MENTAL RETARDATION IN CHILDREN

HANS K:SON BLOMQVIST
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AKADEMISK AVHANDLING
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av

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med lic, fil kand

Umeå 1982

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In an unselected series of mentally retarded children in the county of Västerbotten, Sweden, the annual incidence of children with severe mental retardation (SMR) (IQ < 50) and alive at the age of one year decreased from 5.3 per 1,000 in 1959 - 1963 to 3.1 per 1,000 in 1967 - 1970. This was mainly due to a decrease in the incidence of Down's syndrome. In parallel the proportion of mothers 35 years of age or more at the birth of the child decreased significantly. The prevalence of children with SMR in 1976 was 3.5 per 1,000. The main cause of the SMR was prenatal in 70 percent, perinatal in 8 percent and postnatal in 1 percent. The cause of the SMR was untraceable in 20 percent of the cases. Associated CNS-handicaps occurred in 52 percent of the cases. The annual incidence of mildly mentally retarded children (IQ 50 - 69) registered at the Bureau for Provision and Services for Mentally Retarded was 4.2 per 1,000 and the prevalence in 1979 was 3.8 per 1,000. The cause of the mild mental retardation (MMR) was untraceable in 43 percent. Prenatal causes were identified in as many as 43 percent. Perinatal causes were found in 7 percent and postnatal causes in 5 percent of the cases. Associated CNS-handicaps occurred in 30 percent of the cases.

A syndrome of mental retardation with X-linked inheritance not recognized previously in Sweden was characterized clinically (mainly in boys, machro-orchidism, verbal disabilities) and cytogenetically (a fragile site on the X-chromosomes seen after culturing in special folic acid deficient media) and found to have a prevalence of 6 percent in the population of severely mentally retarded boys. This makes this syndrome the next most common cause of SMR in boys after Down's syndrome. The chromosomal fragility was also identified in female carriers, which has implications for genetic counselling.

Through identification of an untreated phenylketonuric mother giving birth to five severely mentally retarded children, attention was focused on the risks for the fetus of the growing number of phenylketonuric women identified neonatally and treated dietarily but untreated after the age of 10 - 15 years.

Great improvement in intellectual and social ability was seen in a boy with phenylketonuria although the dietary treatment was not introduced until the age of eight years.

Heavy irradiation of a fetus late in gestation caused mental retardation, microcephaly, stunted growth, and eye and teeth abnormalities, although such abnormalities are thought not to result from irradiation after 20 weeks of pregnancy.

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ABSTRACT

In an unselected series of mentally retarded children in the county of Västerbotten, Sweden, the annual incidence of children with severe mental retardation (SMR) (IQ < 50) and alive at the age of one year decreased from 5.3 per 1,000 in 1959 - 1963 to 3.1 per 1,000 in 1967 - 1970. This was mainly due to a decrease in the incidence of Down's syndrome. In parallel the proportion of mothers 35 years of age or more at the birth of the child decreased significantly. The prevalence of children with SMR in 1976 was 3.5 per 1,000. The main cause of the SMR was prenatal in 70 percent, perinatal in 8 percent and postnatal in 1 percent. The cause of the SMR was untraceable in 20 percent of the cases. Associated CNS-handicaps occurred in 52 percent of the cases.

The annual incidence of mildly mentally retarded children (IQ 50 - 69) registered at the Bureau for Provision and Services for Mentally Retarded was 4.2 per 1,000 and the prevalence in 1979 was 3.8 per 1,000. The cause of the mild mental retardation (MMR) was untraceable in 43 percent. Prenatal causes were identified in as many as 43 percent. Perinatal causes were found in 7 percent and postnatal causes in 5 percent of the cases. Associated CNS-handicaps occurred in 30 percent of the cases.

A syndrome of mental retardation with X-linked inheritance not recognized previously in Sweden was characterized clinically (mainly in boys, macro-orchidism, verbal disabilities) and cytogenetically (a fragile site on the X-chromosomes seen after culturing in special folic acid deficient media) and found to have a prevalence of 6 percent in the population of severely mentally retarded boys. This makes this syndrome the next most common cause of SMR in boys after Down's syndrome. The chromosomal fragility was also identified in female carriers, which has implications for genetic counselling.

Through identification of an untreated phenylketonuric mother giving birth to five severely mentally retarded children, attention was focused on the risks for the fetus of the growing number of phenylketonuric women identified neonatally and treated dietarily but untreated after the age of 10 - 15 years.

Great improvement in intellectual and social ability was seen in a boy with phenylketonuria although the dietary treatment was not introduced until the age of eight years.

Heavy irradiation of a fetus late in gestation caused mental retardation, microcephaly, stunted growth, and eye and teeth abnormalities, although such abnormalities are thought not to result from irradiation after 20 weeks of pregnancy.
This thesis is based on the following communications, which will be referred to in the text by the Roman numerals.


Don't let us forget that the causes of human actions are usually immeasurably more complex and varied than our subsequent explanations of them.

Dostoyevsky, The Idiot
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ABBREVIATIONS

B.P.S.M.R. Board for Provision and Services to the Mentally Retarded (Omsorgsstyrelsen)
MR Mental retardation
MMR Mild mental retardation
SMR Severe mental retardation
INTRODUCTION

Mental retardation is a universal problem and the most frequently occurring handicap in children. For the individual concerned independence is often an unattainable goal. For the family it is often a burden, with heavy loading on the stability and aspirations both of parents and siblings. For the society the misery experienced by many of those affected, the often negative attitudes towards mentally retarded people, and the great expenses of domiciliary care, of special programs in education and training, of clinical diagnosis, of biomedical treatment and of underachievement and underproductivity, constitute a real challenge.

There are no simple solutions to the complex problems of mental retardation. Prevention must clearly be given high priority, but there is also a strong obligation to do everything possible to help mentally retarded people to realize their full potentials.

There is an urgent need for knowledge in this area. Epidemiological investigations, among other studies, are prerequisites for rational intervention and planning of services.

Abramowicz and Richardson (1975) critically reviewed 27 community studies concerned with the epidemiology of SMR in children. They noticed differences in definitions, methods used and the reliability of the studies. In most cases SMR was present from early infancy. An increase in prevalence among older children suggested that more cases come to the notice of authorities as children grow older. Thus, rates in older children may come closer to the "true" prevalence and in reliable studies this was about 4 per 1,000. The prevalence rate was somewhat higher in males. About one-half of severely retarded children had significant associated handicaps.

Bernsen (1976) reviewed a number of surveys on the prevalence of mental retardation and found that the SMR prevalence of 3.38 per 1,000 among
children aged 0 - 14 years in the community of Aarhus, Denmark, calculated in her study, was in agreement with other recent figures (Table I) from western countries.

Abramowicz and Richardson (1975) found reports on four community studies of MR in children in which the socio-economic background was evaluated. Only one of these reports (Birch et al. 1970) gave fully comparable figures for families with children of the same age. The latter study indicated that SMR had a random social class distribution, but that MMR was overrepresented in lower social classes.

The causes of the SMR are not completely reported in most of the reviewed studies. Down's syndrome, however, was by far the most frequent etiology and accounted for one-sixth to one-third of the cases. A small percentage were due to other chromosomal abnormalities, metabolic diseases or infections.

The magnitude of the MMR population found in some Swedish studies is given in Table II.

MMR has been considered mainly to consist of the lower end of the physiological distribution of mental ability and for that reason not likely to be preventable. Results of some recent studies concerning the etiology of severe and mild mental retardation are given in Table III. Only a few studies (Czeizel, 1980; Hagberg et al. 1981b) are concerned with possible organic causes of MMR.

The total number of officially registered mentally retarded persons in Sweden on 1st November 1975 was 36,488 or 0.44 percent of the total population (Grunewald, 1979). In the county of Västerbotten 0.61 percent were registered. This was the second highest figure in all Swedish counties; the lowest, 0.32 percent, was found in the county of Stockholm. The age distribution of mentally retarded persons and of the entire Swedish population are given in Fig. 1. The highest prevalence is seen in the age group 15 - 24 years. The total number of officially registered mentally retarded children born in 1959 - 1970 was 5,159; 2,958 were males and 2,201 were females.
### Table 1. Recent epidemiological studies of severe mental retardation in children

<table>
<thead>
<tr>
<th>Authors</th>
<th>Census period or year</th>
<th>Region</th>
<th>Age group (years)</th>
<th>Level of retardation, IQ a)</th>
<th>Prevalence rate per 1000</th>
<th>Number male/female</th>
<th>Sex ratio male/female</th>
</tr>
</thead>
<tbody>
<tr>
<td>McDonald (1973)</td>
<td>1967-1969</td>
<td>Quebec, Canada</td>
<td>8 - 12</td>
<td>&lt;50</td>
<td>3.84</td>
<td>284/223</td>
<td>1.27:1</td>
</tr>
<tr>
<td>Wallin (1974)</td>
<td>1969</td>
<td>Mölndal, Sweden</td>
<td>5 - 19</td>
<td>&lt;51</td>
<td>4.5</td>
<td>14/17</td>
<td>0.82:1</td>
</tr>
<tr>
<td>Bernsen (1976)</td>
<td>1970</td>
<td>Aarhus, Denmark</td>
<td>0 - 14</td>
<td>&lt;50</td>
<td>3.38</td>
<td>96/75</td>
<td>1.28:1</td>
</tr>
<tr>
<td>Gustavson et al. (1977a)</td>
<td>1975</td>
<td>Uppsala, Sweden</td>
<td>11 - 16</td>
<td>&lt;50</td>
<td>2.8</td>
<td>65/57</td>
<td>1.14:1</td>
</tr>
<tr>
<td>Laxova et al. (1977)</td>
<td>1974</td>
<td>Hertfordshire, U.K.</td>
<td>7 - 9</td>
<td>&lt;50</td>
<td>3.1</td>
<td>87/59</td>
<td>1.47:1</td>
</tr>
<tr>
<td>Simpson Smith et al. (1978)</td>
<td>1974</td>
<td>Yorkshire, U.K.</td>
<td>0 - 6</td>
<td>&lt;50</td>
<td>3.4</td>
<td>41/38</td>
<td>1.08:1</td>
</tr>
<tr>
<td>Richardson et al. (1979)</td>
<td>1962</td>
<td>Aberdeen, U.K.</td>
<td>8 - 10</td>
<td>&lt;50</td>
<td>3.6</td>
<td>Not given</td>
<td>Not given</td>
</tr>
<tr>
<td>Linna &amp; Kolviisto (1981)</td>
<td>1979</td>
<td>Öulu, Finland</td>
<td>5 - 19</td>
<td>&lt;50</td>
<td>4.05</td>
<td>194/126</td>
<td>1.53:1</td>
</tr>
<tr>
<td>Present study (1977)</td>
<td>1976</td>
<td>Västerbotten, Sweden</td>
<td>5 - 16</td>
<td>&lt;50</td>
<td>3.5</td>
<td>96/65</td>
<td>1.48:1</td>
</tr>
</tbody>
</table>

a) The intellectual level has been defined in various ways in the studies. To facilitate a comparison in this table the definitions have been roughly converted to IQ values.
Table II. Some Swedish epidemiological studies including mild mental retardation in children

