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progress report on Research
on Human Genetics in Iceland
October 31st, 1980

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PROGRESS REPORT ON RESEARCH ON HUMAN GENETICS IN ICELAND

October 31st, 1980.

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Records of the Icelandic Population are being used to investigate the possible inheritance of disabilities and diseases as well as other characters and the effect of environment on man.

The progress report of reserach covers the period 1977 to 1980. The investigation was begun in 1965 by the Genetical Committee of the University of Iceland and the materials used are demographic records from the year 1840 to present and various medical information. The records are being computerized and linked together to make them effective for use in hereditary studies

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1. Genealogical Register

The progress of the demographic work done in 1977 to 1980 and the punching of various clinical and demographic data is outlined below:

- 1.1 The transcription of genealogical data from the Parish records for the period 1840 to 1910 covered all births during that period and was completed for the whole of Iceland. The transcription was done on forms, where children are grouped and linked with their parents. This work was done by genealogists, mostly at the National Archives. The data have been punched and made available for computer work.
- 1.2 Death records for the same individuals are being added. In it is given the place and date of birth and sometimes cause of death.
- 1.3 The 1910 Census is being used to link birth records from the period 1840 to 1910, as it has previously been linked with the National Register and the death records for later periods.

2. Computer Work Present Status and Future Plan

2.1 Introduction.

After linking the birth records for the period 1911-1966 to the national register, or the death records on the IBM 1620, the linked birth records were transferred to the IBM 360/30 computer in 1976. These records were then organized into an Indexed Sequential File called FSI on the 360. Various checks, corrections, and additions were made in this process. (See Progress Reports 1978 and 1979 for details on FSI.)

Two User Programmes were developed in the period 1977-1979 on the IBM 360/30 for FSI:

(1) Barnaleit (Search for children). This programme finds in the FSI the children of a given couple. This programme has been used in a number of studies, e.g., on cousin-marriages, cancer of the breast and psychiatric diseases.

(2) Makaleit (Search for spouses). This programme finds from the marriage records the spouse(s) of a given individual. The output could then be used as input for the Barnaleit programme (1) to find the legitimate children of the individual. This programme has been used, e.g., in the study of cancer of the breast.

Since Computing Services at the University of Iceland decided to stop using the IBM 360/30 machine at the end of April 1980, some pilot studies began on the PDP 11/60 machine towards the end of 1978. These studies included the design of two test data bases using the SEED (an implementation of the 1971 CODASIL Data Base Task Group Standard. It employs a network structure and is written in FORTRAN IV) data base system (see appendix I). The result was quite encouraging for the committee's project, but because there was not enough space for the whole family-tree data base on the PDP 11/60 discs, it was not possible to install these systems for actual data manipulation.

The PDP 11/60 was, therefore, mostly used for the development of fundamental parts of the future system while IBM 360/30 was still used for actual data manipulation (until April 28, 1980).

In the middle of the summer 1980 Computing Services will transfer all its activities from the PDP 11/60 to a VAX 11/780. Much work has gone into redesigning and implementing the system on each new computer. Much of the system at present installed in the PDP 11/60 machine must be revised and much work must be done to enable utilization of the full potential of the VAX 11/780 machine for the handling of data. On arrival of the new computer and a private disk drive (with 67 MB Disk pack) for the Committee's project it will be possible to keep most of the data on a single device. Moreover, the machine can be used both by batch mode and on-line mode with remote terminals and, therefore, updating, addition and deletion of data will be faster and easier.

The "Family Tree Data Base" will be developed on the VAX 11/780 with a 67 MB disk pack. In addition to the operating system of the computer (VAX/VMS) the data base will be mainly built on SEED data base management system.

2.2 Data

Present status/original data available at time of data base creation.

- A. Census 1910 on tape
- B. Birth records

B-1 mother's records 1840-1910 on cards

B-2 birth records 1910-1966 on tape (FSI)

B-3 birth records 1967-1968 on cards

B-4 birth records 1969-1976 on cards

B-5 birth records 1077-1978 on diskettes.

C. Death records

C-1 death records 1911-1967 on cards

C-2 death records 1968-1977 on tape

- D. Blood groups records on cards
- E. Marriage records

E-1 marriage records 1911-1915 on cards E-2 marriage records 1016-1970 on tape

First-cousin marriage records/control group on tape

G. Twin records.

Of these, birth records play the main role in the project. They contain many details of individuals such as date of birth, place of birth, legitimacy, name of parents (if possible), age/date of parents (if possible), etc. Not all birth records are ready for use as input to the data base. Most of them (B1 - B5) are in different forms and their completeness is variable. A brief data analysis is as follows:

B-1 (Mothers' records 1840-1910):

They are a sort of birth record taken from the mother's register at the child's birth and information about the father is taken from church register. Most of them lack date of birth of parents (sometimes ages/blank). They have not yet been checked. It was proposed to use A (Census 1910) as birth records for the time being, because A is already linked to the National Register/Death records and, moreover, it is possible to make reliable birth records for half of the individuals in Census 1910. B-1 can be linked later. Census 1910 Data Base Model (see Appendix I) is very useful in this context.

B-2 (Birth records 1910-1966):

This part of the birth records was used as FSI on the IBM 360/30. Much work was done to implement B-2. The completeness of the data depends on the era:

 $\underline{1910-15}$: 3 letters are used for names and most of the records lack date of birth of parents.

1916-40: quite reliable concerning names (6 letters) but most records still lack date of birth of parents.

 $\underline{1941-66}$: 3 letters are used for names but records are more complete concerning date of birth of the parents.

- B-3 (Birth records 1967-68): quite complete.
- B-4 Almost all complete, but records do not contain names of parents, but instead their birth number.
- B-5 The same as B-4, except they are on disketts.

Part of Death/Blood group records have been linked to B-2. Of marriage records $\underline{E-1}$ does not contain the dates of birth of married couples.

2.2 Data Base ("Family tree data base").

Present status: Because the data is complex (and incomplete) a complex data base is necessary with 9 seperate interconnected areas (see Fig. 1). The design of this date base is almost complete.

Much work is necessary to build the data base. It may be divided into the following processes:

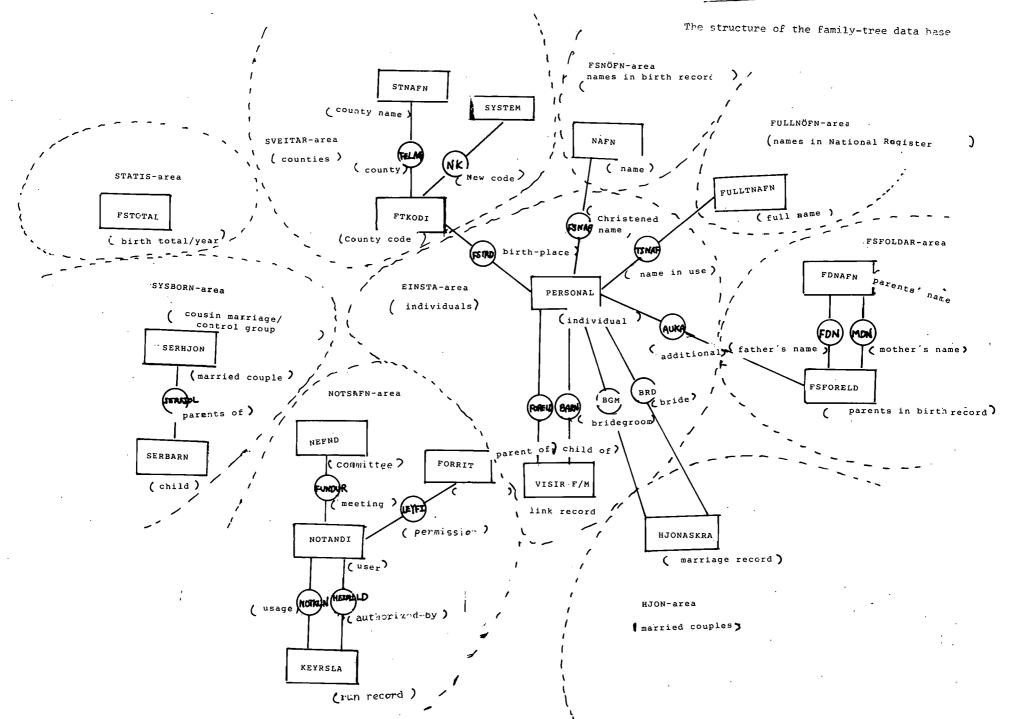
- (1) loading process
- (2) construction of the controllers
- (3) linkage process
- (1) loading process:
 - a) load B-2
 - b) syntax check B-3, then load
 - c) simple syntax check B-4, then load
 - d) load B-5
 - e) Build first Census 1910 Data Base (see App.I Prog. Report 1980) and make birth records out of it for individuals born 1840-1910, load them to the family tree data base.
 - f) check B-1 data, then link them to the data base for addition of information for individuals born 1840-1910.
 - g) load information from the National **Re**gister and link to the individuals alive 1979
 - h) load marriage records.
- (2) Controllers are command routines needed to control the usage of whole Data Base.
 - "Documentater" gives an authorized user the the general information of the SYSTEM.
 - "Reporter" reports the usage of the system/stage of the development of the system.
 - "Guide" helps a user to retrieve, add, change data.
 - "Designer" gives an authorized user information about the structure of the Data Base.
 - "Back up" gives an authorized user the back up situation.

- (3) Linkage process.
 - a) link marriage records to individuals
 - b) interlinkage: children -- parents
 This is the most difficult and time consuming
 process, except for the period 1969-1978.
 A set of programs are necessary for this
 operation.
 - c) link death records (1967-1974) to individuals in the Data Bas-.
 - d) link blood group records to individuals in the vata Base.
 - e) load cousins marriage/control group records.

User Programs

Routines developed for the "Family-Tree Data Base Model" (see App.I, Prog. Report 1980) are available on the PDP 11/60. Transferring them to the VZX 11/780 involves considerable work. Of these routines some (e.g., family tracing routines) may not work powerfully until the data base becomes rather complete, depending on interlinkage process.

Therefore, the transfer of old routines developed for the FSI on the IBM 360/30 machine is also necessary, especially "FIND CHILDREN (barnaleit)" and "FIND SPOUSES (makaleit)". Individual projects, e.g., blood group research may require problem oriented programs.



3. Use of the Demographic Records

The demographic registers are now being used as source of data in various hereditary and ecological studies. Armention may be made of the following 4 projects:

- 1) A study of families of first-cousin marriages was a collaborative effort between many disciplines and institutions, that have collected clinical data, analyzed blood groups and performed chromosome studies of parents and children of 155 families constituting 783 individuals.
- 2) The Genetical Committee has also collaborated in a study of familiality of breast cancer conducted by the Department of Pathology of the University of Iceland and the Icelandic Cancer Registry. This study includes family data of the propositus as far as 3rd degree relatives.
- 3) A study of the possible family agregation of heart disease in Iceland was done by the Chief physician of the Reykjavik City Hospital, in which the Committee's genealogical register was used to collect the families of 150 cases as far removed as 3rd degree relatives, as well as 150 control families.
- 4) Familiality of mental disorders has been investigated as well as the possible inheritance of intelligence as indicated by mean scores achieved at final examination from elementary school.

3.1 First-cousin marriage families.

Data on the first-cousin marriages in the period 1916-1964 were drawn from the demographic records. The children of these couples were extracted from the birth records. The families were then contacted and examined clinically. Initially, the family members were examined personally at the Blood Bank at the same time as a blood sample was drawn for biochemical and immunological studies. Clinical studies concentrated on interviewing a key member of each family and collecting information from the general

practitioners who have been taking care of the families. The study constituted 155 families with 783 individuals.

The collection of clinical data on 117 first-cousin marriage families is now finished and the collected data coded (seeAppendix II). Among the 324 parents there were 44 with psychiatric diagnosis and, in addition, there are 12 parents with CMI indicative of neurotic disorders. The analysis of these data andtheir linkage to the haemato-logical data is now possible.

During 1978 a control group for the first-cousin marriage families was drawn from the Committee's marriage records. This was done by matching every first-cousin marriage with another marriage established in the same year with each of the partners being of the same age as in the first-cousin marriages. By these means, it was possible to compare the fertility of the registered first-cousin marriages with a sample of marriages from the population, where the partners are presumably unrelated. Also, the psychiatric morbidity in the control group could by studied in the same way as among the children and parents of the first-cousin families. Some reports on this study have already been published (see Prog. Report 1977, 1978 and 1979 and Publication list nos. 24,33).

3.2 Carcinoma of breast

The study of possible familiality of breast cancer, conducted by Prof. Olafur Bjarnason and Dr. Hrafn Tulinius at the Cancer Research Society, continued using the Genetical Committee's genealogical register.

The families were constructed around the case as propositus. Relatives were counted all 1st,2nd, and 3rd degree relatives, except great-grandparents. Included in the families are also the spouses of those relatives whose descendants would be covered by the definition above. With each type of relationship the number of breast cancers observed is being compared with the computed number expected to determine, for certain types of relatives, whether the risk of breast cancer is increased in the relatives of breast cancer cases and, if so, how much is it increased.

A report on this study was presented at the Symposium of the Nordic Cancer Union on Genetic Factors in Neoplastic Diseases of Man, Reykjavik June 21st, 1978 (Publication List no 54). Another paper based on this study is presented as Appendix III.

3.3 Heart Diseases

The occurrence of deaths due to ischaemic heart disease among first and second degree relatives of coronary patients and to relatives of equal number of matched controls was studied on the basis of death certificates. The propositi were 108 males and 42 females, who had developed myocardial infarction, males before 65 years of age and females before 70. When compared with controls 1 1/2-fold greater death rate was found among first degree relatives of the propositi and a lower average age at death. The difference in death rate between second degree relatives was not significant, except for maternal brothers. When compared with the death rate due to ischaemic heart disease in the general population the increase in risk to first degree relatives of propositi was nearly 3-fold over the expected value, and $1 \frac{1}{2}$ -fold to second degree relatives. The age of the propositi at onset of myocardial infarction showed no effect on risk to relatives, but the effect of sex was significant. first degree relatives of male propositi the risk increase was up to 5-fold over the expected value. The risk increase was found greatest to first degree male relatives of female propositi, or over 7-fold to fathers and brothers. Mothers and sisters of both male and female propositi showed a 4-5-fold risk increase over the expected value. The risk increase to second degree relatives was 2 1/2-fold over the expected value to maternal brothers of male propositi and 4-fold to maternal brothers of female propositi. The relatives of controls showed a coronary mortality close to that of the general population. Familial clustering of coronary deaths was found in 8.7% of the propositi families and in 4.7% of the controls.

The findings of the present study indicate a substantial genetic component in the overall etiology of ischaemic heart disease, which is more prominent in families of female propositi but hardly of a magnitude that allows genetic counseling. (Publication list no.52)

3.5 Mental Disorders, Intelligence, and Population Structure.

The updating of the psychiatric register has continued. The register has been instrumental in making different studies possible, studies on drinking habits, alcoholics (Publication list no. 23), delirium tremens (Publication list no. 32), incidence of consultations with psychiatrists. The last study has been published as a supplement to the Acta Psychiatrica Scandinavica 1978, Vol.58, and accepted as a D.M. Thesis at the University of Iceland. This study was carried out by Dr. Lárus Helgason. (Publication list no.22). The register has also been useful in follow-up studies of a cohort of the general population (Appendixes IV, V).

Data from the register were used in a paper on the epidemiology of alcoholism published in Advances in Biological Psychiatry, 1979, Vol. 3 (Publication list no. 32 and 31) APP. VI).

A paper was given on epidemiological studies of affective syndromes at a symposium in Arnus, Denmark. This paper includes data on psychiatric morbidity, and especially on affective disorders among children of probands in the cohort study, who had an affective disorder at some time during their 80 years of life and compared with the psychiatric morbidity among children of probands, who never contracted any psychiatric disorder during their life time. (Publication list 29).

The school records have been punched so the Committee now has these on file as far as 1978. Data from these was used in a paper given by Prof. Tomas Helgason at a symposium on primary prevention of mental disorders held by the World Psychiatric Association in Cairo, Egypt, 1978 (Publication list no. 27).

4. Man and the Environment.

The Icelandic data has been considered ideal for investigating the effects of environment on the genetical and medical conditions of man, such as mutation rate and incidence of disease. A study of the effect of the use of geotherman water on man has been discussed. (Publication list no. 20.).

- 4.1 Volcanic eruptions sometimes emit fluoride gases that are carried with the ashfall and contaminate water, soil, and vegetation, and affect both animals and man. A lecture on the fluoride toxicity in Iceland was presented by Dr. Sturla Fridriksson at the University of Athens, Athens, Greece, May 14th, 1979. (Publication list no.18.)
- **4.**2 It has been observed that the incidence of carcinoma of the thyroid gland as indicated by the cancer register has a rather peculiar distribution. This has been investigated by Prof. Olafur Bjarnason and was reported on at a symposium on Geomedicine in Oslo.(Publication list no.1 ξ .)

5. Genetic Marker Studies

The typing of HLA, A, B, and C, red cell blood groups and biochemical markers continues at the Blood Bank.

The association of HLA and diseases was reported on by Dr. Alfred Arnason at a Symposium on Epidemiological Problems in Genetics, June 29-30, 1979, held in Reykjavik by the Nordic Council for Arctic Medical Research.

(Publication list no.2.) The frequency of Gc alleles and a variant Gc allele among Icelanders has been reported.

(Publication list no.47.) Dr. Ólafur Jensson reviewed studies on the genetics and epidemiology of haematological disorders in Iceland. (Appendix VII and Publication List no.42.) Two other reports have been submitted for publication, one on the Genetics and Epidemiology of Cerebrovascular Diseases in Iceland (Publication list no.21) and another on the Investigation of Osteogenesis Imperfecta in Two Families.

Professor Gunnar Gudmundsson read a paper on Hereditary Factor in Intra Cranial Haemorrhage in Iceland, and Dr. Olafur Jensson on HLA types, Gc protein and other genetic markers in multiple sclerosis and two other neurological diseases in Iceland at the 23rd Scandinavian Congress of Neurology 11-14 May, 1980, in Reykjavik (Appendix VIII).

6. Cytogenetics Laboratory Report 1979

The Genetical Committee's chromosome studies are carried out at the Department of Pathology, University of Iceland. The results of work done in 1977-1978 have been reported on in Progress Reports 1978 and 1979. The results of work done in 1979-1980 are shown in the following tables:

TABLE I

Number of Specimens:

Specimen	Number	Diagnosed abnormalities.
Amniotic fluid	239	4
Blood	3 97	29
Skin	5	1
Gonads	3	2
Marrow	4	4
Total:	648	40

TABLE II

Amniotic Fluid Specimens:

Total number of specimens: 239

Diagnosed as normal: 113 Q and 113 0

Re-examined: 6

Not answered: 1

Diagnosed abnormalities: 4

Diagnosed arteficial abnormalities/mother-cell contanimation: 5

Diagnosed abnormalities:

47,XY +G 21 Downs syndrome

47,XXY Klinefelter syndrome

46,XX, del.4p

46,XY, ?9 Same abnormality found in father.

