GENETICAL LINKAGE STUDIES IN MAN

A Study in Applied Statistics.

by

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PREFACE.

This study was designed to search for genetical linkage relationships between the loci of autosomally inherited characteristics in Man. It was wished to illustrate the "odds approach, using likelihood ratio tests, to the problems (a) of calculating the probabilities of linkages between pairs of autosomal loci in large families with multiple generation pedigrees, and (b), if linkage was present, of obtaining an estimate of the recombination fraction.

Grateful acknowledgment is made to my supervisor, Dr. R.A. Robb of the Statistics Department, for his advice and guidance in the preparation of this thesis, and to Professor G. Pontecorvo for providing facilities in the Genetics Department whereby the practical blood grouping tests could be performed.

I am particularly grateful to Dr. J.H. Renwick, Genetics Department, for giving me the opportunity of taking part as Blood Group Serologist in his research project for investigation into genetical linkage in Man, and for permitting me to incorporate some of the blood grouping results in this thesis. I am also indebted to him for providing the results of some of the linkage calculations as determined on an electronic computer. My thanks are given to Miss W.H. Jeffrey for her technical/

technical assistance with the blood group determinations; to Mrs. J.D. Martin for preparing the multiple generation pedigrees from which I traced the copies included in this thesis; to Mr. M.J. Davies, Statistics Department, for his guidance in the estimation of the numbers of degrees of freedom applicable to the χ^2 tests.

I appreciate the generous supplies of blood grouping antisera which I received from Dr. J. Wallace, West of Scotland Regional Blood Transfusion Service. It was with the encouragement of Dr. Wallace that the genetical linkage studies on the Caldwell blood group were embarked upon, this blood group having been discovered by Dr. Wallace and myself.

Blood from rheumatoid arthritic patients was kindly provided by Dr. J.P. Currie, formerly of the Royal Infirmary, Glasgow; Dr. T.N. Fraser, Western Infirmary, Glasgow; and Dr. A. McPhater, Victoria Infirmary, Glasgow. I am grateful to Dr. C. Ropartz, Blood Transfusion Centre, Rouen, France, for confirming the specificity of suitable serum grouping (Gm) reagents, which I selected from these rheumatoid sera. Dr. S.D. Lawler, Royal Marsden Hospital, London, and Dr. A.G. Steinberg, Western Reserve University, Cleveland, Ohio, U.S.A., also sent small supplies of rare Gm grouping sera.

Acknowledgment is also made of small donations of rare red blood cell grouping antisera from the following:-

Dr./

Dr. I. Buchanan, Canadian Red Cross Blood Transfusion Association; Dr. B. Chown, Rh Laboratory, Winnipeg, Canada; Dr. T.E.Cleghorn, South London Blood Transfusion Centre; Dr. H. Hutcheson, Western Infirmary, Glasgow; Dr. P. Levine, Ortho Foundation, U.S.A.; Dr. A.E. Mourant, Blood Group Reference Laboratory, London; Dr. J.P. O'Riordan, National Blood Transfusion Association, Dublin.

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INTRODUCTION

The fundamental object of statistical analysis is the reduction of a mass of data from the crude form in which it is obtained into a more readily intelligible form which highlights any of its special features and relationships. Fisher (1922) defines the purpose of statistics admirably -- "A quantity of data, which usually by its mere bulk is incapable of entering the mind, is to be replaced by relatively few quantities which shall adequately represent the whole, or which, in other words, shall contain as much as possible, ideally the whole, of the relevant information contained in the original data." The purpose of this thesis was the condensation of data concerning human pedigrees in such a manner that genetical linkages between pairs of autosomal loci could be recognised and the appropriate recombination fraction estimated.

The classical theories of Genetics postulate a particulate mode of inheritance by means of genes situated at numerous loci arranged in a specific linear order along pairs of homologous chromosomes. Each locus is occupied by an allele, one of the alternative forms of the particular gene for that locus. In a diploid organism alleles whose loci lie on different pairs of chromosomes segregate and pass to haploid gametes independently of one another at the reduction division of meiosis, but those whose/

whose loci lie on the same chromosome may not do so. Instead, they may appear to segregate in a non-random manner and to show "linkage" to one another. The deviation from independent segregation will be greater the closer the two loci lie to each other on the same chromosome.

