HANDBOOK OF CLINICAL NEUROLOGY

VOLUME 21

SYSTEM DISORDERS AND ATROPHIE
PART I

SYSTEM DISORDERS AND ATROPHIES

PART I

Edited by

P.J. VINKEN and G.W. BRUYN

in collaboration with

J.M.B.V. DE JONG

(内部交流)

Associate Editor

HAROLD L. KLAWANS JR.

NORTH-HOLLAND PUBLISHING COMPANY · AMSTERDAM · OXFORD
AMERICAN ELSEVIER PUBLISHING CO., INC. · NEW YORK

Library of Congress Catalog Card Number: 68-8297

ISBN for the complete set: 0 7204 7200 8

ISBN North-Holland for this volume: 0 7204 7221 0

ISBN American Elsevier: 0 444 10845 9

201 illustrations, 41 tables

PUBLISHED BY:

NORTH-HOLLAND PUBLISHING COMPANY · AMSTERDAM
NORTH-HOLLAND PUBLISHING COMPANY, LTD. · OXFORD

SOLE DISTRIBUTORS FOR THE U.S.A. AND CANADA:

AMERICAN ELSEVIER PUBLISHING COMPANY, INC.
52 VANDERBILT AVENUE
NEW YORK, N.Y. 10017

PRINTED IN THE NETHERLANDS

Foreword to volumes 21 and 22

Quite a number of neurological function disorders have benefited from the considerable advances which have been made since the turn of this century (for example, the discovery of slow-virus disease, dopamine deficiency in parkinsonism and GAD deficiency in Huntington's chorea, immunopathological mechanisms, dexamethasone's protection in serious central craniocerebral trauma, and the value of vascular surgery in occlusive cerebrovascular disease). The application of advanced biomedical methods, procedures and apparatus have necessitated a more simple rearrangement of nervous and muscular disorders along lines which essentially represent cause and pathogenesis, rather than phenomenology. Neurological nosology has, in general, become somewhat more simplified

One fairly large group of disorders has been left behind, however, in this elucidatory process and yet it belongs more or less to the very heart of clinical neurology, i.e. the heredo-'degenerative' disorders. The term degenerative arouses no small amount of opposition amongst a number of our colleagues, due to the supposed pejorative element attaching to it. The Editors are not able to share this view. Their own thoughts on the subject are given in the Foreword to Volume 13 and remain unaltered.

Spinocerebellar degenerations, pyramidal tract degeneration, 'system' degenerations and such like constitute a large field of disorders, the study of which, in the Editors' view, has not progressed much beyond the descriptive level. In general, this is probably due to the fact that it is much less difficult to elucidate the pathogenesis of disorders in which some intermediate metabolite appears as a pathological storage product, than to discover why a part of the nervous system disintegrates without leaving remnants testifying to the nature of the disease process. As a consequence, the treatment of these disorders is alleviatory and palliative rather than rational and effective. Perhaps only a neurologist can experience those particulier feelings of inadequacy which manifest themselves when one is called upon to assume the care of a patient with amyotrophic lateral sclerosis, or progressive spinal muscular atrophy, Strümpell-Lorrain's disease, bulbar paralysis, or olivopontocerebellar degeneration. These volumes embody the current state of our knowledge on these disorders. Neurology has still to find the answers to these diseases and their victims must continue perforce to suffer. The Editors hope, however, that these volumes will contribute

not only to a greater understanding of them, but, hopefully, also to fresh attempts to solve their encumbering riddles.

The main ordinate of lay-out is topographic: firstly, those disorders involving the nerves, followed by those involving the spinal cord, and concluding with those of the cerebellum and brain stem. The Editors have maintained the attitude of reluctant splitters. In their opinion, the moment of lumping together has not yet arrived. Since the knowledge necessary to decide in this matter is not available, they have not forced their view on the authors.