TABLE III

Blood Samples:

Total number of specimens: 397

Motherblood sent with amniotic fluid: 226

Other blood: 171

Diagnosed normal: 71 Q and 51 6

Re-examined: 1

No growth: 1

Diagnosed abnormalities: 29, (15 Q and 14 d)

Diagnosed abnormalities:

Downs syndrome, tri. 21: 2 9, 2 0

Klinefelter, 47, XXY: 5

Turner, 45, XO: 3

Isochromosome X: 2

Inversion on 9: 7 9 and 7 6

? 9: 1

Deletion A2: 1

TABLE IV

SKIN

Total number of specimens: 5

Diagnosed: 3 normal 9

1 47,XXY confirmed diagnosis of amniotic fluid

No growth: 1

GONADS

Total number of specimens: 3

Diagnosed: 2x(XY) woman

1 normal ?

MARROW

Total number of specimens: 4 Diagnosed:

46, XX/47, XX+F Twice examined

46, XX+philadelphia chromosome

 $\mathfrak Q$ with multiple abnormalities.

6. Miscellaneous

Professor John H. Edwards visited the Genetical Committee in June 1978 and 1979 to discuss future work and the First-cousin marriage families'study.

Dr. Elizabeth Thompson from Cambridge, England, visited the Committee in September 1977 to discuss further Icelandic admixture problems, on which she wrote a chapter in her book on "Human Evolutionary Trees", Cambridge University Press 1975.

Dr. Olafur Jensson defended his doctoral dissertation on "Four Hereditary Blood Disorders in Iceland" at the University of Iceland, in June 1978.

Professor Olafur Bjarnason, Professor Magnus Magnusson, Dr. Sturla Fridriksson, Dr. Olafur Jensson, and Dr. Alfred Arnason attended the Symposium of the Nordic Cancer Union, held in Reykjavik, June 21st 1978, at which Dr. Fridriksson gave a paper on "Records of the Genetical Committee" and Prof. Magnusson gave a talk on "Computer Linkage of Birth Records' File in Iceland and its Applications". (Publication list no. 19,51, APP. IX)

A Symposium on Epidemiological Problems in Genetics was held in Reykjavik June 29-30, 1979 by the Nordic Council for Arctic Medical Research. At the Symposium Dr. Alfred Arnason gave a paper on "Association of HLA and Disease in Iceland (Publication list no.2). Prof. Tomas Helgason gave a paper on Mental Disorders and Consanguinity - A comparison of first-cousin marriages and matched unrelated marriages" (Publication list no.33). Dr. Olafur Jensson gave "introductory Remarks on the First-Cousin Study" (Publication list no.34), and a paper on "Genetics and Epidemiology of Haematological Disorders" (Publication list no. 42). Dr. Jensson also co-authored a paper with Dr. Gunnar Gudmundsson on "Genetics and Epidemiology of Cerebral Haemorrhage" (Publication list no. 21). Dr. S. Fridriksson was a co-author with Dr. Oskar Thordarson of a paper on "Death from Ischaemic Heart Disease Among 1st and 2nd degree relatives", which was also presented at the Symposium (Publication list no. 52).

Prof. Olafur Bjarnason attended and presented papers at a symposium on Environmental Causes on Cancer -Documentation and Consequences at Arhus, Denmark, 1979, and the Nordic Association for Forensic Medicine meeting at Sandefjord near Oslo, Norway 1979.

Prof. Olafur Bjarnason and Dr. Sturla Fridriksson attended the Symposium on Geomedical Problems in Oslo, May 22-23, 1978 arranged by the Norwegian Academy of Sciences and presented two papers (Publication list no. 15 and 20).

Sturla Fridriksson attended a Symposium on Toxicology and Protection of the Environment at Athens, Greece
May 13-14, 1979 organized by the NATO Special Program
Panes on Eco-Sciences, and gave a paper on "Fluor Toxicity
in Iceland" (Publication list no. 18).

Prof. Tomas Helgason attended a Symposium on Alcoholism, a Multidisciplinary Approach, arranged by the Interdisciplinary Society of Biological Psychiatry in Amsterdam, May 1978 and gave a paper on Epidemiological Studies of Alcholism (Publication list no. 32). Prof. Helgason also attended a Symposium in Psychiatric Follow-up Research in Hamburg, June 1978 and gave a paper on "Epidemiological Follow-up Research within a Geographically stable Population". Prof. Helgason also took part in a a Nordic training course for research workers on "Longitudinal Prospective Studies of Populations at Risk" in Arhus, Denmark, June 1978 and presented two papers on studies of clinical conorts (Publication list no. 29) Prof. Helgason attended a Symposium on Origin, Prevention and Treatment of Affective Disorders on the occasion of the 50th anniversary of Arhus University, Arhus, Denmark and gave a paper on Epidemiological Investigations Concerning Affective Disorders" (Publication list no. 30) Prof. Helgason attended a Symposium on Treatment and Prevention in Psychiatry, organized by the World Psychiatric Association, December 1978 in Cairo, Egypt, and presented

a paper on "Epidemiology and Primary Prevention"

(Publication list no. 27). Prof. Helgason contributed a chapter on "Estimation of Need on the basis of Case Register Studies: Discussion", in a book titled: Estimation Needs for Mental Health Care, ed. by H. Häfner, published by Springer Verlag, Berlin-Heidelberg-New York (Publication list no 28).

Dr. Olafur Jensson participated in the XIV. International Congress of Genetics in Moscow in August, 1978. Dr. Jensson attended a Symposium on Genetic Diseases in Sparsely Populated Areas of the Nordic Countries and gave a paper on "Examples of Hereditary Diseases in Iceland (Publication list no. 40). Dr. Jensson took part in the 15th European Blood Transfusion course in Frankfurt, 8-18th May, 1979, which included several lectures on blood groups, HLA and complement genetics. Dr. Jensson stayed in England 15-31 May, 1980 to consult with the following collaborators in London and Oxford: Prof. R. Batchelor, Hammersmith Hospital, London (Multiple Sclerosis and HLA). Dr. M. B. Pepys, Hammersmith Hospital, London (Amyloidosis serum amyloid P-component (SAP) and C-reactive protein CRP). Analysis of laboratory results in the Icelandic Family with Macroglobulinaemia. Prof. John H. Edwards, Oxford, regarding analysis of results of genetic marker studies in MS patients in Iceland. Drs. Ruth Sanger and Patricia Tippett MRC Blood Group Unit, University College, London, regarding studies on unusual Rh -D- haplotype in Iceland.

Dr. Alfred Arnason participated in the XIV. International Congress of Genetics in Moscow, August 1978.

Dr. Arnason attended the 17th Scandinavian Rheumatology Congress In Reykjavik, 1970 and gave a paper on Four Rheumatological Diseases in an Inbred Icelandic Family (Publication list no.3). In 1979 Dr. Arnason attended a Course on Blood Transfusion and Tissue Typing in Norway; the X. Nordiske Transplantationsmöde in Reykjavik, and the IV. Congress of the Society of Icelandic Internists, Borgarfjordur, Iceland and presented a paper "Vefjafbokkar (HLA) og insulinindependent diabetes mellitus (IDDM) á İslandi" (Publication list no.10).

Dr. Arnason participated in the Conference on Congenital Adrenal Hyperplasia and HLA in Manchester Sept. 10,1970, and gave a paper on CAH and HLA in Iceland - A crossover between GLO-1 and CAH. Dr. Arnason attended a conference on HLA and Disease in Birmingham Sept. 11-12, 1979 and gave papers on Rheumatological Disease and HLA-Bf in Iceland and IDDM and HLA-Bf in Iceland. Dr. Arnason also attended the following conferences: Scandinavian Conference on Peternity Investigation, Linköping, Sweden, June 8-11, 1980; First Scandinavian Conference in Forensic Science, Linköping, Sweden June 11-13, 1980, and European Complement Workshop, Lund, Sweden, June 13-16, 1980.

Mrs. Takako Inaba, Computer Scientist, attended the 1st International Research Conference on Data Bases, In Aberdeen Scotland, July 1980. The conference was organized jointly by the Dept. of Computing Science of the University of Aberdeen and the British Computing Society.

7. Accommodation:

Administration and offices of the Genetical Committee are at Ingolfsstraeti 5, Reykjavik. Other activities are being conducted at the Blood Bank, the Department of Psychiatry of the University of Iceland at the State Mental Hospital, The University's Science Institute and Computing Services, and the Institute of Pathology, University of Iceland.

8. Scientific Personnel:

Members of the Genetical Committee of the University of Iceland:

Chairman:

Prof. Olafur Bjarnason

Director, Institute of Forensic Medicine,

University of Iceland, Reykjavik

Vice-Chairman:

Dr. Olafur Jensson,

Director, Blood Bank, Reykjavik

Secretary:

Prof. Magnus Magnusson,

Science Institute, University of Iceland,

Reykjavik

Prof. Tomas Helgason,

Director, State Mental Hospital,

Department of Psychiatry,

University of Iceland, Reykjavik

Dr. Sturla Fridriksson,

Geneticist, Agricultural Research Institute,

Reykjavik.

Executive Director of Reserach:

Dr. Sturla Fridirksson.

Co-investigators:

Bjarnason, O., Prof.

Fridriksson, S., Geneticist

Helgason, T., Prof.

Jensson, O., Dr.

Magnusson, M.; Prof.

Consultants:

Prof. Johan H. Edwards,

Genetics Laboratory, Biochemistry Dept.

South Parks Road, Oxford

England

Dr. Howard B. Newcombe,

Head, Population Research Branch

Atomic Energy of Canada Ltd.,

Chalk River Nuclear Laboratories

Chalk River, Ontario , Canada.

Other Personnel:

Office of the Genetical Committee is directed by Dr. Sturla Fridriksson.

Oddny Vilhjalmsdottir, Secretary (1/2)

Key Punch Operator (1/2)

Anna G. Hafsteinsdottir " " (1/2)

Anna Antonsdottir, Supervisor

manual linking (2/3)

Jakobina Petursdottir, manual

linking (1/1)

Working at National Archives:

Gudrun Pordardottir, transferring

demographic data from parish records (3/8)

Lilja Porarinsdottir, manual linking

of demographic data (1/8)

Solveig Gudmundsdottir, manual

linking of demographic data (1/2)

Studies on chromosomes and congenital anomalies are supervised by Professor Olafur Bjarnason at the Institute of Pathology, University of Iceland.

Cerebral haemorrhage with amyloidosis, blood grouping, HLA-tissue typing and other blood group protein marker studies are supervised by Dr. Olafur Jensson and Dr. Alfred Arnason at the Blood Bank in Reykjavik.

Studies on mental disorders, intelligence, and population structure have been supervised by Professor Tomas Helgason.

Computing work has been supervised by Professor Magnus Magnusson and Mrs. Takako Inaba, Computer Scientist.

PUBLICATIONS AND CONFERENCE ABSTRACTS FOR THE PERIOD 1977-1980.

Following is a list of publications and conference abstracts in which use has been made of the Icelandic population records of the Genetical Committee of the University of Iceland during the last three year period:

1. Arnason, A.:

HLA and Bf and their Influence on Disease.

European Society of Human Genetics Oslo Symposium, May 14 and 15, 1977.

2. Arnason, A.:

Association of HLA and Disease in Iceland

Presented at a Symposium on Epidemiological

Problems in Genetics, Reykjavik, June 29-30,
1979, Nordic Council for Arctic Medical Research.

3. Arnason, A.:

Four Rheumatological Diseases in an Inbred Icelandic Family

Presented at the 17th Scandinavian Rheumatology Congress in Reykjavik, 1978.

4. Arnason, A.:

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The application of SEED to the project of the Genetic Committee of the University of Iceland.

Our future plan is to develop a Data Base which contains $q\!$ enetic information on Icelanders from 1840 to the present.

DATA

There are several kinds of records which have been collected by the committee. These are:

- A. The census 1910, which includes about 85000 data records in 10330 residences.
- B. Birth records.
 - B-1 for the period 1848-1910 (about 160.000)
 - B-2 for the period 1910-1966 (about 180.000)
 - B-3 for the period 1967-
- C. Death records.
- D. Blood group records.
- E. Marriage records.

of these, the birth records play the main role in our project. Actually birth records for the period 1910-1966 do exist in index sequential form on IBM 360/30 and have been in use for the last three years, e.g., to find children of a given couple. Some parts of it are linked to Death records, National registers and Blood records.

FAMILY-TREE DATABASE MODEL

The Data base model for the family-tree was developed mainly for the B-2 type of birth record, because others are still in cara forwat and have not yet been read onto tape or disk.

The structure of the family-tree data Dase is as follows:

(See Attabbment No.1)

As one can see, we don't actually need FEDUR, MARDUR area if the original birth records contain 100% complete information about the father and mother of a child. In reality there are not many birth records which can be trusted. That is why we had to add these areas for the time being. Several routines were written for this model. These are:

- 1. a routine to load a birth record into the data base
- 2. a routine to delete a birth records from the data base
- 2. a routing todmodify some items in the data base
- 4. a routine to connect two persons, e.g., child- father/mother
- 5. a routine to trade parents
- 6. a routine to trace children
- 7. a routine to trace ancestors
- 8. a routine to trace descendants
- 9. a routine to trace brothers & sisters
- 10.a routine to trace cousins.

This system has been tested on a family counting of one couple, their 15 children, 62 grandchildren, 26 great-grandchildren and spouses, 137 individuals in all.

CENSUS-1910 DATA BASE MODEL

Another Data base which has been designed recently is for the A type of record. The structure is as follows:

(See Attachment No.2)

The routines designed for this structure are:

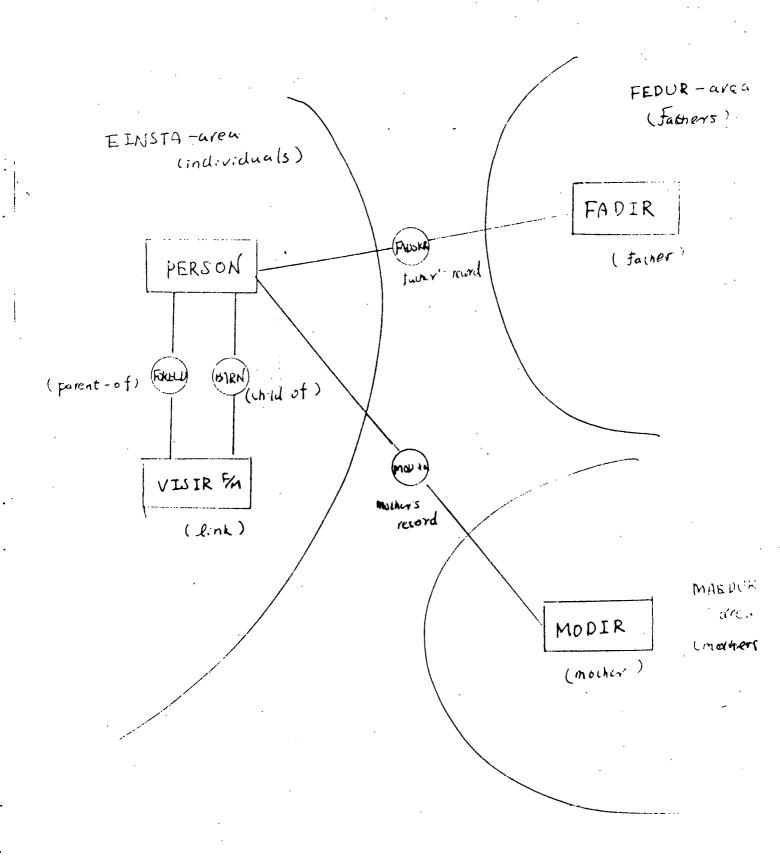
- . Several routines to load Census 1910 data in the Data base.
- Some look up routines, e.g.,

to find personal records by name, house number, lirthday, birth place of combinations of these.

In the near future (i.e., when we get enough disk space) we can store all census records onto the Data base. This Data base will help those who are involved in clerical work at the committee's office. Horeover it as possible to make birth records from this. When both child and parents lived in the same house it is easy to get more precise birth record than the original from the parish records.

EPFDAFRÆDINEFND HÁSKÓLA. ÍSLANDS THE GETTELCAL COMMETTE OF THE UTIVERSITY ÓF ICELAND TEL 11945 HINGÓLESSTRÆTI 5 - REYKJAVÍK - ICELAND

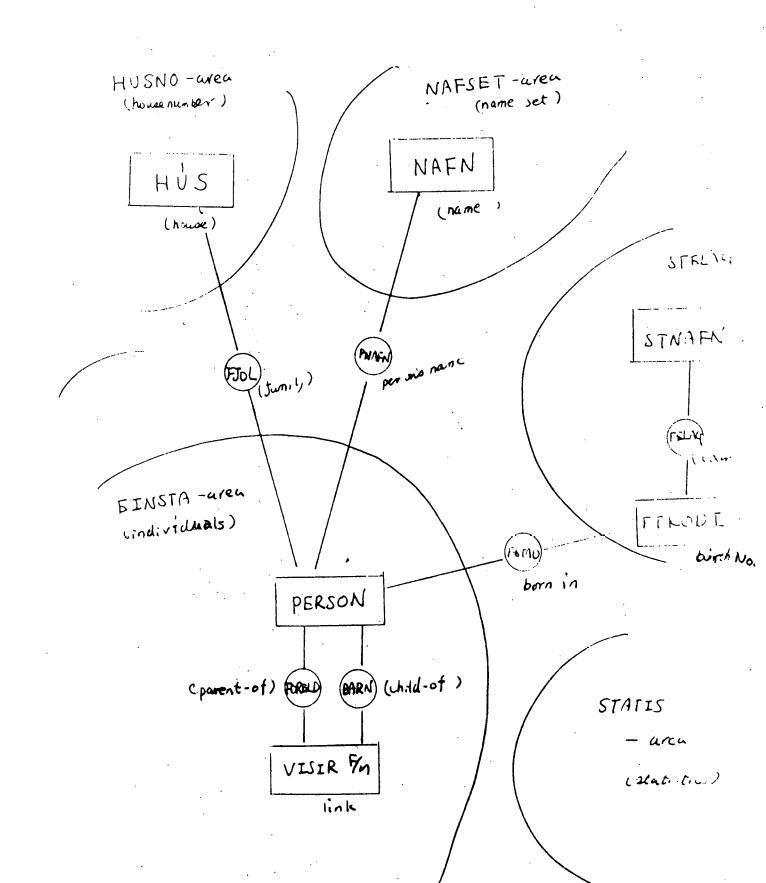
ATTACHMENT NO. 1



The structure of family - cree Database model

ATTAHCMENT NO. 2

The structure of Census10 Date



Hólmfríður Magnúsdóttir

Inngangur.

Pað hefur lengi verið álitið, að geðsjúkdómar væru ættgengir. Athuganir þær, sem gerðar hafa verið benda til þess,
að tíðni geðsjúkdóma sé meiri meðal ættingja prösjúkra en amaarra. Tíðnin er þeim mun meiri, sem skyldleikinn er nánari.
Jafnvel meðal fjarskyldari ættingja þess sjúka, svo sem systkinum foreldra hans og börnum þeirra er tíðnin hærri en meðal
almennings, þótt munur sé ef til vill ekki mikill (ref.8,11,14,16)

Ýmsar kenningar hafa verið uppi um orsakir þessa, svo sem erfðir, umhverfisþættir eingöngu eða hvort tveggja og er síðast-nefnda`kenningin sú, sem menn aðhyllast helzt í dag (ref.2,3,6,4).

