A NOSOMETRIC APPROACH

MULTIPLE SCLEROSIS PROGNOSIS AND TREATMENT

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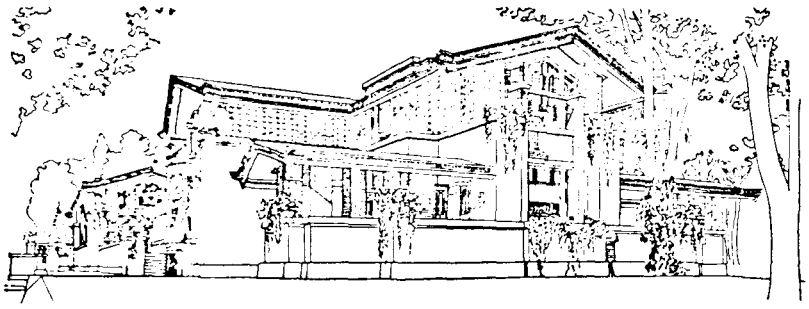

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Man/woman ratio ~ 1/2 pp 14

Symptoms 22

mptoms implying multiplicity of lesions of the central nervous system occurring in the form of acute or gradual attacks not directly attributable to known mechanical, infectious or other external or systemic influences. This definition implies that since no specific test for multiple sclerosis is available, the diagnosis must be based not only on the recognition of the positive characteristics of the disease but also on the exclusion of alternate possibilities that may bring about a similar clinical picture in its cross-sectional appearance although less frequently in its longitudinal course. We have to realize that multiple sclerosis may imitate every known disorder of the nervous system and that a good many of the latter may imitate the appearance and less frequently even the course of multiple sclerosis.

Positive Criteria for Diagnosis

The diagnosis on the positive side must be based not only on the cross-sectional findings, the symptoms and signs, but also on the longitudinal aspects of the disease in terms of the history as well as in terms of subsequent observation. While in a few particularly clear-cut cases, the history and complete examination at intake may settle the diagnosis, repeated examinations over a considerable period of time may be necessary to establish the diagnosis. In some cases this observation may have to be extended as long as four years on the basis of our experience. Even in the hands of the experienced clinician, the diagnosis should be kept continually open to question.

In our studies we utilized every one of the frequent re-examinations of our patients as a means to re-evaluate the diagnosis using these findings to test the consistency of the symptoms and signs with the diagnosis. Evidence from either the cross-sectional and/or the longitudinal views must conform with the clinico-pathologic conception of the disorder, namely the random multiplicity of distribution of the lesions involving a variety of neurological systems, particularly the pyramidal, cerebellar, optic and sensory systems.

Another positive aspect of the characteristics of the disturbances may be their fleeting nature. A serious objective neurological deficit that recovers remarkably promptly without residual in-

capacity is a positive characteristic of multiple sclerosis. An example may be an episode of blindness, diplopia or weakness of a limb with concurrent evidence of pyramidal tract involvement that gives way quite promptly to complete recovery either without residuals and with restoration of normal reflex activity, or leaving in its wake only such telltale marks as slight temporal pallor of an optic disc or absence of one or several abdominal reflexes.

More difficult to diagnose are the progressive cases where the fleeting episodes are harder to distinguish except by careful continuous observation since they tend to coalesce, if less closely followed, into a picture of apparent continuous progression.

A positive item of diagnosis, although by no means specific, may be provided by the spinal fluid findings which Von Storch *et al.*[8] have defined as: a clear fluid with normal or slightly elevated mononuclear count, a normal or moderately elevated total protein concentration (usually less than 75 mg. %), a type D (or CD) gold curve in the presence of negative complement fixation reactions in blood and spinal fluid. According to Freedman and Merritt,[9] however, any particular abnormality may only be present in from 32 to 53% of the cases while at least one abnormality may be shown by 71% of the cases. Hence such positive spinal fluid findings are helpful only if they are strikingly positive while they are not contributory when they are borderline or absent.

Wartenberg[10] points out another feature of the neurological disturbances produced by multiple sclerosis, namely the often observed incongruity between signs and symptoms as compared to their mutual consistency in other organic disorders. This incongruity may be due to the incompleteness with which each function is affected reflecting the patchy nature of the lesions. An example of such incongruity is the presence of a fully positive sign of Babinski in a leg not grossly weakened or otherwise impaired in its motor synergism, occurring practically only in multiple sclerosis with the possible exception of certain cases of infantile cerebral palsy. The reverse type of incongruity may also be seen especially in acute attacks of multiple sclerosis, namely complete paraplegia with normal reflex activity; or retrobulbar neuritis with marked blurring of vision yet without recognizable abnormalities of the optic disc or blood vessels of the fundus.