These volumes, originally planned in 1967, have had to sustain a large number of delays, not the least of which were manuscripts lost in transit, authors who proved more than difficult to reach, and so on and so on. A great blow was dealt by the lamented death of Professor Lumsden, who was to have written a major introductory chapter. In him, neurology has lost an internationally acknowledged expert.

Although it is perhaps inviduous to single out particular authors for special mention, the Editors must use this occasion to confirm their indebtedness to their colleagues Eadie, Sutherland, Tyrer, Zeman, Norris and Dubowitz. To them and our other colleagues, the Editors owe their sincere thanks for the excellence of the contents of these volumes.

In a somewhat unusual departure from custom, the Editors are happy to acknowledge the debt they owe to the three desk editors concerned with these volumes, Mrs. L. Philipp, Mrs. W. H. Posthuma, and Mr. R. W. Stanley, for having helped us with their production. Their sense of purpose was of great encouragement in our labours.

Having concluded our paean, we must leave it to the reader to determine whether we are right in believing that these two volumes provide that level of coverage needed for a group of syndromes essentially constituting the main challenge to current clinical neurology.

P. J. V.
G. W. B.
J. M. B. V. de J.

Acknowledgement

Several illustrations and diagrams in this volume have been obtained from other publications. Some of the original figures have been slightly modified. In all cases reference is made to the original publications in the figure caption. The full sources can be found in the reference lists at the end of each chapter. The permission for the reproduction of this material is gratefully acknowledged.

List of contributors

C. Andrade
Institute of Neurology, St. Anthony's Hospital, Oporto 119

Martin Bergstedt
Otological Clinic, Central Hospital, Karlskrona 383

A. Biemond †
Amsterdam 377

A. Roger Bobowick
Epidemiology Branch, National Institute of Neurological Diseases and Stroke, National Institutes of Health, Bethesda, Md. 3

François Boller
Department of Neurology, Case Western Reserve University Medical School, Cleveland, Ohio 389

Jacob A. Brody
Epidemiology Branch, National Institute of Neurological Diseases and Stroke, National Institutes of Health, Bethesda, Md. 3

Jan Cammermeyer
Laboratory of Neuropathology and Neuroanatomical Sciences, National Institute of Neurological Diseases and Stroke, NIH, PHS, U.S. Department of Health, Education and Welfare, Bethesda, Md. 231

Jean de Recondo
Department of Neurology, Saint Anne Hospital Center, Paris 271

Dorsey Dysart
New Orleans, La. 563

M. J. Eadie
Department of Neurology and University Department of Medicine, Royal Brisbane Hospital, Brisbane 365, 403-459

Gordon J. Gilbert
St. Petersburg, Fla. 509

Wayne Hill
New Orleans, La. 563

D. A. Howell
Department of Neurology, The Churchill Hospital, Headington, Oxford 467

Jean Lapresle
Hospital Centre of Bicêtre, Le Kremlin Bicêtre 171

R. G. Lascelles
Department of Neurology, Royal Infirmary, Manchester 145

Mohsen Mahloudji
Department of Neuropsychiatry, Pahlavi University School of Medicine, Shiraz 555

Elliott L. Mancall
Division of Neurology, Hahnemann Medical College and Hospital, Philadelphia, Pa. 477

J. J. Martin
Department of Neuropathology, Born-Bunge Foundation, Berchem-Antwerp 587

W. B. Matthews
Department of Neurology, The Churchill Hospital, Headington, Oxford 467

Richard F. Mayer
Department of Neurology, University of Maryland School of Medicine, Baltimore, Md. 87

Sigvald Refsum
Department of Neurology, Rikshospitalet, University of Oslo 181

Maria Salam
Department of Neurology, Massachusetts General Hospital, Boston, Mass. 573

Pedro Salisachs
Hospital Centre of Bicêtre, Le Kremlin Bicêtre 171

Franz Seitelberger
Neurological Institute, University of Vienna 43

Jose M. Segarra
Department of Neurology and Neuropathology, Boston University School of Medicine, Boston, Mass. 389