Það hefur ekki enn tekizt að sanna um hvers konar erfðir er að ræða og hafa ýmsar kenningar eða tilgátur komið fram, svo sem einþátta erfðir (monogen: þar sem galli er í einu geni) og erfist samkvæmt Mendels lögmáli.

Þær erfðir skiptast í ríkjandi (dominant) og víkjandi (recessiv) erfðir með mismunandi sýnd (penetrans) við arfblendi (heteropysotu). Þessar erfðir eru ýmist bundnar kynlitningum eða ekki.

Fjölþættar erfðir (polygen) ákvarðast af mörgum ásamt umhverfisþáttum.

Þar er talað um þröskuldsgildi (stundum fleiri en eitt). Þá er talið að þeir sem sýna erfðaeiginleikana offan við þröskuld: -gildið, en hinir neðan við, og ættingjur þeirra þá taldir nær þröskuldsgildinu en almenningur.

Meðal afkomenda náskyldra skipta víkjandi (recessiv) og 1961þættar (polygen) erfðir meira máli en ellu.

Viò víkjandi (recessiv) Mendelian erfòir er hætta á dö "gen" frá sameiginlegum forföður komi fram, þótt ekkert sé sapt í ættarsögu. Við fjölþættar (polygen) erfðir er hætta á dð hluti "gena" verði arfhreinn, þannig að einstaklingurinn ýrist nær eða fari yfir þröskuldsgildið, ef foreldrar hans voru þar nærri, þátt ekki hafi borið á neinum einkennum hjá þeim.

Li selek

Kynbundnar ertðir geta einnig komið hér til greina, þannig að fleiri konur en ella fengju þennan "eiginleika", ef hann kæmi fram í báðum kynlitningum (X) (ref.10).

Rannsóknir á tíðni geðsjúkdóma meðal afkomenda skyldra hafa flestar farið fram á þann hátt, að athugaður var skyldleiki foreldra geðsjúklinga, og tíðni geðsjúkdóma síðan könnuð meðal attingja þeirra.

Pessar rannsóknir hafa í flestum tilvikum byggst á athugunum á sjúklingum sem legið hafa á geðsjúkrahúsum og náð yfir ákveðið árabil (ref.5,7,13).

Böök athugaði íbúa afskekkts svæðis í Norður-Svíþjóð m.t.t. inngiftis og afleiðingar þess á andlegt og líkamlegt heilbular. Athugun sú, sem hér er greint frá, fór fram á annan hátt. Hér er valinn hópur skyldra (tvímenninga), giftra á ákveðnu tímabili.

Börn þessarra hjóna eru fundin með því að tengja fæðingaskrár og giftingarvottorð hjóna í skýrsluvélum.

Tíðni geðsjúkdóma er síðan athuguð meðal foreldra og barna þeirra.

Markmið þessarar athugunar er:

- 1. Er munur á tíðni geðsjúkdóma meðal tvímenningsfjölskyldha og sambærilegs hóps óskyldra (foreldra og barna þeirra)?
- 2. Ef einhver munur er á geðsjúkdómum ofangreindra hépa, byggist hann þá á víkjandi(recessiv) erfðum?
- 3. Er munur á geðsjúkdómsgreiningum tvímenningsfjölskyldna, þegar allir einstaklingar fjölskyldnanna eru taldir með og geðsjúkdómsgreiningar byggjast á fleiru en skráðum upplýsingum eins og er í lið l og ná einnig yfir lengra tímabil?
- 4. Er tíðni geðsjúkdóma meðal skyldra hér svipuð og komið hefur fram við skyldleikarannsóknir í öðrum löndum?

Efniviður og aðferðir.

Á árunum 1916-1964 voru 378 tvímenningsgiftingar skráðar í öllu landinu.

Af þeim hópi voru valdar fjölskyldur til nánari athugana og blóðrannsókna, en ætlunin var að sú rannsókn tæki til a.m.k. 500 einstaklinga í 100-150 fjölskyldum. Tvennt réði vali:

- 1. Að hjónin ættu börn.
- 2. Búseta í eða í nánd við Reykjavík, þar eð einstaklingarnir þurftu endurgjaldslaust að koma sér á rannsóknarstað.

VORU SCHO.

Skoðun og blóðpróf fóru fram í Blóðbankanum í Reykjavík, eftir að þáttakendur verið sent bréf með útskýringum um athugunina og beiðni um þátttöku í henni.

Jafnframt skoðun fengu allir eldri en 16 ára með sér heilsufarsspurningalista "CMI" (en þessi listi er þýddur á íslenzku eftir Cornell Medical Index). Þar eru 195 spurningar um líkamlegt og andlegt heilsufar.

Blóðpróf voru síðar tekin hjá 22 fjölskyldum til viðbótar við þær sem athugaðar voru í upphafi, og þar var 4 fjölskyldum bætt við sem ekki voru skráðar áður / þeirra 378, til þess að ná hæfilægum fjölda til blóðsýna, svo nú fjölgaði fjölskyldum í 382.

Jafnframt voru send "CMI" til allra einstaklinga eldri en 16 ára í þessum viðbótarfjölskyldum og einnig til þeirra einstaklinga, sem ekki höfðu þegar svarað spurningalistanum.

Rannsóknarlok voru nú ákveðin 31.12.1975. Upplýsinga var síðan aflað um heilsufar allra lifandi einstaklinga fram til þess tíma, og látinna að andlátsdægri.

Heimilislæknum voru sendir sérhannaðir heilsufarsspurningalistar. Athugaðar voru sjúkraskrár þeirra, sem legið höfðu á sjúkrahúsum,

dánarvottorð látinna, svo og "CMI" svör þeirra sem svarað höfðu, en þau voru alls 427.

Samband var haft við 150 fjölskyldur í þessari athugun, en einstaklingar 138 fjölskyldna hafa verið í blóðrannsókn.

3 af þeim fjölskyldum varð að sleppa, þrátt fyrir "CMI" svör flestra fjölskyldumeðlima, þar eð ekki tókst að afla frekari upplýsinga um einstaklinga þessarra fjölskyldna vegna samgönguerfiðleika (fjarlægðar, almenns sveitasíma osfrv.).

Er farið var að athuga skyldleikann nánar hjá þessum fjölskyldum kom í ljós, að ein fjölskylda voru afkomendur erlendra systkina og féllu þar með úr athuguninni ásamt 25 öðrum fjölskyldum, sem ekki voru tvímenningar, en skyldar á annan hátt.

3 fjölskyldur neituðu þátttöku og var skyldleiki þeirra ekki kannaður nánar, og fjórðu fjölskyldunni (tvímenningum) var sleppt, þar eð samvinna náðist ekki við alla fjölskyldumeðlími.

int

Kliniskar upplýsingar fengust um flesta einstaklinga,
lifandi og látinna í 117 fjölskyldum (680 manns, sem athugun
þessi nær til), en allmargir einstaklingar 109 þessarra fjölskyldna voru í blóðrannsókn á árunum 1972-1974.
ll6 eru látnir af hópnum: 83 foreldrar og 33 börn.
293 komu sjálfir í viðtal og skoðun (43% alls hópsins, en 🚜 ?
51,7% lifandi einstaklinga, en við aðra var talað eða fengnar
upplýsingar frá ættingjum og í flestum tilvikum fleiri en einum
ættingja, ef í náðist til að fá sem nákvæmastar upplýsingar.

Samanburðarfjölskyldur voru valdar m.t.t. upphaflegu 378 fjölskyldnanna eftir giftingarári og aldri tvímenninganna, og mátti í sambandi við aldur ekki skeika meiru en 12 mánuðum, þ.e.a.s. + eða ÷ 6mánuðum.Fjölskyldurnar voru síðan paraðar við tvímenningana og hlutu sömu fjölskyldunúmer.

3 fjölskyldur af 117 sem getið er um áður féllu þar með strax á brott, en þær höfðu hærri númer en 378. Öllum barnlausum samanburðarfjölskyldum var sleppt og eftir voru þar 103 barnafjölskyldur í hvorum hópi.

Efniviðnum er skipt í tvennt, til þess að fá sem bezt samræmi milli tvímenningsfjölskyldna og samanburðarfjölskyldna.

- A. 117 fjölskyldur (680 manns) merkt hópur III.
- B. 103 A-fjölsk. (551 manns) hópur I.

 og jafnmargar samanburðarfjölskyldur (546 manns) hópur II.
 Samræmi B-hópa var fengið:
- 1. Með fækkun á fjölskyldum, sbr. áður.
- Með fækkun á börnum.
- 3. Með fækkun á geðsjúkdómsgreiningum, sbr. neðan.
- 1. Fækkun á fjölskyldum hefur verið lýst að ofan.
- 2. Öll börn hjóna, einnig þau sem dóu ung, eru talin með í hópi III. Fjöldi þeirra barna var fenginn, þegar talað var við viðkomandi fjölskyldu, en sum þeirra voru ekki á listum E.H.Í. þar sem öll börn höfðu ekki tengst í skýrsluválunum. Fullkomnir listar sem ná yfir 117 fjölsk. voru þar af leiðandi ekki notaðir, en listar E.H.Í. bæði fyrir hóp I og II, þar sem þeir höfðu verið unnir á sama hátt, og í báðum tilvikum var vitað að vantaði börn á listana.
- 3. Sjúkdómsgreiningar hóps III ná fram til 31.12.1975, og eru geðsjúkdómsgreiningar einnig frá sömu árum, en ekki tókst að afla geðsjúkdómsgreininga samanburðarhópsins (II) nema til og með ársins 1973.

Geðsjúkdómsgreiningar hóps ÎÎI eru viðar að en hópa I og II, en í síðastnefndu hópunum eru geðsjúkdómsgreiningar frá geó-læknum, geðdeildum, almennum sjúkrahúsum eða vottorðum frá Tryggingastofnun ríkisins, þ.e.a.s. skráðum upplýsingum. Viðbótargreiningar í hópi III eru flestar frá ofangreindum aðilum, en nokkrum greiningum var bætt við, ef samræmi var milli upplýsinga sjálfs, heimilislæknis, klinisks mats og ákveðinna svara í M-R hluta "CMI" (þeim hluta spurningalistans, sem snerti andlega heilsu).

Helzt var kosið, að allt samrýmdist, sem áður var talið, en í sambandi við ofneyzlu áfengis voru upplýsingar sjálfs og/eða náins ættingja ásamt upplýsingum heimilislæknis lítið negja, til að byggja á sjúkdómsgreiningu, svo og krufningsskýrsla í einu tilviki.

Örfáar taugaveiklunargreiningar voru settar að ofangreindum líkum, þar sem a.m.k. þrennt ef ekki allt bar að sama brunni. Greiningar þessar eru mjög fáar.

Samræmi milli hópa I og II var fengið á þann hátt, að öllum sjúkdómsgreiningum frá árunum 1974 - 1975, svo og þeim greiningum sem settar voru að líkum , var æinungis stuðst við skráðar heimildir.

Allar geðsjúkdómsgreiningar eru skráðar skv. ICD 8. revision og var þeim greiningum sem ekki voru skráðar á þann hátt breytt í núgildandi form.

Ein geðsjúkdómsgreining er hjá hverjum einstaklingi, og verður annars getið síðar, ef ástæða þykir til.

Í þriðja lagi, allar fáanlegar sjúkraskrár einstaklinga úr samanburðarfjölskyldunum, sem legið höfðu á geðsjúkrahúsum voru athugaðar, eins og áður hafði verið gert við einstaklinga tvímenningsfjölskyldnanna.

Í fjórða lagi, aldursdreifing lifandi einstaklinga, þ.e.a.s. er þeir hverfa úr rannsókn 31.12.1975 er flokkuð í 10 ára aldursflokka og sýnt í töflum I og II.

Niðurstöður:

Fjöldi lifandi einstaklinga kemur fram í töflum I og II.

Fjöldi látinna einstaklinga kemur einnig fram þar, en ekki er getið andlátsaldurs.

Foreldrar eru flestir lifandi á aldrinum 70-79 ára. Afkomendur eru flestir lifandi á aldursbilinu 40-49 ára, eða 31,3% í hópi I og II og 31,4% í hópi III, sjá töflu II. Látnir meðal afkomenda í hópi I eru 6,4%, í hópi II: 10,3% og í hópi III: 7,4%.

Flestir afkomenda hafa látist innan við 10 ára aldur.
Barnafjöldi í fjölskyldum er sá sami í hópum I og II, eða 3,3 börn í fjölskyldu, en 3,8 börn í fjölskyldu í hópi III, en þar eru öll lifandi börn talin með.

Tafla III sýnir hversu margir hafa fengið geðgreiningu og eru flokkarnir taldir 5: geðveiki, taukaveiklun, ofnotkun áfengis, lág greind (def.int.).

Það sem ekki tilheyrir þessum 4 flokkum er undir " aðrar greiningar", en þar eru talin psychosomatisk einkenni, geðræn einkenni með vefrænum taugasjúkdómum og annað.

Annarra greininga er ekki getið, eins og t.d. misnotkun lyfja (ICD.304), en þeirri greiningu er sleppt, þar eð enginn þessaarra einstaklinga telst þar.

Tölfræðilegan marktækan mun er ekki hægt að fá en nokkur munur er á niðurstöðum, en tölur eru allar mjög smáar og þar af leiðandi er erfitt að draga niðurstöður af þeim. X^2 getur ekki marktækan mun og heldur ekki samanburður á heildartíðni geðrænna sjúkdóma.

Tafla III sýnir, að fleiri konur hafa geðgreiningu en karlar meðal tvímenninga og afkomenda þeirra (hópa I og III). Geðveiki mæðra svo og taugaveiklun allra kvenna valda mismuninum.

Fleiri karlar en konur eru með geðgreiningu meðal samanburðarhjóna og er það geðveiki feðra, svo og áfengisneyzla sem orsakar þá aukningu, en jafnt er kynja meðal afkomenda þeirra (hóps II), þótt karlar séu heldur fleiri drykkjumenn en konur taugaveiklaðar.

Dálkurinn aftast í þessari töflu sýnir hve margir eru látnir af þessum einstaklingum.

Sjálfsvíg eru 2, hvort tveggja í samanburðarnóp.

Tafla IV sýnir innbyrðis geðgreiningar:

<u>Geðveiki</u> (psychosis): greinist eingöngu meðal kvenna tvímenninga og er þunglyndi algengasta greiningin sbr. töflu VI. Geðklofi: enginn.

Samanburðarhjón hafa 7 greiningar, þar af kurlar 5. Þunglyndi er hér mun minna áberandi en meðal tvímenninga og "depressio endogenica" einungis meðal karla (1 greining, sjá töflu VI). Geðklofi l einstaklingur.

Afkomendur tvímenninga eru mun fleiri geðveikir en afkomendur samanburðarhóps og eru konur ívíð í meirihluta eða 6 af 11. Flestar eru þær þunglyndar(aðalæga depressio endogenica) sjá töflu VI.

Afkomendur hóps II eru jafnmargir af hvoru kyni. Þunglyndi er mun minna áberandi og 'depressio endogenica" kemur einungis fyrir hjá körlum, sjá töflu VI.

Geðklofi greinist hjá afkomendum á eftirfarandi hátt: 1 úr hópi II og III.

Enginn úr hópi I.

113/1 canney 7:00

Enginn þeirra einstaklinga, sem nefndir eru hér urðu geðveikir í sambandi við ofnotkun áfengis eða annarra vímugjafa.

Taugaveiklun (neurosis): tvímenningar eru taugaveiklaðri en samanburðarhjón og eru konur þar í meirihluta.

16 greiningar sem getið er um meðalsamanburðarhjóna okiptast jafnt milli kynja.

or really

Par eru æðasjúkdómar í heila og Parkinsonismus algengastær meðal foreldra.

4 einstaklingar úr hópi I og II hafa þessar greiningar og bætist engin við í hópi III.

Kynskipting er þannig: 75% samanburðarforeldra eru konur, en 75% tvímenninga karlar.

Afkomendur tvímenninga eru einir með þessa greiningu og eru það allt konur. 2 eru í hópi 1 og ein greining bætist við í hópi III og eru hinar greiningarnar: sequale encephalitis, epilepsia? post trauma og sequale thrombosis cerebri.

Ofnotkun áfengis (alkoholismus): er algengari hjá körlum en konum, og mun algengari meðal samanburðarhóps en tvímenninga og afkomenda þeirra, jafnvel þar sem víðtækasta greiningin í hópi III er notuð (sjá skýringar undir Efniviður og aðferðir). Skipting milli fjölskyldna er:

Í hópi I - 3 einstaklingar í 3 fjölskyldum.

1 hópi II-10 einstaklingar í 8 fjölskyldum.

1 hópi III 7 einstaklingar í 5 fjölskyldum.

Fimm afkomendur hafa ofneyzlu áfengis ásamt öðrum greiningum. Þrírþeirra tilheyra hópi I, og sá fjórði bætist við í hópi III en aðal greiningar þeirra eru: geðveiki (1) taugaveil lunar-einkenni (3) þar af 'þunglyndur.

Einnafkomandi í hópi II fær þessa greiningu með taugaveiklunarþunglyndi, en annað foreldri og eitt systkini hafa áfengisvandamál. Allt eru þetta karlmenn.

Léleg greind (def.int.) Fjórirá þessa greiningu í hópi I, og sá fimmti bætist við skv. upplýsingum ættingja og heimilislæknis í hópi III.

Tveiraf þeim fyrrtöldu fá greiningu skv. upplýsingum T.R., annar innan tvítugs, en hinn á sextugsaldri. Hinir 2 hafa einnig vefræna taugasjúkdóma.

Kynskipting er jöfn í hópi I, en karlar verða fjölmennari í hópi III. Allir þessir einstaklingar eru lifandi í rannsóknarlok.

Einn afkomandi er í hópi II og deyr hann innan tvítugs af einkennum sínum.

Tafla VI er samantekt á öllum þunglyndisgreiningum, en skil virtust ekki alltaf glögg milli geðveiki og taugaveiklunar. Tvímenningar virðast heldur þunglyndari en samanburðarhjón, og hafa mun fleiri geðveika, en þær greiningar eru einungis meðal kvenna og í flestum tilvikum er um"depressio endogenica" að ræða.

Þeim greiningum fjölgar um helming frá hópi I til III, er mæðrum fjölgar.

Geðveikisgreiningar eru jafnmargar eða jafnfáar meðal samanburðarhjóna, en depressio endogenica kemur einungis fyrir meðal karla.

Meðal foreldra er taugaveiklunarþunglyndi algengara hjá körlum en konum, og eru 100 tvímenningsfeðra í þessum flokki, svo og um það bil 80% samanburðarfeðra.

Taugaveiklunargreiningar eru jafnmargar í hópi I og II (6)

Hvað þunglyndi snertir meðal afkomenda, þá eru konur fleiri en karlar í öllum 3 hópunum, en kynmunur er minnstur í hópi II.

Punglyndi skiptist nokkuð jafnt milli geðveili og taugaveiklunar í hópi I, en konur eru í yfirgnæfandi meirihluta.

