HEAVY METALS AND THE BRAIN

By

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BLACKWELL
SCIENTIFIC PUBLICATIONS
OXFORD

Published simultaneously in the United States of America by Charles C Thomas, Publisher, 301–327 East Lawrence Avenue, Springfield, Illinois.

Published simultaneously in Canada by the Ryerson Press, Queen Street West, Toronto 2.

First printed in 1959

Printed in Great Britain for Blackwell Scientific Publications Ltd.
by A. R. Mowbray & Co. Limited in the City of Oxford
and bound at the Kemp Hall Bindery

PREFACE

WHEN Dr. Charles Aring suggested to me that I should write a book on heavy metals and the central nervous system, one special difficulty at once emerged. The list of heavy metals that appears in any elementary book on inorganic chemistry contains many more chemical elements than are commonly met with in either clinical neurology or in toxicology. However, excluding those that have recently received special attention, three metals—copper, mercury and lead—are known to cause pathological abnormalities affecting the brain. This volume is devoted then to the consideration of hepatolenticular degeneration, a disease associated with a disordered copper metabolism; also to the intoxications caused by mercury and lead, but only in so far as they affect the brain.

I am deeply grateful to all of my colleagues who have assisted me in discussions. A special word of praise and thanks must go to Miss J. Genower and to Mrs. S. Clements for their secretarial assistance, and to the former for her ability in the translation of some manuscripts. I would also like to thank Mr. J. A. Mills for his skill in photography.

May, 1958

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PART ONE

COPPER

HEPATOLENTICULAR DEGENERATION

CHAPTER 1

INTRODUCTION AND HISTORICAL NOTE

Toxic signs of excessive copper intake have been known for a number of centuries, in fact Thomas Percival[360] in 1785 described the intestinal lesions associated with the consumption of pickled samphire containing large amounts of copper, which led to the death of the seventeen year old girl ten days later.

Later in the nineteenth century Devergie was asked to investigate a fatal case of copper poisoning and he and his colleagues wrote a number of articles concerning this problem.[117 118 119] More recently there has been a review of the general effects of metallic poisoning including copper.[202] All these authors described intestinal symptoms unassociated with nervous lesions.

However, during the past decade it has been found that an abnormal copper metabolism is associated with one neurological condition, now commonly known as hepatolenticular degeneration or Wilson's disease and a brief historical note regarding this condition will first be given.

The published records will be discussed chronologically even though these have not always been correctly interpreted at the time of publication, and it is only in retrospect that one can judge with any degree of accuracy the march of progress.

Frerichs in 1858[150] probably described the first case that would now fall into this category. It was that of a young boy of ten years who had cirrhosis of the liver, an enlarged spleen, no obvious cerebral lesion but who during life showed symptoms suggesting an extrapyramidal lesion.

In 1883 Westphal[525] described two patients with tremor, difficulty in speech and as among other points there was no nystagmus they were considered not to be suffering from multiple sclerosis, but from a condition for which the new term of pseudosclerosis was coined. At the postmortem no obvious cerebral lesion was seen, nor was there any mention of cirrhosis of the liver.

In 1888 Gowers[178] described the clinical condition of a boy of ten years under the title 'tetanoid chorea.' Clinically this was discerned by Wilson to fall into the same type of case that he

described later, and at the postmortem on this boy a liver cirrhosis was found, although again the brain was not said to be abnormal. However, the liver cirrhosis in this case was not described until 1906. Gowers noticed that the disease might be familial, for he found that the sister suffered from the same disorder and she died at the age of sixteen years; another brother was also affected as mentioned by Wilson. Ormerod in 1890[353] described another boy of ten years who showed rather similar clinical features to those described by Gowers, but in whom at the postmortem not only was cirrhosis of the liver present, but there was also a bilateral softening in the putamen. Homén in 1890 and again in 1892[223 224] described a family of two brothers (aged nineteen and twenty-four years) and their sister (aged twenty-six years) all of whom had a tremor rather akin to chorea, but who at postmortem showed liver cirrhosis together with softening of the putamen. However Homén considered syphilis a possible aetiological factor, but this was prior to the days of the Wassermann test.