Consider one pair of homologous chromosomes carrying the loci for the genes A and B, the individual concerned being heterozygous AaBb. In fig. 1a the alleles A and B (or a and b) are in "coupling" (they lie on the same chromosome of a pair), with A and b in "repulsion" (they lie on different homologous chromosomes).

During the early stages of the first meiotic division the homologous chromosomes pair exactly and come to lie adjacent to each other. Each chromosome then duplicates itself along its entire length, except at the centromere where it remains single, (fig. 1a). If a chiasma has formed between the chromatids (fig. 1b), an exchange of segments results from the crossing-over (fig. 1c). Each bivalent (pair of chromatids) then passes to different spermatocytes or oocytes, and the second meiotic division proceeds -- the centromeres divide and the separate chromatids pass to different gametes. The four possible haploid chromosomal arrangements from the original diploid heterozygote AB/ab are AB and ab (non-recombinant types) with Ab and aB (recombinant types) (fig. 1d).

For/

For linked loci a 1 : 1: 1: 1: ratio for the products of meiotic cell division is thus not observed, the usual measure of the degree of linkage being the recombination fraction, θ.

$$\text{Recombination fraction}, \theta = \frac{\text{no. of recombinant progeny}}{\text{total no. of progeny}}$$

In fig.1 the recombinant types Ab and aB would each occur with a frequency of $\theta/2$, while the non-recombinants AB and ab would each have a frequency $(1-\theta)/2$. It is sometimes possible to count directly the certain recombinant and certain non-recombinant progeny in a multiple generation pedigree, and in this way obtain the maximum likelihood estimate of θ. In fact, this procedure was adopted with little loss of linkage information in one of the families studied for linkage between the ABO and Nail-Patella loci.

As the distance between loci on the same chromosome becomes greater the value of θ increases till it reaches 0.5, the figure for independent segregation or "no linkage". It is usually very difficult to say, without extensive information, whether genes with an apparently high recombination fraction, say $\theta > 0.4$, are loosely linked on the same chromosome, or whether they are on different chromosomes. Increasing knowledge of the linkage groups of an organism eventually enables chromosome maps to be drawn showing the order of the gene loci with their map distances apart. Map distance, being defined in terms of cross-overs/

cross-overs in the interval between loci, can be derived from the recombination fraction (Bailey, 1961).

In Man there are 46 chromosomes (22 pairs of autosomes and the sex chromosomes, XX in the female and XY in the male) and to date there is information regarding four autosomal linkage groups. Firstly, Mohr (1951 a,b) found indications of a linkage with a cross-over value of 5.6% between the Lutheran and the Lewis blood group loci. Later this was amended by Sanger and Race (1958) to linkage between the Lutheran and the ABH Secretion loci, because of the relationship between an individual's ABH Secretor genotype and the Lewis phenotype of his red cells. Further information on Lutheran-Secretor linkage will be presented in this thesis.

Secondly came a report by Goodall, Hendry, Lawler and Stephen (1953) of linkage between the loci of the genes for Elliptocytosis and the Rhesus blood groups. Further families were tested but as evidence of heterogeneity was found in the data, Morton (1956) concluded that there are two loci for genes producing Elliptocytosis, only one of which is linked to the Rhesus blood group locus with a recombination frequency of 3.3%.

Thirdly, Renwick and Lawler (1955) recognised a linkage showing 10.4% recombination between the ABO blood group and the Nail-Patella loci. Data from three new families /

families with the Nail-Patella syndrome will be presented, giving a similar estimate of the recombination fraction.

Fourthly, Renwick and Lawler (1963) have detected a probable linkage between the loci of a congenital zonular cataract and the Duffy blood group.