Geðveiki fjölgar ekki frá hópi I til III, þrátt fyrir fjölgun
einstaklinga og/auknum heimildum hvað geðgreiningar snertir,
en aukning verður á taugaveiklun, aðallega meðal kvenna.

Taugaveiklunarþunglyndi er algengast í hópi 11 og"depressio
endogenica"kemur einungis fyrir meðal karla.

Kynmunur er ekki eins áberandi og meðal tvímenningsafkomenda, þótt konur séu heldur í meirihluta.

Í töflu VII er sýnt hvernig geðgreiningar skiptast á milli fjölskyldna í hópum I, II og III.

Umræða.

Tvímenningsfjölskyldur þær, sem hér er greint frá eru úr Reykjavík og nágrenni.

Hér ætti því að vera um þá einstaklinga að mæða, sem auðveldast ættu með að fá geðlæknisþjónustu, og þar af leiðandi hafa flestar geðsjúkdómsgreiningar (ref.4).

Alíta má, að flestir með mjög lélega greind eða slæma geðveiki hafi fengið sjúkdómsgreiningar sínar hjá einhverjum þeirra aðila, sem áður er getið, hvaðan svo sem þeir eru af landinu.

Geðveikisgreiningar einstaklinga tvímenningsfjölckyldna eru í 43,7% tilvika af sjúkrahúsum, en í 69% hjá samánburðarfjöl-skyldum. Allir aðrir einstaklingar nema l, sem er með grein-ingu frá T.R. hafa fengið geðveikisgreiningar sínar hjá geð-

læknum.

Tvímenningsafkomendur hafa greiningar af sjúkrahúsum í 54% tilvika, en afkomendur samanburðarhópsins í 66,6%/til-vika.)

Geðveikum og greindarskertum fjölgar ekki, þegar litið er á hópa I og III með auknum heimildum og fjölgun einstaklinga, en taugaveiklun og drykkjuvandamál aukast aðallega. Aukningin er tæp 2% og er heldur meiri meðal afkomenda en foreldra.

Tvímenningar verða geðveikari eldri en samanburðarforeldrar. Það sama á við um afkomendur þeirra, þótt þeir veikist yngri en foreldrarnir.

Enginn tölfræðilegur munur er á hópunum (I, II, III).

Konur eru í meirihluta með geðgreiningu meðal tvímenningsfjölskyldnanna og veldur því geðveiki mæðra og taugaveiklun- gallra kvenna, eins og áður er getið.

Karlar eru í meirihluta meðal samanburðarhjóna vegna geðveiki og áfengisneyzlu, en kynmunur er eiginlega enginn meðal afkomenda þeirra, þótt konur séu heldur taugaveiklaðri og karlar lívið drykkfelldari í þeim hópi.

Samanburðarforeldrar eru eins og áður er getið geðveikari en tvímenningar, karlar eru í meirihluta og einir með depressio endogenica og geðklofa.

Geðveiki er einungis meðal kvenna tvímenninga og eru flestar þeirra þunglyndar (aðallega depr.end.). Enginn geðklofi. Tvímenningar eru taugaveiklaðri en samanburðarhjón. Konur eru í meirihluta. Enginn kynmunur er meðal samanburðarhjóna. Taugaveiklun greinist sem þunglyndi hjá jafnmörgum einstaklingum í hópi I og II. Karlar eru fjölmennari en konur. Þunglyndi tvímenningsfeðra er eingöngu sem taugaveiklun og svo er hjá rúmlega 80% samanburðarfeðra.

Ofneyzla áfengis er mun meiri meðal samanburðarhjóna en tvímenninga. Yfirvægi er á körlum beggja hópa.

Tvímenningsmæður virðast lausar við áfengisvandamál, þar eð engin þeirra fær þá greiningu hér eða er netnd í sambandi við drykkjuvandamál afkomenda.

Karlmenn eru í meirihluta meðal tvímenninga með geðræn einkenni með vefrænum taugasjúkdómum en konur meðal samanburðarhjóna 75% í hvoru tilviki

Afkomendur tvímenninga eru geðveikari en afkomendur samanburðarhjóna. Konur eru í meirihluta meðal skyldra, en jufnt

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er kynja meðal óskyldra.

Punglyndi (depr.end.) er algengasta greining tvimenningsafkomenda, einkum kvenna. Fjöldi þunglyndra er sá sami meðal beggja kynja samanburðarafkomenda, en depressio endogenica kemur einungis fyrir meðal karla.

Fleiri tvímenningsafkomendur eru greindarskertir og með geðræn einkenni með vefrænum sjúkdómum en afkomendur samanburðarhjóna. Jafnt er kynja meðal þeirra fyrri, en eingöngu konur meðal þeirra síðari.

Ofneyzla áfengis og taugaveiklun aðallega sem þunglyndi er algengara meðal samanburðarafkomenda en tvímenningsafkomenda. Karlar eru heldur fleiri meðal þeirra fyrrnefndu en konur taugaveiklaðri.

Punglyndi, hvort sem um geðveiki eða taugaveiklun er að ræða er algengari í sumum fjölskyldum en öðrum.

Ekki er munur á skyldum og óskyldum, hvað fjölda slíkra fjölskyldna snertir, en þær eru jafnmargar í hvorum hópi (3), og jafnmargir einstaklingar eru með greiningar í þessum fjölskyldum (8).

Munur er þó á skyldum og óskyldum, þar sem 6 af 8 skyldum teljast geðveikir, en 1 af 8 óskyldum, en tuugaveiklaðir ella. 5 af 8 afkomendum tvímenninga í lið aí töflu VI teljast til tveggja þessara tvímenningsfjölskyldna, en foreldrar þeirna hafa ekki þunglyndisgreiningu.

Ofnotkun áfengis virðist einnig algengari í einstaka íjölskyldum, þótt þær greiningar séu ekki alltaf fyrir hendi, en afkomendur beggja hópa sem upplýsingar fengust frá, segja annað foreldri sitt verið vínhneigt.

Allaríkonur áttu vínhneigða feður, hvort sem um skylda eða óskylda er að ræða, en enginn þeirra fær þá greiningu hár.

Samanburðarfjölskyldur hafa fleiri geðgreiningar en tvímenningsfjölskyldur (Tafla V) eða 89 einstaklinga í
53 fjölskyldum, en tvímenningar 83 einstaklinga í 51 fjölskyldu.

Þessi munur er svipaður, hvort sem l eða fleiri en l einstaklingur er með geðgreiningu í fjölskyldu, nema þar sem fleiri en l er geðveikur. Þar eru 4 tvímenningsfjölskyldur á móti l samanburðarfjölskyldu.

Í þessum 4 tvímenningsfjölskyldum eru 56,2% allra geðveikra, eða 63,6% allra geðveikra tvímenningsafkomenda.

Geðveiki er í ll tvímenningsfjölskyldum, en 12 samanburóar-fjölskyldum.

Sérstaka athugun þyrfti að gera á þeim fjölskyldum, þar sem fleiri en l fjölskyldumeðlimur er með greiningu, þar sem hér er einungis um athugun á 2 ættliðum að ræða.

Einnig væri fróðlegt að vita, hvað vefjaflokkun sýndi í þessum fjölskyldum.

Munur á hópum I og III, þar sem fjöldi einstaklinga eykst og upplýsingar eru víðar að en í hópi I og ná ytir lengra tímabil.

Geðveiki minnkar tiltölulega, nema meðal mæðra, þar í jölgar þunglyndisgreiningum (depr.end.) um helming.

Tvær af mæðrunum féllu brott með fækkun fjölskyldna, en l ný greining bættist við á þessu árabili.

Taugaveiklun eykst nokkuð meðal mæðra, en minnkar hjá feðrum, einnig fækkar þunglyndisgreiningum.

Ofneyzla áfengis eykst um helming meðal feðra, en þeir eru enn einir með þá greiningu.

Meðal afkomenda verður tiltöluleg fækkun geðveikra og greindarskertra, en aukning á taugaveiklun einkum kvenna, og er ca. 40% þeirra viðbótargreininga þunglyndi.

Ofneyzla áfengis eykst hjá báðum kynjum, svo og psychosomatisk einkenni karla.

Ekkert virðist benda til víkjandi erfða, þegar hópar I og II eru athugaðir m.t.t. geðgreininga.

Afkomendur tvímenninga ættu þá að hafa fleigi geðgeriningar en samanburðarafkomendur og jafna kynskiptingu, en hafa færi greiningar og yfirvægi á konum (N.S.&.S.H.& S.L.) & 7,13

Í athugunum (ref.5 og 13) er þunglyndi, það er að segje geðveiki algengara meðal afkomenda skyldra en óskyldra, og kemur það einnig fram hér.

Ofangreindar athuganir telja einnig þunglyndi algengara með öðrum greiningum meðal skyldra en óskyldra, en ekki er hægt að fá það fram hér.

× nomment

Skert greind (mental defect) (ref.1, 13). er algengari meðal afkomenda skyldra en óskyldra, og kemur það fram hér. Athuganir Bööks og Nixon og Slater sýna aukningu á geðklofa meðal afkomenda skyldra, og byggja þeir síðastnefndu erfða-"kenningu" sína á geðklofa á þeim mun (rec.autosom gen). Hér fæst ekki sá munur fram.

Einn einstaklingur meðal óskyldra afkomenda hefur þessa greiningu, en enginn afkomandi skyldra í hópi I. Ein geðklofagreining er í hópi III eða meðal 446 afkomenda, en hún er mjög vafasöm.

Herlofsen et al.(ref.5) og Shields et al.(ref.13) fundu engan mun á ofneyzlu áfengis og taugaveiklunar meðal afkomenda skyldra og óskyldra, og geta þeir sérstaklega, að þeir fái ekki þá aukningu á taugaveiklun meðal skyldra sem Julia Bell hafði fundið 1940 (ref. 13).

Hér kemur aftur fram greinileg aukning á taugaveiklun og áfengispfneyzlu meðal óskyldra, og jaðrar við að munurinn sé marktækur, hvað áfengisneyzlu snertir.

ander in our suggester !

Útdráttur.

2701

Athugun á geðsjúkdómsgreiningum tvímenningsfjöldkyldna og valinna samanburðafjölskyldna sýndu engan tölfræðilegan marktækan mun, en nokkur munur er á niðurstöðum. Geðsjúkdómar eru algengari meðal kvenna í tvímenningsfjölskyldunum meðal karla samanburðarhjóna, en nokkuð jafnt skipt milli afkomenda þeirra.

Samanburðarfjölskyldur hafa flesta einstaklinga með geðgreiningu og flestar fjölskyldur þar sem einn eða fleiri
fjölskyldumeðlimir eru geðsjúkir nema þar sem fleiri en
einn er geðveikur í fjölskyldu þar eru tvímenningsfjölskyldur
í meiri hluta eða 4 fjsk/l. Eru 56,2% allra geðveikra (einstaklinga) eða 63,6% geðveikra afkomenda tvímenninga í
þessum fjórum fjsk. Geðveiki, greinarskortur (def.int.) og
geðræn einkenni með vefrænum sjúkdómum eru algengari meðal
afkomenda tvímenninga en samanburðarhjóna. Geðveikin er í
flestum tilvikum þunglyndi og er heldur algengari meðal
kvenna en karla.

Ofneysla áfengis og taugaveiklun aðallega sem þunglyndi eru algengari meðal samanburðarafkomenda. Karlar eru heldur fjölmennari í fyrra tilvikinu en konur í því seinna.

Konur eru þunglyndari en karlar, ef allar þunglyndisgreiningar eru teknar saman (geðveiki og taugaveiklun). Kynmunur er ekki mikill meðal afkomenda samanburðarhjóna en talsverður meðal tvímenningsafkomenda.

Þunglyndi virðist fjölskyldubundið. Enginn munur er á skyldum og óskyldum, hvorki hvað fjölskyldufjölda eða fjöldareinstaklinga í þessum fjölskyldum snertir en meðal skyldra er geðveiki algengari en meðal óskyldra taugaveiklun.

Geðveiki er einnig algengari í einstaka fjölskyldum og er það áberandi meira meðal tvímenningsfjölskyldna eins og ofan greinir.

Ofneysla áfengis virðist einnig fylgja fjölskyldum beggja hópaskyldra og óskyldra.

Ekkert kemur fram sem bendir til víkjandi erfða.

Við samanburð á öðrum skyldleikaathugunum, kemur það sama fram hér og hjá Herlufsen & Ödegård og Shields & Slater, að þunglyndi er algengara meðal afkomenda skyldra en óskyldra og skert greind "mental defekt" sem Shields & Slater og Böök fá fram. Aukning geðklofa meðal skyldra sem Nixon & Slater og Böök. sýna fram á í athugunum sínum kemur ekki fram hér. Herlofsen & ödegård geta þess, að ofneysla áfengis sé svipuð meðal skyldra og óskyldra. Það sama kemur fram þjá Shields & Slater, sem finna heldur ekki neinn mun tauga-veiklunar meðal skyldra og óskyldra, og geta þess sérstaklega að þeir geti ekki sýnt fram á aukna taugaveiklun meðal skyldra sem Julia Bell hafi sýnt fram á 1940. Hér kemur aftur á móti fram aukin tíðni taugaveiklunar og ofneyslu áfengis meðal afkomenda óskyldra og liggur við að munurinn sé marktækur hvað áfengisneysluna snertir.

Hvort val hópanna í þessum athugunum hefur eitthvað að segja skal látið ósagt, en hópurinn sem hér er ræddur er úrtak "heilbrigðra" (skyldra og óskyldra) en ofangreindar athuganir byggja flestar á geðsjúklingum eða íbúum afskekkt héraðs. *******

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Tafla I.

Foreldran

Aldur	Hopur L	Hópur II	Hopur III
29,	0	0	0
30- 39	4	4	. 4
40- 49	15	13	1.8
50- 59	28	26	31
6069	31	34	33
70- 7/9;	41	44	4 9
80- 89:	13	15	16.
90-	0	a	0
	· · · · · · · · · · · · · · · · · · ·		
LIFANDI	132	137	.151
LATNIR	7.4	69:	. 83
	<u> </u>	<i>a</i>	
Vlls	206	206	234
			territaine (Continue de la continue

TAFLA II.

AFKOMENDUR				
ALDUR	HOPUR I	HOPUR II	HOPUR III	
			· · · · · · · · · · · · · · · · · · ·	
			·.	
1- 9	0	2	9.	
10-19	37,	33	49.	
20-29	46	40	57 .	*
30-39	74	80	- 88	
40-49	108	104	140	
50 - 59	5 7 :	46	68	
60-69	ı	0	2	
70-	0 .	0	0	
LIFANDI	323	305	413	
LATNIR	22	35 [,]	33	
		•		
ALLS	345	340	446	
	•		•	

FJÖLDI GEÐGREININGA		KARL	KONA	LATNIR b.a.			
Foreldrar	· · · · · · · · · · · · · · · · · · ·	1 ,		ka	ķo		
I	, 35	15	20	· · 4	6		
: II	34	20	14	10 [×]	3		
III	44.	18	26	- 4,4	6		
Afkomendu	<u></u>	·					
I .	48	20	28	0 .	2		
II	5.5	28	27	2 ×	2		
III	7 2	31	#1	1	2		
*							

x) l suicid.

	FOREL	DRAR		AFKO!	ENDUR		
	. I .	II	III	I	11	1.71	
Psykosur	5	7	8	11	6	12	
Neurosur	22	16	25	26	3.5	39	•
Aðrar di (306-309	agn.6	īt.	. 7	14	3	vg	
Alk.	2	7	ц	3	10	7	
Def. int	. 0	0	0	4	1:		
Total	35	34	t 1 t4	48	5.5	7?	-
Fj.hópur	206	206	234	345	340	448	
% m. D:	.16,9%	16,5%	18.8%	13,9%	16,2%	16,1%	

TAFLA V.

FJÖLSKYLDUR MEÐ OG ÁN GEÐGREININGA

Hopur	MEĐ GEĐGREININGU	%	An	GEÐGREINING	GAR %	ALLS
1 Day	51	49.5		52	50 • 5	103
II.	53	51.5		50	48.5	103
III	71	60.71	.	46	39•3	117/

Samantekt á þunglyndisgreiningum.

- a) 296.2 (Depressio endogenica)
- b) 298.0 (" reactiva)
- c) 300.4 (" neurotica)

Foreldrar:

<u> </u>				·II			III .		
	Ka	Ко	Alls	Ka	Ko	Alls	Ka	Ko	Alls
a)	0	3	. 3	1	0	1	0	6	δ.
p)	0	1	1	. 0	1	· 1	0	1	1
c)	4	2	. 6	. 5	1	6	4	2	6
Alls	s 4	6	10	6	2	. 8	ц	9	13

Afkomendur:

	<u> </u>			-	II			III		
	Ka	Ко	Alls	Ka	Ко	Alls	Ka	Ко	Alls	
a)	3	5	8	1 -	0	1	. 3	5 .	8	
b)			0						0 .	
c)	3	6	9	7	9	16	4	10.	14	
Alls	6	11	17	8	10	18	7	15	22	

Running title:
FAMILIALITY OF BREAST CANCER
IN ICELAND.

A POPULATION BASED STUDY ON FAMILIAL AGREGATION
OF BREAST CANCER IN ICELAND, TAKING ACCOUNT
OF SOME OTHER RISK FACTORS

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Kristin Grímsdóttir and Guðrún Bjarnadóttir.

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Introduction.

Genealogical information is of high quality in Iceland and so is information on health for the latest scores of years. The Icelandic population is willing to participate in surveys and screening operations (1,2). There is no need, nor is there time, to review carefully what has been published (3) on familial risk of breast cancer.

Most, but not all, authors find the relative risk increased. The increase in risk found is usually small, or 2-4 fold, however, it has been shown that under particular circumstances this relative risk can be considerably higher, approaching 10 fold (4,5,6). This is when cancer is bilateral and one of the cancers of the two breasts has a premenopausal onset.

This, the excellent genealogical information in Iceland, and the general acceptance of familiality as a portion of the risk for breast cancer, prompted us to start investigations aimed at showing whether the familial risk is important in the Icelandic population and whether it can be measured accurately.

We felt obliged to investigate first some other known risk factors, so whatever we find on the familiality, can be put in the perspective of the other risk factors.

When speaking of familial increase in risk, one has to take into account, that this increase, if found, can be genetic, environmental, or both.

We first showed that the increase in breast cancer risk with time is very marked in Iceland (7). This was possible, because of complete records of all breast cancer cases diagnosed since 1910, now numbering 1740. The incidence has steadily risen during this period. When we separated the population into decades of birth, that is, we looked at all those born between 1840 and 1849, all those born between 1940 and 1949, and all the intervening decades, we can plot age distribution curve for each decade of birth cohort. When doing so, we found, that the cohort specific incidence is rising very rapidly. Over this span of 110 years, the incidence has more than 10 folded (see table 1). We also found that the increase

in incidence affects not only the higher age groups, the post-menopausal, as had been postulated by other researchers, (8,9,10) but it equally affects the younger age groups. This means, that whatever factor is changing in the population it must determine the breast cancer risk when the patients are relatively young.

