was restarted. After the last time it was stopped she deteriorated noticeably.

#13, M.H.: This patient showed no improvement on anticoagulant therapy but was in the therapeutic range for only four days.

Projected Course of the Thirteen Patients Without Anticoagulant Therapy

Since for this series there is no control group, it might be of interest to project what, judging from previous experience with such patients, their clinical course would have been without therapy. This is outlined in TABLE III. One patient (9) began improving on hospitalization and before therapy had begun. There is a slim possibility that he could have improved.

TABLE III

Comparison of course of thirteen patients with senile dementia treated with Dicumarol with projected course of same patients if left untreated, judging from previous clinical experience.
enough to be sent home on long visits without the anticoagulant treatment but his relatives told me that his memory following treatment had become better than it was even six months prior to hospitalization. This would not likely have occurred in the normal course of events without anticoagulant therapy. As for the other patients, if we had tried reducing the tranquilizer without instituting anticoagulant therapy there might have been four or five who could have tolerated such a reduction and had improvement in their mental functioning without the anticoagulant. The series probably would not have reached the figure of eleven who actually did improve under therapy enough to allow a reduction and even in some a complete discontinuance of the tranquilizer.

Without treatment I would have expected four to deteriorate (2, 3, 8, 11) almost certainly, and probably also 1, 4, 7, 8, and 12. Under anticoagulant therapy none deteriorated; in fact, many showed definite improvement. The fact that three died soon after therapy was discontinued tends to confirm my finding that anticoagulant therapy does prevent deterioration. Under twelve months of observation and without anticoagulant therapy I feel that twelve will almost certainly deteriorate: 9 might maintain his improvement but even he is in a precarious situation and is in constant danger of a recurrence. These patients will be followed for the next year with this in mind.

Of the five patients who were incontinent, I would have expected none to become fully continent without therapy. Under therapy, one patient did become fully continent and she had been on the ward for thirty-five days prior to treatment without showing any improvement. The possibility of improvement being due to psychological factors seems remote since she was so deteriorated that she could say only one word, “good,” and could not even respond to her name until after anticoagulant therapy was begun.

At the beginning of treatment four patients were unable to feed themselves; at the end of treatment three were able to feed themselves due to their improved mental functioning. Without treatment, I doubt if any of these patients would have become able to feed themselves.

**Discussion**

The very high percentage of improvement and the 100 percent lack of deterioration in these patients with senile dementia while on Dicumarol is impressive. Such optimistic findings are likely to create immediate skepticism in the minds of most readers. Few treatments, especially those involving drugs, produce this type of result. And where senile dementia is concerned, heretofore a rather hopeless and poorly understood condition, eyebrows will certainly be raised. Yet the results are very similar to those of my first series of eleven patients with arterial insufficiency of the brain also treated with Dicumarol.2

Such results demand an explanation for they strain the credulity of the most optimistic clinician. Can we, in our present state of knowledge, explain the reasons for such encouraging results? Let us examine some possibilities. First, we are using a specific treatment (prevention of blood coagulation) to combat a specific pathological condition (the intravascular coagulation of blood). If we did not find such results, if only 50 percent stopped deteriorating, we would be very suspicious of the etiological hypothesis. We can compare this specificity to the action of insulin in reducing hyperglycemia in patients with diabetes. The comparison, though not perfect, seems rather good in that insulin can lower the blood sugar below normal and to a dangerous level, as the anticoagulant can lower the prothrombin in the blood to excessively dangerous levels. But despite the specificity of the treatment, I would not be so foolish as to suggest that all senile dementia patients in a mental hospital will recover on anticoagulant therapy. They will all cease to deteriorate, but many will not improve because of irreversible brain damage. This again is similar to diabetes: the blood sugar of a patient with neglected diabetes will always improve with insulin, but despite this he may still be left with a residual disability such as a retinal degeneration or gangrene of the foot.