<table>
<thead>
<tr>
<th>Authors</th>
<th>Census period or year</th>
<th>Region</th>
<th>Age group years</th>
<th>Level of retardation, IQ a)</th>
<th>Prevalence rate per 1000</th>
<th>Number male/female</th>
<th>Sex ratio male/female</th>
</tr>
</thead>
<tbody>
<tr>
<td>Börjeson &amp; Klackenberg (1960)</td>
<td>1958</td>
<td>Stockholm, Sweden</td>
<td>11 - 14</td>
<td>50 - 70</td>
<td>3.5</td>
<td>212/143</td>
<td>1.48:1</td>
</tr>
<tr>
<td>Åkesson (1961)</td>
<td>1959</td>
<td>Southern, Sweden</td>
<td>5 - 15</td>
<td>&lt; 68</td>
<td>23.8</td>
<td>28/19</td>
<td>1.47:1</td>
</tr>
<tr>
<td>Jonsson &amp; Kölvesten (1964)</td>
<td>1954</td>
<td>Stockholm, Sweden</td>
<td>8 - 17</td>
<td>50 - 70</td>
<td>4.5</td>
<td>220 males</td>
<td></td>
</tr>
<tr>
<td>Granat &amp; Granat (1973)</td>
<td>1970</td>
<td>Stockholm, Sweden</td>
<td>19</td>
<td>&lt; 70</td>
<td>22.1</td>
<td>males</td>
<td>d)</td>
</tr>
<tr>
<td>Hagberg et al. (1981a)</td>
<td>1978</td>
<td>Gothenburg, Sweden</td>
<td>8 - 12</td>
<td>50 - 70</td>
<td>3.7</td>
<td>58/33</td>
<td>1.76:1</td>
</tr>
<tr>
<td>Present study (1981)</td>
<td>1979</td>
<td>Västerbotten, Sweden</td>
<td>8 - 19</td>
<td>50 - 70</td>
<td>3.8</td>
<td>110/61</td>
<td>1.80:1</td>
</tr>
</tbody>
</table>

a) The intellectual level has been defined in various ways in the studies. To facilitate a comparison in this table the definitions have been roughly converted to IQ values.

b) Including cases with IQ below 50

c) 0 - 19 years

d) at registration for military service
Table III. Percentage distribution of mentally retarded children among etiological groups given in or calculated from some recent reports

<table>
<thead>
<tr>
<th>Authors</th>
<th>IQ a)</th>
<th>No. of children</th>
<th>Years of birth</th>
<th>Prenatal</th>
<th>Perinatal</th>
<th>Postnatal</th>
<th>Psychosis</th>
<th>Untraceable</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Genetic</td>
<td>Unknown</td>
<td>Acquired</td>
<td></td>
<td></td>
</tr>
<tr>
<td>McDonald (1973)</td>
<td>&lt; 50</td>
<td>507</td>
<td>1958</td>
<td>44</td>
<td></td>
<td></td>
<td>10 - 14</td>
<td>9 - 12</td>
</tr>
<tr>
<td>Turner (1975)</td>
<td>&lt; 50</td>
<td>1000</td>
<td>1930-1970</td>
<td>25</td>
<td>18</td>
<td>8</td>
<td>17</td>
<td>3</td>
</tr>
<tr>
<td>Gustavson et al. (1977b)</td>
<td>&lt; 50</td>
<td>122</td>
<td>1959-1970</td>
<td>43</td>
<td>20</td>
<td>10</td>
<td>10</td>
<td>3</td>
</tr>
<tr>
<td>Lexova et al. (1977)</td>
<td>&lt; 50</td>
<td>146</td>
<td>1965-1967</td>
<td>47</td>
<td>14</td>
<td>1</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Simpson-Smith et al. (1978)</td>
<td>&lt; 50</td>
<td>74</td>
<td>1969-1975</td>
<td>35</td>
<td>16</td>
<td>8</td>
<td>18</td>
<td>10</td>
</tr>
<tr>
<td>Freyers and Mackey (1979)</td>
<td>&lt; 50</td>
<td>401</td>
<td>1961-1977</td>
<td>60</td>
<td></td>
<td>1</td>
<td>12</td>
<td>11</td>
</tr>
<tr>
<td>Van Den Berghe et al. (1980)</td>
<td>&lt; 50</td>
<td>650</td>
<td>not given</td>
<td>38</td>
<td>4</td>
<td></td>
<td>14</td>
<td>8</td>
</tr>
<tr>
<td>Czelizel et al. (1980)</td>
<td>&lt; 50</td>
<td>1060</td>
<td>1957-1965</td>
<td>26</td>
<td></td>
<td>5</td>
<td>34</td>
<td>12</td>
</tr>
<tr>
<td>Hagberg et al. (1981a)</td>
<td>&lt; 50</td>
<td>73</td>
<td>1966-1970</td>
<td>34</td>
<td>12</td>
<td>8</td>
<td>15</td>
<td>11</td>
</tr>
<tr>
<td>Czelizel et al. (1980)</td>
<td>50 - 70</td>
<td>304</td>
<td>1957-1965</td>
<td>8</td>
<td>1</td>
<td>1</td>
<td>17</td>
<td>6</td>
</tr>
<tr>
<td>Hagberg et al. (1981b)</td>
<td>50 - 70</td>
<td>91</td>
<td>1966-1970</td>
<td>5</td>
<td>10</td>
<td>8</td>
<td>18</td>
<td>2</td>
</tr>
<tr>
<td>Present study (1977)</td>
<td>&lt; 50</td>
<td>161</td>
<td>1959-1970</td>
<td>52</td>
<td>8</td>
<td>8</td>
<td>8</td>
<td>1</td>
</tr>
<tr>
<td>Present study (1981)</td>
<td>50 - 70</td>
<td>171</td>
<td>1959-1970</td>
<td>31</td>
<td>4</td>
<td>8</td>
<td>7</td>
<td>5</td>
</tr>
</tbody>
</table>
Fig. 1 Age distribution of mentally retarded persons and of the entire Swedish population, in 5-year age intervals, in 1975 (total population 31st December 1975 = 8,208,442).

From Grunewald (1979). The figure is used with permission of the printing company Almqvist & Wicksell AB, Stockholm, Sweden.
CRITERIA AND DEFINITIONS

The criteria for a diagnosis of MR have distinctive characteristics in different countries depending on factors such as tradition, social complexity, cultural philosophy, including degree of tolerance to deviation, and the availability of services. No single set of criteria will find acceptance in all countries at any point in time. Any criteria for MR must be arbitrary, as the behavioral characteristics lie on a continuum. Concerning the criteria for SMR there is fairly close agreement between different societies. With regard to MMR, however, there are considerable differences. Thus, persons with MMR often experience difficulties in an industrial urban setting, whereas their retardation may pass unnoticed in a simple agricultural society.

However, the society needs criteria for demarcation of MR when planning for provisions, services and care for intellectually handicapped persons. Strict definitions of MR are also needed in most research work.

The classification and nomenclature of MR are discussed in the WHO Expert Committee on Mental Health (1968). The committee considered that taken in conjunction with social factors, the subclassification of the mentally retarded should be associated with the following approximate IQ ranges: mild: -2.0 to -3.3 standard deviations from the mean of 100, i.e. IQs 50 - 70; moderate: -3.3 to -4.3 standard deviations from the mean, i.e. IQs 35 - 50; severe: -4.3 to -5.3 standard deviations from the mean, i.e. IQs 20 - 35; and profound: more than -5.3 standard deviations from the mean.

The guiding principles in the care of mentally retarded persons in Sweden consist in active field programs, normalization, integration, service facilities nearby and day programs for all. Since 1968 these activities have been regulated under a special law, the Act on Service and Provisions for Mentally Retarded Persons.
The needs of the individual subject determine whether he or she receives the support of the B.P.S.M.R. No IQ definition of mental retardation is given in the above-mentioned Act. Standardized psychomotoric tests are often used, however, as one part of the evaluation and children with an IQ level above 70 are usually referred to other authorities outside the B.P.S.M.R. for support for any needs.

In the present study mental retardation was defined according to the principles of the WHO classification (1968) and for the purpose of the study it should have been present before the age of 18 years. For practical reasons, however, and in the absence of exact IQ values at these intellectual levels the subclasses moderate, severe and profound were combined under the heading severe mental retardation (i.e. persons with an IQ below 50). Persons with mild mental retardation were defined as those with an IQ between 50 and 70 and once registered at the B.P.S.M.R.
AIMS OF THE INVESTIGATION

The aims of the investigation were to study

the incidence and prevalence of mental retardation in an unselected population of children;

the etiology of mental retardation in these children;

the frequencies of associated CNS handicaps in these children;

the prevalence of the fragile site X chromosome in severely retarded boys;

the clinical findings in some specific etiological entities of mental retardation;

and to obtain data useful for the authorities in the planning of provision and services for the mentally retarded individual and his family.
MATERIAL AND GENERAL METHODS

The area investigated covered the northern Swedish county of Västerbotten (Fig. 2) with a population of 240,000 - 233,000 in 1959 - 1970 and a total area of 55,000 square kilometers. The population was genetically heterogeneous owing to the different elements - Swedes, Finns and Lapps. The vast majority of the population, however, were quite familiar with Sweden and the Swedish language. The north-western part of the county was characterized demographically by sparsely populated rural areas and small geographically isolated villages. The rest of the county was more densely populated, but the population density in the total county was only 4 inhabitants per square kilometer.

The purpose was to trace every child with MR born between 1959 and 1970 in the county of Västerbotten of a mother registered there for census purposes.

The registers of the B.P.S.M.R. in all Swedish counties, case records of children with possible MR who had received care at the Departments of Pediatrics or the Department of Child Psychiatry in the county of Västerbotten and the death registers were scrutinized.

All children who satisfied our criteria for MR were included in the series. However, children not alive at the age of one year were excluded because of the difficulties in confirming mental retardation before that age. The epidemiological investigation was divided into two parts; one concerning SMR (Paper I) and the other concerning MMR (Paper II). The numbers of children in the population studied and in the two series were 40,871, 161 and 171 respectively (Table IV).

The children were grouped according to certain criteria depending on the predominant etiological factor: 1) prenatal, 2) perinatal, 3) postnatal and 4) psychosis. Children in whom the etiology of the MR was not obvious were placed in a fifth group "untraceable etiology". In cases with two or more possible etiologies a special ranking list (Table V) was used to establish the most probable main etiological factor.
Fig. 2 Map of Scandinavia showing the area of the investigation.

Table IV. Severe mental retardation (IQ < 50) and mild mental retardation (IQ = 50 - 70) in children born in the county of Västerbotten, Sweden in 1959 - 1970 and alive at the age of one year.