In the same manner, we have investigated reproductive factors by linking the breast cancer file with records collected by the Cervix Cancer Detection Clinic, which has operated in Iceland since 1964 (1). By so doing we could confirm the previous finding of the importance of age at first pregnancy, or first life birth, in determining the risk of breast cancer (11) but we could also show that the risk was substantially and significantly altered by parity, another reproductive factor, which had previously not been found to be of importance (12). Having done this, we feel capable of analysing the information we have on the actual familial risk.

Material and methods.

The material on which we based this investigation was collected partly by genealogists who have worked for this study using interviews of family members and published information, series A, and partly by the office of the Genetical Committee of the University of Iceland, from the records already collected by that committee, series B. For the two groups uniform rules have been used throughout . although the extent of the genealogical tree collected has been different. For the 1740 cases we have on file, we have collected the genealogical information for little over 550 of which we have computerized records for 477 proposity. Of this 130 were collected by the genealogists and 347 by the office of the Genetical Committee. sets we have collected information on male and female members and we have also collected information on the spouses of the family members so that we have a group of inwed non-relatives in the same file. Those can be used for internal control. The families collected by the genealogists, series A, have been collected for all first, second and third degree relatives, except for the greatgrand-parents and the grand-parents sibs. Series B we have

confined to parents, sibs, parents'sibs, grand parents, and their spouses.

Selection of proband cases.

The Icelandic Cancer Registry which has been in operation since 1955 (13,14,15) has supplied a complete list of breast cancer cases diagnosed since that date. Prior to 1955, a list of all breast cancer cases diagnosed in Iceland has been established independently (16).

Series A consist of every eighth case diagnosed between 1955 to 1972, subsequently supplemented with thirty cases born between 1900 and 1916 and five cases born 1864 or 1865 and five cases born 1875. These cases are 130.

Series B consist of all 347 cases born 1916 or later, diagnosed before the end of 1977.

(The two series have some members in common, but can be treated as distinct).

Construction of family trees.

Series A. The family trees for series A include parents, sibs, children, parents'sibs, parents'parents, sibs'children, sibs'childrens'children. The family trees include inmarried, not blood-related, individuals. The records of the Genetical Committee, other informative documents including the numerous published family histories and direct interviewing were used to establish the families.

Series B. The family trees for series B include parents, sibs, parents'sibs, parents'parents and children. Inmarried individuals are included. The initial information came from the files of the Genetical Committee later supplemented by information from other sources as described for series A. Estimation of the degree of incompleteness of the Genetical Committee records will be an important subsidiary finding.

For both series, date of birth and date of death, if dead, were recorded. Whether death had occurred was ascertained from the complete national death records, those not appearing in the population roster being searched for in the death records to verify their status.

Ascertainment of breast cancer cases among the families.

Matching was initially performed by the computer, using date of birth and first four letters of forename and surname, a considerable margin of error was allowed. The possible matches were verified by personal examination of one of the genealogists (K.G.) and a member of the staff of the Cancer Registry (G.B.).

Factors included in the risk estimation for each female family member.

The factors to be taken into consideration are decade of birth, age, age at first birth, and parity. Each factor is taken to have an independent, multiplicative effect, as shown previously (12). The risk associated with decade of birth and age come from Bjarnason et al, 1974 (7), as later corrected by Breslow and Day 1975, (17). The risk associated with age at first birth and with parity are from Tulinius et al, 1978, (12) (see table 1). For sisters and aunts from series B whose children were not included in the ascertained family trees, information on age at first birth and parity were obtained, when available, from the records of the Icelandic Cervix Cancer Detection Clinic (1,12).

Results.

The total number on the case file is 1740 and the number of cases for whom family information is used is 477. The total number of female relatives 10601, contains 249 cases of breast cancer or 2,3% whereas the 3788 females related by marriage on the family file contain 69 cases or 1,8% breast cancer cases, see table 2. small difference between 2,3% and 1,8% would increase if the fact were taken account of that the family file contains a large number of children, whereas to be among the females related by marriage the person has to be married, see later. In table 3 the number of each type of relative is given and the number and % of relatives with breast cancer. For the 1st degree relatives (table 3a), the total % is 4.9, with mothers contributing 5,8%, sisters 5,0% and daughters only 1,6%. difference among the 1st degree relatives reflects the different age distribution and will be taken care of by

standardization. For the second degree relatives the total percent is 2,2% or half that of the 1st degree relatives. The greatest number come from the maternal and paternal aunts, 3% of them are breast cancer cases. This is comparable to the mothers among the 1st degree relatives, being the same generation, and therefore of similar age distribution as the aunts. interesting to note that the percentage is practically the same on the maternal and paternal side. For the 3rd degree relatives the total percentage is 1,4, the greatest number of these are 1st cousins who have 3,2% matched on the maternal side and 2,5% matched on the not pure maternal side. Cousins are the same generation as cases and their sisters and this percentage of matching for first cousins should be compared to 5% for sisters.

As mentioned earlier the group of inwed females on the file can not be compared to the blood relatives directly since in order to be married to someone you have to be of marriage age. For that reason we have prepared table 4a and 4b where only those 25 years and older are counted. In table 4a we see again the same kind of gradient in risk when we compare within generations, mothers with 5,8% and aunts with 4,3%, or in the generation of the case, sisters with 5,9%, and cousins, or 3rd degree relatives, 3,3%. Table 4b also gives all mothers of the offspring of the male Here this gradient between first, second relatives. and third degree is lost, for example the brothers wifes having 3,2% matching and the cousins wifes having 3,0% The fathers wifes have 2,0% matching, the uncle's wifes having 1,2% matching. Comparing between the tables, one finds very little difference in the 3rd degree relatives where the blood related cousins have 3,3% matching, 46 out of 1396 and the wifes of the male cousins have 3,0% matching 36 out of 1207.

In order to answer the question whether the reproductive factors, which we have previously shown to have an important risk contribution (12), influence the risk contributed by familial aggregation, we looked

for information on age at first birth and parity for certain relatives of breast cancer cases. The information was obtained from the Cervix Cancer Detection Clinic of the Icelandic Cancer Society (1). Table 5 gives some of this information, 5a on age at first birth, and 5b on parity. In general one can see that the reproductive habits of sisters resemble those of cases to a certain degree.

Table 6 shows observed and expected rates of certain family members and a relative risk. Account has been taken of the contribution made by decade of birth and age in all the computations, but only for sisters can we measure the contribution by the reproductive history. This contribution turns out to be minimal, or its effect is to reduce the relative risk of sisters from 2,91 to 2,74.

Conclusions.

The preliminary conclusions that may be drawn from this are the following:

- 1. The frequency of breast cancer among relatives by blood, or by marriage, to breast cancer cases, can be measured in the data bank collected for that purpose.
- 2. When the risk of breast cancer is compared between degrees of relatedness one can see that there is a constant gradient, so that the nearest relatives have greater risk than those more distantly related. In this manner it can be seen that there is an increase in risk of breast cancer among close family members of breast cancer cases.
- 3. No consistent difference was found in the likelihood of matching for relatives depending on whether they were related to the case through a pure maternal line or the relationship was, at least partly, paternal.
- 4. In trying to evaluate how much this risk is above that of the general population we have compared the percentage of breast cancer cases between comparable groups of blood relatives and relatives by marriage. From that, one can see that in the relatives by marriage there is no gradient between first, second, and third degree relatives, however, the total risk in the relatives by marriage seems to be of a comparable size to

that of the third degree relatives. One may therefore conclude that the little difference in risk between close relatives and the general population is confined to first and second degree relatives and is lost when the genetic dilution has come down to one-eighth common genes, or third degree relatives.

5. Little is known about familiality of reproductive factors. We have looked at reproductive factors among sisters of breast cancer cases and found that their reproductive habits resemble those of the cases to a certain degree, however, when this information is used for internal standardization of the relative risk, this contribution turns out to be minimal or altering the relative risk of sisters from 2,91 to 2,74.

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Risk for breast cancer in Iceland associated with various individual characteristics

Adjusted standardised morbidity ratio by cohort : decade of birth

1	1840-	1850-	1860-	1870-	1880-	1890-	1900-	1910-	1920-	1930-	1940-
	0.252	0.345	0.558	0.886	0.995	1.067	1.257	1.568	1.541	2.392	4.350

Adjusted age-specific incidence rates per 100.000 person-years : Age

20-	25-	30-	35-	40-	45-	50~	55 -	60-	65	70-	75-	80-
1.0	2.6	8.2	21.6	45.7	71.4	76.1	88.8	94.8	146.1	116.3	175.3	238.1

Rel. risk associated with Age at first birth (in years)

<20	20-24	25-29	30-34	35+
1.00	1.53	2.27	2.00	2.91

Rel. risk associated with Parity

1-2	3-4	5
1.78	1.25	1.00

Risk of nulliparous, relative to parity 5+, age at first birth

TABLE 2

<20 = 4.55

TOTAL NO FEMALE BREAST CANCER ON FILE

1740

NO OF FAMILIES TRACED, SERIES A 130

" " " SERIES B 347 . 477

	•		
		MATCHED	7
FEMALE RELATIVES	10601	249	2,3
MALE RELATIVES	11118		·
FEMALES RELATED BY MARRIAGE	3788	69	1,8
MALES RELATED BY MARRIAGE	4006	• • • • • • • • • • • • • • • • • • • •	
	29513	318	

TABLE 3 A

FEMALE RELATIVES ON FILE

·	IST DE	GREE	
	N.	MATCHED	%
MOTHERS	468	27	5,8
SISTERS	972	49	5.0
DAUGHTERS	187	. 3	1.6
TOTAL 1ST DEGREE	1627	79	4,9

gd ⁱ	2nd DE	GREE	•			
•	MATERN	AL		PATERN	AL	
•	N,	MATCHED	% .	N.	MATCHED	7,
GRAND MOTHERS	461	4 .	0,9	461	10	2.2
AUNTS	1260	38	3.0	1278	39	3.1
HALF SISTERS	70	0		114	2	1.8
NIECES	371	5	1.3	509	11	2,2
GRAND DAUGHTERS	163	0		209	0	
TOTAL	2325	47	2.0	2571	62	2,4
	TOTAL	2nd Degree		4896	109	2,2

FABLE 3R

FEMALE RELATIVES ON FILE

3rd Degree

	MATERNA	L	•	NOT PU	RE MATERNAL	٠
	N.	MATCHED	. %	N.	MATCHED	%
GRAND PARENTS SISTER (1)			•	6	0	·.
PARENTS HALF SISTER (2)	80	3	3,8	295	. 5	1.7
FIRST COUSIN ⁽³⁾	472	15	3.2	1244	31	2,5
HALF SIBS DAUGHTER (4)	24	0		172	2	1,2
SIBS GRAND DAUGHTER ⁽⁵⁾	367	0 .		1225	3	0,2
GREAT GRAND DAUGHTER (6)	_ 36	0		156	0	
TOTAL	979	18	1.8	3098	41	1.3
TOTAL 3RDDEGREE FEMALE RELA	TIVES -			4077	59	1.4

FATHERS FATHERS SISTER AND FATHERS MOTHERS SISTER.

PATERNAL, FATHERS FATHERS DAUGHTER, FATHERS MOTHERS DAUGHTER AND MOTHERS FATHERS DAUGHTER.

³⁾ PATERNAL, FATHERS BROTHERS DAUGHTER, FATHERS SISTERS DAUGHTER, MOTHERS BROTHERS DAUGHTER.

⁴⁾ PATERNAL, FATHERS SONS DAUGHTER, FATHERS DAUGHTERS DAUGHTER, MOTHERS SONS DAUGHTER.

⁵⁾ PATERNAL, BROTHERS SONS DAUGHTER, BROTHERS DAUGHTERS DAUGHTER, SISTERS SONS DAUGHTER.

⁶⁾ PATERNAL, SONS SONS DAUGHTER, SONS DAUGHTERS DAUGHTER, DAUGHTER SONS DAUGHTER.

RELATIVES, 25 YEARS AND OLDER, BY GENERATIONS

TABLE 4a

GEN.	lstDEGREE	MATCHED	8	2ndDEGREE	· · · · · · · · · · · · · · · · · · ·	MATCHED	 8	3rdDEGREE MATCHED
- 2				GRAND MOTHER	905	. 14	1,5	
-i	MOTHER 464	26	5,6	AUNT	1803	7 7	4,3	PARENTS HALF SISTERS 272 8 :
0	SISTERS 831	49	5,9	HALF SISTER	152		1,3	COUSINS 1396 46
1	DAUGHTER 141	3 .	2,1	NIECE	696	16	2,3	DAUGHTERS OF HALFSISTERS 136 2
2								SIBS GRAND DAUGHTER 517 3 (

WIFES OF RELATIVES, 25 YEARS AND OLDER, BY GENERATIONS*

GEN.	lstDEGREE	E	MATCHED	8	2ndDEGREE		MATCHED	Qo	3rdDEGREE		MATCHEL)
-2					GRAND FATHER	155	1	0,6				
-1	FATHER	102	2	2,0	UNCLE	433	5	1,2	PARENTS HALF BROTHER	87	2	2
0	BROTHER	313	10	3,2	HALF BROTHER	63	3 .	4,8	COUSINS	1207	36	(*)
1	SON	147	. 2	1,4	BROTHERS SON	198	3	1,0	SONS OF HALF SIBS	.114	1	С
2									SIBS GRAND SON	376	1	0

^{*} WIFES INCLUDES ALL MOTHERS OF THE RELATIVES OFFSPRING e.g. SINGLE MOTHERS.

Table 4a: RELATIVES,
25 YEARS AND OLDER, BY GENERATIONS

Gen	1st Deg	ree .	Matched		કૃ
-2.4					
-1	Mother	464	23	,	5,6
0	Sisters	831	49		5,9
1	Daughter	141	3		2,1
2					

Table 4b: WIFES OF RELATIVES,
25 YEARS AND OLDER, BY GENERATIONS*

lst Dec	gree	Matched	કુ
			•
Father	102	. 2	2,0
Brother	313	10	3,2
Son	147	. 2	1,4
		•	٠,
	Father Brother	Brother 313	Father 102 2 Brother 313 10

*WIFES INCLUDES ALL MOTHERS OF THE RELATIVES OFFSPRING e.g. SINGLE MOTHERS.

Table 4a: RELATIVES,
25 YEARS AND OLDER, BY GENERATIONS

Gen	2nd Degree	Ma	tched .	90
-2	Grand mother	905	14	1,5
-1	Aunt	1803	. 77	4,3
0	Half sister	152	2	
1	Niece	696	16	
2				

Table 4b: WIFES OF RELATIVES,
25 YEARS AND OLDER, BY GENERATIONS*

Gen	2nd Degree	Mato	ched	0,0
- 2	Grand father	155	1	0,6
-1	Uncle	433	, 5	1,2
0 .	Half brother	63	3	4,8
1	Brothers son	1,98	3	1,0
2				

^{*}WIFES INCLUDES ALL MOTHERS OF THE RELATIVES OFFSPRING e.g. SINGLE MOTHERS.

Table 4a: RELATIVES
25 YEARS AND OLDER, BY GENERATIONS

3rd Degree		Matched	90
PARENTS HALF SISTERS	272	8 .	2,9
COUSINS	1396	46	3,3
DAUGHTERS OF HALFSISTERS	136	2	1,5
SIBS GRAND DAUGHTER	517	3	0,6
	PARENTS HALF SISTERS COUSINS DAUGHTERS OF HALFSISTERS	PARENTS HALF SISTERS 272 COUSINS 1396 DAUGHTERS OF HALFSISTERS 136	PARENTS HALF SISTERS 272 8 COUSINS 1396 46 DAUGHTERS OF HALFSISTERS 136 2

Table 4b: WIFES OF RELATIVES, 25 YEARS AND OLDER, BY GENERATIONS*

Gen	3rd Degree	•	Matched	%
-2			. •	
-1	PARENTS HALF BROTHER	. 87	. 2	2,3
0	COUSINS	1207	36	3,0
1	SONS OF HALF SIBS	114	1	0,9
2	SIBS GRAND SON	376	1	0,3

^{*}WIFES INCLUDES ALL MOTHERS OF THE RELATIVES OFFSPRING e.g. SINGLE MOTHERS.

REPRODUCTIVE EXPERIENCE OF DIFFERENT RELATIVE TYPES, AND OF THE DETECTION CLINIC POPULATION, BY DECADE OF BIRTH

1. AGE AT FIRST BIRTH : % OF WOMEN IN EACH CATEGORY

Table 5a

DECADE OF BIRTH	<i>.</i>	S	ISTERS				AUNTS					DETECTION CLINIC POPULATION				
	NP	<20	20-29	>30		NP	<20	20-29	>30		NP	<20	20-29	>30		
<1840		. ,				22,0	0	51,2	26,8							
1840 - 59						17,7	1,3	48,1	32,9							
1860 - 79	27,8	11,1	55,5	5,6		22,9	1,1	42,5	33,5		·		:			
1880 - 99	23,9	2,8	59,2	14,1	:	27,9	4,3	49,5	18,3					·		
1900 - 09	29,2	0	.50,8	20,0		13,3	0	66,7	20,0		12,3	4,3	65,8	17,9		
1910 - 19	11,1	8,9	55,6	24,4		11,1	. 0	88,9	0		10,5	8,2	66,5	14,8		
1920 - 29	21,4	14,3	50,0	14,3		0	0	100,0	Ö		7,7	14,0	69,9	8,4		
1930 - 39	20,0	20,0	50,0	10,0							6,3	25,7	65,8	2,2		

Table 5b

REPRODUCTIVE EXPERIENCE OF DIFFERENT RELATIVE TYPES, AND OF THE DETECTION CLINIC POPULATION, BY DECADE OF BIRTH

2. PARITY: % OF WOMEN IN EACH CATEGORY

DECADE OF BIRTH		SISTERS			AUNTS			DETECTION CLINIC POPULATION				
	NP	< 3	3-4	> 5	· NP	< 3	3-4	> 5	NP	< 3	3-4	> 5
< 1840					22,0	14,6	14,6	48,8				
1840 - 49					17,7	31,6	12,7	38,0				
1860 - 79	27,8	5,6	5,5	61,1	22,9	26,3	20,7	30,2			:	
1880 - 99	23,9	22,5	29,7	23,9	28,0	22,6	24,7	24,7				
1900 - 09	29,2	30,8	26,2	13,8	15,1	20,0	40,0	26,7	12,3	29,1	34,4	24,2
1910 - 19	11,1	37,8	22,2	28,9	11,1	22,2	55,6	11,1	10,5	24,9	36,9	27,7
1920 - 29	21,4	35,7	14,3	28,6	0	50,0	50,0	. 0	. 7,7	21,1	40,9	30,3
1930 - 39	20,0	50,0	20,0	10,0					6,3	33,5	44,6	15,6

OBSERVED AND EXPECTED RISK OF
BREAST CANCER CASES BY RELATIVE TYPE
Corrected for decade of birth and age.