TABLE 2

MALE-FEMALE RATIO OF MULTIPLE SCLEROSIS CASES WITH ONSET IN YEARS 1939-1948

	Male	*Female*	*Total*
DENVER (Kurland[16])	25 (27.8%)	65 (72.2%)	90 (100%)
WINNIPEG (Kurland[15])	27 (38.6%)	43 (61.4%)	70 (100%)
BOSTON (present sample)	125 (38%)	204 (62%)	329 (100%)
TOTAL	177 (36%)	312 (64%)	489 (100%)
	$\chi^2 = 3.41$	df = 2	$P \cong .20$

TABLE 3

MALE-FEMALE RATIO OF MULTIPLE SCLEROSIS CASES IN OUR SAMPLE

	Male	*Female*	*Total*
Onset 1939-1948	125 (38%)	204 (62%)	329 (100%)
Onset other years	77 (34%)	148 (66%)	225 (100%)
Total	202 (36.5%)	352 (63.5%)	554 (100%)
	$\chi^2 = 0.82$	df = 1	$P \cong .40$

sex distribution with respect to the periods of time noted here. We may conclude, therefore, that our sample as a whole represents adequately the sex distribution of multiple sclerosis in the areas and times studied here.

Age at Onset

Accuracy of determination of age at onset in multiple sclerosis is often questionable because of two difficulties:

(1) Initial symptoms may be fleeting and often attributed to other causes.

(2) Determination of age at onset is usually retrospective.

In the present study, control of these factors has been attempted by questioning the patient repeatedly about onset. Only after the patient has become sophisticated with respect to symptoms, and

only after he has presented a consistent account of first symptoms has the time of onset been accepted. Often the time of onset was remembered precisely by the month or time of year. When the patient remembered only the year, the date of the first clinic visit was presumed to be an anniversary of the date of onset.

As a further check on accuracy of determination of age at onset, we argue as follows: since determination is retrospective, we would expect errors of memory to result in a reported age at onset that is *later* than the true age at onset. Moreover, we would expect that such errors should increase as the time of onset becomes more remote. A greater error in determination should occur when onset occurred many years prior to observation. Thus later ages at onset should be indicated by those patients who report onset in earlier calendar years than by those who report onset in later calendar years.

Conversely, no difference in age at onset should be noted between such groups if the retrospective error is minimal.

For this analysis, the total group was divided roughly at the median calendar year of onset into two groups with onset within or prior to 1942 (269 cases) and with onset within or subsequent to 1943 (285 cases).

If the retrospective error is not significant, these two groups should not differ in age at onset. If the retrospective error is significant, the group with onset within or prior to 1942 should show a higher mean reported age at onset than the group with onset within or subsequent to 1943.

The distributions of ages at onset for the two groups are given in Figure 1 and the statistical constants for the two distributions are shown in Table 4.

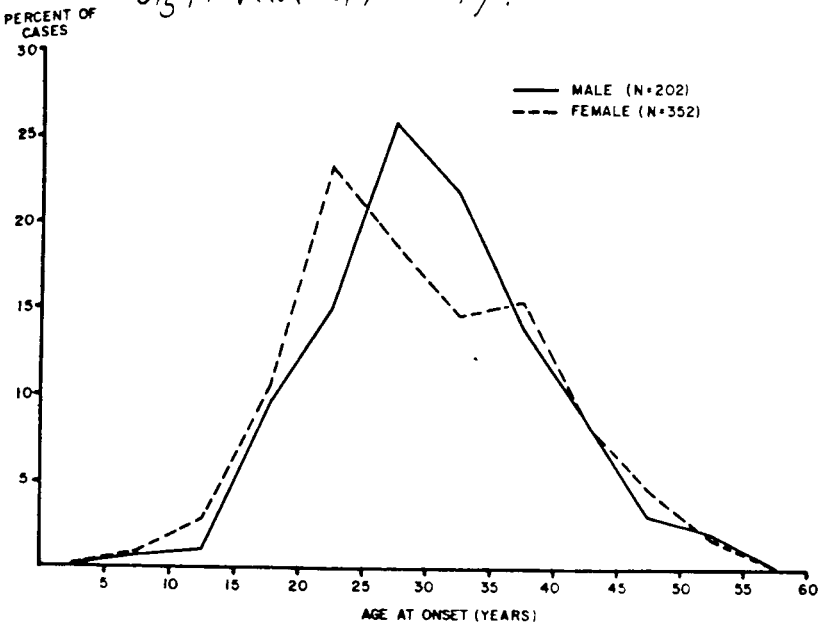
The distributions for the two groups are only trivially different. The slight difference in means noted below is contrary to the hypothesis of inaccuracy based on remoteness.