Complications due to uncertainty regarding the mode of inheritance of the conditions being tested for linkage or to misclassification of the children were deliberately sidestepped in the present investigation by intentionally restricting the study to those whose inheritance was clear. Family material was tested for genetical linkages between the loci of rare autosomal dominant conditions and other more common autosomal characteristics, such as the blood, saliva and serum groups. The selected autosomal dominant conditions -- the Cl^a (Caldwell) blood group antigen and the Nail Patella syndrome -- appeared from the observed segregation ratios to be manifest regularly in the heterozygous state in both sexes. (For the Nail-Patella allele it is not even certain that the homozygous affected state is compatible with life). The blood, saliva and serum groups have been sufficiently deeply studied in the past for it to be recognised that they show regular autosomal inheritance with complete penetrance (Race and Sanger, 1962).

Also presented in this thesis are the phenotype distributions/

distributions of the blood, saliva and serum groups as observed in the grouped material compared with those for Britain in general, and Scotland in particular. These findings served to a certain extent as useful checks on the accuracy of the practical blood grouping tests and on the purity of the reagents used.

The basic principle underlying the linkage calculations used in this thesis was that an estimate of the recombination fraction could be arrived at through knowledge of the likelihood of actually finding in the general population families with the observed distribution of children. The likelihood of obtaining the observed family data at a recombination fraction θ was compared with the likelihood when there was no linkage at $\theta = 0.5$ (for $\theta = 0.5$, the value of the likelihood ratio was thus 1). For convenience of manipulation in calculations it was easier to work with such likelihood ratios in logarithmic form as "lods". Lod or z scores for unrelated families were added to give the total lod score, $Z(\theta)$, for the whole data. Morton (1955) has published a series of tables of lod scores when $\theta = 0.05$, 0.1, 0.2, 0.3 or 0.4 for various mating types with families of different size. Reference was made to these tables in the analysis of the Lutheran-ABH Secretor data in the present investigation. An IBM 7094 computer was used for most of the remaining lod score calculations (Renwick and Schulze, 1964).

By/

By the Theorem of Bayes (1763) the distribution of the likelihood (antilog of $Z(\theta)$), given θ, could be interpreted as the distribution of the probability of θ, given the observed data. Assuming that the recombination fractions for linked loci are equally distributed throughout all parts of the range $0 \leqslant \theta \leqslant 0.5$ (Morton, 1955), and knowing the average likelihood of θ in this range, the final probability could be calculated that linkage was present between any tested pair of autosomal loci by taking into consideration the low a priori probability of about 1/22 of autosomal linkage (Smith, 1959).

Such reasoning, when applied to data concerning the inheritance of the MNSs and Cl^a (Caldwell) blood group antigens, led to the conclusion that the MNS and Cl sites are closely linked. In the two families studied linkage was complete, no certain recombination between Ms and Cl^a being observed. Thus, in these families the presence of the Cl^a antigen on the red cells, by marking most effectively those individuals who are carrying a particular Ms chromosomal arrangement, increased the efficiency of the MNS locus in further linkage studies involving the blood, saliva and serum group loci. The observed probabilities of linkages, $0 \leqslant \theta \leqslant 0.5$, between the combined MNSCl locus and these other autosomal loci will be discussed, together with the much smaller probabilities of linkages closer than $\theta = 0.3$.

The/

The maximum likelihood value of the recombination fraction is that value of θ which maximises the likelihood of having obtained the family data as observed. The 95% confidence limits for the observed maximum likelihood values of the recombination fractions between the ABO and the Nail-Patella loci, and between the MNS and Cl (Caldwell) sites, were determined and the results will be discussed.

Thus, by using Smith's (1959) approach to the interpretation of linkage data, it was possible to determine the probability of autosomal linkage between pairs of loci and simultaneously to estimate, where applicable, the value of the recombination fraction.

