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A genetic register system (*RAPID*)

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Summary. Justification is given for establishing a genetic register system as a means of ascertaining and preventing genetic disease. Such a computerized register system, referred to by the acronym '*RAPID*' (*R*egister for *A*scertainment and *P*revention of *I*nherited *D*isease), has been established in Edinburgh.

The system involves ascertaining individuals in the population at risk of having a child with a serious genetic disorder through various record systems and statutory registers. Procedures for contacting and following up individuals found to be at risk are discussed.

Computer methods for the recording, storage, and retrieval of individual and family data are described.

Because of population mobility and the geographical dispersal of family members a Genetic Register System is more likely to be effective if organized on a national basis and the authors would therefore welcome the collaboration of other geneticists in this venture.

The effect of genetic counselling in reducing the proportion of cases of genetic disease in the population has been examined theoretically (eg, Smith, 1970; Motulsky, Fraser, and Felsenstein, 1971) and the results of such calculations have shown that unifactorial disorders offer the best scope in prevention. Genetic counselling would be expected to have much less effect in reducing the proportion of cases of multifactorial or chromosomal disorders because in general the number of individuals at high risk of having affected children in these families is small.

To gain some idea of the extent of the problem, families with *serious* genetic disorders referred to the Department of Human Genetics, Edinburgh, for counselling were studied. The results confirmed theoretical expectations that the main scope for preventing genetic disease lies with the simply inherited disorders (Emery and Smith, 1970). Secondly it was found that only a relatively small proportion (14%) of individuals at risk of having affected children (or carrier daughters in the case of X-linked disorders) in these families were referred specifically for genetic counselling (Emery, 1972). Many affected children were born to parents who, *a priori*, were at high risk of having affected children but had never been counselled and were therefore unaware of the risks. Others were referred for counselling only after the birth of an affected child which might otherwise have been prevented.

Thus it seemed to us that, on the basis of these findings, a greater proportion of cases of serious unifactorial disorders might be prevented if more individuals at risk in the population could be ascertained so that they might be given appropriate genetic advice. At present there is no defined procedure for tracing and following up such individuals, and it was decided that an answer to this problem might be found in the use of a genetic register system.

In recent years a number of investigators have argued the need for some form of genetic disease register (Miller, 1964; Newcombe, 1966; Renwick, 1968; McKusick, 1969; Wertelecki, Lawton and Gerald, 1969; Oliver, 1970; Welch, 1972). Most of these reports however, have been concerned with identifying affected individuals for welfare purposes or for research. Yet a more pressing problem is the need for a register system to help trace individuals at risk so that they can be counselled (Oliver, 1970;

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Welch, 1972). A recent report of a WHO Scientific Group (World Health Organization, 1972) has in fact recommended that medical genetics centres should set up registers of genetically determined disorders for this reason. Such a register was initiated in this Department in 1970, and is referred to by the acronym *RAPID*: *R*egister for the *A*scertainment and *P*revention of *I*nherited *D*isease. For ease of storage, updating, and retrieval of family data it has been necessary to computerize the register system.

Organization of a Genetic Register System

The first step in establishing the Genetic Register System was the *ascertainment* of individuals at high risk (greater than 1 in 10) of having a child with a serious genetic disorder where counselling would be appropriate. Ascertainment of such individuals depends primarily upon the detection of affected individuals within the population. This information may be obtained directly or indirectly. The more usual *direct* method of ascertainment may be through population screening programmes or as a result of routine diagnosis when a disorder is recognized to be genetic and the individual is then referred by the general practitioner or hospital consultant. With few exceptions (eg, phenylketonuria) population screening for unifactorial disorders is impractical because of their rarity. Individuals at risk can also be ascertained *indirectly* from data stored in other record systems and registers, such as hospital in-patient records, various public health records, and certain statutory registers (Fig. 1). The relative values of these various sources will be discussed later.

The second step in the genetic register system was the assessment of the risks of ascertained individuals having affected children. These risks are based upon genetic principles or empiric risks (Smith, Holloway, and Emery, 1971).

