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A NOSOMETRIC APPROACH

MULTIPLE SCLEROSIS PROGNOSIS AND TREATMENT

By

LEO ALEXANDER, M.D.

Director, Multiple Sclerosis Research Clinic and Neurobiologic Unit, Division of Psychiatric Research, Boston State Hospital; Assistant Clinical Professor of Psychiatry, Tufts University Medical School, Boston, Massachusetts

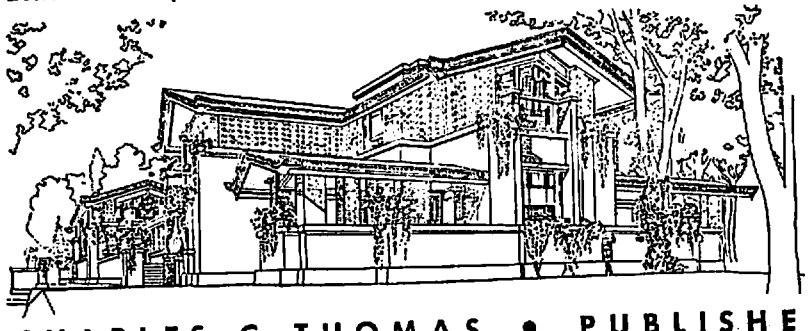
AUSTIN W. BERKELEY, Ph.D.

Professor of Psychology
Boston University

and

ALENE M. ALEXANDER

Administrative Assistant
Multiple Sclerosis Research Clinic
Boston State Hospital



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symptoms 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.

tumors. These signs of mental deterioration consisted of general slowing of thinking processes, deterioration of memory, of fund of recent knowledge and of judgement in one case and marked memory disturbance and vague generalized mental impoverishment and slowness in the other. One of them was the above mentioned patient with right acoustic neurinoma, the other a case of epidermoid tumor of the right temporal lobe. In verified multiple sclerosis patients we have never found such marked mental deterioration occurring before there is significant interference with the ability for independent ambulation. In any patient who shows this sequential pattern, careful study for brain tumor is indicated.

The only clinical sign which by itself may rule out multiple sclerosis is complete homonymous hemianopia. Visual field disturbances in multiple sclerosis are usually patchy or incomplete, including scotomata and various degrees of hemiamblyopia. The only patient among the 660 cases who came to us with the preliminary diagnosis of multiple sclerosis who was found to have a complete left hemianopia demonstrable even by simple finger perimetry turned out to be a case of brain tumor, namely the patient with the epidermoid tumor of the right temporal lobe mentioned above. The absence of complete homonymous hemianopia in verified cases of multiple sclerosis had been reported by Oppenheim in 1887,[12] by Uhthoff in 1890[13] and recently confirmed by Savitsky and Rangell[14] in the large clinico-pathological material of the Montefiore hospital.

The rarity of purely unilateral involvement in multiple sclerosis should also be emphasized. The only patient in our case material whose sensori-motor symptoms remained consistently unilateral, on the left throughout the entire four years of her clinic observation (apart from occasional nystagmus in either direction, but more consistently to the right, and temporary fluctuation of visual acuity of the right eye) was found by subsequent ventriculographic study followed by operation to have been suffering from a cholesteriniferous cyst of the right parietal lobe, measuring 8 cm. in diameter, its wall measuring 0.2 cm. in thickness. There was a remarkable degree of recovery after operative removal of the cyst by Dr. Samuel Lowis.

We believe that the combination of independent preliminary diagnosis and subsequent prolonged clinic observation may have resulted in our having at our disposal for this study as pure a culture of multiple sclerosis patients as may be obtainable by the study of living patients.

Study of the Representative Character of the Sample

Thus screened, there remained a total of 554 multiple sclerosis patients. These patients were studied over periods varying from one to eight years, the average being three years. The study was based on repeated quantitatively scored neurological examinations. Five thousand, six hundred and thirty-five such examinations were carried out in the course of one thousand, four hundred and twelve illness years, distributed over a duration span from the first to the twenty-sixth year of the illness.

Source of Referral

Of these five hundred and fifty-four patients, three hundred and fifty-two came from the clinic and two hundred and two from private practice, which means 36.5% private patients. This is consistent with 36.7% found by Kurland[15] in the Boston, New Orleans and Winnipeg studies.