<table>
<thead>
<tr>
<th>Years of birth</th>
<th>No. of children alive at one year of age in the studied population</th>
<th>Severe mental retardation (I)</th>
<th>Mild mental retardation (II)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>No. of children</td>
<td>Per thousand</td>
</tr>
<tr>
<td>1959 - 1962</td>
<td>13 981</td>
<td>74</td>
<td>5.3</td>
</tr>
<tr>
<td>1963 - 1966</td>
<td>13 973</td>
<td>47</td>
<td>3.4</td>
</tr>
<tr>
<td>1967 - 1970</td>
<td>12 917</td>
<td>40</td>
<td>3.1</td>
</tr>
<tr>
<td>1959 - 1970</td>
<td>40 871</td>
<td>161</td>
<td>3.9</td>
</tr>
</tbody>
</table>
Table V. Ranking list of predominating etiological factors in the classification of mental retardation. A factor with a lower classification number disqualifies factors of higher number.

<table>
<thead>
<tr>
<th>Etiological factor</th>
<th>Group and numbers of classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Genetic</td>
<td>Prenatal 1A</td>
</tr>
<tr>
<td>2. Recognized syndrome</td>
<td>Prenatal 1B</td>
</tr>
<tr>
<td>3. Prenatal stigma</td>
<td>Prenatal 1B</td>
</tr>
<tr>
<td>4. Prenatal infection</td>
<td>Prenatal 1C</td>
</tr>
<tr>
<td>5. Postnatal defined cause</td>
<td>Postnatal 3A</td>
</tr>
<tr>
<td>6. Perinatal infection</td>
<td>Perinatal 2A</td>
</tr>
<tr>
<td>7. SGA ($&lt;-2$ SD of the mean)</td>
<td>Prenatal 1C</td>
</tr>
<tr>
<td>8. Severe perinatal asphyxia ($\text{Apgar} &lt; 3$ at 1 min; cerebral hemorrhage)</td>
<td>Perinatal 2B</td>
</tr>
<tr>
<td>9. Toxlicosis, bleeding during pregnancy, major placental infarction</td>
<td>Prenatal 1C</td>
</tr>
<tr>
<td>10. Perinatal asphyxia ($\text{Apgar} &gt; 3 &lt; 7$ at 1 min)</td>
<td>Perinatal 2B</td>
</tr>
<tr>
<td>11. Low birth weight (&lt;2500 g) and AGA without complications</td>
<td>Perinatal 2C</td>
</tr>
<tr>
<td>12. Infantile psychosis</td>
<td>Psychotic 4A-B</td>
</tr>
<tr>
<td>13. Neglect</td>
<td>Postnatal 3B</td>
</tr>
<tr>
<td>14. None of the above</td>
<td>Untraceable 5A-B</td>
</tr>
</tbody>
</table>

$SGA =$ small for gestational age

$AGA =$ appropriate for gestational age
The prenatal group was divided into subgroups A) genetic, B) prenatal unknown and C) prenatal acquired (Table VI). The genetic group was further divided into chromosomal (chromosomal aberrations) and monogenic (mutant-gene) disorders.

Cases where environmental factors had affected the fetus were referred to the group prenatal acquired. This group included children small for gestational age (SGA), i.e. children with a birth weight below -2 SD of the mean for the age. Cases with a history of bleeding during the pregnancy with a major placental infarction, with toxaemia or with maternal diabetes, i.e. with fetal deprivation of supply (FDS) (Hagberg et al. 1976), were also included in this group.

Children with prenatal stigmata not referable to any of the above groups were placed in a separate group "prenatal unknown".

The perinatal group comprised children in whom obvious abnormalities had been caused during or within seven days after delivery. Children born with a low birth weight but appropriate for gestational age were also assigned to this group if the pre- and postnatal histories were normal and if the child had no stigmata.

Postnatal factors were considered to be the cause of the MR in cases with defined brain-damaging events occurring after the age of seven days. In the MMR study cases with prolonged severely inadequate stimulation or neglect were classified as postnatal in the absence of other known causes.

Children without a convincing etiology of the MR and with a primary psychosis were grouped separately.

The rest of the children were assigned to the group "untraceable etiology". These children were born at term, had a birth weight that was more than -2 SD of the population mean, had uneventful pre-, peri- and postnatal histories, and did not exhibit prenatal stigmata. None of the first-degree relatives had mental retardation of an untraceable cause.
Table VI. Etiological distribution of children with severe mental retardation (SMR: IQ < 50) and mild mental retardation (MMR: IQ 50 - 70) born 1959 - 1970 in the county of Västerbotten, Sweden and alive at one year of age

<table>
<thead>
<tr>
<th>Classification/etiology</th>
<th>SMR</th>
<th>MMR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of</td>
<td>Percentage</td>
</tr>
<tr>
<td></td>
<td>children</td>
<td>of cases</td>
</tr>
<tr>
<td>1 Prenatal</td>
<td>112*</td>
<td>70</td>
</tr>
<tr>
<td>1A Genetic</td>
<td>86*</td>
<td>53</td>
</tr>
<tr>
<td>1Aa Chromosomal</td>
<td>56</td>
<td>35</td>
</tr>
<tr>
<td>1Ab Neurometabolic</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td>1Ac Neurocutaneous</td>
<td>5</td>
<td>18</td>
</tr>
<tr>
<td>1Ad Other progressive disorder</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1Ae Other hereditary cause</td>
<td>18**</td>
<td>10</td>
</tr>
<tr>
<td>1Af Multifactorial causes</td>
<td></td>
<td>26</td>
</tr>
<tr>
<td>1B Unknown</td>
<td>12</td>
<td>7</td>
</tr>
<tr>
<td>1Ba Recognized syndrome</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>1Bb Other prenatal stigmata</td>
<td>11</td>
<td>6</td>
</tr>
<tr>
<td>1C Acquired</td>
<td>14*</td>
<td>9</td>
</tr>
<tr>
<td>1Ca Prenatal infection</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>1Cb FDS</td>
<td>11</td>
<td>10</td>
</tr>
<tr>
<td>1Cc Prenatal &quot;Intoxication&quot;/Irradiation</td>
<td>2*</td>
<td>2</td>
</tr>
<tr>
<td>2 Perinatal</td>
<td>13</td>
<td>8</td>
</tr>
<tr>
<td>2A Perinatal infection</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>2B Asphyxia/cerebral hemorrhage</td>
<td>12</td>
<td>9</td>
</tr>
<tr>
<td>2C LBW/AGA</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>2D Hypoglycemia</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>3 Postnatal</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>3A Defined organic causes</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>3B Neglect</td>
<td>-</td>
<td>3</td>
</tr>
<tr>
<td>4 Infantile psychosis</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>4A Infantile autism</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>4B Other primary psychosis</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>5 Untraceable</td>
<td>32*</td>
<td>20</td>
</tr>
<tr>
<td>5A with epilepsy/cerebral palsy</td>
<td>18</td>
<td>9</td>
</tr>
<tr>
<td>without &quot;-&quot;</td>
<td>14*</td>
<td>65</td>
</tr>
</tbody>
</table>

1 - 5
161     99       171     100
Notes to Table VI

FDS = fetal deprivation of supply
LBW = low birth weight
AGA = appropriate for gestational age

*Three boys with MR initially described as "untraceable" (Paper I) were later found to have fragile site X chromosomes (Papers III and IV). Subsequently they were classified as "prenatal, genetic, other hereditary". Three other boys with the fragile X syndrome were already referred to this group.

†One boy with MR classified as "prenatal other hereditary cause" (Paper I) was later found to be a son of a mother with an untreated phenylketonuria (Paper V). Subsequently he was referred to group prenatal, acquired and subgrouped "intoxication".

**One girl with MR classified as "chromosomal" (46,XX/47,XX,+18, mosaicism) (Paper II) was reinvestigated and then found to have a normal chromosomal karyotype and diastrophic dwarfism. The MR was considered to be due to the chromosomal aberration.
In the MMR series, children with an untraceable etiology of the MR were allocated to a subgroup "multifactorial" if a first-degree relative had MR or borderline intellectual ability of unknown origin.

During the time of our first study (Paper I) it became obvious that further investigations with new methods might give additional knowledge concerning the etiology of the MR and possibly be of value for treatment and prevention.

Two boys, one in the SMR series (Paper I) and one in the MMR series (Paper II) had pedigrees suggesting an X-linked inheritance. They became index cases in families with the fragile X syndrome (Paper IV).

It seemed possible that 40 boys in the SMR series (Paper I) might possess a fragile X chromosomal constitution. Twenty-nine of these were examined in this respect. Seven of the 40 boys were dead and four were not examined for other reasons (Paper III).

No specific causal factor was evident in 62 children in the SMR series (Paper I). Forty-eight of the mothers of these children were analysed concerning aminoaciduria. In 10 cases urinary samples were not obtained, two mothers were excluded for ethical reasons and two mothers could not be traced (Paper V).

One late-diagnosed phenylketonuric boy in the MMR series (Paper II) was followed up clinically and with psychometric evaluations during a 10-year dietary treatment period (Paper VI).

One girl in the SMR series (Paper I) was damaged by irradiation in late gestation. She was investigated cytogenetically and followed up clinically for 13 years (Paper VII).

Case records of all children in the series were scrutinized for associated central nervous system handicaps in the form of epilepsy, cerebral palsy, other motor disorders, and severe impairment of vision and hearing.
Epilepsy was defined as recurrent epileptic seizures. Convulsions during the first month of life, febrile convulsions before the age of five years and unclassified types of fits were excluded. Cerebral palsy was defined as "a disorder of movement and posture due to a non-progressive defect or lesion of the immature brain" (Bax, 1964). Obvious motor disorders were recorded, clumsiness and minor motor disturbances were not included. Known severe impairment of vision and hearing was recorded.

LABORATORY METHODS

Chromosome analyses by routine methods were performed in most children with Down's syndrome. They were also undertaken in most other cases with prenatal stigmata. Since 1975 G-banding techniques have been used in the analyses.

In selected cases (Papers III and IV) the chromosomes were studied in lymphocytes cultured in a special MEM-FA medium containing no folic acid (Sutherland, 1979) and supplemented with 5% fetal calf serum, phytohemagglutinin and antibiotics for 72 hours. The pH was adjusted to 7.6 with IN NaOH, 24 hours before harvesting. Colcemide was added 1½ hours before harvesting. The cells were harvested in the usual way and slides were prepared by air-drying without heating. The slides were stained with Giemsa stain and then destained and G-banded for identification of the fragile X chromosome.

Urinary metabolic screening included the following tests: AlbustixR, ClinisticR, PhenistixR, ClinitestR, Brand's reaction, Cuprizone reaction, Nitrosonaphthol reaction and Azur-A reaction. The screening was performed in almost all children (except children with Down's syndrome) in the two series with the aim of detecting errors in amino acid, carbohydrate and glucosaminoglycan metabolism (Hambraeus and Holmgren, 1974). In addition, in a few patients plasma and urinary samples were examined by gas-liquid chromatography and an automatic amino acid analyzer for the detection of errors in amino acid and lipid metabolism.
Serological analyses. In a small number of cases with signs indicating a prenatal infection, serological analyses regarding toxoplasmosis, rubella, cytomegaly and herpes simplex (TORCH) were performed. In a few cases urinary samples for isolation of cytomegalic virus were obtained.