The third step was the development of procedures for contacting and following up individuals who were considered to be at high risk of having an affected child. This presents perhaps the most difficult problem. After careful consideration we have adopted the following procedures which we feel offer protection to the individual's right to privacy yet have proved practical in operation. In the case of families ascertained through individuals referred directly to the genetic clinic, other family members deemed to be at risk are contacted only with the express permission of the individual seen in

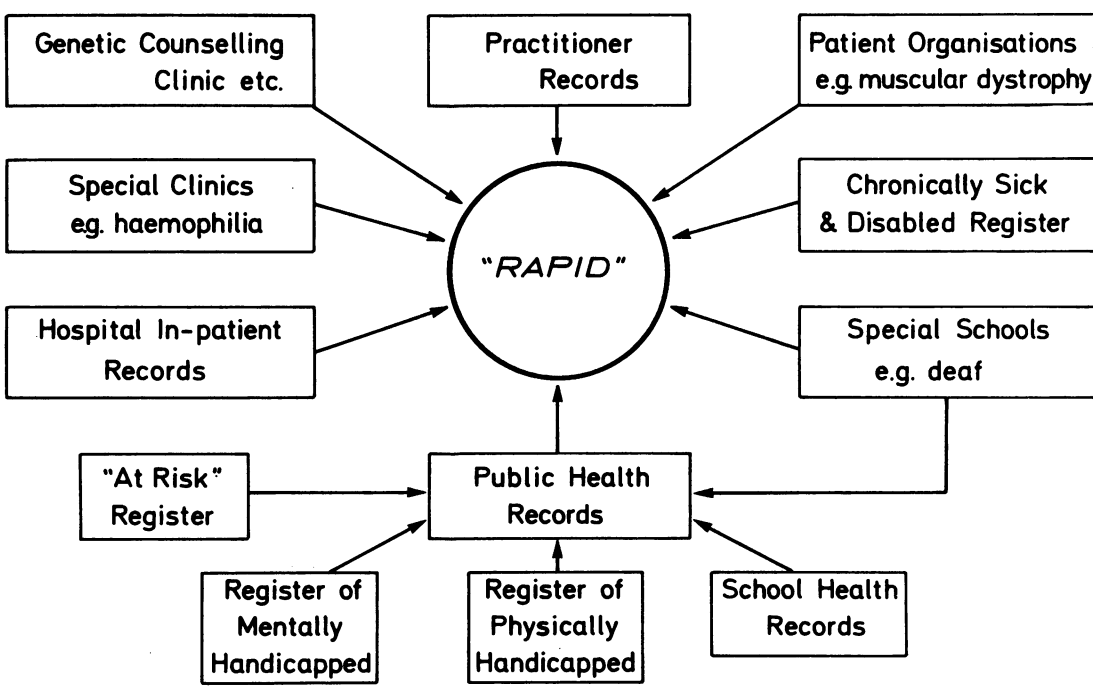

FIG. 1. Methods of ascertaining individuals and their families with serious genetic disorders.

the clinic. When this permission is given then relatives at risk are contacted, not directly, but through their general practitioner. This is considered important as there may be factors unknown to the geneticist or individual seen in the clinic which might make it unnecessary or even imprudent to contact certain family members. The relative's general practitioner can be identified provided the name and address of the relative is known because each local Executive Council (National Health Service) holds a list of patients in any particular area along with the practitioners with whom they are registered.

In the case of individuals ascertained in other ways, they are not approached without first obtaining the permission of their practitioner and often the consultant as well.

The problem whether individuals should be told they are at risk of having an affected child when this information has not been requested has recently been considered at length both from the ethical (Lappé, Gustafson, and Roblin, 1972) and scientific (Littlefield, 1972) points of view. We feel that parents have a right to know these risks. However, we also believe that the general practitioner is usually a good guardian of the individuals' interests in this regard. A discussion of the genetic risks and their implications first between the geneticist and the practitioner is therefore, in our opinion, the best approach to the problem. In the case of individuals ascertained indirectly through other registers and record systems it also allows the geneticist to determine how precisely a particular diagnosis has been established.