Sex Distribution

The proportion of males to females among patients with onset of illness during the years 1939-1948 among the group represented in our sample does not differ from those proportions reported by Kurland for Denver[16] and Winnipeg.[15] Kurland's data for Winnipeg, Canada for the years 1939-1948, and his corresponding data for Denver, Colorado are presented in Table 2 together with our data.

Thus our Boston, and Kurland's Denver and Winnipeg samples do not differ with respect to sex distribution more than could be expected on the basis of random sampling error.

This finding could be generalized to our entire sample if the sex distributions were the same for those with onset in years other than the period 1939-1948. Table 3 indicates that this is the case.

Thus our present sample may be considered homogeneous in

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%)
	$x^2 = 3.41$	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%)
	$x^2 = 0.82$	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

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.

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

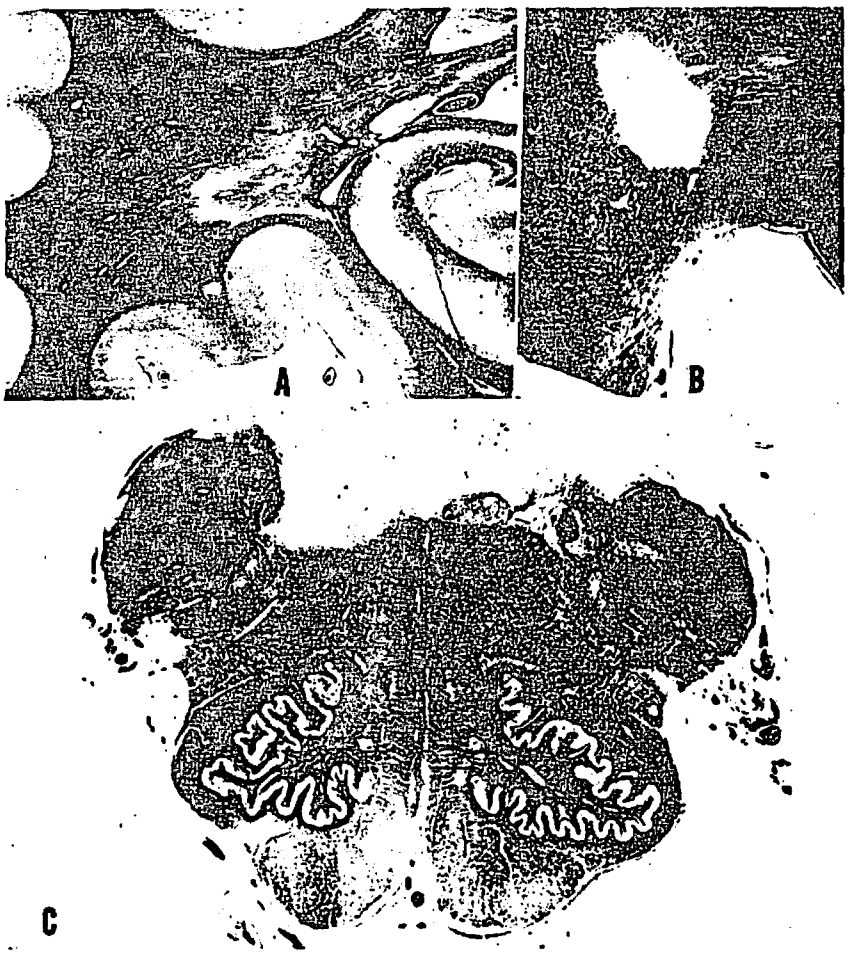

Figure 30. Representative sections from the brain and spinal cord of the patient whose course of illness is illustrated in Figure 29. Myelin sheath stain (modified Heidenhain method).