Neuroradiological examinations were carried out mainly in children with prenatal stigmata, but also in some other cases. The examinations included skull X-ray, pneumo-encephalography, carotid and vertebral angiography, and in a few cases computerized transaxial tomography (CTT).

Electroencephalography was performed in children with suspected or confirmed seizures.

Audiometry was done in children with suspected hearing impairment.
RESULTS

Severe mental retardation (Paper I)

For the period 1959 - 1962 the incidence of SMR in children was 5.3 per 1,000 children alive at one year of age, and 3.4 and 3.1 per 1,000 in 1963 - 1966 and 1967 - 1970 respectively. The mean yearly incidence was 3.9 per 1,000 (Table IV).

The incidence of Down's syndrome in the material decreased from 2.2 per 1,000 in 1959 - 1962 to 0.8 and 0.9 in the following two 4-year periods.

The proportion of mothers 35 years of age or more at the birth of the child decreased both in the total material (39, 30 and 31 percent) and in the group with Down's syndrome (74, 45 and 45 percent) in the three 4-year periods studied. Corresponding figures for mothers in the total population were 16, 14 and 10 percent for the county of Västerbotten and 13, 10 and 8 percent for the whole of Sweden respectively.

The mortality rate in the material was 11.8 percent, compared with 0.9 percent for the general population of the same age group in Sweden. The prevalence of SMR among children 5 - 16 years of age was 3.5 per 1,000 (30th June 1976).

The proportions of children in different etiological groups are presented in Table VI and Fig. 3. The main cause of the SMR was prenatal in 70 percent of the cases, perinatal in 8 percent and postnatal in one percent. A primary psychosis was seen in one percent. In 20 percent of the cases the cause of the mental retardation was not evident. The subclass "genetic causes", 53 percent, constituted the largest group. Within that group, chromosomal aberrations (mostly Down's syndrome) were found in 35 percent. Monogenic disorders were seen in 18 percent. Prenatal acquired and prenatal but otherwise unknown causes were found in 9 and 7 percent respectively.
In the total material there were 96 males and 65 females, giving a male excess sex ratio of 1.48:1. In the prenatal etiology group the male excess was 1.66:1.

The mean birth weight in the total material was 3,110 g, as against 3,550 g in the Swedish population. The proportion of SGA children was higher than expected. Thus 8.7 and 27.3 percent had a birth weight equal to or lower than -2 SD and equal to or lower than -1 SD, compared with the expected proportions 2.3 and 15.9 percent, respectively.

Associated CNS handicaps (Table VII) were seen in 52 percent of the children, mostly in cases with a prenatal etiology of the retardation. Thirty-six percent of the children had epilepsy, 19 percent had cerebral palsy and 16 percent had both these conditions. Severe impairment of vision and severe impairment of hearing were found in 10 and 6 percent of the cases, respectively.

Table VII. Some associated CNS handicaps in 161 children with severe mental retardation (IQ < 50) and 171 children with mild mental retardation (IQ 50 - 70).

<table>
<thead>
<tr>
<th>Handicap</th>
<th>SMR</th>
<th>MMR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of children</td>
<td>Percentage of cases</td>
</tr>
<tr>
<td>Epilepsy</td>
<td>58</td>
<td>36</td>
</tr>
<tr>
<td>Cerebral palsy</td>
<td>30</td>
<td>19</td>
</tr>
<tr>
<td>Epilepsy and cerebral palsy</td>
<td>26</td>
<td>16</td>
</tr>
<tr>
<td>Severe impairment of vision</td>
<td>16</td>
<td>10</td>
</tr>
<tr>
<td>Severe impairment of hearing</td>
<td>9</td>
<td>6</td>
</tr>
<tr>
<td>One or more associated handicaps</td>
<td>84</td>
<td>52</td>
</tr>
</tbody>
</table>
Fig. 3 The distribution, according to the etiology of the mental retardation, of 161 severely mentally retarded children (Paper I) and 171 mildly mentally retarded children (Paper II) born in the county of Västerbotten, Sweden, in 1959 - 1970 and alive at the age of one year.
Mild mental retardation MMR (Paper II)

The incidence of MMR in children born in 1959 - 1970 was 5.4 per 1,000 children alive at one year of age in the period 1959 - 1962 and 3.1 and 4.1 per 1,000 in the following two 4-year periods. The mean yearly incidence was 4.2 per 1,000 (Table IV).

At the time of the delivery 18 percent of the mothers in the series were above 35 years of age, compared to 13 and 10 percent in the populations of Västerbotten and Sweden, respectively.

Since four children had died and 10 other children were removed from the B.P.S.M.R. register because of improved intellectual performance, the prevalence of MMR among children 8 - 19 years of age was 3.8 per 1,000 (1st January 1979).

The proportions of children in different etiological groups are given in Table VI and Fig. 3. Forty-three percent of the children were considered to have a prenatal and seven a perinatal factor as the main cause of their MR. A postnatal factor was found in five percent of the cases. Two percent of the children had a primary psychosis. In forty-three percent of the cases no convincing etiologic factor could be traced.

There were 110 males and 61 females in the material, giving a male excess sex ratio of 1.8:1. In the prenatal group the male excess was 1.8:1 and in the genetic subgroup it was 2.1:1.

The mean birth weight in the whole material was 3,350 g. The lowest mean birth weight was seen in the prenatal and the perinatal etiological groups. The percentage of children in the series born before 38 complete weeks of gestation was the same as in the Swedish population, 10 percent. Six children in the series (3.5 percent) were one of twins, compared to 1.25 percent in the Swedish population.
Associated CNS handicaps (Table VII) were present in 30 percent of the children. Epilepsy occurred in 18 percent and cerebral palsy in 7 percent. Nine and two percent had severe impairment of vision and hearing, respectively.

Prevalence of fragile X syndrome in severely mentally retarded boys (Paper III)

The boys in the SMR series (Paper I) who had been classified into groups without an unequivocal diagnosis were considered for chromosomal analysis in special cultural medium in order to determine the prevalence of boys with fragile site X chromosomes in this series. Out of the 96 boys in the total series, 40 belonged to such groups: untraceable (20); prenatal, genetic subgroup "other hereditary" (11), prenatal unknown with stigma (8) and primary psychosis (1). Out of these 40 boys seven were dead and four boys could not be investigated for other reasons. Six of the 29 boys examined were found to have fragile site X chromosomes. It is unlikely that there were any boys with marker X chromosomes in the other etiological groups. The prevalence of the fragile X chromosome syndrome in severely mentally retarded boys was thus 6 percent (6/96).

Families with fragile site X chromosomes (Paper IV)

In the epidemiological studies of SMR (Paper I) and MMR (Paper II) male excess ratios of 1.5:1 and 1.8:1 respectively were found and it was suspected that an X-linked mode of inheritance might have contributed to this finding.

An association between X-linked mental retardation and X chromosomes with fragile sites was originally reported by Lubs in 1969. Eight years later Sutherland (1977) pointed out the need for special cultural conditions for expression of the fragility of the X chromosome (Xq 28). Keeping this in mind, two boys born in 1961 and 1968 with possible X-linked mental retardation, and their families, were examined. In one
family (Family G) the mother was married twice. In both marriages boys with MMR were born. A male first cousin of the mother and a male first cousin of her boys were also mentally retarded. Fragile site X chromosomes were identified in the proband and his half-brother and in their retarded male cousin. The same was also found in the mother of the proband and in two 21-year-old twin sisters of the mother. The fragility was not observed in another sister, a younger brother or two female cousins of the mother. In the other family (Family P) two brothers and a male first cousin on the mother's side were severally mentally retarded and had macro-orchidism. A fragile site X chromosome was identified in both the brothers and their mother. The rest of the family refused examination.

The chromosomes were analysed in two laboratories (Umeå, Sweden and Glostrup, Denmark). There was a good accordance between the two laboratories with regard to the existence of fragility of the X chromosomes, but differences were noted in the individual cases in respect to the frequencies of the fragile X chromosomes.

A survey of the literature and of our own cases revealed a fragile site X chromosome in 53 males in 26 families. The fragility was seen in 2 - 50 percent of analysed cells. Fourteen of the boys were severely and 39 were mildly mentally retarded. Macro-orchidism was present in 28 of 31 reported cases. The fragile site X chromosome was seen in 0 - 35 percent of the analysed cells in 19 out of 24 examined mothers of the affected boys.

Maternal phenylketonuria (Paper V)

In the epidemiological series of 161 SMR cases (Paper I) neither a diagnosis nor a cause of the MR was found in 62 cases. Urinary samples were obtained from 48 mothers of these 62 children. At metabolic screening for amino acids one of the mothers showed an increased urinary excretion of phenylketones. The serum phenylalanine value from the same mother exceeded 1,200 μmol/l. Thus the mother had a classical type of
phenylketonuria (PKU). The index case was a boy born in 1959 as the youngest of five siblings, all severely mentally retarded. None of the children had PKU. Three of the children were born "small for gestational age", three were microcephalic, one had a microphthalmia and four had convulsions and/or abnormal EEG.

Late introduced dietary treatment in PKU (Paper VI)

An eight-year-old mildly mentally retarded boy born in 1961 - the youngest of four siblings - was referred for clinical examination because of great learning difficulties at school. Urine and plasma analysis of amino acids led to a diagnosis of PKU of the classical type. Later it became known that an older sister and an older brother also had PKU and were severely mentally retarded, both with IQs of 25. Despite the late diagnosis in the proband, a modified low phenylalanine diet was introduced at the age of eight years. During a 10-year observation period the boy made marked progress with respect to his social and mental capacity, with a rise in IQ score from 59 to 82.

Radiation therapy during late fetal life (Paper VII)

In 1966 a pregnant woman received radiotherapy for carcinoma of the uterine cervix. The fetus was heavily irradiated during the 30th to 33rd week of gestation. A total of 40 Gy were given over the pelvic area of the mother, including the head of the fetus, with an excellent effect on the tumor. A girl was delivered by cesarean section in the 36th week of pregnancy. There was no asphyxia and no congenital defects were visible. The subsequent psychomotor development, however, was retarded. Before her death, at the age of 13 years, the girl was microcephalic and had developed SMR, stunted growth, microphthalmia, retinal degeneration, cataract and defective dentition. Cytogenetically the frequencies of both chromatid and chromosome breaks were increased.
GENERAL DISCUSSION

Epidemiological aspects

On the basis of the work of Penrose (1963), mentally retarded individuals have often been referred to either the "physiological" or the "pathological" group, the two basic entities which together account for the total number of retarded. The intelligence in the physiological group is assumed to have a Gaussian distribution, with a mean IQ of 100 and a standard deviation of 15 points. An IQ of 70, i.e. the IQ mean minus two standard deviations, is often regarded as the upper limit of the mentally retarded population and is in accordance with the WHO recommendations (1968).

