October 10, 1963

CEREBELLAR ATAXIA

[redacted])

This patient was born in [redacted]. There was no evidence of abnormality at birth. The first 6 years of his life he developed normally but was noted to be clumsy in his gait about the time he started school. To the gait difficulty was added a tremor of neck and trunk with coarse and irregular to and fro movements of the head. Eating and drinking became progressively impaired over the next 6 years and he took to moving around on hands and knees. He could not go to school and appeared intellectually dull. Because of tongue tremor his speech became very difficult to understand.

When seen in consultation 1959 he was sitting on the floor, rocking back and forth with his head shaking at a different rate. His speech was slurred and limited to a few expressions. He had no telangiectasias and no skin rash. His cranial nerves were intact. Muscle strength was good. No atrophy or fasciculations were noted. Sensory appeared intact. No contractures. Stretch reflexes in the legs were absent. Babinski's sign was not present.

Intense physical therapy improved his ability to feed himself and take care of himself and even speech therapy was moderately successful. Psychological testing revealed, however, that his IQ was below 30 and his ability to cooperate in the training program lessened rapidly. After about a year he returned to his previous status. His disease remained stationary over the next three years. During 1963 he had repeated infections, became bedridden and developed contractures. Wasting of muscles became apparent but could be attributed to deficient food intake. His face became mask-like and he had repeated "choking" spells when eating and drinking. For the first time seizures were noted and he was admitted because of these in [redacted] 1963. Shortly after discharge he developed high fever, had pneumonia on x-ray and had to be readmitted. While in the hospital he had several episodes of hypotension and Cheyne-Stokes respiration and he expired suddenly. No post-mortem.

PMH [redacted]

This 38 y/o [redacted] female was in good physical shape until 1960 when she noted the onset of walking difficulties consisting of staggering and falling to either side. She felt weak and dizzy, particularly when changing position. When admitted she was noted to have considerable static tremor of arms and legs. Her handwriting was very poor and previous specimens on the chart dating from 1947 and 1954 showed that a marked deterioration had taken place. She was ataxic on testing, left more than right. Objective strength was normal as were cranial nerves, sensory system and reflexes.

Further work-up included normal pneumoencephalogram, normal total spinal fluid protein with a relative increase in the α-2 fraction. Urine amino acids were normal. An increase in spinal fluid glutamic and aspartic acids was noted.

PMH [redacted]

33 y/o [redacted] female with normal development until age 21 when onset of rhythmical head tremor was noted. This remained the only sign of disease until 6 years ago when her

legs began to feel unsteady and her handwriting rapidly worsened. She also developed recurring muscle spasms in legs and shoulders with no visible fasciculation and no EMG evidence of denervation. On examination in 1957 she was moderately ataxic with marked static tremor of head and tongue. She had no sensory changes, was strong and had normal reflexes. Her pupillary reactions were sluggish. Serology was normal. She had one normal daughter, two miscarriages and a stillborn male infant. She has been getting worse steadily but slowly and no new systems of the brain have become involved. She has normal amino acid patterns in urine and spinal fluid and normal serum electrophoresis.

REFERENCES

Few electrophysiological studies have been added since last review and the main advances can be found in the following three references which also contain summaries of earlier work on cerebellar function.

1. Granit, R. Receptors and sensory perception. Yale Univ. Press. 1955. Chap. 7.

2. Dow, R. S. Some aspects of cerebellar physiology. J. Neurosurg. 18: 512-530. 1961.

3. O'Leary, J. A litre and a half of brains II. Arch. Neurol. 8: 35-49. 1963.
Hereditary and/or familial ataxia in animals.

4. Schut, J. W. Olivo-ponto-cerebellar atrophy in a cat. J. Neuropath. Exp. Neurol. 5:77-81. 1946.

5. Brouwer, B.: Familial, olivo-ponto-cerebellar hypoplasia in cats; Psychiat. Neurol. Bl. 38:352-367. 1934.
Similar disease in children, see Ford. p. 400 Ed. 3. 1952.

6. Sawin, P. B., Anders, M. V., and Johnson, R. B. Ataxia, a hereditary nervous disorder of the rabbit. Proc. Nat. Acad. Sci. 28: 123-127. 1942.

7. O'Leary, J. L., P. B. Sawin, S. Luse, A. B. Harris and L. S. Erickson: Hereditary ataxia of rabbits. Arch. Neurol. 6: 123-137. 1962.
Onset at age 60 days with 10-90 days duration and always fatal. Single recessive gene. Cerebellar, vestibular, cochlear motor cranial nerves. Globular dilatation of terminal arborisations of axons, involving the myelin sheath and leaving the axon intact for some time. Little glia involvement or reaction. Enzyme studies and amino acid secretion studies have been normal.

