# MECHANISM OF DEMYELINATING DISEASES OF THE CENTRAL NERVOUS SYSTEM

## *A Therapeutic Approach with Anticoagulants*

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Ten years after Arthus[1] presented the histopathology of a local anaphylactic reaction in the skin of sensitized animals, Rachmanow[2] described degenerative alterations in the neurone cells of animals that had died in anaphylactic shock. That the Arthus phenomenon could be produced in the brain was demonstrated when rabbits sensitized to horse serum were shocked by intracerebral injection of that antigen. The site of the injection became one of violent pathology, for hemorrhages, thrombi, necrosis, scavenger cells, and microglial and oligodendroglial infiltrations were demonstrated.[3]

Experimental cerebral anaphylaxis in monkeys produced neuropathologic changes comprising two types of lesions.[4] The first was at the site of injection of the shocking dose of antigen and was similar to that described above. The second type of lesion was that of a disseminated encephalopathy in which the areas of demyelination were perivascular. The microscopic picture of these dispersed lesions revealed (1) perivascular infiltration by a variety of cellular elements; (2) axis cylinder destruction; (3) occlusion of small blood vessels by thrombi and endarteritic processes, and (4) intra and perivascular edema. Chronicity of the condition and protracted sensitization with the antigen were reflected in a change in the nature of the perivascular reaction. The change in reaction was from that of an acute hemorrhagic type associated with an exudate of polymorphonuclear leukocytes to the more chronic picture involving lymphocytes and finally granulomas and giant cells.

Basically the similarities and identities between the pathology of experimental cerebral allergy and the pathology of demyelinating diseases such as multiple sclerosis are these:[5]

1. The demyelinating process is chiefly perivascular in both conditions.
2. Hemorrhages are a major finding in the acute processes, while a paucity of hemorrhages characterizes the chronic stages of each.
3. Degeneration and necrosis of blood vessel walls are common to both.

4. Thrombus formation is seen in the acute stage of a demyelinating disease, while experimental anaphylaxis involving any tissue includes all stages of thrombus formation in the pathologic picture.
5. The perivascular reaction is predominantly perivenous, although it may involve arteries and capillaries.
6. Necrosis is a frequent feature of both processes.
7. In general, the patchy or diffuse gliosis of the demyelinating process is viewed as the equivalent of the scar tissue repair in other organs. Patchy gliosis has been reported in the later stages of experimental cerebral anaphylaxis.

The greatest disagreement among neuropathologists seems to arise from the etiology of the demyelinating process. Ferraro[5] has presented his argument based on the analogy of the cerebral pathology of demyelinating diseases and that of cerebral anaphylaxis. With this approach he hopes to open new avenues of investigation. Putnam[6] has introduced a different theory based on a peculiar disturbance in the clotting mechanism of the blood of patients suffering from multiple sclerosis. There is experimental evidence to show that demyelinating lesions can be produced through retrograde obstruction of cerebral venules, and thrombi, among other changes, are regularly seen in the acute lesions of multiple sclerosis in man.[7,8] Thrombi have also been noted in other body organs in acute or progressive cases where encephalomyelitic changes were taking place.[9] Putnam has summed up his theory as follows: "There are individuals who suffer from a peculiar lability of the clotting mechanism of the blood. Whether this is congenital or acquired is not clear. If it exists, however, any slight disturbance of the equilibrium of the body may precipitate a shower of minute thrombi in various tissues. Most of these cause no permanent damage, but any that occur in the brain leave a permanent landmark behind and a local vascular abnormality which predisposes to further clotting. If the process is sufficiently stormy, a widespread destruction is produced, and the patient dies with the manifestations of 'encephalomyelitis'."[6]

Irrespective of the cause, it is generally agreed that each sclerotic plaque of multiple sclerosis goes through an acute state. It is in these acute lesions that thrombi are most frequently seen. Putnam reasoned that any gain from specific treatment must be directed toward preventing relapses and that this might best be done through depressing the ability of the blood to form thrombi. Thus he turned to the use of anticoagulants, and his group has recently reported a series of multiple sclerosis

cases that were continuously treated with the anticoagulant, dicoumarin, over a long period of time.[10]

The origin of plaques through thrombus formation does not necessarily eliminate the explanation of the pathologic picture of demyelinating diseases as a part of an allergic reaction. The formation of thrombi may be only a step in the march of events in the pathologic parade. The consistent production of thrombi in cerebral anaphylaxis has been pointed out by many workers, as previously mentioned. Putnam suggested that the instability of the clotting mechanism might be one aspect of allergy.[9] During an allergic reaction damage may occur to blood vessel walls in the form of periarteritis, or intimal changes may be induced which in turn would encourage thrombus formation in such vessels. It is possible, too, that vessels may be compressed by perivascular edema resulting from an allergic reaction, thereby indirectly causing thrombi to form in them.[11] An unexplained thin sheathing of the retinal venules in a group of 34 patients has been reported by Rucker.[12] This vessel abnormality was especially noticeable toward the periphery of the ocular fundi. Twenty-one of these patients were subsequently diagnosed as having multiple sclerosis, while 7 others were suspected of having a related disorder. Spasms of fundus arterioles have been observed directly with the Morton ophthalmoscope in cases of multiple sclerosis. These spasms were accompanied by the subjective visual impairments of shimmering and scotomata.[13]

Once the initial pathologic process has been established, the relapsing nature of this group of diseases may well be the result of subsequent, specific, antigen-antibody reactions for which the brain and cord are the shock organs. Kennedy[11] states that many things about multiple sclerosis suggest paroxysms of localized allergic edemas. Among these are the episodic character with intermissions, curability of the acute crises, and attacks on the optic nerve.