Recording, Storage, and Retrieval of Family Data

Data on all ascertained individuals and their relatives deemed to be at risk are recorded on specially designed cards. For each individual there are four cards (see Appendix): the first deals with personal details, the second with disease details, the third with medical (general practitioner, consultant, and hospital) details, and the fourth with genetic details. The information is vetted, encoded, and then stored in the computer file. A pedigree is taken at interview but this is not stored in the computer

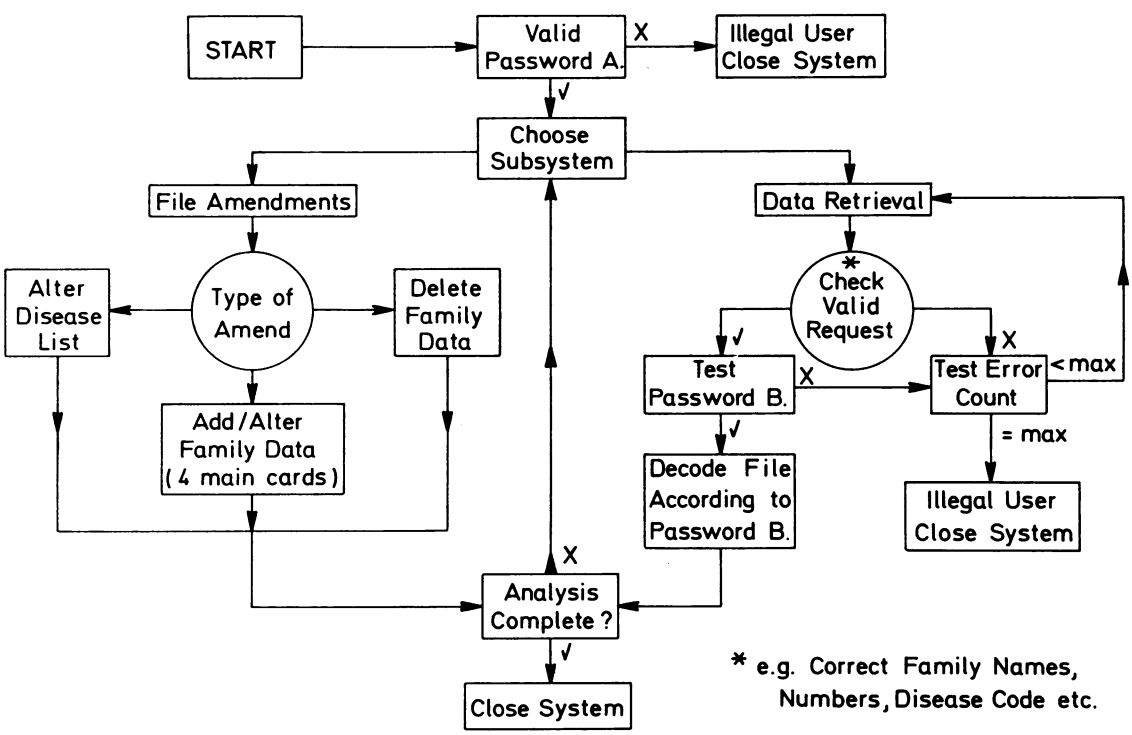

FIG. 2. Simplified outline of the *RAPID* system.

since it is not essential to the system, though this information can be computerized if necessary (Krush *et al*, 1970).

Each family is allotted a code number (eg, 247/–) and each individual at risk in the family is then numbered accordingly starting with the first individual contacted (eg, 247/1). Specific disorders are coded by adding a fifth digit to the code given in the International Classification of Diseases (ICD). This may prove somewhat restrictive in the future as the number of recognized genetic disorders increases but it has proved simple and convenient in use over the last 3 years. A coding based on the ICD has the advantage that it includes both multifactorial as well as unifactorial disorders. An example of the extended ICD coding is illustrated in the case of the spinal muscular atrophies (330·1):

Infantile type	330·11
Intermediate type	330·12
Juvenile type	330·13
Adult type	330·14
Distal type	330·15, etc.

The code numbers for families, individuals in the families, and diseases are used in all subsequent manipulations of the data. A computer program for recording and retrieving individual and family data has been produced, details of which are available (Moores, 1972). The file system is at present capable of storing data on between 25 and 30 thousand individuals. Access to the data is through a teletype terminal using the Edinburgh Multi-Access System (EMAS) on an ICL 4–75 computer.

Because of the need to maintain strict confidentiality of the information in the register a number of security checks have been incorporated into the system. Access to the system by anyone working with the register is only possible when a valid password A has been used (Fig. 2). One may then directly choose to amend the file data. Since this does not involve data retrieval, no further checks of this subsystem are necessary. If, however, the operator wishes to retrieve data the request must first be checked for its validity, ie, correct family names, numbers, and disease code, etc. A legitimate user may on occasion make an error, and for this reason an error count is introduced into the system. Finally, a second password B is needed. This allows data to be retrieved at different levels depending on the particular operator's password. For example the clinician dealing with a family has access to all the genetic and medical information on the individuals in the family. On the other hand a genetic field worker who is concerned with tracing relatives may only retrieve pedigree data.