Strümpell in 1898 and 1899[459 460] described three cases clinically similar to those of Westphal and once more used the latter's term of pseudosclerosis, a name which unfortunately became popular especially in the German literature for a miscellaneous and mixed group of diseases.

In 1902 Kayser[246] described a zone of corneal pigmentation in a case which was diagnosed as multiple sclerosis, and this was followed a year later by Fleischer's[140] description of a similar lesion. This last author in 1909[141] described the histopathology of the zone we now know as the Kayser-Fleischer ring or zone. Salus in 1908[408] was, I believe, the first to point out the connection of this corneal zone of pigmentation with pseudosclerosis, to be followed four years later by Fleischer[142] who noted the same connection.

Anton in 1908[12] described the rather similar clinical findings in a girl of fourteen years, but there was thought at postmortem to be a gumma in the brain, and this case although included in my list may in fact not be one. Three years later Völsch[508] described the clinical findings in a girl of seventeen years who showed tremor, dysarthria and rigidity with dementia but with an absence of pyramidal signs. At postmortem, although cirrhosis of the liver was present, the brain presented no abnormality.

Wilson published in 1912 his paper which is accepted as of considerable importance.[526] He described four patients seen personally with details of two others which were related to Gowers' and to

Ormerod's cases respectively. He reviewed the relevant literature especially citing Gowers, Ormerod, Homén and Völsch. As well as an exhaustive clinical description of his cases he described the post-mortem findings in three of the four cases, in which he found not only liver cirrhosis, but also softening of the basal nuclei with cavitation also present. Histological studies were made and the results were given in considerable detail. Wilson further discussed possible aetiological factors, discarding most of the previously suggested theories—such as syphilis—but retaining the hypothesis that the cause was the result of a non-microbial toxin.

Hösslin and Alzheimer in 1912[229] described the histological changes, and especially the glial abnormalities in the brain, in pseudosclerosis. Since that time the name of Alzheimer has been attached to two types of cell found in the brain in this disease. Spielmeyer in 1920[444] re-examined the brain in a case of Fleischer's and found lesions in it similar to those already described by Wilson in his cases, so that the histology of both conditions, now known as hepatolenticular degeneration, was proved to be identical for all practical purposes.

Cases were now being described in many countries with occasional monographs such as those of Hall[196] and of Lüthy.[299] Hall was the first to use the term hepatolenticular degeneration, and he showed the unity of Wilson's disease and of pseudosclerosis. Unfortunately, during the first four decades of this century many cases have been described under one or other of these terms which do not belong to the group at all; especially is this true of cases of hepatic coma and of various forms of encephalitis which have been misdiagnosed, and have mistakenly been recorded as cases of hepatolenticular degeneration.

Other landmarks ought to be mentioned, such as the finding by Rumpel in 1913[403] of an increased copper content in the liver. Vogt in 1929[505] in one of Lüthy's cases, demonstrated an increased copper in the liver and brain, and Haurowitz recorded in 1930[203] the same finding. These copper abnormalities have been confirmed and will be discussed later in more detail.

Uzman and Denny-Brown in 1948[493] found an increased amino acid and Porter[379] an increased copper content in the urine, while in 1936 Policard *et al.*[370] proved the presence of copper in the Kayser-Fleischer zone.

Cumings in 1948[98] suggested that BAL should be used in therapy,

the value of which both he[99] and Denny-Brown and Porter[115] reported upon in 1951.

Scheinberg and Gitlin in 1952[415] reported the absence or gross diminution of caeruloplasmin in the sera of patients with this disease. Since 1951 many reports on biochemical features have been published which will be discussed in later chapters.