The reader may not have too much difficulty, then, accepting this factor of specificity of treatment to account for the prevention of deterioration; but how does one explain the large percentage of patients showing improvement? The answer is that this study was carefully designed to include mainly patients who had a good chance to improve with anticoagulant therapy. The criteria used for this selection have been discussed earlier. Again let us make a comparison with diabetes. An aged, neglected diabetic with gangrene of the leg and retinal deterioration will not improve as dramatically as will a young, new diabetic when first started on insulin. Though in both patients the blood sugar will be adequately controlled, the neglected diabetic will remain disabled, whereas the new diabetic will function almost normally. In a like manner we could expect better results in patients with senile dementia if we could treat them in the early stages of the disease, before hospitalization was needed. Stopping deterioration at that level would mean preserving useful function.

Of the reader may ask a more difficult question, one which puzzled me for several years: How can patients improve when they have already suffered brain damage, for we know that nerve tissue cannot be regenerated? A partial answer appears to be that these patients must have some viable but nonfunctioning areas of brain tissue which exist in such a state because sludging of the blood in a narrowed artery will not allow sufficient circulation to permit this brain tissue to function fully, yet there is enough blood supply to prevent actual death of this tissue. There are various reports in the literature to support this theory. Very illustrative is that of Debaker and Lockard7 who work with Knisely, the originator of the term “blood sludging.” These workers studied twenty-two patients with cerebral vascular insufficiency and were able to correlate decreased neurologic signs and symptoms with a demonstrable decrease in the sludging of the blood, which was accomplished by antimalarial drugs. Other reports confirm this relationship between blood sludging and brain function but what has not been documented is the corollary: that the sludging may be confined to one area—distal to a constriction in an artery (Fig. 1). Such a stenosis may be in an internal carotid artery in the neck, in a smaller artery inside the skull or a combination of both, or even many areas combined. The effects will be harmful, though more localized than if sludging is generalized throughout the body. In such localized conditions, however, the sludging will not be visible outside the skull, as in the scleral vessels for example. It could be present in the meningeal vessels as demonstrated by Meyer8 using a method which can-
Fig. 1. Abstract anatomical demonstration of the main arterial supply to the brain, showing various sites and combinations of stenosis and occlusion.

not be used clinically. In most patients with senile dementia, particularly in the younger age group, the blood in general is normal, but I have little doubt that if we could place a plastic window in an internal carotid artery, distal to a stenosis blocking over 50 percent of the lumen, we would see turbulence, stagnation and blood sludging in various degrees. This sludged blood must flow distally into the smaller arterioles and capillaries of the brain where it may plug the vessels in various areas with varying degrees of damage. If there happens to be a second stenosis, say in the anterior cerebral artery, then the effect may be compounded distal to the second stricture (Fig. 2). If a motor area of the brain is affected, paresis, tremor, incoordination or rigidity may result. If a so-called "mental area" of the brain, such as the frontal lobe, is affected mental symptoms will result. If a sensory area is affected, such as the occipital lobe, visual reception or its interpretation will be disturbed. The second type of lesion, perhaps combined with the third, is likely the primary lesion in senile dementia; but the combinations and permutations of the brain areas which may be affected are almost endless.

This theory fits well with the clinical picture of senile dementia in which patients' signs and symptoms, so much so that it is next to impossible to find two patients alike. Senile dementia, then, may represent an example of a condition called "diaschisis" by von Monakow and described by Kampinsky as a "depression of function of one region of the central nervous system due to a localized injury in another region." There is a blocking of synaptic transmission between regions connected by fiber tracts. Clinically the phenomenon may be observed as the initial flaccid weakness and depressed consciousness relieved when other tracts take over the function. This is an alternative explanation to relief of sludging as an explanation of improvement, but there seems to be no reason why both cannot occur, either separately or together.