8. Locke, S. and J. M. Foley. A case of cerebellar ataxia, with a discussion of classification. Arch. Neurol. 3: 279-289. 1960.
Progressive cerebellar, dorsal ganglia and pyramidal signs. Purkinje cells lost, cerebellipetal fibers affected, cerebellifugal fibers left intact. On the basis of the pathological findings, the authors propose a spinal, a cerebellipetal and a cerebellifugal classification.

9. McHenry, Jr., L. C., J. M. Foley and O. S. Marin. Focal cortical cerebellar sclerosis. Arch. Neurol. 3: 46-54. 1960.
Focal areas of varying size with complete loss of all cell types and myelin. Intense gliosis. No clinical signs.

10. Victor, M., R. D. Adam, and E. L. Mancall. A restricted form of cerebellar cortical degeneration occurring in alcoholic patients. Arch. Neurol. 1: 579-688. 1959.
Clinical picture dominated by leg involvement with rapid evolution followed by years of stability. Heavy drinkers of at least 7 years duration (the majority over 25 years). Nutritional depletion occurred in many but not all. All neurocellular elements in the cortex involved with lesions limited to anterior and superior portions

of the cerebellum. Although in older people a slight decrease in cell-population always takes place the reduction seen in these cases amount to 75-80%. No deep nuclei involvement. There is no indication that the areas involved can be separated from others by virtue of any unique enzymatic, biochemical or pharmacological properties. A reversible, week-long, transient ataxia is seen in alcoholics after severe drinking. For discussion of the latter, see

11. Decker, J. B., C. E. Wells and F. McDonell; Cerebellar dysfunction associated with chronic alcoholism. Neurology 9: 361-366. 1959.

12. Friede, R. L. Cerebellar edema. Arch. Neurol. 8: 67-81. 1963.
Relevant data from this work indicate a uniform distribution of oxidative enzymes between different regions of the cerebellum with smaller amounts in the molecular layer. Anaerobic glycolysis with lactic acid formation leads to granular layer edema with marked swelling, tearing of Purkinje axons, and subsequent degeneration of the cell bodies.

Agents capable of inducing cerebellar lesions include nitrogen chloride, DDT, thiophene, organic mercury compounds, Dilantin, heat and anoxia.

13. Hunter, D. and D. S. Russell. Focal cerebral and cerebellar atrophy in a human subject due to organic mercury compounds. J. Neurol. Neurosurg. and Psychiat. 77:235-241. 1954.

14. Cruickshank, E. K. Neurological disorders in the tropic. In Modern Trends in Neurology. 3. ed. Williams. Butterworths, Wash. 1962. Chap. 12.
Minamata disease which affects among many other parts of the brain also the granular cells but not Purkinje cells. It is actually the result of organic mercury poisoning.

15. Hoffman, W. W.: Cerebellar lesions after parenteral Dilantin® administration. Neurology 8:210-219.1958.
Dilantin effect in the case has been questioned by Victor et al (ref.) and could be anoxia.

16. Krainer, L. Lamellar atrophy of the Purkinje cells following heat stroke. Arch. Neurol. Psychiat. 61:441-444.1949.

17. Brain, W. R., P. M. Daniel and J. G. Greenfield. Subacute cortical cerebellar degeneration and its relation to carcinoma. J. Neurol. Neurosurg. and Psychiat. 14:59-75.1951.

Active destructive process with microglia and neutral fat. Olives usually spared (time course?).

18. Siebert, R. G., H. M. Keith and F. R. Dion: Ataxia-Telangiectasia in children. Proc. Staff. Meet. Mayo Clin. 34:581-587.1959.
Apparent onset with the beginning of walking. Mild choreo-athetosis. Oculocutaneous telangiectasias beginning at age 3 in conjunctiva, butterfly area of face and flexor areas of limbs. Mental deterioration after age 9. Purkinje cell degeneration.

19. Korein, J., P. A. Steinman and E. H. Senz. Ataxia-telangiectasia. Arch. Neurol. 4: 272-280. 1961.
Temporary improvements seen in the ataxia and mental impairment develops late. The recurrent sinopulmonary infections are very dangerous.

20. Gutmann, L. and L. Lemli. Ataxia-Telangiectasia associated with hypogammaglobulinemia. Arch. Neurol. 8:318-327.1963.

Gamma globulins in three siblings with similar manifestations ranged from 0.1-0.6 G/100 ml with normals given as 0.75-1.2 G/100 ml. One case had no antibody response to typhoid but an anti-B titer of 1:2. The lowered gamma globulin is proposed to explain the tendency to recurrent infection.