J. K. Smith
Department of Neurology, The Permanente Medical Group, Kaiser Foundation Hospital, Walnut Creek, Calif. 519

Gilbert B. Solitaire
Department of Pathology, Yale University School of Medicine, New Haven, Conn. 107

G. Stewart
Medical Research Council Unit for Human Biochemical Genetics, University College, London 145

P. K. Thomas
Department of Neurology, Royal Free Hospital, London 145

John H. Tyrer
Medical Professorial Unit of Queensland University, Royal Brisbane Hospital, Brisbane 263, 319

C. E. C. Wells
University Hospital of Wales, Cardiff 73

Wolfgang Zeman
Department of Neuropathology, Indiana University, Indianapolis, Ind. 535

Contents

CHAPTER 1

General pathogenetic mechanisms of the systemic atrophies

The Editors had intended to open Volumes 21 and 22 with an introductory review of biochemical, infectious and nutritional pathogenetic mechanisms in the systemic atrophies.

Professor C. E. Lumsden, M.D., F.C.Path., Head of the Department of Pathology at the University School of Medicine at Leeds accepted the onerous task to write such a chapter. In view of the numerous and aetiologically very heterogeneous disorders collected in the present volumes, the Editors had arranged with him that his contribution would be written after the manuscripts for all other chapters had been received.

In the summer of 1974, Neurology sustained a grievous loss in Professor Lumsden's sudden death after a brief illness that ended a fruitful and very active scientific career.

During the years of close connection with the Editors, Professor Lumsden showed himself to be a most amiable and witty man, a deep-thinking writer and at all times a gentle and courteous man. He was, indeed, a man for all seasons and we have no doubt that much of this was due to the influence of his alter ego, Jacqueline. His letters and conversations were invariably a source of delight. We shall miss this as so many other things in his passing. One of the secrets of his beautiful scientific prose was that his manucripts were cast like statues, not knit like socks. He would have been sad to have known that he would be taken from us at the time when he had finished collecting his material and was all set to bring forth the fruit of his labour. Over a period of 35 years Professor Lumsden rendered an impressive contribution to the body of neurological knowledge, as witnessed by his authorship of more than 70 original papers and about 15 books. He never squandered his energy on trivial problems, and concentrated mainly on the investigation of multiple sclerosis, demyelinating disorders, immunopathology of the central nervous system and leprosy. To these fields he brought numerous new techniques of investigation. It is doubly sad that his dearest wish, to be alive when the enigma of multiple sclerosis would at last be unraveled, has not been granted. The Editors can only hope that some reader of this page may be equal to the task which Professor Lumsden's death has caused to be left unfinished.

The Editors

CHAPTER 1

General pathogenetic mechanisms of the systemic atrophies

Epidemiology of neurodegenerative system disorders

A. ROGER BOBOWICK
and
JACOB A. BRODY

Epidemiology Branch, National Institute of Neurological Diseases and Stroke, National Institutes of Health, Bethesda, Md.

This discussion will be limited to the population characteristics of this group of neurodegenerative disorders. The purpose is to mention the problems of classification, to discuss the application of epidemiologic methods and to examine to what extent these epidemiologic methods have been applied.

For convenience, the neurodegenerative disorders considered here were grouped under 3 general headings: hereditary neuropathies, hereditary spinocerebellar degenerations, and motor neuron diseases. Tables 2, 4 and 8 offer a survey by tabulating the most widely recognized syndromes in these groups. The tables are a convenient frame of reference and are not intended to be a definite classification system.

There may be considerable clinical and pathologic overlap among these disorders and for the past 70 years neurologists have lamented the resultant nosologic tangle. Ultimately a disease classification should be based on etiology. However when etiology is being sought observational data either biochemical, morphologic, genetic or clinical must be used. With hereditary diseases phenotypic expression may vary while the genotype is relatively constant. Because of the limitations of current knowledge one is faced with numerous interpretations which have resulted in an almost unmanageable profusion of syndromes.