The object of this investigation was to get a complete picture of MR in a total population of children. Good prerequisites for the study were the relatively stable population, the ten-digit identity number allotted to all residents in Sweden, a well developed system of social welfare and health care for mentally retarded children, and the two well equipped departments of pediatrics in the county. Most probably all children with SMR were identified through relevant registers and records. As it was not possible to test all conceivable mildly mentally retarded children, we had to use an operational definition of MMR. The B.P.S.M.R. plans and provides social and educational facilities and services for training and habilitation of mentally retarded persons according to a special Swedish law. It is highly probable that all children in need of these services were registered by this authority. A few children might be registered by B.P.S.M.R. although they have an IQ higher than 70 and a number of children with an IQ just below 70 might not be included in the B.P.S.M.R. register. However, we choose to define MMR as an intellectual ability corresponding to an IQ of 50 - 70 and once registered by the B.P.S.M.R.

The assignment of borderline cases to the SMR or the MMR series gave no difficulties in most cases; only three children classified as MMR were borderline to SMR low IQ cases.
Children who had died before the age of one year were excluded from the series. This might, of course, have had an impact on our figures, but during the period of this study the perinatal and infant mortality rates were decreasing in Sweden and a retrospective approximation of the prevalence of MR at birth as proposed by Freyers and Mackay (1979) must be very uncertain.

The mean annual incidence of SMR in children was 3.9 per thousand. There are few comparable studies. McDonald (1973) gave an incidence of SMR of 4.6 per thousand for Canadian children born in 1958 and alive at one year of age and Gustavson et al. (1977a) reported an incidence of 2.9 per thousand in children born in Uppsala, Sweden in 1959 - 1970 and alive at one year of age. The incidence of SMR in the county of Västerbotten decreased during the study period (Table IV). This decrease was mainly referable to a reduction in the incidence of Down's syndrome to one-third between the two periods 1959 - 1962 and 1963 - 1966. Simultaneously there was a considerable reduction in the frequency of mothers more than 35 years of age giving birth to children in our study, in the county of Västerbotten and in the whole of Sweden. Another contributory cause of the lower incidence in the younger groups may be the accumulative increase in the incidence of SMR with increasing age (Fig. 1). Early antenatal diagnosis had no impact on the incidence of MR, as no prenatal diagnostic studies were performed in the country before 1970.

The estimated prevalence of SMR of 3.5 per thousand in our series is lower than the figure of 4.5 per thousand found in an earlier Swedish study (Wallin, 1974) and is also somewhat lower than that in a recent Finnish study (4.05 per thousand) and in most British studies, but somewhat higher than the prevalence found in Denmark (3.58 per thousand) and the estimated prevalence of 2.8 per thousand in the Uppsala study (Table I). There are differences between these studies, however, as regards definitions, case-finding systems, the ages of the children and the census dates, and comparisons must be made with caution.
The mean annual \textit{incidence} of MMR was 4.2 per thousand (Table IV). The fluctuations between the three 4-year periods may reflect a real change in the "true" incidence of MMR but may also be due to changes in the policy for registration of retarded children at B.P.S.M.R.

The \textit{prevalence} of MMR in our series, 3.8 per thousand, is very low compared with the theoretically expected value (23 per thousand for IQs of 50 - 70) and compared with the results of most other studies (Table II). However, Börjeson and Klackenberg found a similar low mean prevalence - 3.5 per thousand among 11 - 14-year-old children born in 1944 - 1947 and registered at the B.P.S.M.R. in Stockholm, and Hagberg et al. reported a prevalence of 3.7 per thousand for MMR in 8 - 12-year-old children born in 1966 - 1970 in Gothenburg. In the latter study known borderline cases in ordinary schools as well as all such children in special schools were reviewed and cases "in doubt" according to the intellectual level were retested. In this way 18 children (0.7 per thousand) with an IQ of 71 - 75 in special schools and 19 children (0.8 per thousand) with an IQ of 50 - 70 in ordinary schools were found. In special schools there were 72 children (0.29 per thousand) with an IQ of 50 - 70. Thus altogether 91 children (3.7 per thousand) in this population of school children had an IQ of 50 - 70.

One possible reason for the very low prevalence figure for MMR in our study, as well as in the Gothenburg study, might be general changes in the IQ distribution among Swedish children in the course of time. Unfortunately no recent information is available concerning the IQ distribution in an unselected population of Swedish children, but in a relatively recent Danish study a mean IQ of 110 and a standard deviation of 15 points were found (Rönne-Jeppson, 1971). One reason for an increase in the registered IQ in our study could be that the tests used were old-fashioned, as they were standardized 40 years ago. Earlier and more intensive developmental stimulation during the last decades by television, nursery schools etc. might have elevated the level of knowledge of most children in Scandinavia, which in turn could have been reflected in the testings. An IQ mean of 110 and a standard deviation
of 15 will theoretically put 3 per thousand of the population in the IQ range 50 - 70. This figure is rather near to the MMR prevalence of 3.7 per thousand reported from the Gothenburg study and to the figure of 3.8 per thousand found in the present study in Västerbotten.

The policy for registration of a child at the B.P.S.M.R. could also have an impact on the prevalence figure of MMR in our series, as such registration was used as a criterion of MMR. In view of the principles of normalization and integration it is possible that some children with an IQ below 70 were not officially identified as mentally retarded. On the other hand, some of the children registered at the B.P.S.M.R. might - as was the case in the Gothenburg series - have had an IQ above 70. As these two categories most probably were of similar size also in our series the MMR prevalence figure of 3.8 per thousand is probably reliable.

In a review in 1974 Clarke and Clarke claimed that mild subnormality of non-pathological origin is for some individuals a transitory condition. The 10 children in our series removed from the B.P.S.M.R. because of improved intellectual performance support this opinion. The possibility that this phenomenon might have had an impact on the prevalence figures is illustrated in Fig. 1. The significance of social and cultural conditions in this context is under debate. In Sweden, however, the number of persons living in unfavorable social conditions with a subsequent risk of cultural deprivation has decreased considerably since the 1940s and the low incidence figures in our series may in fact reflect a real decrease in the prevalence of MMR in children.

However, until extensive examinations of the intellectual capacity of a total, unselected population of Swedish children have been performed, the exact current percentage of mildly mentally retarded children (defined in IQ terms) remains uncertain.

Nowadays the society has great demands on its members. Although a decreasing number of children was labelled mildly mentally retarded, an
intellectual ability corresponding to an IQ between 50 and 70 should not be considered as a mild handicap. Many of these children have problems in everyday life, at school and in different working situations. Furthermore, in our modern, technocratic society there are indications that the proportions of "functionally retarded" people will increase further.

Earlier studies, e.g. by Åkesson (1974), indicated that the prevalence of MMR was much lower in urban areas than in rural ones. Västerbotten is characterized by sparsely populated rural areas and geographically isolated small villages. The prevalence of cases with MMR and registered by the B.P.S.M.R. in the county, 3.8 per thousand, is higher than the figure of 2.9 per thousand found in children 8 - 12 years of age with an IQ of 50 - 70 and registered at the B.P.S.M.R. in the Swedish city of Gothenburg. Thus there still seems to be a somewhat higher prevalence of MMR in rural than in urban areas in Sweden. A real and progressive decrease of this difference is probable, as a result of improvement and levelling of socio-economic conditions and advances in such factors as education, antenatal and postnatal care, and communications.

Etiological aspects

Diagnostic efforts to elucidate causes in cases of MR have sometimes been limited. One reason has been lack of knowledge in the field, and another a defeatistic view regarding the possibilities of helping the individual and the family. However, a reliable etiologic diagnosis is a necessary basis for realistic planning of care and habilitation of the child, for judging the prognosis, and for genetic counselling of the parents and other relatives, and sometimes it may open possibilities for preventive measures and treatment.

In some disorders it is possible, by antenatal investigations, screening of newborns, etc., to predict MR in the child before or soon after delivery. In many children MR cannot be confirmed until several years
after birth. In such cases attempts at diagnosis may rely on uncertain and sometimes uncontrollable information and in many cases it is not possible to establish the etiology of the MR.

MR is a symptom, not a disease in itself. Many different causes may lead to dysfunction of the brain and a general lowering of mental ability. Although the etiology of MR is known in many cases, e.g. cases with chromosomal abnormalities and PKU, the pathogenesis remains to be elucidated.

With increased knowledge and with the availability of new and more reliable diagnostic methods, it was considered important to make an up-to-date survey of the etiological factors in MR in an unselected child population.

**Prenatal etiologies**

In our series as well as in other recent materials (Table III) the etiology was most commonly prenatal.

**Chromosomal aberrations**

The genetic contribution to SMR largely consisted of unbalanced autosomal chromosomal aberrations (35 percent). In comparison the contribution of chromosomal aberrations to MMR was rather small (8 percent, Table VI, Fig. 3). Most of these patients had Down's syndrome. The incidence of Down's syndrome in our SMR study and the proportion of cases with this syndrome in the etiological panorama decreased markedly during the study period from 2.2 per thousand in 1959 - 1962 to 0.8 per thousand in 1963 - 1966. This decrease in incidence was correlated with a simultaneous reduction in maternal age at child-birth.

In the period 1968 - 1970 the incidence of Down's syndrome in the whole of Sweden was 1.32 per thousand (Lindsjö, 1974) and in the period 1968 - 1977 1.28 per thousand (Lindstén et al. 1981). The mean maternal age at child-birth decreased in Sweden between 1968 and 1977. Fewer older
mothers gave birth to children and consequently the number of children with Down's syndrome born to older mothers decreased. In the county of Västerbotten, however, the proportion of older child-bearing mothers during the time of the present study (1959 - 1970) was higher than in the whole of Sweden. According to Lindstén et al. (1981) the risk that Swedish mothers of different ages would bear a child with Down's syndrome did not change significantly over the period 1968 - 1977. Nowadays most children with trisomy 21 are born to younger women. The impact of amniocentesis for fetal chromosomal investigation in older women on the incidence of chromosomal aberrations in the newborn will thus be relatively small. This procedure is highly recommended, however, for the individual older pregnant woman.

For prenatal diagnosis of a major proportion of chromosomally unbalanced fetuses a screening procedure would be necessary. In the future, isolation and analysis of fetal cells from the maternal circulation might be possible. Several technical and ethical problems remain to be solved concerning this matter.

Recently several authors (Eriksson and Bjerkedal, 1980; Stene et al., 1981) have reported that elderly men also run an increased risk of having trisomy 21 offspring. This question was not investigated in our series or in the total Swedish series of Lindstén et al. (1981).

In our series (Papers I and II) there was an excess of males of 1.6:1 among children with Down's syndrome. A similar male excess in Down's syndrome has been observed by other authors (see Lindstén et al. 1981). The reason is not known, but a change in the primary sex ratio is one possibility.

In most of the cases in the present series chromosomal analyses were performed before the introduction of the banding technique. It is highly probable that chromosomal reinvestigations with this technique would point out some more cases with chromosomal aberrations so far not identified. Such an investigation has not been considered ethically, however, in most cases.
Neurometabolic disorders

Many children with neurometabolic disorders will not survive the first year of life, but some of them do. In every case an unequivocal diagnosis is very important, as it may be possible to treat the child or to establish the diagnosis prenatally in future pregnancies. In our series there were eight children with neurometabolic disorders who had survived one year of life. Seven of them had SMR. Two boys with Krabbe's disease and one boy with the infantile form of Gaucher's disease died before the age of two years. One boy with the Spielmeyer-Vogt syndrome and one boy with an unspecific neurometabolic disorder were still alive in 1981.