This raises practical problems in assigning diagnostic labels. Often enough similar combinations of symptoms and signs occur so that the patients can be grouped. Those exhibiting a certain such combination of symptoms are then said to be suffering from a certain syndrome or disease, such as Alzheimer's disease, Pick's disease or Jakob-Creutzfeldt disease. Or the name may refer to the type of pathological lesion, such as "spastic pseudosclerosis," the synonym for Jakob-Creutzfeldt disease. Such names and syndromes are very useful to the diagnostic, prognostic and research work of medicine, allowing the organization and comparison of knowledge by various workers. There comes a time, however, when these names are apt to impede progress by giving us the feeling that we know a great deal about the condition. A good example is the diagnosis "acroparesthesia," a formerly untreatable condition which now has become the "carpal tunnel syndrome," an easily cured condition.

It seems to me that some of the diagnostic labels of brain lesions may have diverted our attention from the main problem—the inadequacy of the circulation of the brain. When we think of the many arteries supplying the brain, the individual variations and anomalies of these arteries, the many possible sites of narrowing or occlusion, the variations in efficiency of the collateral blood supply, the changes in blood pressure, the changes in the blood constituents themselves, (from anemia to polycythemia, from less viscous to very viscous sludged blood), we can begin to appreciate that a great variation in symptoms might result
from an infinite combination of brain lesions. As if this were not enough, the damage to the brain tissue initiates the phenomenon of diaschisis. But we have still not reached the end of this complicated situation for we must add to the picture the patient's emotional reaction to his tissue damage and this may overshadow all his other symptoms. This emotional reaction may vary from calm acceptance through hysterical anxiety to a psychotic delusional reaction with paranoid ideation. We can now realize that a host of complicated and seemingly unrelated symptoms can arise from a single physiological dysfunction—arterial insufficiency of the brain.

This would appear to be a useful diagnostic label: "Arterial Insufficiency of the Brain" (A.I.B.). It has a sound physiological and pathological basis and puts the blame where it originally belongs—on the arteries. Not that the patient does not have a paranoid delusional reaction, or a dementia, or a severe anxiety reaction—these he may have. The diagnosis of A.I.B. stresses the primary origin of these symptoms—a deficient arterial blood supply to the brain. We can now proceed to attack the disease at its source, which is the clotting or sludging of the blood beyond the narrowed or occluded arteries.

Other similar terms are used but do not seem quite as applicable as A.I.B. "Ischemia of the brain" is shorter and accurate but seems to switch the attention from the arteries to the brain itself. "Cerebrovascular insufficiency" may be more accurate in that it includes the venous drainage, which may be important in a small percentage of patients, but it does not in practice focus much attention on the veins and it neglects an emphasis on the arteries and the rest of the brain, being concerned only with the "cerebrum" whereas the primary lesion may be in the cerebellum or some other part of the brain.

In the final analysis it seems best to consider A.I.B. and its clinical counterparts as a type of pluricausal disease so well described by Selye in his book on thombohemorrhagic phenomena. Each patient may be considered from a primary etiologic viewpoint (arterial stenosis), a secondary etiologic viewpoint (blood sludging, thrombosis, anemia, polycythemia, weak heart action), and a symptomatic viewpoint (psychologic: paranoid, anxiety, denial reactions). Therapeutically, one or more of the causes may then be attacked—excise the stenosis, anticoagulate the blood, tranquilize the mind or reduce the mental stress.

The approach in the series of patients presented in this paper was with these principles in mind with the exception that surgery was not contemplated. Ideally these patients should have a four-artery arteriogram to disclose any surgically correctable lesion of the carotid or vertebral arteries. So far as I know, no one has studied dementia from the surgical viewpoint—it might be worth doing. The general condition of the patients is important too—including digitalization, control of diabetes where necessary and adequate exercise: all of these influence the circulation and nutrition of the brain. For this reason I think these patients should primarily be under the care of a general physician who can look after these factors at the same time that he controls the anticoagulant therapy, where this is necessary. Such an arrangement could be the most efficient for the doctor and the patient, and the most economic in terms of both money and doctor-time. We must not, however, neglect "mental exercise" for the patient but keep him in contact with normal people and performing normal functions so as to reorient him to reality situations.

Placebo Effect, Tranquilizer Effect, Prothrombin Level Control

There are three other aspects of this particular series that warrant discussion: the placebo effect of treatment, the beneficial effect on mental function of reduction in the tranquilizer dosage and the type of anticoagulant and degree of control of the prothrombin time.