Cobb and Bereday (1953) attempted to organize the chaos in the neurological literature by pointing out that among the familial system diseases of the neuraxis there were 8 main syndromes among more than 50 clinical pictures that had been described. The syndromes are: infantile muscular atrophy (Werdnig–Hoffmann); familial spastic paralysis (Freud–Jendrassik); hypertrophic neuritis Deierine–Sottas); peroneal muscular atrophy (Charcot–Marie–Tooth); familial areflexic dystasia (Roussy–Lévy); spinal ataxia (Friedreich); cerebellar ataxia (Marie) with or without optic atrophy; optic atrophy (Leber) with familial spastic paralysis, hypertrophic neuritis, or peroneal muscular atrophy.

The authors also listed 4 secondary characteristics often found combined with one of these syndromes. They are: pes cavus, scoliosis epilepsy, and dementia.

The syndromes seem to be the functional result of various combinations of 14 localizable lesions in the neuraxis which they listed: retinal degeneration; optic atrophy; mid-brain lesions with pupillary dysreflexia; mid-brain lesions with progressive ophthalmoplegia externa; cerebellar atrophy, nuclear; pontine atrophy; olivary atrophy; cochlear degeneration; degeneration of dorsal tracts of the cord; spinocerebellar tract degeneration; pyramidal tract

References p. 36

degeneration; ventral horn cell degeneration; radicular neuropathy; hypertrophic neuropathy.

This attempt to balance the excessive separation ('splitting') of disorders with a simplified grouping ('lumping') was welcomed by Woodworth et al. (1959) who suggested converting the Cobb and Bereday classification of heredofamilial diseases into a code for designating the clinical and anatomic features.

However, the anatomic substrate is frequently unknown and classification must be based on semiology (symptoms and signs) alone. Recently Drachman (1968 and Vol. 22 of this Handbook) has provided an example of the pitfalls of present-day nosologic systems, based on semiology.

Nevertheless, overlapping observations are the data that must be worked with to understand obscure disease. A composite of most of the pathologic, semiologic and laboratory observational data that might enter into a classification of these system disorders is offered in Table 1.

The epidemiologist relies on the proper identification of the clinical entities he is to measure. However, pathologic taxonomy is the basis of disease classification today. Consequently there is a disturbing distance between the common classification system and the actual data observed. Feinstein (1967) has lucidly detailed the implications of these problems in taxonomy. While recognizing that pathologic taxonomy is established as a unifying diagnostic language, he would also have the clinician classify his 'observations' rather than his 'inferences' about pathology. Problems of criteria would thus be simplified and the dimension of time or natural history could be included. In this way the illness that is the interaction of host and disease would be classified rather than one or the other. Using Boolean mathematical concepts of union, intersection and complementation of sets and Venn diagrams, Feinstein has offered a model for the total spectrum of human disease. Patients are grouped into those with clinical complaints who therefore seek medical attention and those who escape attention because they do not complain – termed 'lanthanic' (from the Greek 'lanthanein' – to escape notice). A second grouping is based on the presence of primary or secondary features of the disease. Finally the total spectrum of human disease will include a group discovered only at death and a 'core' of undiscovered disease. These concepts have been put into diagrams by Feinstein with the view-

TABLE 1

Observational data operant in a classification of neurodegenerative system disorders.