The administration of anticoagulants in the treatment of multiple sclerosis, whether it be based on Putnam's theory or on the Ferraro concept of cerebral allergy, is directed against the formation of thrombi. Such treatment is justified since thrombus formation is one of the links in the chain of events leading to demyelination, and preventing their formation offers a logical attack against the progress of the pathologic process. On this basis the information accumulated in the treatment of 12 cases of multiple sclerosis using the anticoagulant, dicumarol, (3, 3′–methylenebis [4-hydroxycoumarin]) deserves passing review.

All patients were hospitalized and a prothrombin time determined before dicumarol was given. The Quick method of determining the prothrombin time was used throughout this series. All dicumarol was

given orally. Treatment was inaugurated by a dose of 300 mg. the first day and 150 mg. the second day. A prothrombin time was determined on the third day and the succeeding dose governed by the effect of the drug given thus far. After the first three days a maintenance dose ranging between 50 to 100 mg. every other day was found to be sufficient to maintain the prothrombin time at the desired level of 50 per cent of normal (normal = fifteen seconds). It was essential to do prothrombin time determinations at least two or three times weekly until the maintenance dose of dicumarol became established. Later in a few cases this procedure was reduced to once a week, especially when the maintenance dose of dicumarol required to keep the prothrombin time at the desired level became fairly constant. It was deemed wise to keep the patients under close hospital observation for the first two weeks of treatment, during which time a safe plan for continuing the drug over a long period of time could be determined. An attempt was made to keep the prothrombin time as close as possible to 50 per cent of normal for the duration of the treatment.

Of the 12 patients treated by this method, 7 were women (58.3 per cent) and 5 were men (41.7 per cent). The average age of patients at the start of treatment was 34 years. The oldest was 55 years and the youngest 23. In the average case, the disease had been in progress forty-six months before being treated with dicumarol. One patient had had symptoms attributed to the disease for sixteen years prior to treatment.

Six patients (50 per cent) gave a personal or family history of allergy. Three such histories are related below.

**Case 1.** A white woman, aged 35, had had recurrent bouts of hives all her life. She was found to be sensitive to rayon and wool. Questioning revealed that she had had asthma and hay fever in 1935. The patient was skin tested for undulant fever in 1945 and gave a markedly positive reaction to this test. A course of undulant fever vaccine therapy had to be discontinued because of the violence of reaction. A year later another attempt was made to give her graduated doses of brucellin, but because of the untoward reaction with high fever this treatment had to be stopped. This patient believed she had had her most crippling relapse of multiple sclerosis after the fourth injection of brucellin. This case has been diagnosed elsewhere by a very competent neurologist as an allergic encephalomyelopathy. He has prescribed an autogenous vaccine made from sinus washings and tonsil swabbings. The patient has been on a desensitizing program for several months using this vaccine. One communication from the patient (January, 1947) revealed subjective improvement.

**Case 2.** A beauty shop operator, aged 32, had had a rather severe contact dermatitis on her hands when she presented herself for dicumarol therapy. Patch tests revealed that she was very sensitive to tobacco and to two hair waving lotions which she was using in her daily work.

**Case 3.** A white woman, aged 38, on whom the diagnosis of multiple sclerosis was made, revealed that she had had hives for the first time in August, 1945. The urticaria appeared intermittently throughout the following summer until November, 1946. The responsible allergen or allergens were not known. The patient stated that while the hives were at their height of severity she suffered a marked exacerbation of the symptoms which were characteristic of multiple sclerosis.

With cooperation of the department of allergy a series of patients suffering from multiple sclerosis and its related disorders is being skin tested. Stock mixed respiratory vaccine, stock mixed stool vaccine, and individually tested common bacterial invaders are the antigens being used. It is hoped that some information can be gathered with which a desensitizing program can be worked out for selected cases. A report of this work will appear at a later time.

The average length of treatment was forty-two days, the shortest being a fourteen-day period and the longest a one hundred fifty-day period at the time of this report. In this study any one of the three following reasons was considered sufficient for stopping the treatment: complications from hemorrhage, especially into the kidney; inability to establish a safe program for administering dicumarol during the two-week hospitalization period, and instances where it was impossible to check the patient's prothrombin time regularly after he left the hospital. At present 8 (66⅔ per cent) of the patients are still on treatment. Several more patients have been added to the series since this report was written.

Ten of the patients (83⅓ per cent) expressed subjective improvement. This has been noted as early as seven days after treatment was started. Improvement in vision is one of the first things the patient will proffer. Expressions, such as, "My hands do not tingle so much," "I'm steadier on my feet," or "I feel that I can walk better" are frequently heard. These may only be unbased enthusiasms released from persons who, in their mind's eye, had already consigned themselves to life in a wheel chair.

Unfortunately, objective evidence of improvement is not so prevalent. Two patients (16⅔ per cent) showed evidence of objective improvement. The most striking change was noted in a 29-year-old white woman who could not urinate spontaneously and had required daily catheterizations by her family physician prior to coming to the hospital. During the second week of dicumarol treatment she was able to void spontaneously and has had no difficulty in this respect since.

In another patient, a 30-year-old white woman, the bilaterally positive Hoffman sign and sustained ankle clonus were changed to unilateral findings.

## Conclusions

It is concluded that the results of dicumarol treatment of multiple sclerosis have been indifferent to slightly encouraging in a small series of cases. More information concerning the value of this method of treatment is becoming apparent as prolonged therapy continues in most of these patients and in additional patients with the diagnosis of multiple sclerosis.

A quick review of this small sampling should serve to evoke further interest in the use of anticoagulants in the treatment of multiple sclerosis, and, what is equally important, should stimulate a continued interest in the role of allergy in this stubbornly mysterious demyelinizing process.

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