TABLE 4

MEANS AND STANDARD DEVIATIONS OF AGES AT ONSET IN PATIENTS REPORTING ONSET IN 1942 OR EARLIER, AND THOSE REPORTING LATER ONSET

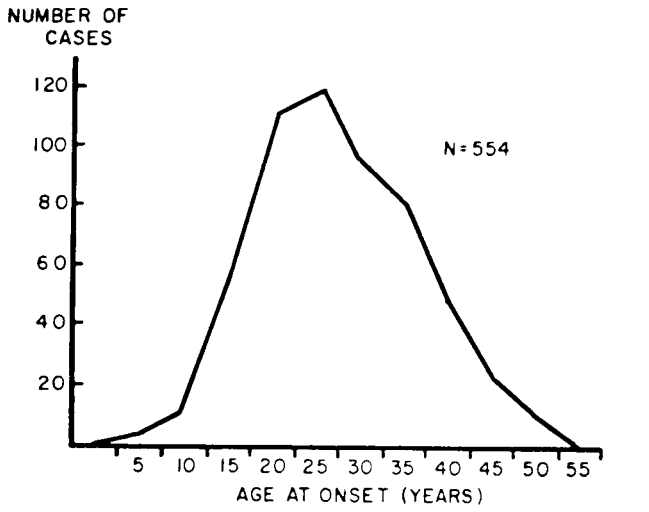
	Onset ≤ 1942	*Onset* ≥ 1943
N	269	285
Mean	27.85	30.59
Standard Deviation	8.16	9.25

big increase at puberty.



DISTRIBUTIONS OF AGE AT ONSET SEPARATELY FOR THE SEXES.

Figure 2.



FREQUENCY DISTRIBUTION OF AGE AT ONSET IN YEARS IN THE TOTAL SAMPLE

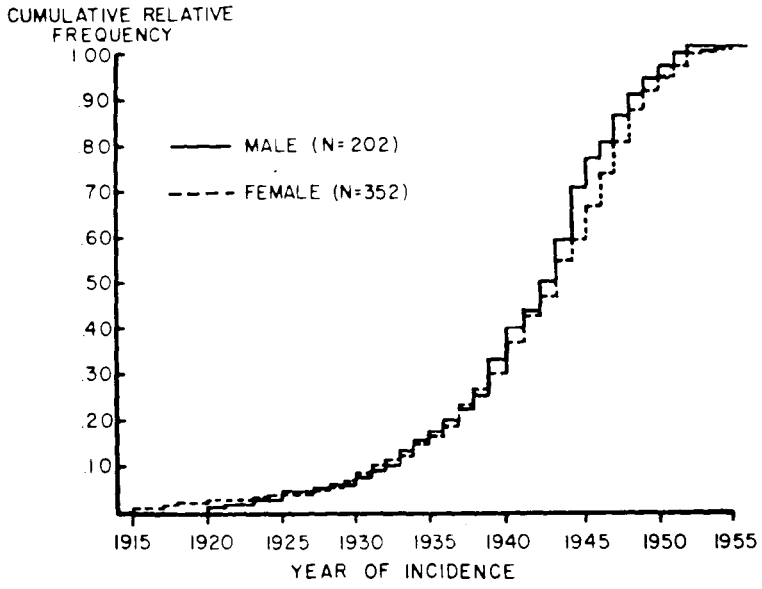
Figure 3.

See pp 29-30

Annual Incidence

We ask first whether the distribution of annual incidence is the same for male and female patients. The cumulative distributions of annual incidence separately for the sexes and covering the years of incidence available in our material are given in Figure 4. It appears from this figure that annual incidence does not differ appreciably in the sexes and this conclusion is supported by the Kolmogorov-Smirnov test of the difference between the two distributions. On the basis of this test, the probability of occurrence of the obtained differences between the two distributions is approximately .10 and, by the usual standards of significance, we may conclude that the sexes do not differ in annual incidence. This lack of difference between the sexes permits combining the groups for further analysis.

We have not found published data covering the entire span of years of incidence represented in this sample. Therefore we cannot evaluate the representativeness of this sample over the entire



CUMULATIVE YEARLY INCIDENCE OF MULTIPLE SCLEROSIS SEPARATELY FOR THE SEXES SHOWING REGULAR ANNUAL INCIDENCE IN YEARS WITH ADEQUATE SAMPLES

Figure 4.