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

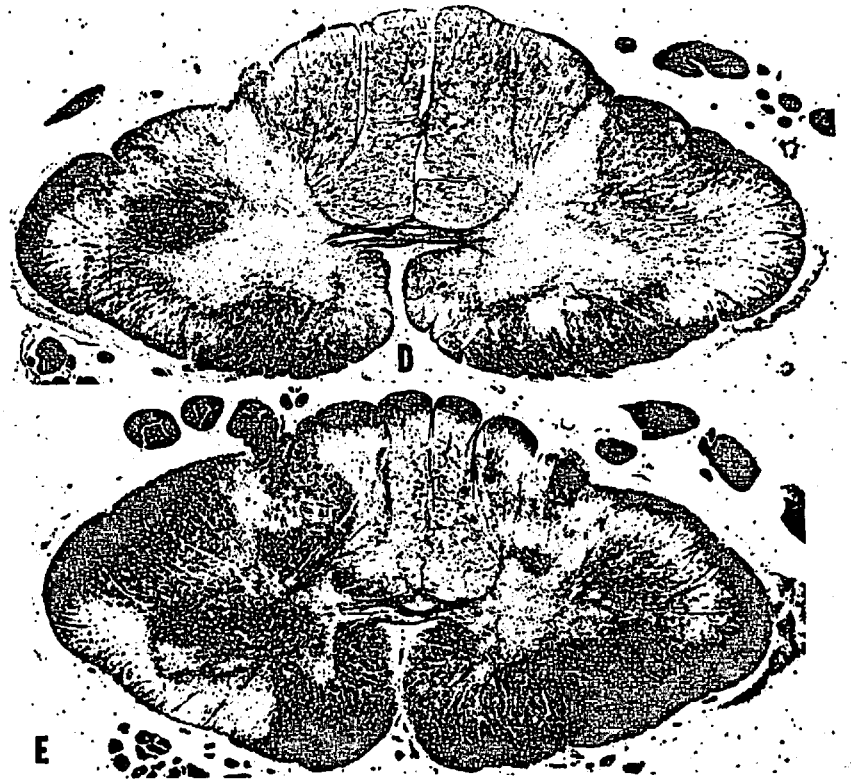

Figure 30 (continued).
D. Fifth cervical segment. Enlargement eight times.
E. Eighth cervical segment. Enlargement eight times.

and histological indication of marked variety in duration of the lesions in this patient.

It would be very important for the practical life plans of our patients if we could predict the future course of the disease on the basis of the early course up to a critical point such as the five year mark. Such a prediction applicable to the individual case can be envisioned as obtainable by our method of study if we can extend it to a new large sample of patients seen over an identical, prolonged span of illness years. Reliable prediction, hence, for the individual case is yet to be perfected in the future. However, the average curve described above could well be used as a standard for judging the course of any particular patient in that it allows the conclusion as to whether he appears to have average, below

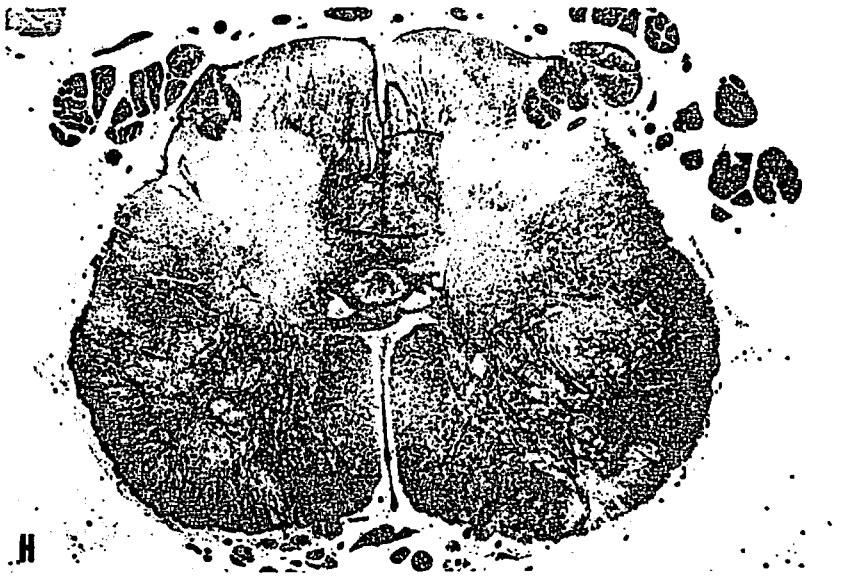

Figure 30 (continued).
H. Fifth lumbar segment. Enlargement nine times.