The only child with PKU in the series (Paper VI) was born in 1961, i.e. before the general screening for this disorder was introduced in our country. Despite the late diagnosis a diet low in phenylalanine was introduced at the age of eight years and subsequently the boy's intellectual ability improved. Previous reports (Bruhl, 1966; McKeen, 1971) have documented an improvement in the behavior but no progress of the mental development of older PKU patients on introduction of a low phenylalanine diet. In a double-blind study, Hambraeus et al. (1971) did not find any positive effects of a low phenylalanine diet in seven older mentally retarded PKU patients. Once MR has been established it can rarely, according to Knox (1966, 1972), be improved by the introduction of a diet low in phenylalanine. In the present case, however, there was obvious improvement both in the child's school performance and at repeated IQ testing. The improvement could possibly be explained by a favorable PKU phenotype in the boy.

The positive effects of dietary treatment in this patient underline the importance of a correct diagnosis in such cases and encourage similar dietary trials also after the first years of life in children with PKU. The importance of continuing a low phenylalanine diet in PKU children who have been treated earlier is evident from a comparative study in London and Heidelberg (Smith et al. 1978). The introduction of a normal diet between the ages of 5 and 15 years in the English PKU children
caused a significant fall in the recorded mean IQ, while this was not seen in the German PKU children who received a prolonged low phenylalanine diet.

In other biochemical disorders a dietary treatment introduced at a later age may also be effective. Thus Gröbe (1980) reported a striking improvement in the behavior and intellectual development of eight homocystinuric patients 11 to 27 years of age, in close correlation to the biochemical normalization after the introduction of pyridoxine or a low methionine diet with supplemental L-cystine. A low protein diet has also been recommended in histidinemia (Corner et al. 1968). Levy et al. (1974), on the other hand, found a normal development in 20 children in spite of the fact that no treatment was given.

After the introduction of the neonatal PKU screening program in 1965, four PKU children born in 1965 - 1970 in the county of Västerbotten, were identified. Through early dietary treatment they have all achieved a normal psychomotor development.

**Neurocutaneous disorders**

The neurocutaneous syndromes, sometimes called phacomatoses, include several conditions with certain common characteristics, among them cutaneous manifestations. Five of the eight children with neurocutaneous syndromes in our series were severely mentally retarded (Table VI). Two children had tuberous sclerosis, five had the Sjögren-Larsson syndrome (MR, congenital ichthyosis and spastic di- or tetraplegia) and one had a syndrome with MR, ichthyosis and epilepsy. In the comparable study of SMR in the county of Uppsala (Gustavson et al. 1977a) there were no cases of neurocutaneous syndromes and in the study of MMR in Gothenburg (Hagberg et al. 1981b) there was only one case in this subgroup, a girl with xeroderma pigmentosa.

The relatively high incidence of neurocutaneous syndromes in our study can partly be explained by the high incidence of Sjögren-Larsson syndrome in Västerbotten. This syndrome - originally described in Sweden
had a mean incidence of 10.2 per 100,000 in 1901 - 1977 in the county of Västerbotten, compared to 0.6 per 100,000 in the whole of Sweden (Jagell et al. 1981). The high incidence of some disorders with an autosomal recessive inheritance in Västerbotten might be due to a genetic founder effect. Owing to a decline in the death rate, the prevalence of Sjögren-Larsson syndrome (2.6 and 0.4 per 100,000 in 1978 in Västerbotten and Sweden, respectively) is expected to increase somewhat in the future.

Other progressive disorders
The heading "other progressive disorders" was adopted from the Uppsala study (Gustavson et al. 1977a). In the present series, however, no child surviving one year of age belonged to this subgroup.

Other hereditary causes
The original series of SMR (Paper I) was further investigated (Papers III, IV and V) and altogether 19 children with SMR and 10 with MMR (Table VI) were assigned to the subgroup "other hereditary disorders".

Of special interest are the cases of fragile X syndrome, not previously recognized in Sweden. This syndrome comprised a minimum of 6 percent of the male cases in the SMR series and next to trisomy 21 was the most common single cause of SMR in boys (Paper III). In the review of previously published cases (Paper IV) 25 percent of the boys with the fragile X chromosome were found to have SMR and 75 percent had MMR. Thus it is reasonable to conjecture that there is a higher percentage of the fragile X syndrome among mildly mentally retarded than among severely mentally retarded boys. Macro-orchidism after puberty and verbal disabilities seem to be important clinical signs of the syndrome.

Diagnosis of index cases and female carriers with the marker X syndrome gives a fundamental basis for genetic counselling and should have considerable impact on the future prevention of MR. Furthermore, a method of identifying the marker X chromosome in cultured fibroblasts has been published (Jacky and Dill, 1980). Such a method could make prenatal
diagnosis of the syndrome possible and recently this have been done (Jenkins et al. 1981; Webb et al. 1981; Shapiro et al. 1982). However, various reports must be considered in this connection. For example Darker et al. (1981) describe a fragile site on the X chromosomes in two brothers with normal intelligence, Webb et al. (1981) report transmission of the fragile X site from a male, and Turner et al. (1980) found that fragile site X chromosomes occurred in mildly mentally retarded females. Prevention of the disorder by intrauterine treatment might be possible in the future. There are indications pointing towards an association between a defect in the thymidine synthetase in the folic acid metabolism and the fragile X syndrome (Tommerup, 1981). Postnatal treatment with high doses of folic acid have also been tried in a few patients with this syndrome, but so far with no convincing effect (Sutherland, personal communication 1981).

**Multifactorial causes**

When assigning a child to an etiological group, only one cause of the MR was considered. The use of the ranking list of main causative factors (Table V) might be criticized as a simplification not taking into account multifactorial mechanisms and unduly favoring prenatal factors. In the SMR study (Paper I), however, in most cases the main cause was quite distinct in the specified classification groups. Furthermore, in the comparative Uppsala study (Gustavson et al. 1977a) clashes giving rise to doubt concerning group were unusual. The same can probably be said for the present study, as the same classification system was used in the two investigations. In the MMR study (Paper II) 19 percent of the children, mostly boys, were referred to the group "multifactorial etiology". No main cause of the MR could be identified in these cases, but all the children in this group had a first-degree relative with MR or with a borderline low mental ability of unknown origin. The marked male dominance in the multifactorial group indicates a possible presence of X-linked mutations, i.e. males with the fragile X syndrome, and this question will be further investigated.

Besides an adverse polygenic inheritance leading to developmental insufficiency of the brain and intelligence, a possible lack of stimul-
ating factors in the environment must also be considered. Familial
cases of mental subnormality and MR may be aggravated by a lack of
postnatal stimulation in sensitive periods of the development. In most
families in the present study it was not possible to evaluate the sig-
nificance of such environmental factors. In three children, however,
neglect was recorded as the main cause of the MR (Table VI).

"Prenatal unknown" causes
In 8 percent of the children with SMR and in 4 percent of those with
MMR the MR was considered to have a prenatal but otherwise unknown
etiology. The children had associated major and/or minor abnormalities
of prenatal onset. One child had the syndrome of Prader-Willi and
another had the Elfin face syndrome, but in the other cases no exact
diagnosis has so far been established. Among the latter there may be
cases with unidentified minor chromosomal aberrations and gene muta-
tions as well as cases with unidentified or still unknown teratologic
or brain-damaging factors.

An increased frequency of MR has been reported among children with congenital hypo-thyroidism (Andersen, 1961). In Sweden congenital hypo-
thyroidism has been calculated to have an incidence of 1:6,900 live
births (Alm et al. 1978). In the present series, however, only one
child had congenital hypothyroidism as the main cause of the MR. In
this case the diagnosis was not confirmed until the age of two years.
In the etiological classification the child was not referable to the
genetic group nor to the subgroups "prenatal infection", "fetal depriv-
ation of supply" or "prenatal intoxication/irradiation". For this
reason the child was referred to the group "prenatal unknown", but
could as well have been placed in a group of his own. Four additional
children born in the county during the period of this study (1959 -
1970) had congenital hypothyroidism, but in these cases the diagnoses
were confirmed at an early stage and with subsequent therapy the child-
ren were not classified as mentally retarded.
A neonatal screening program for congenital hypothyroidism was first introduced in Canada (Dussault et al. 1975) and positive effects have been reported from other countries, including Sweden (Engberg et al. 1978). Since the introduction in 1976 up to 1981, seven cases of congenital hypothyroidism were identified through the screening in the county of Västerbotten; with thyroid substitution therapy these children seem to have developed quite normally.

The high incidence of congenital hypothyroidism, the serious effects on the mental development and the excellent treatment possibilities make a nation-wide screening program highly indicated and such a program linked to PKU screening is under evaluation in Sweden (Alm et al. 1981). A child may, however, develop hypothyroidism after the neonatal period and great responsibility will still be placed on the child health care to look for cases with symptoms and signs of this condition.

Prenatally acquired mental retardation
The population is increasingly being exposed to injurious environmental influences such as consequences of industrialization, changes in the way of living, and exposure to infections, drugs, radioactivity, and so on. Questions concerning the sensivity of the fetus to different environmental factors have thus been brought to the fore (Nordström and Beckman, 1981; Nordström et al. 1981).

Prenatal infections
In the epidemiological studies (Paper I and II) an attempt was made retrospectively to identify prenatal infections (the TORCH syndrome, i.e. toxoplasmosis, rubella, cytomegaly or herpes simplex), fetal deprivation of supply and any maternal intoxicating effects which might have caused the MR. In only three children (0.9 percent) (Table VI) was it possible to demonstrate that the MR was caused by prenatal infections. One severely mentally retarded boy had a cytomegalic infection and two mildly mentally retarded girls had a prenatal toxoplasmosis and a rubella infection, respectively, as the causes of the MR. This must be considered a comparatively low incidence. Conceivable teratogenic
infectious agents in the area studied during the time in question were not looked for systematically, however, and children referred to other groups might also have had a prenatal infection as the origin of the MR.

The incidence of diagnosed prenatal infections causing MR was low in other studies also. Thus in only 2 out of 122 cases (1.6 percent) with SMR in Uppsala (Gustavson et al. 1977a) and in none of 91 cases with MMR in Gothenburg (Hagberg et al. 1981b) was the MR caused by an identified prenatal infection. Laxova et al. (1977) reported only one case (0.7 percent) with a causative prenatal infection in a series of 146 children with SMR in England, Turner (1975) 23 cases (2 percent) in a survey of 1,000 Australian patients with an IQ below 51 and Hunter et al. (1980) 10 cases (2 percent) in a study of 406 children with SMR in Canada. In a review article, Lechtig et al. (1979) estimated the prevalence of intrauterine infections to be 0.3 - 5.0 percent in industrial countries. They considered that intrauterine infections were responsible for approximately 13 percent of all cases with MR in the USA.