TABLE 5
WEIGHTING CHART

VISION	
Corrected—less than 20/200	20
20/200-20/100	15
20/70-20/50	10
20/40-20/25	5
PUPILS	
Pupillary asymmetry	2
Abnormal reaction to light or accommodation	5
EYE MOVEMENTS	
Marked (such as eye muscle palsies, diplopia)	10
Moderate or slight (such as disturbance of convergence)	5
NYSTAGMUS	5
Unsustained	2
TONGUE—Deviation	2
FACIALS	
Asymmetry—Marked	5
Slight	3
OPTIC DISCS	
Pallor—Marked	15
Moderate	10
Minimal or Slight	5
Blurring	10
VISUAL FIELDS	
Restricted—Marked	15
Moderate	10
Minimal or Slight	5
Scotoma (not to be scored if vision is less than 20/200)	10
SPEECH	
Defect—Marked	15
Moderate	10
Minimal or Slight	5
POSTURE	
Inability to Stand	15
Abnormal—Marked	10
Slight	5
STATUS	
Bedridden	20
Wheel Chair	15
Walking with Support of Other Person	10
Crutches	8
Cane	7
Walking Unaided with Abnormal Gait	5
COORDINATION	
Tremor at rest and during static innervation, intentional tremor and ataxia with goal directed movements with eyes closed and with eyes open, scored separately and for each extremity. Marked	10
Moderate	5
Minimal or Slight	2
ADIADOCHOKINESIS +	5
Slight or ±	2
BRADYTELEOKINESIS +	5
±	2
ROMBERG +	10
±	5
STRENGTH*	
Paralysis	20
Weakness—Marked	15
Moderate	10
Slight	5
TONUS** (Increased or Decreased)	
Marked	15
Moderate	10
Slight	5
ABNORMAL MOVEMENTS	
Marked	10
Moderate	5
Slight	2
TENDON REFLEXES +++	1
++++	2
Absent	2
CLONUS + ++ +++	4
±	3
MAYER—Absent	2
HOFFMAN +	5
±	3
ABDOMINALS—(Per Side)—Absent	15
Partially Preserved	10
CREMASTERIC—(Per Side)	
Absent	15
+	10
BABINSKI—(Per side) Fully Positive	20
Equivocal	10
ABSENT PLANTAR REFLEX WITHOUT BABINSKI	5
OTHER ABNORMAL TOE PHENOMENA	
Each	5
SPHINCTERS	
Incontinence	20
Occ. Incontinence	10
Retention	10
Frequency	5
Urgency	5
Difficulty in starting stream—occasional retention	5
SENSATION—Per Side—Per Quality	
Absent	10
Diminished	5
Hyperesthesia or focal pain	10
Paresthesia or subjective numbness	5
IMPOTENCE	15
OTHER SIGNIFICANT SIGNS	10
Exophthalmus due to retrobulbar neuritis with pain of eyeball	
Temperature differences	
Paravertebral spasm, etc.	

*STRENGTH is scored for extension and flexion of each important group of muscles separately. The following groups are distinguished: hip, knee, foot, shoulder, elbow and hand with wrist. Thus, a complete triple flexion paralysis of the leg would be scored 60; moderate weakness of extension of one hip, 10; or marked weakness of grip of one hand, 15; or slight weakness of extension of one wrist, 5.

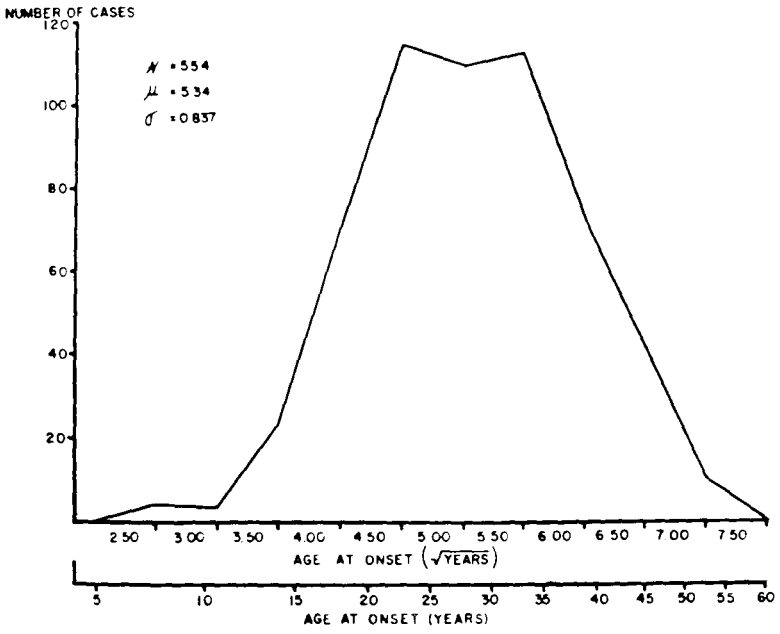
**TONUS—Scored per extremity.

support this assumption. Chi-square with 17 degrees of freedom is 36.31 which yields a probability of less than .005. Thus the assumption of normality is not tenable if age at onset is measured in years. We have seen that the mean year is 29.2, but the median is 27.7 years. Since the distribution of years is non-normal the median year is the more appropriate measure than the mean.

Again we have transformed the age at onset in years to the square root of years. The distribution of these measures is given in figure 8. The mean of these values is 5.34 and the standard deviation is 0.837. The Chi-square test of goodness of fit to a normal distribution yields a value of 20.28 with 17 degrees of freedom. The probability of departure from normality is .26 and the assumption of normality is therefore seen to be tenable. In further analyses of age at onset, the measure employed will thus be the square root of the age at onset in years.

Duration of illness

The duration of illness is defined by the number of years



THE DISTRIBUTION OF THE SQUARE ROOTS OF AGE AT ONSET IN YEARS AND THE CORRESPONDING SCALE IN YEARS

Figure 8.

shown in Figure 28 died six years after onset, after crossing the 300 mark in the fourth year of his illness. The patient whose graph is shown in Figure 29 crossed the 400 mark in the fifth year of her inexorably progressive illness, became bedridden during the fifth year and died in the thirteenth year of her illness. Figure 30, A-H, illustrates the great number, wide-spread distribution