Bassen-Kornzweig Syndrome

Cerebellar ataxia, proprioceptive loss, myopathy(?), retinitis pigmentosa and acanthocytosis.

21. Bassen, F. A. and A. L. Kornzweig. Malformation of the erythrocytes in a case of a typical retinitis pigmentosa. Blood 5:381-387.1950.

18 y/o female. Had few menses, male type of hairgrowth, arched palate. Younger brother studied later. Both ataxic.

22. Mier, M., S. O. Schwartz and B. Boshes. Acanthocytosis, pigmentary degeneration of the retina and ataxic neuropathy: A genetically determined syndrome with associated metabolic disorder. Blood.16:1586-1608.1960.

Onset at age 17. Had a persistent diarrhea as a child just as the case of Bassen and Kornzweig. Refsum's disease does not come with blood abnormalities, but has the other manifestations.

23. Schwartz, J. F., L. P. Rowland, L. A. Edes, P. M. Marks et. al. Bassen-Kornzweig Syndrome. Trans. Am. Neurol. Assoc. 1961. p. 49-53.

In the discussion Korey contrasts this disease (β-lipoprotein deficiency) with α-lipoprotein deficiency (Tangier disease). He also raises the questions if (1) there is a linked deficit, since absorption or transport disturbance would not explain CNS abnormality because most of its lipids are made from small molecules, or (2) if (as Eder has indicated) the thorny cell appearance is reversible by adding a lipid emulsion, is the whole neurological picture one of membrane disturbance? Is it (asks Korey) a β-lipoprotein deficiency or a conjugation deficiency?

24. Salt (1960) found β-lip.↓↓ (50%). Blood. 16.1960.p.1814.

25. Centervall, W. R. and M. M. Miller. Ataxia, telangiectasia and sinopulmonary infections. J. Dis. Child. 95.385-396.1958.

Photosensitivity may be a factor because of the 20 cases known in 1958; 9 were from Southern California. Normal Laboratory values, including amino-acids. Neuroectodermal syndrome, with some relation to Von Hippel-Lindau.

26. Schwartz, J. F., L. P. Rowland, H. Eder, P. Marks, E. F. Osserman, E. Hirschberg and H. Anderson. Bassen-Kornzweig Syndrome. Deficiency of serum β-lipoprotein. Arch. Neurol. 8.438-454.1963.

27. Fine, D. Y., K. D. Barron and A. Hirano. Central nervous system lipidosis in an adult with atrophy of the cerebellar granular layer. J. Neuropath. Exp. Neurol. 19:355-369. 1960.

Clinical course: Progressive cerebellar dysfunction and muscular atrophy over 17 years. No amaurosis and no mental deterioration (excellent chess player). Intraneuronal lipid deposits in spinal cord, anterior horn cells and granular cells with staining characteristics of protein bound ganglioside. Purkinje cell dendrites were distended by lipid.

28. Gilbert, G. J., W. G. McEntee III and G. H. Glaser. Familial myoclonus and ataxia. Neurology 13.365-372.1963.
Unexplained finding of elevated spinal fluid uric acid with otherwise normal serum values and normal amino acid pattern in urine. Normal serum electrophoresis. Latest reported cases of the group originally described by

29. Hunt, J. R.: Dyssynergia cerebellaris myoclonica. Brain 44:490-538.1921.

Marinesco-Sjögren Syndrome.

Cerebellar ataxia, congenital cataracts, retarded mental and physical maturation; (skeletal anomalies).

30. Marinesco, G., St. Draganesco, and Vasilu, D.: Nouvelle maladie familiale caractérisée pár une cataracte congenitale. L'Encephale 26:97-102.1931.

31. Sjögren, T.: Hereditary congenital spinocerebellar ataxia accompanied by congenital cataracts and oligophrenia. Neurol. 10.293-305.1950.

32. Alter, M., O. R. Talbert and G. Croffead. Cerebellar ataxia, congenital cataracts, and retarded somatic and mental maturation. Neurology 12.836-847.1962.
Autosomal recessive disease with pronounced limb ataxia, dysarthria and nystagmus. A few of the cases have had low blood calcium values.

33. Milne, M. M., M. A. Crawford, C. B. Girao and L. Lochridge. The Metabolic abnormality of Hartnup disease. Quart. J. Med. 29:407-422.1960.
Defective tryptophan transport with decreased amount or efficiency of tryptophan pyrrolase. Therefore an abnormal excretion of indolic acids. See also

34. Gepson, J. B. and M. G. Spiro. Hartnup disease. in The metabolic basis of inherited disease. McGraw-Hill. 1960. Chap. 43.