There is no doubt that the extra attention given the patient in the form of daily blood tests, frequent interviewing, possible change in attitude on the part of the staff and so forth could alter the patients' behavior. This is the reason many people ask for controls and for large numbers of patients, which at first thought is a most logical request. But since equivalent controls are most difficult if not impossible to find, we might first ask: what can we do to understand these various factors and how can we limit their influence on our results? First, it seems to me that most of our patients were too confused to be very much influenced by venesection and interviewing, since they forgot about
it almost immediately and had no understanding of what the purpose was. Such procedures might make a patient worse rather than better by adding to his confusion. As for the attitude of the staff, with most it was great skepticism rather than enthusiasm; again more likely to interfere with than to stimulate improvement. The best way of dealing with this problem, it seems to me, is to assess the effect of these multiple factors on an individual basis using clinical judgment. While there is always room for error, accepting this risk seems preferable to using no judgment at all, relying solely on mass statistics. It is usually not difficult to distinguish the difference between a patient who realizes what the medicine he is getting is for and imagines it is helping him, from a patient who takes orange juice, norepinephrine, and any medicine in it, and becomes continent and able to feed himself after four weeks of treatment. As for the extra attention of the staff, they were so busy that one could say that little extra care was given; in fact the patients who became able to feed themselves received much less attention.

The beneficial results in mental function which may occur from a reduction in the dose or elimination altogether of a major tranquilizer is a different problem. The medicine could reduce mental alertness, hence the patient would tend to become more alert when not taking it. But he could also become more agitated and anxious, thus negating the beneficial effects of increased alertness. I feel that the anticoagulant, by improving mental function, reduced the confusion and anxiety enough to allow reduction in the dose of tranquilizer, thus producing a doubly beneficial effect.

As for the anticoagulant treatment itself, warfarin sodium may be used in future trials since it has several advantages: it is water soluble and can be given by injection when the patient is unable to swallow; it is now more widely used so that more doctors are familiar with its use; it is said to have a more reliable action and thus makes control easier; its action is faster—within twenty-four hours as compared to forty-eight to seventy-two hours for Dicumarol; it comes in a variety of strengths tablets allowing more accurate dosage. The last two may also be disadvantages: if a patient misses a dose he will lose the anticoagulant action faster, the increased number of tablet strengths can lead to confusion over which strength the patient took, although this is avoided to some extent by the different strengths tablets being of distinctive colors and having the number of mg. marked clearly on the tablet. There is a chance, however, that warfarin sodium may not be as effective as Dicumarol in reducing blood sludging; no studies have been done on this problem. The failure of a warfarin sodium treated series of patients to show beneficial results would not negate the results with Dicumarol herein reported. At present three of the thirteen patients have been restarted on anticoagulant therapy, this time using warfarin sodium**, so that we shall have some chance to compare the therapeutic action of the two drugs.

The optimum level at which the prothrombin time should be kept is still not agreed upon for coronary artery disease and it may be different for senile dementia. I chose the level of two to two and one-half times the control time because this had been the level used in the successfully treated eleven patients mentioned earlier* and is the level recommended by most clinicians treating coronary artery disease or transient ischemic attacks. When we have sufficient number of patients under therapy for a long period, different levels of control may be tried to discover if a higher level would be effective since it would give less chance of hemorrhagic complications. It may be, however, that some patients will require even lower levels such as the "bleeding close" technique described by Per Udden. 12

It is not always easy to keep the prothrombin time in the therapeutic range. This was emphasized by Hutton et al., 12 whose study revealed that of a group of hospitalized patients on anticoagulant therapy, less than 50 percent were well controlled. Obviously the effectiveness of control will have a great influence on the results of anticoagulant treatment.

We may also change to the thrombotest instead of the prothrombin time, since it offers certain advantages as outlined by Vigran 14 in his comprehensive book on anticoagulant therapy, that is, greater safety and more flexibility in doing the test.