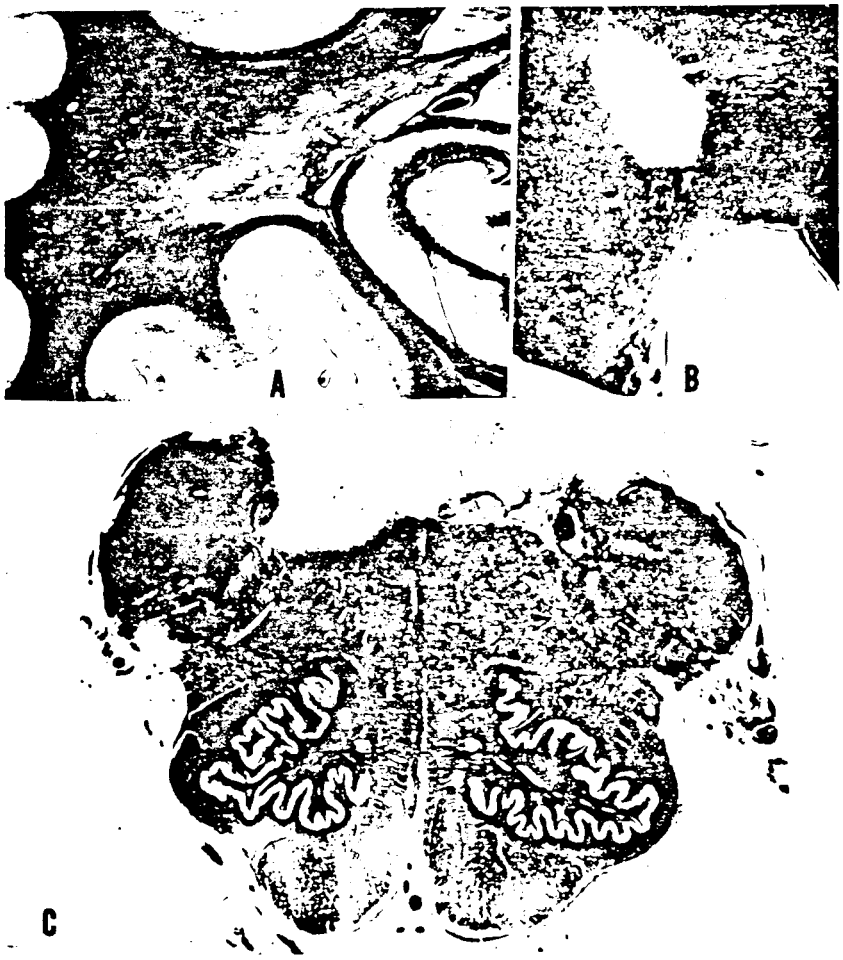


Figure 30. Representative sections from the brain and spinal cord of the patient whose course of illness is illustrated in Figure 29. Myelin sheath stain (modified Heidenhain method).

A. Left temporal lobe. Enlargement four times.
B. Left occipital lobe. Enlargement four times.
C. Medulla oblongata. Enlargement four times.

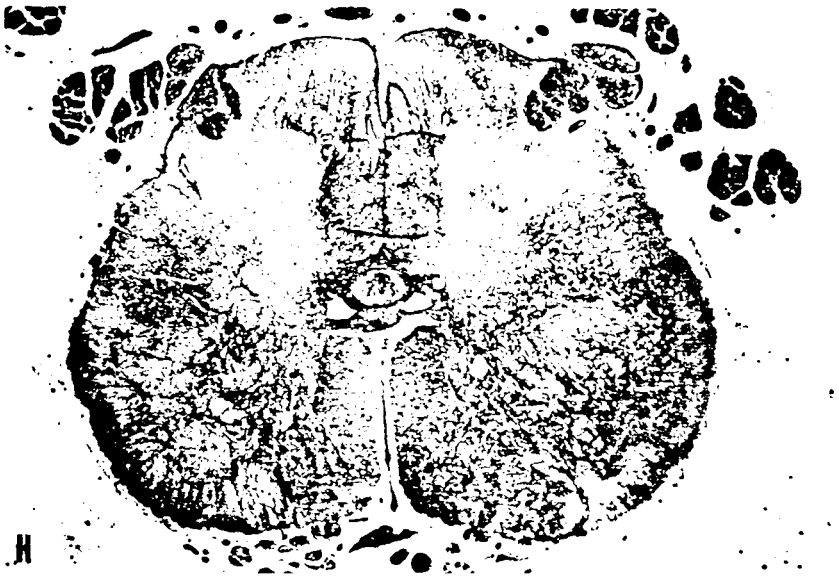


Figure 30 (continued).
H. Fifth lumbar segment. Enlargement nine times.

is +.89. If these findings are substantiated in a different sample of patients, it would mean that we could predict quite effectively from illness year the average score of a group of patients.

Our present material however, already yields data enabling us to examine some factors which may affect the average course in large groups of patients.