Terminology

It will be apparent to those studying the literature that many terms have been used to describe one condition. These names include pseudosclerosis, tetanoid chorea, torsion spasm (of Thomalla), progressive lenticular degeneration and hepatolenticular degeneration. Discussion raged furiously about this nomenclature in the first few decades of this century, and cases were allotted to specific groups. Yet as late as 1921 Wilson[527] claimed that his disease and pseudosclerosis were different. However, similarities were evident, for almost all correctly diagnosed cases coming to postmortem showed liver cirrhosis and, as already mentioned, on cerebral histology Spielmeyer found the same changes in pseudosclerosis as Wilson did in his material. Further, the Alzheimer cells, and even more the Opalski cell, said to be characteristic of pseudosclerosis, have been found in the brains of cases of hepatolenticular degeneration. Again, although the Kayser-Fleischer zone was described in a case of pseudosclerosis, Pollock in 1917[373] found it in a case of Wilson's progressive lenticular degeneration. The abnormal biochemical findings have also been found in all varieties of the disease.

The use of the term pseudosclerosis has been fairly and adequately discussed by Denny-Brown[114] while the remarks on this subject by Wilson[530] are somewhat biased. As many clinicians know, and as has been conclusively proved biochemically, there is a form of the disease to which the adjective pseudosclerotic can well be applied. It is of interest that Hall[196] was able to quote in his monograph not only examples of typical cases, but also those of a transitional nature. Seletski in 1924[431] and again in 1926[432] agreed that the term pseudosclerosis should be abandoned in so far as this name was intended to indicate a specific disease entity.

It is therefore intended in this volume to use only the name *hepatolenticular degeneration* to cover all types of cases.

CHAPTER 2

CLINICAL FEATURES

Definition

The disease, until recently regarded as a fairly rapidly fatal malady, is characterized by the progressive development of widespread tremor and rigidity, together with other signs to be mentioned later. Much of the rigidity is of the type commonly found with lesions of the basal ganglia with signs which are almost entirely extrapyramidal in nature in uncomplicated cases. The condition is usually found in adolescents and in young adults.

Pathologically there is a liver cirrhosis, and cerebral lesions are also present, while biochemically there is an abnormal copper metabolism and an aminoaciduria.

Incidence

Number. The number of patients who have been described and can be considered with some degree of certainty as suffering from this disease is probably about 600. Table 1 gives the list of the cases I have been able to review, but of these there are a very few which might be regarded as doubtful, for I have included those reported by Anton, Strümpell and Westphal. This list is incomplete, for a few Italian, a few South American and some Russian cases recorded in the literature are not available to me. Konovalov (personal communication) tells me he has seen some forty patients and he has recently published a report on the results of treatment in eighteen cases.[259] Kurinnaya[268] also refers to a number of previous U.S.S.R. publications, which were unobtainable. The table includes the sex and age where known, the presence or absence of a Kayser-Fleischer ring and whether an autopsy was performed.

Sex. It is seen from Table 1 that males predominate, there being 309 males to 212 females.

Age. The age given in the table is that at which the patient died, or the age when last seen. Cassirer[82] recorded findings in a boy whose first symptoms began at the age of four years and Bielschowsky and Hallervorden[40] and Zappert[542] have on record cases of children of seven years of age. It has been suggested that an

TABLE 1

LIST OF PUBLISHED CASES OF HEPATOLENTICULAR DEGENERATION

Reference	*Name of Author*	*Sex*	*Age*	*K.F.*	*P.M.*
1	Abély and Guyot	M	45		
4	Alajouanine *et al.*	M	26	+	+
5, 6	Altschul and Brown	M	9		+
		M	18		+
7	Amelia	F	14		
8	Amyot	M	19		+
		F	24	+	
		M	20	+	
		M	21	+	
9, 10	André	M	30	+	+
		M	37	+	+
		M	25	+	
10	André and van Bogaert	M			+
		M	9		
12	Anton	F	14		+
13	Archangelskÿ	F	11	+	
15 (also 465)	Babcock and Brosin	M	20	+	
18, 437	Barkman and Sjövall	F	12	+	+
19, 20, 21, 22	Barnes and Hurst	M	12		+
		F	14	+	+
		F	10	—	+
		M	11	—	+
23	Bäumler	M	10		+
24	Bau-Prussakowa and Mackiewicz	M	20	+	+
		M	18		+
27	Bearn and Kunkel	F	30	+	
		M	19	+	
		M	19	+	
		M	32	+	
		M	50	+	
		M	30	+	
		M	24	+	
		M	42	+	
		M	31	+	
		F	34	+	
		M	12	—	
		F	28	+	
		M	18	+	
		M	37	+	
31	Benda	M	16		
33	Bergonzi	M	15		
34	Bergonzi and Rossini	M	15	+	
35	Berretta	F	48		