Type of relative	Observed	Expexted	Rel.risk	P .
Mothers	24	12,48	1,92	0,01
Grandmothers	14	12,33	1,14	N.S.
Maternal grandmo	others 4	6,63	·	
Paternal grandmo	others 10	5,70		•
Aunts	67	43,15	1,55	0,01
Maternal aunts	31	21,13		0,05
Paternal aunts	36	22,02		0,01
Sisters.	30 .	9,92	3,02	0,01
Daughters	3.	1,74	1,72	N.S.
First cousins		•		
2246 series A	13	9,14	1,42	N.S.
" В	2	0,88	2,27	N.S.
2236 " A	9	8,10	1,11	N.S.
" B	. 0	0,92		N.S.
2146 "A	10	8,69	1,15	N.S.
" B	2	0,91	2,20	N.S.
2136 " A	9 .	7,55	1,19	N.S.
" В	1	0,39	2,56	N.S.
First cousins total	al 46	36,58	1,26	N.S. (<0,08

Table 6b

OBSERVED AND EXPECTED RISK OF BREAST CANCER CASES BY RELATIVE TYPE Corrected for decade of birth and age.

Series A

Type of relative	Observed	Expected	Rel. risk
Mothers	5	2,65	1,93 N.S.
Aunts	12	9,40	1,28 N.S.
Maternal aunts	. 7	5,04	•
Paternal aunts	5 .	4,36	
Sisters	20	6,87	2,91 S.

Excluding those born before 1890, and corrected for decade of birth, age, and reproductive history.

Mothers	1	0,39		
Aunts	2	2,77		
Sisters	18	6,74	2,74	s.

Sisters Corrected for decade of birth and age
Relative risk 2,91

Sisters Corrected for reproductive history

Relative risk 2,74

Tómas Helgason

The purpose of this paper is to review some of the findings in a retrospective psychiatric study of a birth cohort and a more prospective follow-up study of the same cohort and to consider the methodological problems inherent in the studies. The studies are biographical in their approach and limitations since they involve the collecting of both recorded data and data memorised by a number of individuals, and the verification of the latter. The advantage of this method is that health information is collected on every member of the cohort during his lifespan from all available sources. the collection of data starts with information on the mother's health during pregnancy and a history of the individual's birth and possible complications during this period. From then on the growth and the development of the person should be followed during childhood and adult life until senescence. Provided adequate records are available, it should be possible to reconstruct and summarize the psychiatric-medical history of any individual and assess whether he has had a psychiatric illness or not. But such records are only exceptionally available for persons who have reached an advanced age. Therefore a compromise has to be made between the ideal and the obtainable. Furthermore, the amount of information required, especially about the early life, depends on

To be published in a book on longitudinal studies in medicine this year.

the purpose of the study. If it is etiological, the necessity is obvious, but if it is limited to the more descriptive epidemiological, such information is of less importance when the main focus of interest in on comparing the morbidity between various social and demographic groups.

A considerable proportion of psychiatric disorders are not seen by psychiatrists. These are often, but not necessarily, the so called minor disorders. factors which determine whether a patient sees a psychiatrist or not are far too often of a non-medical nature. These may be of an environmental, physical, or social nature relating to the accessability of the service or the social stigma attached to seeking psychiatric assistance. The advent of new therapeutic techniques may work both ways, either by increasing or decreasing the demand for service. If a new technique is relatively simple to apply and resembles other techniques applied by general practitioners, they will probably attempt to treat more patients without referral to a psychiatrist. On the other hand the patients will be referred if the patient and his doctor believe in the efficacy of the specific psychiatric treatment.

It is necessary to combine information from general practitioners and other key-informants in the community with information from hospitals and psychiatrists to improve the epidemiological data necessary for evaluation of the psychiatric morbidity in the population. The uniformity of the data can to some extent be secured by having the same psychiatrist collecting them and evaluating the mental health of all the probands. Ideally the same psychiatrist should interview all the members of the cohort. This is difficult in a large cohort followed over a lifetime. Longitudinal studies are of either a pro-

spective or a retrospective nature; or a combination of both. Certain characteristics of the population can be followed in retrospect and from then on the population can be followed either continuously or at certain intervals. The studies which are to be reviewed briefly here are of the combined type, i.e. a birth cohort has been followed retrospectively from the age of 13-15 years until the age of 60-62 years and then followed-up until the age of 74-76 years and finally until the 80th birthday of every member of the cohort.

METHOD AND MATERIAL

The cohort was selected and investigated according to the principles of <u>Klemperer's</u> (1933) "biographical" method. This method is not applicable except under special external circumstances. Given these circumstances, as in Iceland, the method is most effective and should give information for the determination of disease expectancy as reliable as possible in retrospective investigations. The essentials and main advantages of the method are:

- 1) The initial probands are an almost unbiased sample of children in the population to be investigated, i.e. persons who have not entered the usual manifestation period of the major psychoses;
- 2) The health of each individual is investigated as thoroughly as possible during his lifespan or until he has passed the manifestation period of the disorders to be investigated.

The only bias in the sample itself is that all the probands belong necessarily to one age group, selected by the fact that those alive at the time of the investigation should have passed the manifestation period. Therefore, it is not possible to draw the primary material by random sampling in many age groups; a suitable number of probands born during one or as few years as possible has to be obtained, possibly by including every person born in these years. This very selection is most helpful in collecting the necessary information about the probands. It makes possible the search of all official registers and hospital files, whereas this work would have been practically impossible if the initial study were carried out for the same number of persons drawn or apletely at random.

Information is collected on each proband, living or dead, to find all those who may have been sick or abnormal during the observation period and to find out what they have suffered from, when their illness started, how long it lasted, and how serverely they were affected. Furthermore, information is collected on social status, family and other aspects which might affect the health and development of the individual.

It is obvious that information on mild disorders in persons who have died forty years ago may be missed. Information on such disorders could only be obtained with complete certainty in a prospective investigation where every minor illness was registered at the time of its occurrence from early adolescence until old age. The difficulties inherent in such a project are evident. The second best choice, when an exploration of a long period is necessary, is a retrospective investigation involving the collection of as much information as possible. The results obtained from such a study

concerning minor disorders will have to be regarded as minimal figures.

In longitudinal studies such as the present, it is essential to compromise between two standpoints if the investigation is to achieve its purpose. On the one hand, the probands of the cohort have to be born so long ago that those still alive at the time of the investigation have passed the manifestation period of the diseases to be investigated. As one of the main purposes of the present investigation was to find the disease expectancy for manic-depressive psychoses, the probands should preferably have been born 70-75 years before the time of investigation. This is also desirable in the investigation of the risk of senile dementia and other diseases which do not make their appearance until at an advanced age. On the other hand, it is important for the reliability of the information obtained that the number of probands who died long ago should not be too large.

In compliance with these considerations it seemed most appropriate to select probands who were born 60 years before the first study was carried out although about one fourth of the probands who were in the age range of 13-15 years in 1910 would have died by 1957 when the study begun. It could be expected that there would still be many persons alive who had known the dead probands well enough to give reliable information on their health. It was also considered more valuable to obtain information about major diseases appearing when the probands were in their fifties than to try to concentrate on minor disorders among those who died at an early age.

(1947) selected their probands Klemperer and Fremming from birth registers, but only persons who had reached the age of 10 or more were included in the psychiatric survey. In the Icelandic study it was intended to proceed in the same way. But unfortunately some of the parish records which contained the necessary birth registers had been lost by fire. Therefore the only way to obtain a complete sample of the population in the, necessary age group was to draw the names of the probands from the population census registers. census register from 1910 contained all the necessary identification data on each person. This register was, therefore, used to draw the sample, i.e. all Icelanders born in Iceland during the years 1895-1897 and living there on December 1st, 1910. The probands were thus 13-15 years of age at the beginning of the observation period. As the sample includes all Icelanders of a certain age group alive on a certain date there is no question about the national representativity.

The primary sources of information about the probands health were the general practitioners who had been taking care of them. For the dead and emigrated probands, information was also collected from relatives and acquaintances of the probands as well as from various key-informants in each community. Some probands were approached directly, either in writing or personally, and a number of probands, especially those with more serious psychiatric problems, who were still alive, had been seen in psychiatric consultation. The information thus obtained was amplified and verified by searching the files of all hospitals in the country, both general and special, the files of the State Disability Insurance Board, the files of nursing and old age homes, the police records, the files of clinics for alcoholics and the files of a psychiatrist who had been in practice in Iceland during 30 years of the first 47

The first stage of the study (<u>Helgason</u> 1961 and 1964) covered 47 years i.e. the period from December 1st, 1910 to July 1st, 1957, when the probands still alive were at the age of 60-62 years. Owing to the very extensive sources of data, it was possible to acquire knowledge of 99.4 per cent of the 5,395 probands alive on December 1st, 1910, sufficient to determine if they had had mental disorders or not, and most often to diagnose what sort of mental disorder.

The second stage (<u>Helgason</u> 1973, 1978, 1979) of the study covers a period of 14 years from July 1st, 1957 to July 1st, 1971, when the probands still alive were at the average age of 74 years. The information in the second phase of the study was collected very much in the same way as during the first stage, except that by this time a psychiatric register had been established comprising those who had been seen by a psychiatrist in Iceland from 1908 and those who had been admitted to departments of neurology or internal medicine and nursing homes after 1960 and assigned psychiatric diagnoses.

The third stage of the study involves a follow-up of all the members of the cohort until the age of 80. A fourth phase (Helgason 1979) which has just started is aimed at identifying the children of the members of the cohort and studying the mental disorders among these in relation to those of their parents.

The material for the first stage of the study comprises all Icelanders born during 1895-1897 who were still alive in Iceland on December 1st, 1910, a total of 5,395 probands. During the period 1895-1897,

7,209 children were born alive in Iceland (Stjórnartíðindi 1896-1898). Thus, 74.8 per cent of the birth cohort survived in Iceland until the age of 13-15 years.

Only 0.2 per cent of the probands of the study could not be traced after 1910. And with regard to another 0.4 per cent it was not possible to obtain sufficient information of psychiatric relevance except that they had been functioning socially. Thus, it was possible to trace 99.8 per cent of the cohort and to secure relevant data on the health of 99.4 per cent. During the period 1910-1957, 27.8 per cent of the probands died, while 0.8 per cent disappeared alive from observation. (Table 1). The emigration was minimal, i.e. 4.5 per cent during this period.

Table 1

During the second stage of the study, 0.7 per cent of those alive in 1957 could not be traced, and 26.9 per cent died before July 1st, 1971. Thus, almost one half of the original cohort was still alive and available for follow-up in the third phase of the study. In the second stage of the study those who had emigrated were excluded.

Table 2

Demographic data collected to which the morbidity can be related include age at death or disappearance from observation, causes of death, birth place, migration, residence at the beginning of the observation period, and at the various cross-sectional dates, occupation, social class, and marital status.

The morbidity in the study is expressed as disease

expectancy incidence during certain age periods, and lifetime prevalence. Disease expectancy is defined as the probability of an individual of a given age to develop a specified disease at some time during his life or previous to a certain later age, provided that he survives the manifestation period of the disease or to the specified age. Incidence refers to the number of new cases in the cohort during a specified period of time. Lifetime prevalence is the number of active and previously active cases in the population alive at at certain point in time. If there is no excess mortality among those contracting the disease under study, the lifetime prevalence should be the same as the disease expectancy, otherwise the disease expectancy will be higher than the lifetime prevalence, provided the case finding among the deceased is as efficient as among those alive.

Disease expectancy is thus an age-corrected expression of morbidity, independent of mortality in various groups at various times. Therefore, it is suitable for comparison of morbidity. For methods of calculation of disease expectancy the reader is referred to the main report on the studies (Helgason 1964)

In the present paper the morbidity is calculated for broad diagnostic groups only. These are, in the results from the first stage of the study, functional psychoses (i.e. schizophrenia, manic-depressive psychosis and psychogenic (reactive) psychoses), neuroses, alcoholism and drug abuse, organic mental disorders, and other functional mental disorders (i.e. personality disorder, intellectual subnormality and unspecified mental disorders). In the results of the second stage the incidence of organic mental disorders and functional

RESULTS

During the first stage of the study, which was purely retrospective, 1,543 probands were identified with mental disorders occurring before the age of 60-62 years or before the proband's disappearance from observation. The available information was sufficient to assign a diagnosis to the majority of these probands. Only 5.8 per cent of them could not be given a specific diagnosis and were labelled unspecified mental disorder, which probably is most often some form of personality disorder. Besides this group there were also 7.4 per cent of the probands with mental disorders, where there was some uncertainty with regard to which diagnostic category they belonged to. In table 3 they are included with the group which at that time was thought to be most likely. Table 3 comprises only main diagnosis and it is therefore possible to add the expectancy of developing different forms of mental disorders to obtain a total estimate of developing a mental disorder before the age of 60-62 years. This is probably slightly higher for women than for men. Women have higher expectancy of developing functional psychoses or neuroses before the age of \$0-62 years, while men have much higher expectancy of developing alcoholism. With regard to the other disorders, the difference between the sexes is not significant. Within the group of functional psychoses, manic-depressive psychosis is the most frequent according to the results of the studies, followed by psychogenic psychoses. Manic-depressive psychosis and psychogenic psychosis are more frequent among women than among men.

The disease expectancy varies according to socio-demographic factors as shown in table 4 and table 5. However, it is not possible to decide from this study whether the mental disorder or the sociodemographic status is the antecedent factor. to be born in mind that in the present study the socio-demographic variables are classified according to the probands' own achievements. Thus it is obvious than disorders which have developed at an early age and impair social achievements will result in the probands' low socio-economic status, and his remaining unmarried. According to able 4, the expectancy of alcoholism tends to be highest in social class I, while the expectancy for all other disorders tends to be highest in social class III. In these tables, intellectual impairment, personality disorders, and unspecified mental disorders are taken together as other Their common factor is that they functional disorders. have developed at an early age and characterize the person for most of his life. These disorders explain the much higher total expectancy of developing a mental disorder in social class III. The morbidity pattern is slightly different among men and among women as the expectancy of neuroses among women tends to be slightly higher in social class III than in the other social classes, while among men it is highest in social class I.

Table 4

Table 5

The expectancy according to marital status is

calculated only for those who have remained single during their life and for those who are or have been married. The divorced and widowed are thus included with the married under the heading ever-married. expectancy for alcoholism and neuroses is fairly similar among the never-married and among the ever-married, while the expectancy of functional psychoses and especially of the other functional mental disorders is much higher among the never-married than among those who have married. Again, a large proportion of the difference in the total expectancy of mental disorders is explained by the much higher expectancy of unspecified and personality disorder and intellectual impairment among those who have remained single during their life. In connection with the organic mental disorder, it should be remembered that epileptics, who most often have developed their disease at an young age, are included in this group, and this probably explains the higher expectancy of organic mental disorders among the never-married in comparison with the ever-married.

The livetime prevalence at the cross-sectional date of the first stage of the study is shown in table 6. At the probands average age of 61 years the total lifetime prevalence of mental disorders was 30.9 per cent, probably slightly higher among women than among men. The lifetime prevalence comprises those who have had a mental disorder at some time during their life, but are not necessarily ill at the time of the study. The lifetime prevalence of disorders which have an excess mortality is lower than the disease expectancy while the prevalence of disorders without excess mortality is the same as the lifetime prevalence.

The second stage of the study included those of the original cohort who were alive in 1957 in Iceland at the age 60-62 years. Information was collected on this group until their death or until they reached the age of 74-76 years, i.e. over a period of 14 years. Besides giving an epidemiological description of the mental disorders occurring during this period of life, this part of the study provided answers to the question of whether those with previous functional mental disorders were more prone to develop age related organic mental disorders than probands without a mental disorder. During this period 534 new psychiatric cases were identified. About 55 per cent of these were diagnosed as organic mental disorders related to cerebro-vascular disturbances or degenerative processes in the brain occurring with advancing age. Of functional disorders identified during this age period depressive syndromes were most common, accounting for almost one fourth (22.6 per cent) of all new cases identified. In addition to the new cases with depressive syndromes, 173 cases which had previously had a psychiatric diagnosis with depressive or other symptoms, were now classified as depressive. Thus, 8 per cent of the probands who had reached the age of 60-62 years had a depressive illness after this age and before the age of 74-76 years. More than one half of these cases had at some time been seen by a psychiatrist or admitted to a hospital.

Table 7

The incidence of organic and functional mental disorders during this period is shown in table 7. In spite of allegedly intensive case identification during the first stage of the study, 62 cases were identified during the second stage which actually had an earlier onset.

These are considered here as having an onset at the age of 61. The incidence of organic mental disorders rises with age, especially after the age of 70, while the incidence of functional disorders other than depressive decreases after this age. The sum of the incidence rates or disease expectancy is 16.7 per cent for men and 16.5 per cent for women. By adding these rates to the expectancy rates calculated from the results of the first stage of the study the overall expectancy of a person at the age of 14 to develop a mendal disorder before the age of 75 years can be estimated to be 49.2 per cent for men and 51.8 per cent for women. But it could be maintained that it was more correct to calculate the incidence rate only for the previously mentally healthy probands. is done for the age group 61-74, the incidence rates are approximately 27 per cent for men and 28 per cent for women instead of 16.7 and 16.5 per cent, respectively, thus inflating the estimate of the overall disease expectancy by 10 per cent

Table 8

Besides new cases identified during the second stage of the study a number of previously diagnosed cases were assigned a new main diagnosis, most often an organic mental disorder. Table 8 shows that a similar proportion of previously mentally healthy probands and probands who previously had a functional mental disorder, were diagnosed as having organic mental disorder during the age period 61-74 years. On the other hand a similar proportion of previously organic cases were now given a main diagnosis of functional mental disorder. Almost 30 per cent of the probands who had previously had a functional mental disorder were not assigned any diagnosis after the age

of 61. These were mostly probands with an earlier diagnosis of neuroses. These results do not give any support to the notion that people with functional mental disorders are more prone to develop organic mental disorders with advancing age.

Table 9 and 10 show the distribution of patients identified during the follow-up in the second stage of the study according to social factors, compared with those without mental disorder. There are proportionally more unmarried and fewer married patients with functional disorders than in the general population, which reflects the findings from the first part of the study, while the marital status among those with organic syndromes is fairly similar to that of the general population and not very different from that of those without mental disorders. A greater proportion of both patients with organic and functional disorders than persons without mental disorder belong to social class III. bands without mental disorders belong to social class II, while a similar proportion of patients and probands without mental disorders belong to social class I.

Table 9

Table 10

Table 11 compares the outcome of those having a diagnosis of mental disorder during the age period of 61-74 years with those without such a diagnosis. An excess proportion of deaths and disability is found among those with organic mental disorders and also, but to a less extent, among those with functional mental disorders. Disability is defined as a reduction in working capacity which would entitle a person to

Social Security Benefits, i.e. a disability rating of more than 50 per cent. Psychiatric disability is higher among women, both among those with organic and functional disorders, while a greater proportion of men is deceased in both illness groups. The high mortality among men with functional mental disorders is mainly accounted for by the alcohol abusers, almost exclusively a male disorder in this cohort. Of the group without mental illness 63.5 per cent were still alive at the average age of 74 years and not disabled, while 43.5 per cent of those with functional mental disorders were still alive and not disabled and only 29.6 per cent of those with organic mental disorders were still alive and classified as not disabled.

Table 11

In the first stage of the study, suicide accounted for 3.4 per cent of the deaths. In the second part it accounted for 1 per cent of the total number of deaths, while in the third part of the study only one proband had committed suicide out of approximately 600 deaths. Almost 90 per cent of the probands who had committed suicide had been mentally ill. From these data, the expectancy of committing suicide before the age of 75 years can be estimated to be approximately 2 per cent for men and 1 per cent for women.