Symptomatology
blindness
dementia
rigidity and choreoathetosis
pupillary dysreflexia
ophtalmoparesis
ataxia of gait, limb, speech
tremor
myoclonus
nystagmus
deafness
sensory loss
spasticity
areflexia
amyotrophy
motor weakness
Laboratory findings
spinal fluid protein
nerve conduction and electromyography
serum abnormalities of lipid metabolism, or immunoglobulins
Associated findings
pes cavus
kyphoscoliosis
cataracts
epilepsy
cutaneous abnormalities and trophic changes
cardiac and visceral disorders
Pathology
retinal degeneration
optic atrophy
cerebral cortical atrophy
basal ganglia neuronal loss
midbrain neuronal loss
cerebellar degeneration
pontine neuronal loss
olivary degeneration
cochlear degeneration
posterior column degeneration
spinocerebellar tract degeneration
pyramidal tract degeneration
anterior horn cell loss
spinal ganglion cell degeneration
hypertrophic neuropathy

point of different observers included (Fig. 1).

An appropriate illustration of the spectrum of a disease is seen in peroneal muscular atrophy (Charcot–Marie–Tooth disease). There is a large lanthanic population of uncomplaining people who escape medical attention. The secondary feature of pes cavus accounts for another population of patients who may or may not seek medical attention. The primary feature of a benign slowly progressive distal motor-sensory neuropathy overlaps with these subpopulations to complete the spectrum of disease. Complete ascertainment of these subsets is necessary in order to describe, classify and index patients, using various modes of detection and taking into account the general clinical stage in which the patient is seen (Fig. 2).

In the light of present knowledge and approaches, these idealized concepts of the spectrum of human disease are relevant and workable only rarely for the disorders considered here. Application of these principles however, would allow a more accurate description of the population dynamics of disease – that is, better epidemiology.

Epidemiology is the study of the distribution of disease in a population and all the environmental and host factors affecting the distribution. It is the aim of the epidemiologist to determine meaningful correlations between the appearance of specific syndromes in given populations which could lead to a better understanding of the etiology and prevention of the disease. With many of the neurodegenerative system disorders, major reliance must also be placed on the geneticist to achieve a more complete understanding.

Epidemiologic observations on the chronic neurologic diseases considered here are sparse and for the most part limited to studies of general population characteristics. Such descriptive data are of limited value because of the difficulties of case ascertainment using precise comparable clinical definitions and classifications. Most investigations have been confined to individual patient series and mortality data. There have, however, been several careful surveys in which a population is defined as the denominator among which specific syndromes are identified and using these identified cases as the numerator the rates of given diseases have been calculated. Rates by convention are presented in terms of 'incidence' or the number of new cases per 100,000 people per year, or in terms of 'prevalence' or the number of living cases per 100,000 on a specified day.

HEREDITARY NEUROPATHIES

For the most part the hereditary neuropathies considered here are quite rare and their population characteristics are confined to individual and family reports. The sensory syndromes of childhood as represented by the first 5 entries in Table 2 are particularly uncommon. The nosology of these childhood sensory syndromes is, of course, still being delineated.