It might be considered that such a system of checks is excessive. We feel it is necessary in view of the present justified concern over patient confidentiality, and particularly since information about inherited disease could be subject to possible misuse more than purely clinical information would be. For example, within the register there is information on individuals who, though perfectly healthy at present, may be at risk of developing a genetic disorder in the future (eg, myotonic dystrophy or Huntington's chorea). If this liability were known, perhaps to a prospective employer, this might be to the individual's disadvantage. Information about any individual in the register is only released to physicians and medical geneticists who are directly involved in the management of the patient and his family.

TABLE I

SOURCES OF RECORDS SURVEYED FOR SERIOUS GENETIC DISORDERS AND NUMBERS OF INDIVIDUALS SELECTED FOR CONTACT THROUGH THE REGISTER SYSTEM

(Psychiatric disorders excluded)

Source	Period Covered	No. of Records Surveyed	No. Selected
*Hospital Admissions**	1970–71		
Adult		17,628	117 (0·7%)
Children		4325	67 (1·5%)
Total		21,953	184 (0·8%)
Public Health Registers (City of Edinburgh)			
'At risk'	1964, 1969–70	4837	68 (1·4%)
Mentally handicapped	1964, 1967–72	285	33 (11·6%)
Physically handicapped	1964, 1967–72	180	53 (29·4%)
Chronically sick and disabled	1972–73	4868	161 (3·3%)
Special Schools			
Donaldson's School for the Deaf, Edinburgh	1960–67	150	26 (17·3%)

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Feasibility of a Genetic Register System

The feasibility of various aspects of the *RAPID* system is currently under investigation, but limited so far to individuals and their families residing in this region.

An attempt has been made to assess which sources of patient data are likely to yield the greatest number of individuals at risk of having affected children. Obviously special clinics for particular genetic disorders (eg, haemophilia) and referrals to the genetic clinic yield a large number of families in which there are individuals at risk (Emery and Smith, 1970). Screening of other registers and record systems, by ICD coding and diagnostic classification of diseases likely to include genetic disorders (Table I), indicates that some sources (eg, registers for the mentally and physically handicapped) may be potentially more fruitful than others (eg, 'at risk' registers). School health records have been found to be a relatively poor source of material because of the comparative lack of information on which to delineate genetic disorders.

It is to be expected that the comparative proportions of ascertained individuals with serious genetic disorders will vary with the designation and catchment area of a particular hospital and will probably be greatest in the case of children's hospitals. However, within this region our experience indicates that general hospitals can be usefully surveyed when statistics are computerized and facilities exist to examine relevant case records.

The ascertainment, tracing, and contacting of individuals who had been previously seen in the genetic department has been comparatively easy because, detailed information was already known about them. We have so far been able to trace over 80% of those individuals who we have wished to contact. Of these almost all have been co-operative and where relevant (ie, with a relative at high risk residing in this region) have given permission for their relatives to be approached.

With regard to individuals ascertained from sources other than the genetic department, as would be expected many were unaware of the full implications of the heritable nature of their disorder. Nevertheless after discussion permission to approach relatives has so far been obtained in over three quarters of these cases.

These are preliminary findings and it is appreciated that much more information will be needed to determine fully the feasibility of the register system.

Further Uses of a Genetic Register System

Apart from the prevention of genetic disease, a genetic register system could be valuable in a number of other ways which have been enumerated by McKusick (1969). By ascertaining individuals at risk of developing a serious genetic disorder, or at risk of having affected children, this could lead to early and correct diagnosis and even the institution of proper treatment in rare genetic disorders. It could also be of value in alerting individuals with inherited susceptibilities to drugs and for detecting and eradicating life-threatening complications of genetic disease, such as intestinal malignancy in polyposis coli. Many of these functions, however, might only be realized if a genetic register system were linked to other health records.

A linked system of health records has been advocated for many purposes (Acheson, 1967) including the prevention of genetic disease (Welch, 1972). Linkage of various hospital and public health records with a genetic register system could be valuable in a number of ways. For example, through linkage with hospital in-patient records, information on an individual known to be at risk of developing a serious genetic disorder could be made available to the hospital consultant which might be helpful in diagnosis and management of the patient. However, though linkage with other health records could be valuable, many of the functions of a genetic register system in disease prevention are not dependent on such linkage.