DISCUSSION

It has been attempted to make the case-finding in the study of this birth cohort as intensive as possible. This has been done by seeking information on each proband individually from a number of sources where he

or his family may have applied for treatment or assistance. One of the major sources of information has been the present or the last general practitioner who has been taking care of a proband. This practitioner obviously has not been taking care of the proband during the whole observation priod and therefore it is quite possible that he has incomplete information on the proband's state of health prior to his registration on the practitioner's This was borne out by experience during the first stage of the study, when a number of cases were identified through sources other than the general practitioners, who under these circumstances added information on the proband's state of health at the cross-sectional date of the study. The coverage with regard to the identification of psychoses and the more severe form of other mental disorders is probably fairly good. But it is beyond doubt that it has not been possible to identify all cases of minor illness, especially those occurring during the earlier part of the observation period. is clearly borne out by comparison of the lifetime prevalence of these disorders among those still alive at the cross-sectional date of the study with that among the deceased. Therefore, lifetime prevalence among the probands alive at the age of 60-62 years has been taken as the best estimate for the disease expectancy for neuroses and unspecified mental disorders. Also, in the follow-up part of the study a number of cases were identified which had developed during the observation period of the first stage and should therefore have been identified earlier.

On the other hand, the long observation period as well as the follow-up during the second stage of this study makes it unlikely that many cases have been misidentified as psychiatric. In the first stage of the study, some cases were marked as uncertain in view of limited information. Those who survived until the

follow-up period, when further information were collected, proved during the second stage of the study to be psychiatric.

In the second stage of the study, the cases were identified through other psychiatrists, general practitioners and hospital records. The proband or his family has thus had to decide if he was ill enough to consult a physician. Only exceptionally were cases identified through other sources, contrary to what had to be done in the first stage of the study, when cases were also identified through key-informants, family members or by interview with the probands themselves. Therefore it is possible that cases remain unidentified in the population where the initiative to seek treatment or other forms of assistance has not been taken.

Clearly, then, the estimates of disease expectancy presented here are presumably minimal figures. The total disease expectancy for men and women is fairly similar although slightly higher for women. But the morbidity pattern is different for the sexes, especially with regard to neuroses and alcoholism. Neuroses are twice as frequent among women as among men, while alcohol and drug abuse is ten times more frequent among men than among women. The sum of the expectancy of developing either neuroses or alcoholism is almost equal for men and women. Further, the expectancy according to social class and marital status is similar for neuroses and alcoholism. This has been used as epidemiological evidence for the hypothesis that alcoholism and neuroses may have a common etiological factor (Helgason 1970).

Apart from the difference between the expectancy of neuroses and alcoholism, the fact that women have higher expectancy of functional psychoses is accounted

for by manic-depressive psychosis and reactive depressive psychosis.

Disorders other than neuroses and alcoholism occur most frequently among those who belong to the lowest social class and to those who have never been married. Compared to the probands without mental disorders during the age of 61-74 years, more patients in this age group are either single or divorced and belong to social class III. When evaluating these results, it must be considered that a personality disorders, mental subnormality or psychiatric illness contracted at an early age, or for that matter any illness contracted at an early age, impedes the possibilities of an individual to climb the social ladder or get married. Therefore, the frequency of mental disorders is higher among probands socially isolated and with low social status. But it is also likely that the stress related to poverty, social isolation and low social status predispose to the development of mental disorders.

With regard to the outcome among the probands who have survived until the age of 74-76 years it has already been pointed out that alcohol abuse undoubtedly contributes to the higher mortality among men than among women with functional mental disorders. Conversely, the higher frequency of neurosis may explain why more women are disabled for psychiatric reasons at this age. It may be pointed out here that mortality is the only epidemiological criterion considered in this study on which neuroses and alcoholism differ markedly. The lower ratio of physical disability among psychiatric patients is probably more apparent than real. They may be as physically handicapped as the others, although mental illness accounts for the major

part of their disability.

SUMMARY

In a study of a birth cohort of 5,395 Icelanders, followed from the age of 13-15 years until the age of 74-76 years, 2,077 cases of mental disorders were identified. On this basis the expectancy of developing a mental disorder before the average age of 75 years is estimated to be 50.5 per cent, similar for both sexes. The expectancy of committing suicide before this age is two per cent for men and one per cent for women.

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Table 1

Distribution of a birth cohort of Icelanders alive in Iceland at the age of 13-15 years (in 1910) according to sex and survival until the age of 60-62 years (in 1957)

	М	F	M+F	
				•
Not traced	0.2	0.2	0.2	
Disappeared alive 1910-1957	0.8	0.8	0.8	
Deceased 1910-1957	30.7	24.8	27.8	
Alive at the age of 60-62 years	68.3	74.2	71.2	•
Total	100.0	100.0	100.0	
Total no. of probands	2,729	2,666	5,395	

Table 2

The distribution of the birth cohort whose mental health had been studied until the age of 60-62 years (in 1957) according to sex and survival 14 years later (in 1971)

	М	F	M+F	
- Emigrated before 1957	2.5	4.6	3.6	
Not traced all 1957	0.2	1.2	0.7	
Deceased 1957-1971	32.5	21.7	26.9	uže
Alive in 1971	64.8	72.5	68.7	
'Total	100.0	100.0	99.9	
Total no. of probands	1,864	1,979	3,843	

Table 3

Expectancy (per cent + standard error) of mental disorder according to sex and main diagnosis

(Cases i danh field be feel linger of 6 gent)

	Male	Female	M+F
Functional psychoses	3.57 <u>+</u> 0.39	6.19 <u>+</u> 0.50	4.89 <u>+</u> 0.32
Neuroses	9.50 <u>+</u> 0.68	18.04 <u>+</u> 0.86	13.89 <u>+</u> 0.56
Alcohol and drug abuse	8.98 <u>+</u> 0.59	0.89 <u>+</u> 0.19	4.91 <u>+</u> 0.31
Organic mental disorders	2.55 <u>+</u> 0.34	3,45 ± 0.39	3.02 <u>+</u> 0.26
Personality disorders	2.35 <u>+</u> 0.29	2.36 <u>+</u> 0.29	2.35 <u>+</u> 0.21
Intellectual subnormality	3.11 <u>+</u> 0.33	2.74 <u>+</u> 0.32	2.93 <u>+</u> 0.23
Unspecified mental disorders	2.41 <u>+</u> 0.36	1.67 <u>+</u> 0.29	2.03 <u>+</u> 0.23
	00 100 4 3 400	71 216 1 1 02	
Total	32.47 ± 1.00	35.34 ± 1.03	34.02+ 0.72

Table 4

Expectancy (per cent <u>+</u> standard error) of mental disorder according to social class and main diagnosis

	Social class I	Social class II	Social class III
Functional psychoses	4.23 <u>+</u> 0.64	3.89 <u>+</u> 0.49	6.00 <u>+</u> 0.5
Neuroses	14.29 <u>+</u> 1.19	11.76 <u>+</u> 0.88	15.41 <u>+</u> 0.8
Alcoholism and drug abuse	6.78 <u>+</u> 0.79	4.49 <u>+</u> 0.52	4.34 <u>+</u> 0.4
Other functional mental disorders	1.81 <u>+</u> 0.42	5.50 <u>+</u> 0.58	10.92 <u>+</u> 0.6
Organic mental disorders	2.12 <u>+</u> 0.47	2.71 <u>+</u> 0.42	3.69 + 0.4
Total	29.23 <u>+</u> 1.49	28.35 <u>+</u> 1.18	40.36 <u>+</u> 1.1

Table 5

Expectancy (per cent <u>+</u> standard error) of mental disorder according to marital status and main diagnosis

	Never-married	Ever-married
Functional psychoses	8.39 <u>+</u> 0.86	3.85 <u>+</u> 0.33
Neuroses	14.04 <u>+</u> 1.22	13.86 <u>+</u> 0.63
Alcoholism and drug abuse	4.81 <u>+</u> 0.64	4.94 <u>+</u> 0.36
Other functional mental disorders	13.89 <u>+</u> 0.95	4.96 <u>+</u> 0.36
Organic mental disorders	4.03 <u>+</u> 0.62	2.70 <u>+</u> 0.28
Total	45.16 <u>+</u> 1.53	30.31 <u>+</u> 0.80

Lifetime prevalence of mental disorder (per cent <u>+</u> standard error) according to sex and main diagnosis at the age of 60-62 years

	Male	Female	M+F
	`.	·	
Functional psychoses	2.74 <u>+</u> 0.38	4. 95 <u>+</u> 0.49	3.88 <u>+</u> 0.31
Neuroses	9.50 <u>+</u> 0.68	18.04 <u>+</u> 0.86	13.90 <u>+</u> 0.56
Alcoholism	7.46 <u>+</u> 0.61	0.61 <u>+</u> 0.18	3.93 <u>+</u> 0.31
Other functional mental disorders	7.78 <u>+</u> 0.62	6.37 <u>+</u> 0.55	7.05 <u>+</u> 0.41
Organic mental disorders	1.88 <u>+</u> 0.31	2.37 <u>+</u> 0.34	2.13 <u>+</u> 0 \(23 \)
Total	29.36 <u>+</u> 1.05	32.34 <u>+</u> 1.05	30.89 <u>+</u> 0.75

Table 7

Expectancy (per cent <u>+</u> standard error) of mental identified disorders developing for the first time in the population aged 61-74 years according to sex and main diagnosis

	М		F	M+F
Organic mental disorders	10.67 <u>+</u>	0.80	8.46 <u>+</u> 0.69	9.49 <u>+</u> 0.52
Depressive mental disorders	3.36 <u>+</u>	0.46	4.11 <u>+</u> 0.48	3.75 <u>+</u> 0.33
Other functional mental disorders	2.66 <u>+</u>	0.39	3.91 <u>+</u> 0.46	3.30 <u>+</u> 0.30
Total	16.69 +	0.95	16.48 + 0.90	16.54 + 0.65

Distribution of mental disorders occurring from the age of 61 to 74 years according to diagnosis before the age of 61 years

Diagnosis before 61 years of age

Diagnosis at the age 61-74 years	None Per cent	Organic Per cent	Functional Per cent	Total Per cent	No. of proban
None .	78.8	12.5	29.5	63.0	2315
Organic	11.8	75.0	13.0	13.5	497
Functional	9.4	12.5	57.5	23.5	865
Total	100.0	100.0	100.0	100.0	3677

Table 9

Comparison of marital status among probands with psychiatric diagnosis and without psychiatric diagnosis from the average age of 61 - 74 years

	Single	Married	Widowed	Divorced	Total	No. of probands
•	Per cent					
Organic mental disorders	20.5	50.9	23.5	5.0	99.9	497
Functional mental disorders	27.4	41.8	24.5	6.2	99.9	4 6 5
Without mental disorders	18.6.	53.8	24.1	3.5	100.0	2315
Total	20.9	50.6	24.1	ц.ц	100.0	3677
Chi square	52.59 DI	F= .6 I	< 0.001			· ·

Table 10

Comparison of social class among probands with psychiatric diagnosis and without psychiatric diagnosis from the average age of 61-74 years

	Social class I	· Social class II	Social class III	Total No	o. of proband
	Per cent	Per cent	Per cent	Per cent	
	•				
Organic mental disorders	23.7	31.0	45.3	100.0	497
Functional mental disorders	21.3	31.3	47.4	100.0	865
Without mental disorders	22.2	37.0	40.9	100.1	2315
Total	22.2	34.8	43.0	100.0	3677

Chi square 16.03

DF= 4

D < 0.01

Table 11

Outcome among probands with psychiatric diagnosis registered during the age period 61-74 years, compared with outcome among those without psychiatric diagnosis during this age period

	Or	Psychia ganic	atric diag	nosis tional		sychiatri gnosis	C ,	
		cent		cent		cent		
	M	F	М	F	М	F		
	•							
Not disabled	28.7	30.5	39.6	46.9	60.5	66.3		
Psychiatric disability	23.1	27.6	11.5	21.8	· -	· <u>-</u>		
Other disability	8.8	6.9	٤.1	9.4	• 10.0	12.5		
Dead	39.4	35.0	40.8	21.8	29.4	21.2		
m	. 300 0	: 400 0	3000					
Total	100.0	100.0	100.0	99.9	99.9	100.0		
No. of probands	251	246	407	458	1155	1160		

GENETICS AND EPIDEMIOLOGY OF HAEMATOLOGICAL DISORDERS

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INHERITED RED CELL ABNORMALI-TIES

Two main types of hereditary haemolytic anaemias have been studied in Iceland for the last 20 years, hereditary elliptocytosis and hereditary spherocytosis (4). The findings as to the number of families involved and the individuals diagnosed and their ethnic origin are summarized in Table I.

TABLE I. Inherited red cell abnormalities.
Hereditary haemolytic anaemias.

	•		
Condition	Families	Affected	Origin
Hereditary elliptocytosi	3 8	90	Icelandic (1) Algerian (1) Icelandic/ Danish/ Eskimo (1)
Hereditary spherocytosi	14 s	35	Icelandic (14)
Total	. 17	125	

Three families with hereditary elliptocytosis containing over 90 affected individuals have been examined more closely. The largest of these, with over 80 affected members, is Icelandic, another is of Algerian origin, and the third, which is cur-

rently under investigation for a gene for elliptocytosis, is from one of three possible sources, Icelandic, Danish or Eskimo.

A total of 14 Icelandic families with 35 diagnosed cases of hereditary spherocytosis have been identified. The population of Iceland, at present approx. 224,000 (Dec. 1st 1978), contains at least 125 individuals with these 2 types of hereditary haemolytic anaemia diagnosed during the period studied.

Pedigree studies indicate that all the affected members of the large Icelandic elliptocysis family are descendants of a common ancestor. The hereditary pattern is typical for a dominant, autosomal gene with full penetrance. A high incidence of signs and/or symptoms of haemolysis (over 57 per cent) is found among the affected at one time or another. No haptoglobin was detected in 80 per cent of the affected individuals investigated. The age distribution of the affected members at the time of diagnosis shows an increase in the incidence of anaemia with age. Splenectomy has been performed with satisfactory results in three cases. The loci for elliptocytosis and the Rhesus system are not closely linked in this family.

Thirty-five members with typical hereditary spherocytosis (HS) and over 90 apparently unaffected members belonging to the 14 families have been studied. Pedigree studies on one of the families indicate that the HS gene or genes have been transmitted through six generations over the past 200 years (4). A marked deficiency is present in the number of affected members compared

of the HS families. The most striking example of the uneven genetic ratio is a sibship of 15 members investigated haematologically, with only one suffering from typical HS. Much reduced penetrance of the HS gene or the presence of the socalled smild forms is upheld as the main explanation for the unevenness in the genetic ratio. Some families are also involved, however, in which abortions and death at an early age indicate that selection against the affected could also disturb the genetic ratio in HS families.

INHERITED COAGULATION DIS-ORDERS

A total of 85 individuals in 14 families have been diagnosed with different forms of hereditary

hereditary bleeding disorder in Iceland is von Willebrand's disease, more than half of the cases belong to this category (4, 6). The number of haemophilia A and B bleeders are similar to the frequencies found in England (Oxford) and Scandinavia, 4-6 per 100,000 inhabitants.

Factor VII deficiency causes bleeding in homozygous and some heterozygous family members. 4 homozygous and 19 heterozygous members are therefore entered sen blocs in the Table II. The parents in this family are second cousins (11). Hageman factor deficiency has been found in one large sibship of 12 (10). Deficiency in this factor has no known pathological consequences, but it is an interesting marker not only from the coagulation point of view, but also because the locus for its gene is thought to be on chromosome No 6.

TABLE II. Inherited coagulation defects in Iceland.

Condition	Deficiency of factor	Families	Affected	Origin	References
von Willebrand's dise ase	VIII vwf	4 (1)	45	Icelandic	4, 6
Haemophilia A	VIII	6	6	Icelandic (4) Swedish (1) Finnish (1)	5
Haemophilia B	IX	1	· 2	Icelandic	5
Factor VII	VII	: 1	23	Icelandic	11
Hageman factor deficiency	XII	1	6	Icelandic	10
Her. hypoprothrombi aemia	n- II	1	1	Icelandic	1
Total		14	85		

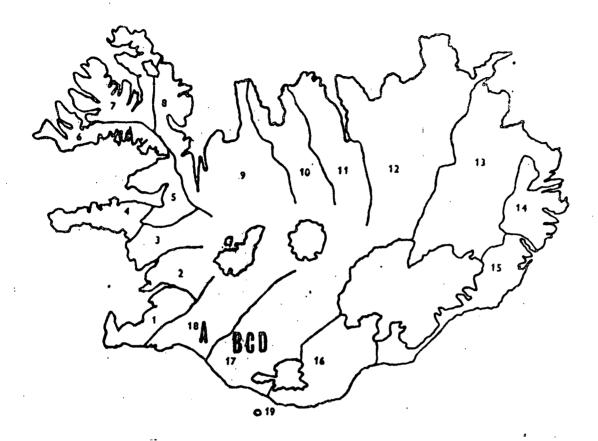


Fig. 1. Home districts of the von Willebrand's disease families A, B, C and D in counties 17 and 18.

Hereditary hypoprothrombinaemia was found to be the cause of excessive bleeding in a woman who also had cerebral aneurysm, as did her brother (3). These and their 4 sibs were children of parents who were first cousins.

All cases of von Willebrand's disease diagnosed so far belong to one of the four families A, B, C and D. It is thought most probable that they are descended from a common ancestor in the south of Iceland. Although the geographical origin of these families is indicated in Fig. 1 as being counties 18 and 17, all four can in fact be traced back to Rangarvallasysla (County 17).

INHERITED PLATELETS AND VAS-CULAR DEFECTS

Four families containing 10 members with the giant platelets syndrome have been investigated, including one family in which the father had married his mother's sister (Table III). The affected individuals have a bleeding tendency due to disturbances in primary haemostasis such as epistaxis, bruises and excessive bleeding from scratches and other small superficial wounds.

TABLE III. Inherited platelet and vascular defects.

Giant platelet syndrome (A).

Hereditary haemorrhagic telangiectasia, HHT (B).

Condition	Families	Affected	Reference
A Giant platelet syndrome(s)	4	10	7
в нит	2	15	2,4

A family with 12 members suffering from hereditary haemorrhagic telangiectasia (HHT) was described in 1973 (2), and the von Willebrand's disease family A (6) contains 3 members with HHT. Both these families have relatives in the same and neighbouring parishes, and in both instances untimely cerebral haemorrhage has been diagnosed in their close relatives (3, 6).

LEUKAEMIA AND CHROMOSOME ABNORMALITIES

Malignancy associated with chromosomal abnormalities has been observed in an increasing number of cases during the last 10-15 years. Chromosomal abnormalities are well known in myeloid leukaemia, particularly in the chronic form with the Philadelphia chromosome.