TABLE 1—*contd.*

Reference	*Name of Author*	*Sex*	*Age*	*K.F.*	*P.M.*
38	Bickel *et al.*	M	14	+	
		F	10	+	+
		F	7	+	
		M	14	+	+
		M	15	+	+
		F	13	+	+
		F	15	+	+
		F	18	+	+
		M	19	+	
		M	25	+	+
		F	40	+	+
38 (also 101, 329)	Bickel *et al.*	M	25	+	
39	Bickel *et al.*	F	29	+	
		F	24	+	
		F	19	+	
40	Bielschowski and Hallervorden	F	17	+	+
		M		+	+
42 (also 158)	Blaha *et al.*	M	13	+	
		M	12	+	
		M	13	+	
		F	11	+	
		M	33	+	
		F	37	+	
		F	40	+	
		F	20	—	+
		M	12	—	
		F	13	+	
		F	15	+	
43	Blažević and Ljuština-Ivančič	M	29	+	
45	Boenheim	M	14		
47, 49	van Bogaert	M	33	+	+
		M	22	+	
46, 48 (also 10)	van Bogaert	M	32	+	+
48 (also 10)	van Bogaert	F	40		
49 (? also 395)	van Bogaert and Willocx	M	17		+
50	Bolten	M	26	+	
53 (also 189)	Borsari and Bianchi	F	12		+
54	Bostroem	M	28		+
55	Bostroem	F	21	+	
56 (also 465)	Bothman and Rolf	M	16	+	
		F	8	+	
		M	13	+	
		M	24	+	

TABLE 1—*contd.*

Reference	*Name of Author*	*Sex*	*Age*	*K.F.*	*P.M.*
58	Boudin *et al.*	F	29	+	
		F	34		
		M	44		
59	Boudin *et al.*	F	18	+	+
60	Bouman *et al.*	M	26		+
64	Braunmühl	F	14		+
65	Bridgman and Smyth	F	14		+
66 (also 98)	Brinton	F	21	+	+
		M	17	+	+
69	Brückner		16		+
		F	9		+
71	Buscaroli and Rizzo	F	14		+
74	Cadwalader	M	18		
		M	36		
75	Cadwalader	F	20		+
76	Cagianut and Theiler	M	14	+	+
79	Carter	F	18	—	
81	Cartwright *et al.*	F	28	+	
		M	15	+	+
		F	10	+	
		M	21	+	
		M	30	+	
		M	20	+	
		F	29	+	
82	Cassirer	M	17	—	
84	Cathala and Olivier	F	14	+	
85	Čenzov	F	20	+	
86	Chambers, Iber and Uzman	F	15	—	+
		F	12	—	
		F	17	+	+
		F	13	+	
		M	12	+	
87	Chasanow	F	34	+	
		F	54	+	
88 (also 366)	Cheng	M	24	+	
		M	24	+	
91	Ciarla	F	27		
93	Cohen and Tamaela	M	46		+
94	Cooper *et al.*	M	21	+	
		M	13	+	
95	Cords	M	33	+	
96	Costa	F	15	+	+
98	Cumings	M	46	+	+
99	Cumings	M	36	+	
		M	24	+	
		M	27	+	
		F	21	+	