The Lack of Prognostic Indication of Sex and Age at Onset

The first of the factors which we considered was the sex of the patient. Since it has been noted in the literature that the incidence rate of multiple sclerosis is higher for women than for men and also that the death rates do not differ, one might expect a difference in the general course of the illness between the sexes. If that were the case, it would be inappropriate to use a single general curve as a standard for evaluating patients of both sexes. We therefore plotted the mean annual examination scores separately for the sexes and fitted logarithmic curves to each of these plots. Figure 31 shows the two log curves on the same graph. It is

basic aspects of supportive management. These included frequent interviews with physicians and social workers who were accessible to the patients by telephone not only during clinic hours but also on a twenty-four hour basis; referral to vocational rehabilitation and supportive psychotherapy at the clinic,[35, 36, 37, 38, 39, 40] and to specially organized group therapy sessions.[41, 42, 43] These factors were a basic service offered to all patients of the clinic.

As stated in Chapter IV, where we discussed the continued attendance versus discontinued attendance groups, it emerged that these treatment facilities were selective in that they were of more obvious potential advantage and hence more utilized by patients in the less severely disabled category. However, since the control groups to be discussed in the subsequent sections were closely matched as to severity with the groups receiving special treatments, this factor does not discriminate between these treatment and control groups.

Muscle Adenylic Acid (My-B-Den) and Thiamine Chloride

100 mg. sustained action type My-B-Den (Shapiro[44]) and 100 mg. thiamine chloride intramuscularly were given three times weekly to a total of 209 patients. In about one-quarter of these patients (54), the dosage was increased to 100 mg. of each daily during attacks. Since there were clearly no differences between these two dosage groups, the groups were combined for the analysis. This treatment was given over periods averaging 6.2 months, the median period of observation being five months and the range being one to twenty-two months.

Of the 209 patients receiving this treatment, thirty-nine cases were eliminated from the analysis because they were not observed frequently enough or had other treatments preceding this one. The remaining cases included seventy males and one hundred females. An equal number of control patients of each sex were selected by eliminating those with the fewest observations and those with other treatments preceding the periods available for control study. For each of the treated cases, the observation immediately preceding the treatment (initial observation) was compared with another as close as possible but prior to termination

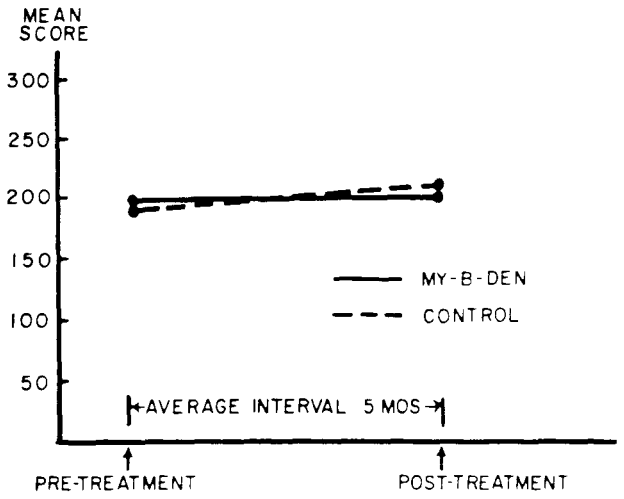


Figure 39. Effect of muscle adenylic acid (My-B-Den) on course of the disease. Mean scores in 170 treated patients and 170 matched control patients.

and the matched 170 control patients who did not receive muscle adenylic acid are shown in Figure 39.

Blood Transfusions

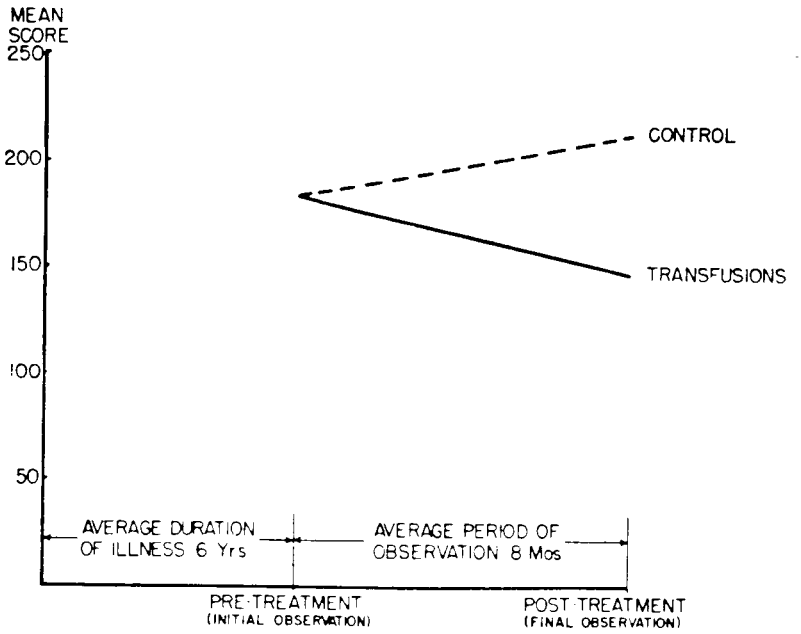
The use of components of blood, serum as well as whole blood transfusions, as a treatment for patients suffering from multiple sclerosis has been undertaken in the past on a number of samples and the result reported in the literature (Dumas and Foix[45], Laignel-Lavastine and Koressios,[46, 47, 48] Stransky,[49-55] Schaltenbrand,[56, 57] Arasa,[58] Alexander, Loman, Lesses and Green,[59] and Vasilesco[60]). Blood transfusions were tried because it was thought or implied by some of these authors[47, 51, 52, 57] that multiple sclerosis was an infectious illness of wide-spread distribution and that those not suffering from it were ipso facto immune and therefore capable of conveying immunity to afflicted persons.