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

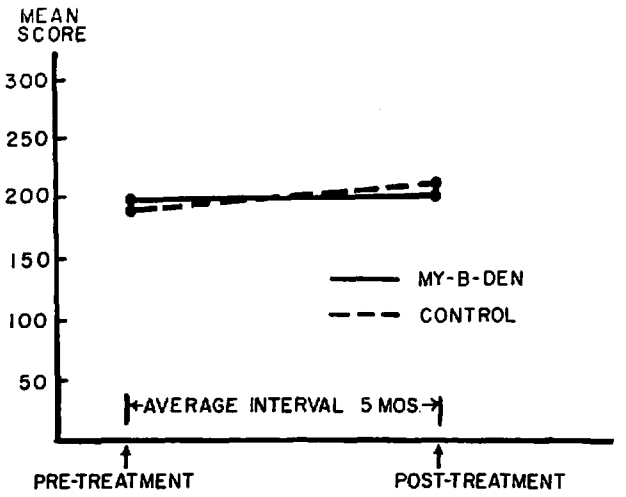

Figure 39. Effect of muscle adenylic acid (My-B-Den) on course of the disease. Mean scores in 170 treated patients and 170 matched control patients.

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,[50] 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.

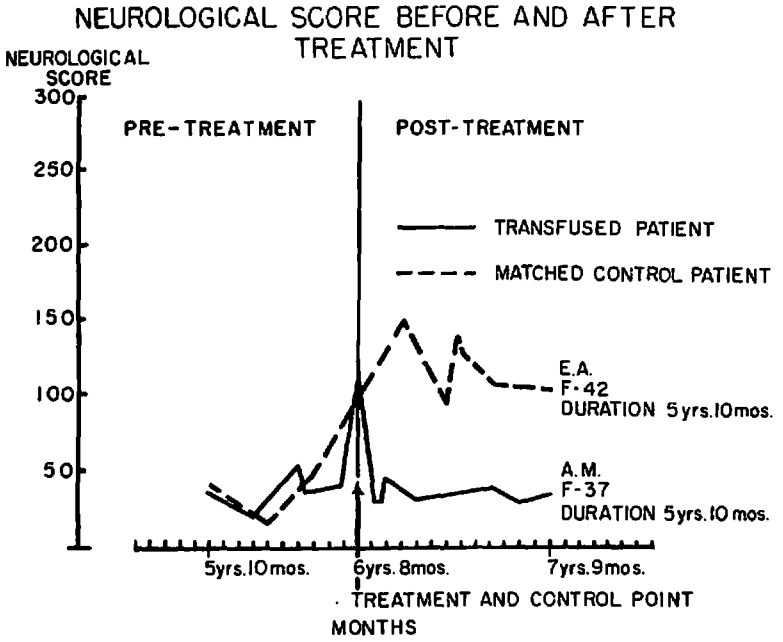

Figure 41.

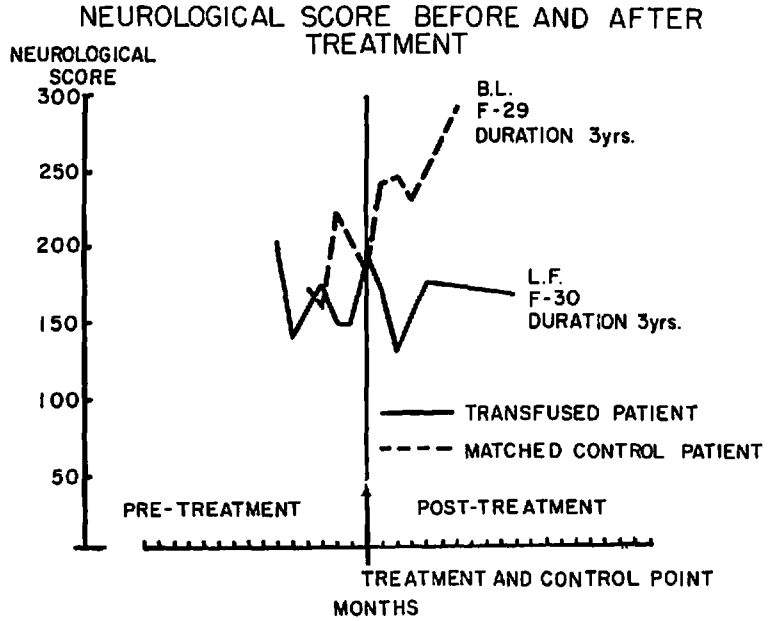

Figure 42.