Two types of chromosome abnormality and leukaemia in Icelanders are recorded in Table IV. The first is an example of familial acute myeloid leukaemia with acquired Pelger-Hüet anomaly and aneuploidy of group C (9). All five members of one generation in an Icelandic family were affected by acute myeloid leukaemia or preleukaemia. Two sibs died of acute myeloid leukaemia and another of myelofibrosis associated with leukaemic changes. The other two sibs are still alive. One of them (the propositus) has haemotological features consistent with preleukaemia, and both have evidence of an abnormal cytogenetic clone in the bone marrow with 47 chromosomes, an extra chromosome in group C. The finding of the acquired Pelger-Huet anomaly in the neutrophils of the two sibs with the bone marrow clone suggests that a specific genetic cell defect has been transmitted with autosomal dominant characteristics. The presence of immunological deficiencies and an undue susceptibility to oncogenic viruses, as suggested by warts affecting three family members, may have played a part in the pathogenesis of the leukaemic process.

SUMMARY

The five categories of inherited blood disorders reviewed are summarized in Table V.

TABLE IV.	Chromosomal abnormalities as-
	sociated with leukaemia.

Condition	Families	Affected	Reference
Myeloid leu- kaemia (3)			
Chromosome		•	
	•	5.	Q
clone (2)	. 1	3	,
Acute leukaemi	4	4	8
Total	· 5	8	

TABLE V. Categories of abnormalities and number of affected individuals.

Type of inherited abnormality	Number of affected
Red cells	125
Coagulation .	85
Platelet and arteries	25
Chromosomes and white ce	lis 8
Total	243

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(ABSTRACT)

ACID PROTEINASE, NEUTRAL PROTEINASE AND B-GLUCURONIDASE ACTIVITY OF CEREBROSPINA FLUID IN MULTIPEL SCLEROSIS

H.O. KILPELÄINEN, T. HALONEN, J. KEKONI, G.K. MOLNÁR AND P.J. RIEKKIN Dept. of Neurology University of Koupio and Dept. of Neurology University of Turku Fin

Neurochemical studies have shown that there is an increase of acid protein and B-glucuronidase in MS plaque areas and sometimes even in the so-ca normal appearing white matter. The activity of neutral proteinase can be creased in the acute phase of plaque formation. Neutral proteolytic activit the cellular fraction of CSF has been found to be elevated in acute MS parallel result has been found for supernatant acid proteinase activity.

We have assayed proteolytic and B-glucuronidase activity in CSF from subject groups (MS in remission, MS in exacerbation, progressive MS, epile and normal controls). CSF neutral proteinase and supernatant acid proteir activities were measured by using human BP as substrate at pH 7.6 and respectively. B-glucuronidase activity in CSF was measured by using phe phthalein glucuronide as substrate at pH 4.5 accc ding to the method by A and Reagan.

Our preliminary results did not show any marked differences in a proteinase activity in different patient groups. Neutral proteinase acti seemed to increase in acute and progressive MS and epilepsy compared with in remission and normal controls. Beglucuronidase activity was decrease acute and progressive MS and epilepsy compared with MS in remission controls.

Neutral proteinase activity seemed to be in connection with the activit disease but in some case there were also low activities in an acute phase of and high activities in controls. The source of this activity is unclear, and activity did not correlate with CSF cell count.

In the further trial we are going to correlate these lyzosomal enzyme activ with basic protein consentration in CSF.

(ABSTRACT)

HLA TYPES, GC PROTEIN AND OTHER GENETIC MARKERS IN MULTIPLE SCLEROSIS AND TWO OTH NEUROLOGICAL DISEASES IN ICELAND

A: ÁRNASON, Ó. JENSSON, I. SKAFTADÓTTIR, B. BIRGISDÓTTIR, G. GUÐMUND!
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Sixty three patients with multiple sclerosis (MS) and fourty of their rela have been typed for HLA A, B and C series of antigens, ten red blood g

systems and ten other biochemical genetic marker systems, including Gc protein by isoelectric focusing. Furthermore, a family of eight including 3 brothers, who have congenital analgesia, have been typed. Most of these marker systems have also been ascertained in 25 individuals belonging to families containing members suffering from hereditary cerebral haemorrhage with amyloidosis (HCHWA). The proportions of the genetic markers in MS patients particular HLA, Bf, C₃, Gc and MNSs are compared with those found in the normal population. Haplotypes of some of the systems investigated have been related to a proportion of patients in the above mentioned three categories to detect association and linkage.

Association of MS and Gc IF; and of MS, HLA B5 and B7 was observed. Both B5 and B7 are linked to Bf S in the MS group. The association of MS and Gc locus suggests, that a-region on chromosome no 4 could be involved in the immune response in MS patients in a similar fashion as is indicated by the Bf locus on chromosome no 6, i.e. MHC region¹. The MNSs antigens coded for on chromosome no 4 have recently been suggested as influential in graft versus host disease.²

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(ABSTRACT)

THE PROGNOSIS OF OPTIC NEURITIS: CLINICAL AND IMMUNOLOGICAL STUDIES WITH SPECIAL REFERENCE TO ITS RELATIONSHIP TO MULTIPLE SCLEROSIS

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47 patients with optic neuritis (ON) which were first seen during 1970 – 1973 were re-examined neuro-ophtalmologically and neurologically after a follow up of seven to 10 years.

During the initial attack of ON the cerebrospinal fluid (CSF) samples and serum/CSF measles antibody levels were analyzed as published earlier (Nikoslelainen, E. et al.: Acta Neurol. Scandinav. 53: 105-119. 1975. Nikoskelainen. E. et al.: Ibid. 51: 347-364, 1975) 19747 of the re-examined patients had an elevated relative IgG (more than 10% of total protein) in the CSF during the ON. According to the Schumacher Committee, 15/47 of these parients had probable and 2/47 possible multiple sclerosis (MS). 28/47 patients had normal relatice IgG in the CSF during ON. 11 of these patients had probable and 7 possible MS. Gelatinized cellulose acetate electrophoresis was abnormal in 19 patients with ON. At the re-examination 14 had probable and three possible

during these days. The corresponding figures for the ethanol-related cases were 14 out of 19 ($X^2 = 6.74$, p<0.01) and for the ethanol-unrelated cases 21 out of 56 ($X^2 = 0.65$, n.s.). Accordingly, the weekly distribution of the bleedings also suggests the influence of ethanol.

In conclusion, ethanol intoxication seems to provoke aneurysmatic subarachnoid hemorrhage.

(ABSTRACT) HEREDITARY FACTORS IN INTRACRANIAL HAEMORRHAGE IN ICELAND

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A particular type of cerebral haemorrhage has been described in several Icelandic families, characterized by a primary amyloidosis of the cerebral arteries. Well over one hundred patients are known to have died of intra cerebral haemorrhage occurring at the age of 15-40. In a proportion of cases there has been a recurrence of the haemorrhage from few months up to several years after the first insult. This hereditary cerebral haemorrhage with amyloidosis (HCHWA) will be reviewed.

A total of 145 patients were diagnosed with cerebral aneurysm during the period 1967-1976. Of these 11 were close relatives, including two members belonging to a family with congenital hypoprothrombinaemia.

From the above mentioned categories it is evident that hereditary factors play a significant role in causing intracranial haemorrhage.

(ABSTRACT) CEREBRAL DYSFUNCTION FOLLOWING OPEN-HEART SURGERY

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One hundred cardiac valvular replacement patients were investigated in a one year's clinical, EEG and neuropsychological follow-up study in order to elucidate the short- and longterm postoperative CNS outcome. Postoperative neurological disorders were observed in 37 cases. Usually the signs were mild and tended to resolve rapidly but one year after surgery 7 patients still displayed residual symptoms. Long perfusion time, presence of preoperative neurological

RECORDS OF THE GENETICAL COMMITTEE

OF THE UNIVERSITY OF ICELAND (CANCER IN TWINS) by

Sturla Fridriksson.

Introduction:

The relatively small population in Iceland, and its isolation through the ages, the extremely good genealogical records, and the high medical standard, render the population very advantageous for a study on human genetics.

Work with general genetical information in view, started in the year 1965 under the supervision of the Genetical Committee of the University of Iceland. The preliminary task was the transfering of the Icelandic population's demographic data to punch cards suited for analysis and linkage by computer (Bjarnason et al. 1967).

Icelandic Population:

Origins:

Iceland is considered to have been uninhabited when it was finally discovered by the people of North Europe. Irish monks may have been the first to discover the island and they settled here in the early 9th century. Later in the 9th century the Norsemen arrived, and the general settlement is considered to have begun in the year 874.

The majority of the settlers probably came from Norway, some from Denmark and Sweden, while others came from the British Isles and were partly Celts. (Fig. 1).

Birth Rate and Population Size:

Various attempts have been made to estimate the size of the Icelandic population at the end of the time of settlement and its fluctuations since. It can be shown that the population was in a direct proportion to the fodder production and that the utilization of the grass crop limited the population. The country gould support about 80.000 people at the beginning of the settlement but with deterioration of the grassland depopulation occurs. Yield of grass was affected by over-grazing and wind erosion, the movement of the Arctic ice towards the country, and several volcanic eruptions resulted in destruction of flocks and caused famine.

The population size was also subject to periodic distortion due to epidemics affecting sometimes animals, sometimes man, which in both cases contributed to the process of depopulation, but between these there would be periods of increase to a level limited by the crop-potential.

number of births in Iceland was approximately 2,000. It reached 2,500 annually in the period 1825 to 1925. In 1941 to 1945 it was on the average 4,720 births per year. At present the population is over 220.000. In the period 1916 to 1960, a total of 144.000 individuals were born in Iceland.

During the period from 1703 to 1916 approximately 430.000 individuals were born. In addition to the individuals alive at the census of 1703, the total population from 1703 and onwards would thus be approximately 700.000 individuals of 10 generations, the majority of whom are on record. Only a small part of the population from 874 to 1703 is known. The total population in the period 874 to 1703 may be roughly estimated at 1,500.000 individuals of over 30 generations.

It may be noted that immigration and emigration have been insignificant during the 1100 year existence of the Icelandic nation. The small number of immigrants has mostly been from Denmark and the emigration from Iceland has been to North America during the last two centuries.

The changes in the growth of the population of Iceland through the ages and the part available on records is shown by the curve in Fig. 2. The figure shows the immigration as lines at the lower end and a few emigrations which took place in the 19th century, when some Icelanders moved to the western world.

The cross lines show the total of 30 to 40 generations that have lived in the country. The hatched lines show the available records dating back, mainly, to the 17th century. Demographic information from earlier periods are indicated by scattered vertical lines. The low part of the population pillar is relatively poorly recorded with scant and unreliable

data, although some families can be traced back to the time of settlement, and most people can hitch their family tree onto it through some prominent historical figure, whose family had been recorded.

The demographic records may be obtained from following sources:

- 1. The Book of Settlement
- 2. Legal Documents
- 3. Annals
- 4. Sagas
- 5. Parish Records
- 6. Censuses
- 7. The National Registry
- 8. Various Occupations Books
- 9. Pedigree Books
- 10. Oral Information.

Censuses:

Although extensive information is available on the Icelanders in the Middle Ages in annals, historical descriptions and legal documents, no general census was taken. The first general census was taken in 1703. In this census the individuals are listed by name, address(farm and county) with information on age, occupation, and often marital status and health. At that time, the population of Iceland was 50.358 individuals. Shortly afterwards the country was struck by plague and famine, and the population was reduced to approximately 35.000. It was not until 1820 that the Icelandic population again reached the number of 50.000 individuals.

In 1729 a second census was taken. It, however, covered only three counties. Then follow special censuses in 1762, 1769, 1785, and a general census in 1801. From 1835 censuses were taken at five-year intervals until 1860, and from then on at ten-year intervals until 1960.

Parish Records:

The earliest continuous parish records date from 1664 and were written in the parish of Reykholt in Borgarfjördur. Another parish, Möðruvallaklaustur in the north, also has continuous records from the year 1694.

In the year 1735, the bishops of Iceland decreed that records of births and deaths be kept in every parish. And, in 1746 a proclamation from the King was issued, demanding that the clergy record all births, marriages, and deaths as well as the literacy of the parishoners.

In 1812 a new proclamation was issued regarding parish records, and now records were standardized and kept in duplicate with a special section for parish censuses. These often included remarks on social status and records of cause of death. Most of these records have been preserved, but some have been lost due to neglect or in fire. The records are kept in the churches as long as they are current, and then sent to the National Archives for permanent storage. There are today about 100 parishes in Iceland's 20 counties.

The parish registers are handwritten by the ministers, and contain the registrations of births marriages and deaths. Of course, the registers differ greatly in precision of entries and handwriting. Boys are entered on the left-hand page and girls on the right.

In the first column is the entry number, then date of birth followed by name, or names, of each child if it was christened (otherwise recorded as stillborn or dead). Next entered is the mother's full name and - in about 50% of the entries - her age, but never date of birth; followed by father is full name but neither age nor date of birth (with a very few exceptions), and occupation though this information is often vague. Also entered are the parents' address, if married, or addresses, and status (mother: fiancée of child's father), and lastly, remarks such as illegitimate or parents married later etc.

Conventional Demographic Records.

A Statistical Bureau was established in 1916 and it collects demographic records on printed forms, i.e.; births, marriages, and deaths that are sent in by ministers. In 1952 the Bureau established a National Registry with birth numbers. These, however did not include information on both biological parents, only the person legally in charge of the child.

The nature of the demographic data can be outlined as follows:

- National Register. A card referring to every person in Iceland defined by his or her name, birth date and a two-digit number, the whole making an identification number of 8-digits, with marital status and address.
- 1) Birth certificates, which also include stillbirths and give the name and birth dates of parents from 1940. Up to that time the details usually consisted of name and age of parents rather than the birth dates.

- Marriage certificates giving the same data as above, in addition to place of birth and consanguinity.
- 4) Death certificates.

Family Records

The Genetical Committee proceeded to use these demographic records to prepare data suitable for genetical studies. Beginning with the birth certificates to record each child's parents and obtaining the registration number from the National Registry as well as information on marriage and death from the respective certificates.

The aim is to obtain the vital demographic data on the basic family triangle, i.e., the child and its parents, in addition to information of a genetic and environmental nature and thus link this related data and arrange all the basic triangles into family trees.

The demographic records of an individual tie him to the parents and to various information of genetical, medical and environmental character.

Handling of the Demographic Registers

The principal work of the Committee, so far, has consisted of the transfer of demographic information to punch cards and to make them available for computer studies.

The transfer of the demographic data covers four major periods, these are:

- 1. Present day to 1916
- 2. From 1915 to 1911
- 3. Individuals alive at 1910 Census
- 4. From 1910 to 1840

The linking has been performed by computer at the University Computing Center as well as manually at the Genetical Committee's office. The birth records were linked to the national register and the death records. Simultaneously, with recording of demographic data at the National Archives, family linking work is being carried out. This work requires continued manual recording from the National Archive by genealogists. these data from 1840 to present total some 360.000 birth records. Approximately 240.000 of these have been transferred onto punch cards or about 70% of the population of that period. Additional 72.000 individuals are on written forms with their parents on the Committee's files giving a total of 312,000 birth records. This means that 87% of the birth records from 1840 to present are on punched cards, or on readily available froms for the Committee. It is therefore, theoretically possible to trace some individuals for 6-7 generations. However, information on the parents'birth dates before the year 1940 is such that it is difficult to link them with their own birth records. A manual linking operation can be carried out however with the aid of the family groupings from the 1910 Cansus. The linking of sibs in the period 1840 to 1910 is facilitated by the simultaneous listing of all children with their mothers.

Use of the Records

Linking the individual demographic data into pedigrees provides good basic material which can be used in various population and genealogical studies. The present linking operation, however, was initiated as the Icelandic data was considered advantageous for various studies in the field of human genetics. Examples of studies, in which the demographic records have been used are:

- 1. Records of blood groups obtained at the Blood Bank in Reykjavik have been transcribed and linked to demographic and medical records for studies on hereditary analysis on blood groups.
- 2. Studies of families of first-cousin marriages are performed as a collaborative effort between many disciplines and institutions. Clinical data and information on blood groups of these families have been collected and analyzed.
- 3. A study of familiality of breast cancer is supervised by the Icelandic Cancer Society and the Department of Pathology University of Iceland in collaboration with the Genetical Committee.
- 4. A study of the possible familial aggregataion of heart diseases in Iceland is performed using material from the Reykjavik City Hospital applying the genealogical register to collect the families of 150 cases as far removed as 2nd degree relatives as well as 150 control families.
- 5. Familiality of mental disorders has been investigated as well as the possible inheritance of intelligence as indicated by mean score achieved at final examination from elementary school.

It is clear that the family registers will be used more extensively in the future, to survey the heritability of various genetic markers, disabilities, and specific diseases, such as cancer.

TWIN STUDIES

The demographic files may be used in various genetic studies. Such as to evaluate effects of heredity and environment on twins. A twin register, which covered the period 1905 to present (1977), was made from the Icelandic records. Multiple births are coded in the birth records, making a listing of all twins possible. They can then be grouped according to sex and cause of death.

In this 70 years period, 2824 twin pairs were born in Iceland. The present pedigree list contains 2206 twin pairs. Of these 550 are of different sex and 1326 of same sex, or 622 feamales ($\frac{92}{1}$) and 704 males ($\frac{66}{1}$), and 330 singles with a co-twin missing from the records (Table 1).

CANCER IN TWINS

For a special study of cancer in twins, a group of twins born during the years 1905-1930 was investigated, i.e., of the 946 twin pairs born in the period 577 pairs were available for the study in the twinregistry.

Mortality of the twins is obtained from the demographic register which included cause of death, classified according to the International Classification of Diseases, Injuries, and Causes of Death.

Among the selected twin-group in this 25 year period were 266 individuals of twins deceased. Of these 26 were registered as having died from cancer.

Table 2 gives the results of cancer cases in twins distributed by sex. Of the deceased individuals 14 males and 12 females had died of cancer. Only in six cases had the co-twin of a cancer individual died and in each case from a different cause than cancer regardless of sex and zygosity (MZ and DZ).

The present study does not offer any indication of prevailing risk of death from cancer to a co-twin of an individual who has died from cancer, nor does this small population sample provide any support to the hypothesis of possible inheritance of cancer.

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TABLE 1

MULTIPLE BIRTHS IN ICELAND 1906 - 1976

PERIOD	BIRTHS					
	Twins	Triplets	Quadruplets	TOTAL		
1906-1910	. 187	2	· · · · · · · · · · · · · · · · · · ·	189		
1911-1920	363	11		374		
1921-1930	396	5	•	401		
1931-1940	315	2		317		
1941-1950	421	: 5	• • •	426		
1951-1960	461	** 7 .	1 .	469		
1961-1970	452	. 8		460		
71	40			40		
72	37		• .	37		
73	. 46			46		
74	35			35		
75	46	1		47		
76	25			25		
TOTAL	2824	41	1	2866		
On Pedigree	Reg. 220	06		•		
o, 5	5.5	30				
9 9	6 2	22				
88	7.0) 4				
Missing co-	twin 33	30				

CANCER MORTALITY OF TWINS IN ICELAND BORN 1905-1930

Sex	Zygosity	Deaths of					
		one twin	(co-twin	from	diff.	cause)	Both twins
88	ΜZ	9	(4)				0
ט ט	DZ			•	. •		
	MZ	6	(1)				0 .
đ	DZ			•			
•	DZ	· 5	(1)			·	. 0
•	DZ	, 6 ·	(0)		. •	· •	0