Although the infectious theory of the cause of multiple sclerosis has not been buttressed by adequate evidence, new evidence concerning a vascular theory (Putnam,[61-64] Brickner,[65-67] Rucker,[68] Haarr,[69] Shulman, Alexander, Ehrentheil and Gross[70] and Swank[71-75]) as well as some evidence suggesting enzymatic defi-

ciency[76] still point to blood transfusions as a method of treatment of potential value in allaying the progression of the illness. A relationship to circulatory factors is inherent in the few definitive facts that we know about the disease such as the greater incidence and severity of the illness in cold than in warm climates. That poor circulation due to vasoconstriction incidental to chilling by low temperatures may account for these geographical differences appears to be supported by the distribution of the lesions in multiple sclerosis, the sites of predeliction of the lesions being the least well vascularized parts of the brain and spinal cord, namely the optic nerves, the upper lateral ventricular angles and the mid-thoracic spinal cord while the best vascularized parts of the brain immediately adjacent to the largest vessels are seldom, if ever, involved (such as the optic tracts). Then, too, the lesions themselves are characterized by venous congestion but arteriolar constriction and poor capillary filling. Thus it was felt that, since this evidence pointed to a vascular factor, blood transfusions might well be a means "to fill the vascular tree". If an enzyme deficiency should play a role, then likewise the introduction of blood from a healthy donor might be expected to make up for such a deficiency. Hence, irrespective of which theory one were inclined to favor, it seemed worthwhile to investigate the effect of blood transfusion treatment; and the hope seemed to be justified that, by the analysis of the ways in which the treatment affected the patients, some new leads as to the nature of the illness might be derived.

Method of Blood Transfusion Treatment

As described in our first pilot study,[59] transfusions of 500 cc. of fresh homologous and compatible whole blood collected in acid-citrate dextrose solution or of its equivalent in freshly spun down blood plasma derived from 500 cc. of fresh homologous whole blood were given once weekly for a period of six weeks. Whole blood was given to start with, but whenever the hematocrit rose above 55% or the red blood count rose above six million per cubic millimeter, plasma was substituted for whole blood. This was usually not found necessary before the fourth transfusion.



THE EFFECT OF BLOOD TRANSFUSIONS ON THE COURSE OF MULTIPLE SCLEROSIS MEAN SCORE IN 64 TREATED PATIENTS AND 64 UNTREATED MATCHED CONTROL PATIENTS

Figure 40.

by analysis of variance at better than the .01 level. The difference between the initial and final scores for the transfused cases is equally significant (by *t* test), as is the difference between initial and final scores for the control cases. Thus these findings represent a significant average improvement in the transfused cases as compared to a significant average worsening in the control patients. The results of this study would lead us to conclude that blood transfusion treatment has a beneficial effect on the course of the disease.

However, we have noted in Chapter III that the acuteness of the attack is related to the outcome, and consequently we wished to rule out acuteness of progression preceding institution of transfusion treatments as a variable which might possibly account for the favorable results reported above. Consequently, we examined only those transfused cases in whom we had a sufficient number of observations to determine the course of the illness preceding

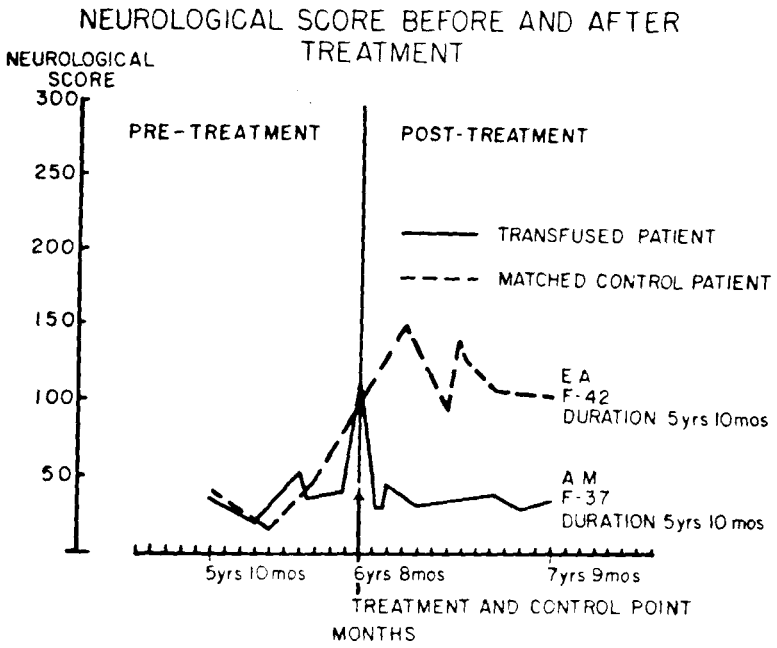


Figure 41.