Finally, because of population mobility and the geographical dispersal of family members, a genetic register system is more likely to be effective if organized on a national basis. Collaboration between genetic centres in different parts of the country would therefore be important.

It is a great pleasure to acknowledge all those who, at one time or another, have played a part in developing this system particularly Miss Susan Holloway, BSc, and Miss Moira Young, SRN. We are also grateful for the invaluable help of Dr J. L. Gilloran, Dr M. A. Heasman, Dr H. E. Seiler and their respective staffs, and Mr W. Jeffrey, Principal of Donaldson's School, Edinburgh.

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APPENDIX

'RAPID' CLINICAL RECORD CARDS

Card 1—Personal Details

Field Content	Cols	Coding
Card number	1	1
Family number	2–6	
Individual number	7–8	
Old/new record	9	O—Old, N—New
Title	10–13	Miss, Mrs, Mr
First name	14–21	
Second initial	22	
Surname	23–33	
Sex	34	M—Male, F—Female
Marital status	35	S—Single, M—Married, W—Widowed, D—Divorced, Z—Not known
Birth Day	36–37	
Month	38–39	
Year	40–41	
Father's initials (if a child)	42–43	
Address (+ postal code)	44–72	

Card 2—Disease Details

Field Content	Cols	Coding
Card number	1	2
Family/Individual number	2–9	As for card 1
Disorder	10–28	
Code number	29–33	
Mode of inheritance	34–35	AD—Autosomal dominant AR—Autosomal recessive XR—X-linked CH—Chromosomal CX—Complex, multifactorial NR—Not resolved NI—Not inherited ZZ—Not known
Code number for any other disorder	36–40	
Mode of inheritance	41–42	
Data ascertained Month	43–44	
Year	45–46	
How ascertained	47–48	GP—Practitioner CO—Consultant GR—Genetic register, etc SE—Self
Number of affected relatives		
Parents	49	
Sibs	50	
Uncles, aunts	51	
Nephews, nieces	52	
Grandparents	53	
Grandchildren	54	
Cousins	55	

Card 2—Disease Details—*continued*

Field Content	Cols	Coding	Field Content	Cols	Coding
Self	56	A—Affected H—High risk of being affected L—Low risk of being affected N—Not at risk	Future children: Risk	64	H—High M—Medium L—Low N—Not at risk
			%	65–66	
Number of living children:			Follow-up By	67	G—GP C—Consultant F—Family
Affected	57				
At risk	58				
Normal	59		Reason	68	D—Diagnosis C—Counselling V—Review
Number of dead children:					
Affected	60				
Normal	61		Date of follow up		
Adopted children	62		Month	69–70	
Information up-to-date	63	N—No D—Dead	Year	71–72	

Card 3—Medical Details

Field Content	Cols	Coding
Card number	1	3
Family/individual number	2–9	As for card 1
General practitioner		
Initials	10–11	
Surname	12–22	
Address	23–45	
Contacted	46	Y, N
Attitude	47	U—Uncooperative I—Indifferent C—Cooperative
Hospital code	48–49	
Patient Hospital number	50–55	
Consultant		
Title	56–57	
Initials	58–59	
Surname	60–70	
Contacted	71	Y, N
Attitude	72	As for col. 47

Card 4—Genetic Details

Field Content	Cols	Coding	Field Content	Cols	Coding
Card number	1	4	Counselling		
Family/individual number	2–9	As for card 1	Advice (1)	49–50	RE—Reassurance SA—Selective abortion AI—Artificial insemination, etc
Employment	10–21				
Social class	22				
Father's birth year	23–24		Advice (2)	51–52	
Mother's birth year	25–26		Method	53–54	FL—Family limitation ST—Sterilization AB—Abortion SA—Selective abortion, etc
Maiden name	27–34				
Own or mother's maiden name	35				
Visit details			Attitude	55	As for card 3 (col. 47)
Visit Number	36		Children wanted	56	Y, N
Date Day	37–38		Comments	57–70	
Month	39–40		Race	71	C—Caucasian N—Negro M—Mongolian, etc
Year	41–42				
Seen By	43–44	Clinicians initials			
For	45–46	DI—Diagnosis CO—Counselling FO—Follow-up OT—Other	Religion	72	P—Protestant C—Catholic J—Jewish, etc
At	47–48	As for card 3 (cols. 48–49)			