Huldt et al. (1979) investigated the epidemiology of toxoplasmosis in Scandinavian populations. They reported a low frequency of positive dye test in small children. The antibodies, however, appeared gradually through childhood into adolescence and adult life. Antibodies were more common in females then in males. There was a familial clustering of the toxoplasmosis, but data indicated that the infection was most often acquired outside the home. Children below one year of age were not examined, since their antibodies are most often passively acquired. In a recent prospective Scottish survey (Williams et al. 1981) the rate of infection with Toxoplasмагондии (seroconversion) among pregnant women was 2.3 per thousand and the incidence of congenital toxoplasmosis not less than 0.5 per thousand. These figures were higher than expected in the area. In Europe, however, the incidence of congenital toxoplasmosis had been estimated as 3 - 6 per thousand and in the United States as 1 - 2 per thousand.
Prevention of infection by the parasite Toxoplasma gondii is difficult. No human vaccine is available. Avoidance of cats and raw pork meat during pregnancy have been proposed. Huldt et al. (1979) found no correlation, however, between the presence of antibodies against toxoplasmosis and the exposure to cats or eating of raw meat. Through early identification of the infection in newborn infants and early and intensive treatment the range of the lesions in the infected child could be restricted.

Gregg (1941) first reported the importance of rubella as a causal agent of birth defects while studying an epidemic of rubella in Australia 1939-1941. The main congenital defects, MR, heart defects, deafness, cataract, and microencephaly that followed major epidemics are nowadays well known (Eriksson et al. 1979).

In order to protect fetuses from rubella infections, vaccination focused on women was introduced in Sweden in 1974. A general vaccination program for both sexes in order to reduce the prevalence of measles, mumps and rubella has just begun in this country. Hopefully this will eliminate these viruses from the Swedish population and consequently the number of children damaged by these infections will be reduced.

The prevalence of cytomegalic infection in Sweden was investigated by Ahlfors et al. (1981a). In an extensive study in the city of Malmö, cytomegalic virus was isolated in 0.4 percent of 4,421 newborn infants. At a follow-up 1½ to 3 years later, three infants (0.07 percent) had neurological sequelæ. All three had impairment of hearing and one also had severe psychomotoric retardation (Ahlfors, personal communication).

The possibility of a vaccination against cytomegalovirus infection has been discussed under the assumption that only a primary infection during the pregnancy is responsible for infection of the fetus (Elek and Stern 1974). However, this assumption has not been proven (Ahlfors et al. 1981b). Furthermore, theoretically a living vaccine could be oncogenic. Thus caution as well as extensive research to solve these problems will be necessary.
Herpes simplex infections in a subclinical or clinical form are one of the most common infections in man. Herpes simplex can be demonstrated clinically in about one percent of all pregnancies; the frequency of clinically demonstrated herpes simplex infections in the newborn, however, is estimated at 1/3,500 - 1/30,000 (Nahmias et al. 1970). Neonatal herpes infections are very serious and if the child survives, one of the sequelæ may be mental retardation.

To date there are no vaccines available for use against herpes simplex viruses. Antibodies against one of the two types do not necessarily prevent infection by the other type. However, preventive measures such as therapeutic abortion, cesarean section and prevention of transmission of the virus during the postnatal period are recommended. No child in our series had an identified herpes simplex infection as a cause of the MR.

The degree of fetal injury depends on the type of infection, fetal age, the severity of the infection, the nutritional status of the fetus and the efficiency of the immune response. Consequently the prevalence of the TORCH syndrome and other infections varies between different populations and quantitatively they are probably more important as causes of MR in developing countries.

The exact proportion of children with sequelæ of intrauterine infections in our series is unknown, owing to a lack of specimens. It is possible that a prenatal infection was the cause of the MR in some additional cases, especially in children with an "untraceable" MR.

Fetal deprivation of supply (FDS)
With the intention of comparing the etiological panorama of SMR in the county of Västerbotten with that of Uppsala (Gustavson et al. 1977a), the classification system used in the latter study was adopted. The subgroup FDS was defined as proposed by Hagberg et al. (1976). The group mainly comprised SGA children. In the SMR series 8 percent of the children were assigned to the FDS subgroup both in the Västerbotten and in the Uppsala study.
In the MMR series (Paper II) in Västerbotten essentially the same definitions and classification system were used as in the SMR series (Paper I). Eight percent of the MMR children in our series were assigned to the FDS group. In the MMR series from Gothenburg (Hagberg et al. 1981b) children with FDS and children with asphyxia/hypoxia were classified together under the heading "perinatal origin" of the MR. Consequently the series are not quite comparable. However, five of the 91 children in the Gothenburg study (5 percent) could be considered as having FDS according to the definition used in the present series (Papers I and II).

FDS children seem to be more prone to be damaged by otherwise normal perinatal events (Hagberg et al. 1976) and in some cases with a history compatible with FDS as well as asphyxia it was difficult to decide which of these was the main etiological factor. Retardation of fetal growth should be looked for and recognized throughout all pregnancies and attempts should be made to identify the cause or causes. Identification and treatment of any disease in the mother, rest in bed, etc., are very important for improving the growth of the FDS fetus.

Prenatal intoxication
Four cases were classified under the heading "maternal intoxication/irradiation". One offspring was damaged in utero by an elevated serum phenylalanine level in the mother (Paper V), two by drugs and one by heavy irradiation (Paper VII).

Maternal PKU is one important acquired cause of MR. An untreated phenylketonuric woman offers a very unfavorable intrauterine milieu to her fetus, with subsequent harmful consequences for its development. Lenke and Levy (1980) reviewed published and unpublished information about maternal PKU and hyperphenylalaninemia in a world-wide survey. They obtained data from 524 pregnancies, including those of the present investigation (Paper V) and concluded that among untreated pregnancies the risk of MR and microcephaly in offspring was increased at all levels of maternal hyperphenylalaninemia, reaching 90 percent or more for maternal serum phenylalanine levels exceeding 170 μmol/l. Treatment
with a low phenylalanine diet during pregnancy has been tried in PKU women. Among 34 pregnancies treated in this way, abnormalities in the offspring were only prevented in a few cases. For an optimal effect, the dietary treatment should be started prior to conception.

Some women may have PKU and - as illustrated by the reviewed cases - may become pregnant. It is thus important that all women are examined concerning PKU before child-bearing ages. Since the introduction of the neonatal PKU screening program in Sweden in 1965 an increasing number of girls with this condition have been identified and given dietary therapy. Many of these girls are not recommended any food restrictions after the age of 10 - 15 years. These girls will soon reach child-bearing ages.

Women with PKU require thorough information before they become pregnant concerning the high risk of serious fetal damage. In patients with a very strong desire to have a child of their own, dietary treatment should be introduced before conception and the women carefully supervised throughout their pregnancy.

Alcohol abuse is a growing health problem and the rediscovered fetal alcohol syndrome gives it a new dimension (Ulleland 1970, Warner and Rosett 1975, Olegård et al. 1979). In our series with severe and mild mental retardation (Papers I and II) no case of MR caused by alcohol abuse was identified. None of the mothers of the mentally retarded children were registered by the authorities because of alcohol abuse and there were no notes concerning alcohol abuse in the records. On clinical grounds, however, in three cases the fetal alcohol syndrome could be suspected. Repeated clinical examinations might possibly reveal additional cases.

In a Canadian study, Hunter et al. (1980) found that only four out of 406 severely mentally retarded institutionalized patients had a history and examination findings compatible with the fetal alcohol syndrome. On the other hand, Hagberg et al. (1981b) considered that 8 percent of mildly mentally retarded children born in 1966 - 1970 in Gothenburg,
an industrial city in the south-west of Sweden, fulfilled very strict criteria for a diagnosis of this syndrome.

The difference in prevalences of the fetal alcohol syndrome between the two Swedish studies could at least partly be explained by differences in the female alcohol consumption. The total amount of alcohol purchased per capita in Västerbotten has traditionally been lower than that in most other counties of Sweden (CAN, 1981). There could also have been differences between the two counties in the policy for registration of alcohol abuse during the period in question.

The alcohol habits in Sweden have changed. Today more women are addicted to alcohol, with consequent risks for the offspring. Increased information concerning the risks to the fetus caused by alcohol abuse is necessary. The preliminary results of extensive alcohol-preventive intervention in maternal health care look promising (Larsson, 1982).

Prenatal irradiation
Through well-planned and carefully accomplished examinations the dose of radiation in diagnostic work is nowadays very low. Also in therapeutic radiology the doses outside the tumor are reduced as much as possible. The girl exposed to heavy intrauterine irradiation (Paper VII) is in one aspect of historical interest. With the present knowledge and equipment for the care of preterm infants the girl should have been delivered by cesarean section before the radiation therapy. It has been thought that after 20 weeks of pregnancy even heavy irradiation of the fetus is not likely to produce severe damage to the fetus (Dekaban 1968). In the present case irradiation caused severe damage as late as in the third trimester, a period in the CNS development characterized by glial multiplication and establishment of synaptic connections (Dobbing 1974). Furthermore, the frequencies of persisting chromatide and chromosome breaks were increased. At her death, 13 years after the irradiation, no signs of malignancy were seen.

Since the intrauterine exposure to radiation was very heavy (40 Gy), it must be considered remarkable that the child survived and reached an age of 13 years.
The clinical characteristics demonstrated in this case might have significance in investigations of children damaged in utero and in decisions concerning therapy in pregnant women with radiosensitive tumors.

Perinatal etiology

The percentages of perinatal causes of MR in the present and some other studies are given in Table III. Perinatal events have usually been considered of great importance as causative factors in mental deficiency and most authors report a higher prevalence of perinatal causes of MR than we found. The classification into the different etiological groups in our series was of course influenced by the ranking list (Table V), in which some prenatal factors were regarded as etiologically more important than some coexisting perinatal factors. Any comparison between the studies must be made with great care. However, the frequency of MR caused primarily by perinatal factors was unequivocally low in both the SMR and the MMR series (Papers I and II). In the same time period the deliveries became centralized and the perinatal mortality decreased in the area investigated, as in the whole of Sweden. Increased survival rates in some groups might possibly have increased the incidence of MR. However, good antenatal care with early identification of pregnancies at risk, improved obstetric methods and advances in neonatological care had obviously not resulted in a higher incidence of MR. On the other hand, it should be noted that 27 children with MR and epilepsy and/or cerebral palsy without observed perinatal problems were referred to the group "untraceable etiology". It is possible that some of these children had an unnoticed hypoxia or neonatal metabolic derangement which caused the brain damage.

Perinatal complications were the main cause of the MR in 7 percent of the present SMR series and in 8 percent of the SMR cases in the Uppsala study (Table III). Seven percent of the cases of MMR in our study were caused by perinatal complications, compared with 18 percent in the Gothenburg study. In the latter study, however, FDS children were also included in this subgroup. In our series there was no case of MR caused
by hyperbilirubinemia, but this condition might partly explain the high proportion of perinatally caused MR in the Hungarian series of Czeizel et al. (34 percent).