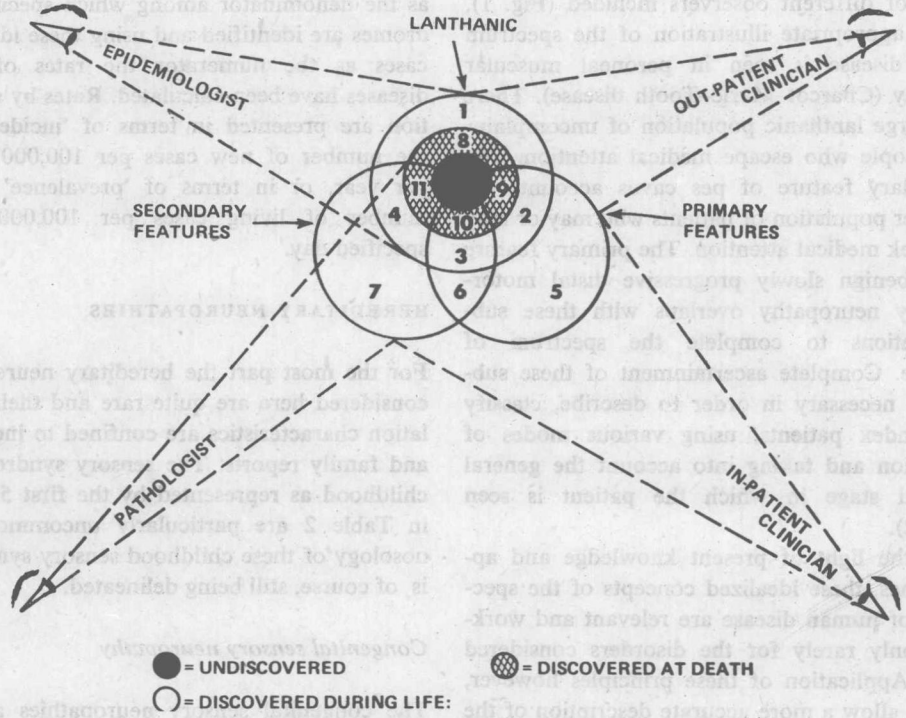
Congenital sensory neuropathy

The congenital sensory neuropathies and the indifference to pain syndrome present with similar clinical pictures of infants and children who have repeated injury due to their failure to avoid noxious stimuli. Careful evaluation of sensory and autonomic function will allow the clinical classification to be made.

Familial dysautonomia

Despite its rarity, familial dysautonomia has been the subject of recent population surveys in Israel and North America. The disease is considered to be inherited as an autosomal recessive trait. Up to 1970, 34 cases of familial dysautonomia had been diagnosed in Israel (Rotem 1970). Moses et al. (1967) in their study of all known living cases of familial dysautonomia in Israel had uncovered 23 individuals all less than 20 years of age. The population at risk according to Israeli census figures for 1964 was 360,000 Ashkenazi Jews in the age group of 0 to 19 years. This gives an age-specific prevalence rate of 6.39 per 100 000. The authors calculated the gene frequency was 0.0091 and the heterozygous carrier frequency

References p. 36



● = UNDISCOVERED ⊗ = DISCOVERED AT DEATH

○ = DISCOVERED DURING LIFE:

1. Lanthanic asymptomatic
2. Lanthanic primary
3. Lanthanic combined
4. Lanthanic secondary
5. Complainant primary
6. Complainant combined
7. Complainant secondary
8. Lanthanic asymptomatic
9. Lanthanic primary
10. Lanthanic combined
11. Lanthanic secondary

Fig. 1. Total spectrum of human disease with the viewpoint of different observers. (Modified from Feinstein 1967.)

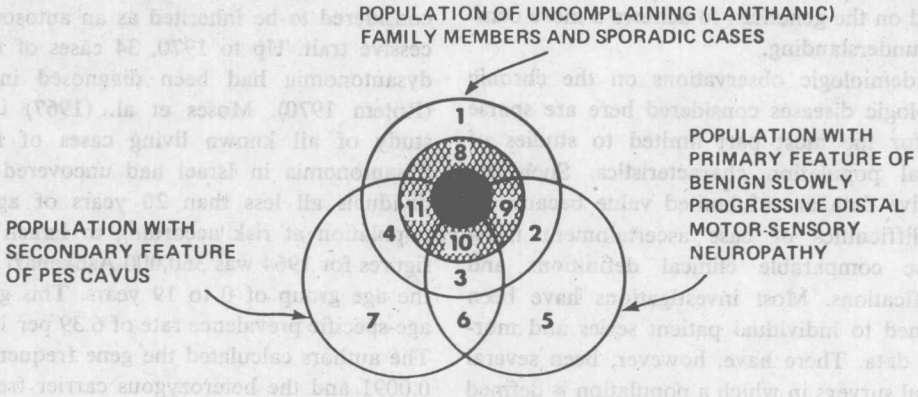


Fig. 2. Spectrum of Charcot–Marie–Tooth disease

References p. 36