35. Bergstedt, M., S. Johansson and R. Müller. Hereditary spastic ataxia with central retinal degeneration and vestibular impairment. Neurology 12.124-132.1962.
Initially leg involvement, then color vision blindness, decreasing visual acuity and on laboratory testing non-reactive labyrinths.

36. Malamud, N. and Cohen, P. Unusual form of cerebellar ataxia with sex-linked inheritance. Neurology 8:261-266.1958.
Male children only with cerebellar ataxia which in the course of 5-10 years was replaced by rigidity and athetosis.

37. Smith, J. K., V. E. Gonda and N. Malamud. Unusual form of cerebellar ataxia. Neurology 8.205-209.1958.
Cerebellifugal degeneration, ballismus and rigidity. Onset in adult life. No other cases in family.

38. Farmer, J. W. and V. M. Mustian. Vestibulocerebellar ataxia. Arch. Neurol. 8.471-480. 1963.
A new entity consisting in periodic attacks of vertigo, diplopia and ataxia beginning in early adult life and continuing over many years before a chronic, slowly progressive cerebellar disease starts. Amino-acids in urine were normal. Nystagmus is rather prominent. A slightly different type with periodic acute ataxia episodes was described by

39. Parker, H. L.: "Periodic ataxia". Coll. Papers Mayo Clin. and Mayo Found. W. B. Saunders Company 1947. Vol. 28. p. 642.
The syndrome is also the one clinically most similar to that described by O'Leary et al. in rabbits (see ref.)

CHART 1.

Porter-family

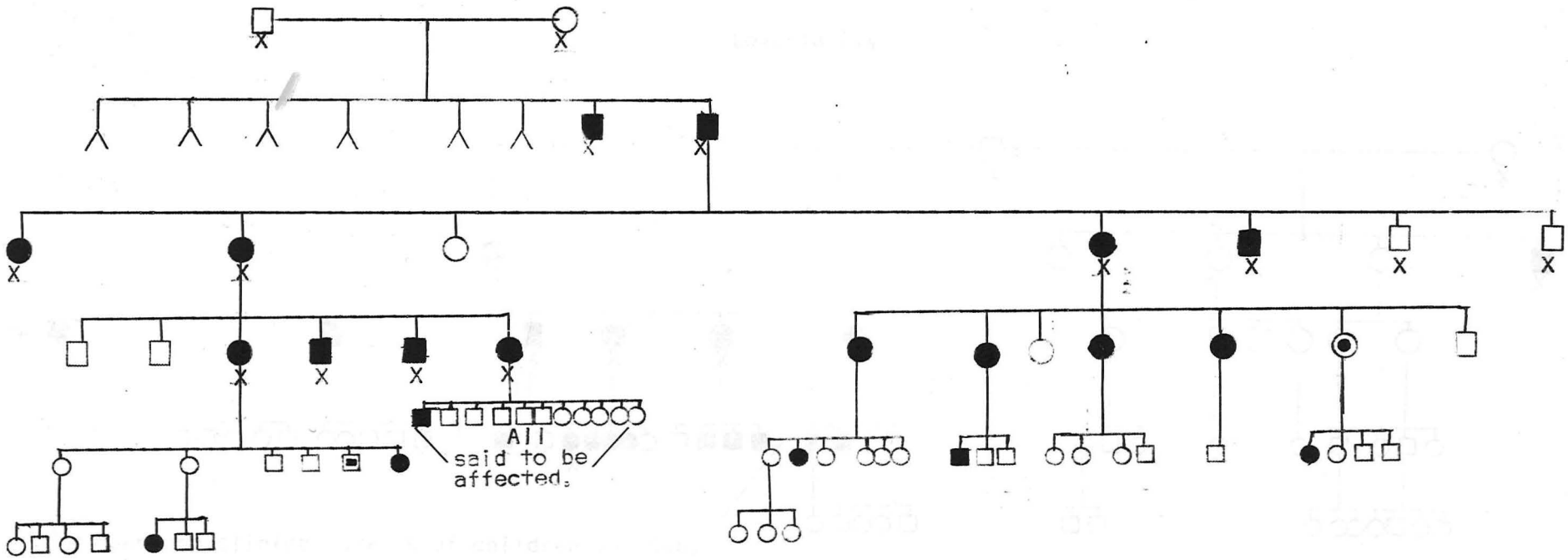

CHART 2.

Love-family