There were only two uncomplicated cases with a low birth weight (LBW) and appropriate for gestational age (AGA) in our total material, one in each series, and none in the series from Uppsala and Gothenburg. The prognosis concerning mental development in the group "uncomplicated LBW/AGA and alive at one year of age" therefore seems good.

With greater improvement in obstetric and neonatal management, the number of children with MR of perinatal origin should be further reduced.

Postnatal etiology of MR

In one percent of the cases in the SMR series (Paper I) and in five percent in the MMR series (Paper II), most of them boys, the MR had a postnatal etiology (Table VI). In two cases of spontaneously arrested hydrocephalus the assignment to the postnatal group can be discussed, as the structural background of the elevated intracranial pressure was probably of pre- or perinatal origin. The mental retardation, however, was considered to be the result of a later intracranial hypertension and consequently classified as postnatal. Only one girl had MR following encephalitis and no single patient had MR after immunization, as has occurred in a fair number of cases in England (Miller et al. 1981). One boy was mentally retarded as a result of a traffic accident. In other studies (Table III) 2 - 16 percent of the children with MR were assigned to a postnatal etiological group. The higher frequency figures given by Czeizel et al. in Hungary and Hunter et al. in Canada included several cases of meningoencephalitis of bacterial or viral origin.

Hunter et al. (1980) reported 5 cases of definite abuse and 3 cases of suspected abuse in their series of 406 children with MR. In an extensive study of 140 children in two subnormality hospitals in the U.K.,
Buchanan and Oliver (1979) found that 3 percent had definitely suffered assaults as babies, which caused brain damage rendering severe mental handicap and 8 percent could possibly have been rendered mentally handicapped as a result of abuse. In a recent review Frodi (1981) suggested that atypical infants/children (with mental, physical, or behavioral abnormalities) are at risk of child abuse, as they may be perceived as adverive and as such may serve as aggression-facilitating stimuli. In our series (Papers I and II) there were no known cases of MR following brain injury from assaults.

In England, in a high proportion of mentally retarded children the MR has been considered to be due to neglect (Buchanan and Oliver 1979). This could not be confirmed in our series, where only two boys and one girl had MMR which was believed to be a consequence of neglect and understimulation. In these cases the lack of stimulation was documented and judged to be the major cause of the MMR. All three children later made progress in mental ability and subsequently they were removed from the B.P.S.M.R. register. Understimulation may of course have an impact in other cases also, especially those with backward parents. In the present study these cases were classified as multifactorial concerning the cause of the MR. In reviewing the long-term effects of early experiences of understimulation, however, Rutter (1980) concluded that because of the maturational changes that take place during middle and later childhood and the effects of beneficial and adverse experiences during all the years after infancy, the residual effects of early deprivation on intellectual and social development are quite small.

With increased knowledge, general improvements in the society and improved child health care in Sweden, many postnatal factors causing or aggravating MR have been reduced and can probably be diminished further.

Primary psychosis

In studies concerning etiological factors in MR, primary child psychosis has sometimes been recorded under a separate heading. It might be
argued that psychosis is not an etiological factor in MR and certainly the pathogenetic mechanisms are unknown in many cases of psychosis, as they frequently are in MR. However, the infantile autism syndrome (Kanner 1943; Rutter 1975) has a characteristic clinical picture and, furthermore, the affected children require a very specific mode of treatment. This is also true for other forms of primary child psychoses. Thus it was considered justified to classify these children separately.

In the SMR study (Paper I), one percent and in the MMR study (Paper II) 2 percent were assigned to the primary psychosis group (Table VI). In other studies (Table III) the psychotic group comprised 1-3 percent of the retarded children. A primary psychosis may be unidentified for several years, but as the youngest children in our study were five years old most cases with primary psychosis should have been recognized. As mentioned previously, in our classification of the main etiology of MR a ranking list (Table IV) was used. Thus, five children with MR and primary psychosis had obvious prenatal stigmata and two others had intrauterine deprivation and were classified according to this. This underlines the multifactorial etiological background in child psychosis.

Untraceable etiology

This group exists as a separate entity primarily through the process of elimination. No demonstrable cause of the MR was detected from the records in as many as 22 percent in the SMR study (Paper I) and 43 percent in the MMR study (Paper II). In both series there was a majority of boys. The proportion of children with SMR of untraceable etiology in some other studies varies between 11 and 37 percent (Table III). In MMR only two comparable studies are available, and show a proportion of untraceable etiology of 55 percent (Hagberg et al. 1981b) and 61 percent (Czeizel et al. 1981) respectively.

Several unidentified etiologies of the MR are possible in this group: unrecognized environmental damage and/or maternal/fetal interaction,
unrecognized small structural chromosome abnormalities, the homozygous state of several different autosomal recessive genes, X-linked recessive mutations, autosomal dominant new mutations, and multifactorial inheritance.

In our supplementary study (Paper IV) three boys with an "untraceable" SMR were shown to have the fragile X syndrome, and were subsequently reclassified to a group with monogenetic inheritance (Table VI). The large excess of boys also in the MMR series indicates additional cases of the fragile site X syndrome in this series.

Mental capacity lies on a continuum and part of the children in the MMR-untraceable group according to the definitions comprise the lower end of the normal distribution. Our and other studies show, however, that pre-, peri- and postnatal factors play a considerable role even in the pathogenesis of MMR. Some of the causative factors of MR are already preventable and others will probably become preventable in the future.
Associated CNS handicaps

Half of children with SMR (Paper I) and one-third of those with MMR (Paper II) had associated CNS handicaps (Table VII). Epilepsy was the most common in the two series (36 and 18 percent), but cerebral palsy was also frequently present (19 and 7 percent) and in many cases these two conditions occurred together.

A combination of MR and epilepsy has also been very common in other series. Out of 243 Finnish children 0 - 19 years with epilepsy, 40 percent had MR (Sillanpää 1973) and 16.4 percent of 9 - 11 year-old English children with intellectual retardation had had seizures, compared with 1.4 percent in non-retarded controls (Rutter et al. 1970). Among severely retarded children in London up to 5 years, 5 - 10 years and 10 - 15 years of age, 25, 18 and 25 percent, respectively, had had seizures (Corbetta et al. 1975). Thirty percent of the 5 - 16-year-old children in the SMR study in Uppsala (Gustavson et al. 1977a) and 12 percent of the 8 - 12-year-olds in the MMR study in Gothenburg (Hagberg et al. 1981a) had epilepsy. In a follow-up study of the mentally retarded population in Aberdeen in Scotland, Richardson et al. (1981) found a history of seizures in 19 percent of retarded people in preschool years and 13 percent in early, late and postschool years up to 22 years of age. No significant correlation was found between the severity of the epilepsy and the severity of the MR. They also noted a significantly higher frequency of seizures among mentally retarded males and speculated upon a higher frequency of CNS damage in the males.

Compared with the above reports, the frequency of epilepsy in our two MR series is somewhat high. The diagnosis of epilepsy in our two series was based, however, on the clinical records and in doubtful cases checked with available electroencephalograms and thus considered reliable. In relation to the male excess in our MR series the proportion of males with seizures was not increased.

Many of the epilepsies were of a severe type, with a high frequency of seizures, and some of the children received several antiepileptic drugs in doses that were sometimes CNS-depressing.
Spastic hemi-, di- or tetraplegia were the most common cerebral palsy syndromes in both our series (Papers I and II). Tetraplegia occurred mainly in children with MR of neurometabolic etiology. Only two children had syndromes of mainly the dyskinetic type.

Most of the cases with cerebral palsy were found in the subgroups "prenatal acquired" and "perinatal asphyxia/hemorrhagia". This is in accordance with a finding that FDS was an important causative factor in cerebral palsy (Hagberg et al. 1976). In the latter study almost one-third of cerebral palsy children born in 1959 - 1970 had an IQ below 70. In a recent study of 183 children with cerebral palsy born in 1960 - 1972 in the county of Malmö, about 25 percent were found to have SMR and about 7 percent MMR (Lagergren 1981). In our series many cases with cerebral palsy were also seen in the group with an "untraceable" etiology, indicating brain-damage events in these cases also.

The programs for preventing deficient intrauterine growth and Rh-immunization, improvements in monitoring deliveries and resuscitating asphyxiated infants, and intensified neonatal care will continue to be important in the attempts to reduce the number of brain-damaged children.

The prevalence of visual impairment, 10 and 9 percent in our SMR and MMR series respectively (Table VII), was much higher than that of one per thousand found among normal Swedish children (Lindstedt 1975). It was lower, however, than the figures of 11 - 15 percent and 25 percent given for severely and very severely mentally retarded children, respectively, in a Danish series (Warburg 1979). In our study only known severe visual impairment was recorded and it is quite possible that additional retarded children had unnoticed visual impairment.

Severe impairment of hearing was found in 6 percent of the children with SMR and in 4 percent of those with MMR (Table VII). There are great problems both in identification and in diagnostic evaluation of hearing impairment in mentally retarded children. In an extensive study of children with MMR in the county of Uppsala (Lerman 1978), 4 percent
were found to have impairment of hearing (≤ 40 dB, 500 - 3,000 Hz in the best ear). In the severely retarded children the corresponding figure was 7 percent. Compared with these figures our data seem valid, but since only known impairment of hearing was recorded and relevant investigations had not been made in many of our cases, the figures must be considered as minimum values.

All mentally retarded children should be examined regularly concerning vision and hearing, with the aid of suitable tests conducted by specially trained persons. In some of the children the handicap situation could probably be reduced by provision of spectacles or hearing aids.

Of the possible CNS handicap, only epilepsy, cerebral palsy, and impairment of vision and hearing were recorded in the present study. In many mentally retarded children other CNS-related handicaps, e.g. behavioral or emotional disturbances, may be the greatest problem. However, since relevant information concerning the magnitude of these problems was often not given in the records, such factors were not included in this study.
GENERAL CONCLUSIONS

1. The prevalence of both severe (IQ below 50) and mild (IQ 50 - 70) mental retardation decreased in 1959 - 1970; nevertheless mental retardation is the most frequent handicap in children and extensive efforts should be made to prevent the handicap situation.

2. The etiology of mental retardation can be determined in the majority of severely retarded children and in many children with mild mental retardation.

3. The preponderance of prenatal causes of mental retardation in children must not lead to fatalism, as both many genetic and some prenatal acquired causes can be prevented. Through further concentration on identification of key cases, on genetic counselling and on antenatal care the number of children mentally retarded from prenatal causes ought to be reduced.

4. Perinatal factors are the main cause of mental retardation in only a minor proportion of children, but such factors may aggravate the outcome of prenatal injurious mechanisms. Further concentration on active obstetric and neonatal care will hopefully diminish the number of children with perinatally caused mental retardation.

5. Postnatal etiological factors cause a small proportion of mental retardation in children in our country. Further efforts to achieve a better environment for children are important, however, in the attempt to further reduce the frequency of mentally retarded children.

6. Efforts instituted to trace the specific etiology of mental retardation in hitherto "untraceable" cases may be successful and important, as the disorder may be treatable and as additional cases of the same disorder in the family may be prevented.

7. The high incidence of multiple handicaps in mentally retarded children underlines the need for multidisciplinary services for this population.
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