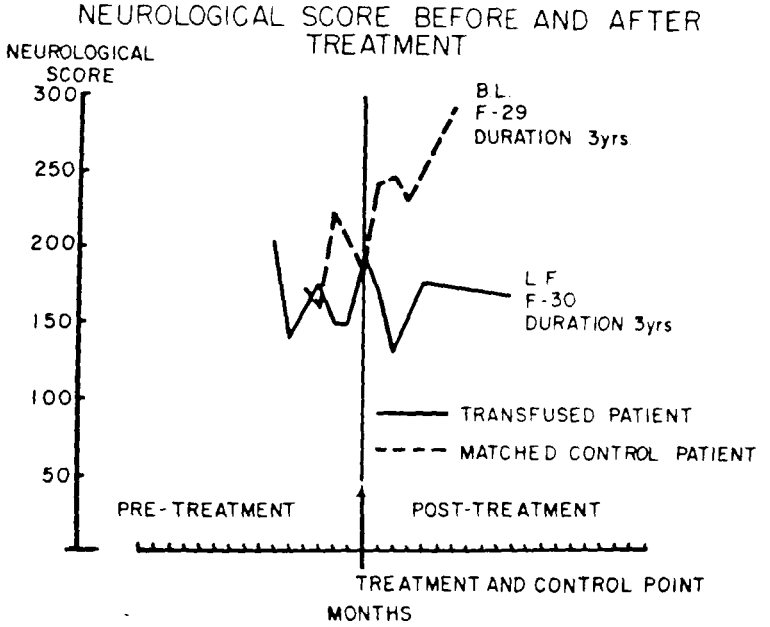


Figure 42.

TABLE 10

COMPARISON OF CHANGES IN NEUROLOGIC STATUS OF TRANSFUSED PATIENTS AND MATCHED CONTROL PATIENTS

		Number of Changes		
Neurological Sign	*Total*	*In Favor of Transfused Patient*	*In Favor of Control Patient*	*P (Two Tail Binomial Test)*
Vision	9	6		.51
Optic discs	13	7		1.0
Nystagmus	4	2	2	1.0
Speech	3	3		.25
Gait	8	4	4	1.0
Romberg	11	9		.07
Coordination, arms	15		11	.12
Coordination, legs	8		6	.29
Strength, arms	7	4		1.0
Strength, legs	18	13		.10
Tonus, legs	9	6		.51
Abdominal reflexes	10		6	.76
Tendon reflexes, legs	4	2	2	1.0
Babinski-plantar reflex, any change	23	13		.68
Babinski, complete reversal to normal plantar reflex	4	4		.06
Rossolimo	10		8	11
Mendel-Bechterew	9		7	.18
Sphincters	7	4		1.0
Sensation, touch	3	3		.25
Sensation, pain	9	6		.51
Sensation, position	8	4	4	1.0
Sensation, vibration, right	13	9		.27
Sensation, vibration, left	14	10		.18
Sensation, vibration, combined	15	11		12

first blood transfusion was treated again in November, 1958 for an attack of only four days duration. This time she again achieved a dramatic improvement during the first transfusion. Her left eye which had been practically blind (vision less than 20/200) suddenly recovered in that she could recognize large objects. Double vision on gaze to the right recovered as well. Three days after the first transfusion she noticed further improvement in vision and twenty-six days later (after her fourth transfusion) her vision was 20/20. Strength of her legs recovered as well and her gait was fully normal within forty-eight days of the first transfusion.

Directions for Blood Transfusion Treatment: Transfuse 500 cc. of fresh whole homologous and compatible blood collected in acid-citrate dextrose solution once weekly over a period of six weeks. Determine red blood count and hematocrit before each new transfusion. If the red blood count is above six million per cubic millimeter, or the hematocrit rises above 55 per cent, substitute 180 cc. of freshly centrifuged plasma prepared from homologous and compatible blood for the 500 cc. of whole blood.

Lately we have tended to give plasma from the outset either freshly spun down from 500 cc. of whole blood or 180 cc. of freshly frozen plasma from homologous and compatible blood. While we do not yet have available a sufficiency of such cases for statistical evaluation, it is our clinical impression that plasma transfusions provide results fully as good as those of transfusions of whole blood, including the occasional instances of sudden and dramatic relief of signs and symptoms which had stubbornly failed to yield to spontaneous recovery. We have lately also treated patients with less than a series of six transfusions, giving only one transfusion at the time of an unyielding attack provided that it was followed by effective relief. We found that such treatment given once or twice a year, as needed, was able to bring about prompt reversal and restoration to pre-attack status. However, these cases are still not numerous enough for statistical evaluation.

Schaltenbrand[78] has gone one step further and reports that 200 cc. of blood may be sufficient for this purpose. In the patients whom we have thus treated, however (four so far), we have given the standard size transfusion. This method of aborting, short cutting or relieving attacks is worth further investigation, because it