TABLE 1—*contd.*

Reference	*Name of Author*	*Sex*	*Age*	*K.F.*	*P.M.*
102	Cumings	M	26	+	
		M	24	+	
		F	16	+	
		F	16	+	
		F	19	+	
		M	45	+	
		F	30	+	
		M	20	+	
		F	18	+	
		M	18	+	
102 (also 329)	Cumings	M	23	+	
107	Curschmann	M	40	—	
108	Curschmann	M	42	—	
112	Degkwitz	F	18	+	
115	Denny-Brown and Porter	F	21	+	
		F	47	+	
115 (also 388)		M	28	+	+
116	Dent and Harris	M	21	+	
120	Díaz *et al.*	F	12	+	+
122	Dimitri and Berconski	F	17		+
123, 124	Dimitz and Vujić	M	36	+	
125	Dina and Serra	F	42	+	+
126	Dunnavan and Motto	F	14	+	
127	Dziembowski	M	22	+	+
		M	26	+	
		M	17	+	
130	Eckhardt *et al.*	M	17	+	+
		M	28	+	+
131	Economo	M	15		+
133	Eicke	F	25	—	
		M	45	—	
		M	14		+
136 (also 10)	Fanielle and Neujean	M	33	—	+
137	Fantiš	M	17		+
		F	11		+
138	Farnell and Harrington	F	19		+
139	Filimonoff	F	19	+	
140, 141, 142, 246, 403, 408	Fleischer	M	29	+	+
		M	32	+	
		M	31	+	+
144	Fleischer and Gerlach	M	25	+	+
145	Fog-Poulson	M	19	+	
146	Fracassi	M	29	+	
147	Frank	M		+	

TABLE 1—*contd.*

Reference	*Name of Author*	*Sex*	*Age*	*K.F.*	*P.M.*
148	Franklin and Bauman	F	22	+	+
		F	35	+	+
		M	23	+	
		F	26	+	+
		M	33	+	+
		M	28	+	
		F	16	+	
		F	25	+	
		M	34	+	+
149	Freedberg	F	26	—	+
150	Frerichs	M	10		
151	Frets	M	27		+
		M	30	+	
153	Froment	M	27		
154, 155	Froment, Bonnet and Masson	F	24	+	
156	Gardberg	M	11	—	+
157	Gartner	M	16	+	
		F	24	+	
		F	34	+	
		F	34	+	
159	Gastager and Spiel	M	13	+	
160	Gaupp				+
161	van Gehuchten	M	21	+	
162	van Gehuchten	F	12		
		M	18		
163	Geissmar	M	17		+
		M	22	+	+
		M	17		+
168, 372	Gerstmann and Schilder-Pollak	M	22	—	+
169	Gijsberti Hodenpijl	M	9		+
		F		+	
		F	11		
		M	14	+	
171	Gilsanz *et al.*	M	20	+	
		M	19	+	
172	Gjonys and Schroder	M	13	+	+
173	Glazebrook	M	17	+	
		M	17		+
175	Goldbach	M	22	+	
		F	13	+	
		M	38		
176 (also 157)	Goodhart and Balser	F	22	+	
		F	21	+	
178	Gowers	M	10		+
		F	16		+

TABLE 1—*contd.*

Reference	*Name of Author*	*Sex*	*Age*	*K.F.*	*P.M.*
179	Graf	F	16	+	
180	Green	M	24	+	+
184	Greenfield, Poynton and Walshe	F	15	+	+
188	Guillain *et al.*	F	45		+
189	Guizetti	M	8		+
190	Günther	F	44	+	
191	Gysin and Cooke	M	22		+
192	Hadfield	F	12		+
193	Hagan and Butt	M	25		+
195	Halford	M	14		+
196	Hall	M	32	+	+
		M	31	+	
		M	36	+	
198	Halpern	M	32		
199	Hamilton and Jones	M	28	—	+
		M	20	—	
200	Haq and Smith	M	22	+	
201	Harrow and Richards	M	11		+
204	Heine	F	45	+	
205, 206	Helman	M	20	+	
		M	18	+	
209	Herz and Drew	M	34	+	
		M	31	+	
		F	23	+	+
		F	33	+	
		M	30	+	
		M	26	+	
		M	39	+	
210	Hessberg	M	18	+	
211, 212	Heuyer *et al.*	F	14	+	+
213	Higier	M	22		
		M	35		
215	Holloway	M	27	+	
216	Holloway and Long	F	34	+	
221, 222	Homberger and Kojol	M	18	+	+
		M	20	+	
		F	19	+	
		M	39	+	
223, 224	Homén	M	24		+
		M	19		+
		F	26		+
225	Hood and Fagerberg	F	10		+
		M	12		
		F	13	+	
		F	10	+	