Conclusions

The results of treatment with Dicumarol in these thirteen patients with senile dementia confirms the earlier impression that it may be possible to arrest the progress of this disease. Furthermore, the improvement in this selected group indicates that in certain patients the condition is to some degree reversible. If these two findings can be confirmed it means that patients developing senile dementia, if treated early enough with Dicumarol, may never develop the disease to a serious degree, and hence may never become disabled by it. In others, already disabled but having some viable though non-functioning tissue, worthwhile improvement might be possible. In a third group, already disabled by irreversibly damaged brain tissue, improvement could not be expected but prevention of further progress of the disease could make worthwhile their limited rehabilitation by maximum development of their remaining mental abilities, similar to the way in which a patient with hemiplegia is rehabilitated.

This study also shows that anticoagulant therapy can be a practical proposition in a large mental hospital if a minimum of extra facilities is supplied. The extra cost should be more than offset by the need for less burdensome forms of care in the form of feeding patients and cleaning up after their incontinence, as well as by the greatly reduced amount of tranquilizer requirements. Besides the direct benefits, the availability of a treatment which offers prevention of further deterioration and even the possibility of improvement will greatly reduce the hopelessness often felt by the nursing staff who have to care for this type of patient. Their increased enthusiasm may not only be beneficial to the treatment of the patient but may also aid in the recruitment of more staff.

A longer trial of therapy in a larger number of patients, with controls if possible, will be required to confirm these conclusions. In a small number of patients in such a study I think it would be advisable to do four-artery angiograms. Another promising area of investigation would be the evaluation of the circulation time through the brain. In this regard Oldendorf and Kitano 16 have shown that in a group of normals over age forty the brain circulation resulting from such tests might show clearly the further progress of the disease in the brain is 9.75 seconds, whereas for a group with a history of cerebral infarction it is 14.3 seconds. A seventy year old senile man had a time of 29 seconds, which indicates a severe interference with the circulation of the brain. Such tests might show clearly and objectively increased efficiency of the brain circulation resulting from anticoagulant therapy in patients with senile dementia.
senile dementia and could also be of diagnostic value.

At this point it seems pertinent to refer to the study of Whittier et al., 17 on the use of Dicumarol in the prevention of degenerative disease: even though it was done with a different purpose in mind it involves much the same type of patient and a similar institution but it has the advantage of having a control group and of being carried on over a longer period. Their results show a very definitely beneficial effect of Dicumarol in preventing degeneration: the mortality rate in the treated group was 11 percent compared to 28 percent in the placebo group—a 50 percent reduction—and the survival time was over twice as long in the treated group. Although our studies differ in many respects they both show that Dicumarol definitely delayed what we may refer to as the "degenerative process," unsatisfactory as the term is. And we must note that Whittier's patients were not selected—careful selection might result in even more impressive beneficial results.

Finally, it should be mentioned that other and safer drugs than the anticoagulant may be worth a trial. Their use can be based on the same principles—to improve the blood supply to the brain. Vasodialators have been used with very little success and have fallen into disrepute, but they may have a beneficial effect in a few patients. What has not been tried are the antimalarial drugs which have been shown to break up the sludge in the blood. 7 In a patient in whom sludging is the main problem they might be effective.

Summary

The beneficial results of continuous anticoagulant therapy in eleven of thirteen patients with senile dementia are described. Various features of the etiology, diagnosis and treatment are discussed in view of the controversial nature of the subject and the newness of some of the concepts such blood sludging and stenoses of the carotid and vertebral arteries. The fact that no patient deteriorated while on anticoagulant therapy and eleven improved during treatment is further confirmation of the hypothesis that the various senile dementias are due to arterial insufficiency of the brain. The theory that this insufficiency is partly due to coagulation or sludging of the blood beyond the stenosed arteries leading to the brain seems to be confirmed by the beneficial effects of anticoagulant therapy. The resumption of deterioration in many of the patients after the anticoagulant therapy was stopped offers further confirmation that this theory is correct. The logical implication, that senile dementia can now be prevented in some patients and improved or arrested in others, is discussed.

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