FAMILY MATERIAL

The Family Material can be divided into 2 categories :

A Families tested for previously recognised linkage relationships

a) Linkage between the Nail-Patella syndrome and the ABO blood group loci Families Sau 1, 2 and 3

b) Linkage between the Lutheran blood group and the ABH Secretor loci Families Bak, Bla, For, N-p H, MoG, Oak and Sau 1

B Families tested for a new linkage relationship

For linkage between the MNS and Cl(Caldwell)blood group loci

For linkage between the MNSCl and the ABO, P, Rh, Lu, K, Fy, Jk, Se or Gm loci

Families Cal and Gil

A Families tested for previously recognised linkage relationships

a) Linkage between the Nail-Patella syndrome and the ABO blood group loci

Families Sau 1, 2 and 3 (Figs. 2, 3 and 4)

The clinical features of the Nail-Patella syndrome or Hereditary Onycho-osteodysplasia include dystrophy of the finger-nails, sometimes even complete absence of thumb and index nails, patellar absence or hypoplasia, posterior dislocation of the head of the radius and the presence of an iliac horn projecting from the middle of the iliac bone. The condition is manifest from birth in affected persons (Renwick, 1956). For the purposes of his investigations Dr. J.H. Renwick diagnosed the condition by clinical examination of the finger-nails, elbows and knees.

Families Sau 1, 2 and 3 all have the same surname, most come from the Midlands of England, but no inter-relationship between them has yet been established. The last 5 generations, at least, have no such relationship. Family Sau 1 was first described clinically by Cotterill and Jacobs (1961).

The findings regarding the genetical linkage in these families between the ABO and the Nail-Patella loci were/

were included in a conference paper concerning the different rates of recombination at meiosis in the human male and female (Renwick, 1963).

b) Linkage between the Lutheran blood group and the ABH Secretor loci

Families Bak, Bla, For, N-p H, McG, Oak and Sau 1 (Figs. 5-13

These families were all examples of sibships with Lutheran (a+) children, who had also been tested for their salivary ABH Secretor status.

With the exception of Family N-p H the families in this category are all being reported for the first time. Family N-p H was the Nail-Patella family N of Lawler, Renwick and Wildervanck (1957) with new information on the Lutheran blood groups and ABH Secretor status of III 30 and III 38.

B Families tested for a new linkage relationship

For linkage between the MNS and Cl(Caldwell) blood group loc

For linkage between the MNSCl and the ABO, P, Rh, Lu, K Fy, Jk, Se or Gm loci

Families Oal and Cil (Figs. 14 and 15, Tables 1 and 2)

The initial discovery of the rare blood group antigen, Cl^a (Caldwell), has been reported and its basic serology described/

described by Wallace and Izatt (1963), in a paper of which a reprint is included in this thesis. However, the present report is the first detailed description of the family linkage studies which led to the conclusion that the Cl and MNS loci are closely linked.

Throughout the investigation no difficulty was experienced in the detection of Cl (a+) individuals. To group the red cells a potent saline-agglutinating anti-Cl^a from a group AB donor was used in tube tests at $+4^oC$, and the results read microscopically.

In family Cal, the Caldwell family itself, it is unfortunate that no trace could be found of the proposítus' father and his relations. Several cousins on his mother's side of the family were grouped, but none were Cl(a+).

The family Gil were of Northern Irish (Ulster) extraction 6 generations ago, though the 4 more recent generations have lived in the Glasgow area. Examination of the pedigree (figs. 15a, b and c) shows that it must have been II 17 who introduced Cl^a into the family.

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The Cl^a(Caldwell) Antigen : a New and Rare Human Blood Group Antigen related to the *MNSs* System

Two unrelated families have been found to demonstrate the inheritance of a new and rare red cell antigen, the specificity of which appears to differ from that of all other antigens so far described. It is proposed that the new antigen be named Cl^a(Caldwell). The close genetical linkage of *Cl^a* to the *MNSs* system has been established. In the two families here reported the coupling of *Cl^a* is with *Ms* throughout.

The propositus, Mr. Caldwell, had donated blood on six occasions, each time being grouped as O. On testing his seventh donation it was found that his red cells were weakly agglutinated by the anti-B grouping serum in routine use. Caldwell's cells were not polyagglutinable, nor were they agglutinated by any of a battery of high-titre anti-B sera known to be potent in detecting an 'acquired' B antigen[1], nor by a panel of high titre anti-A + B (group O) sera.

Initially we tested 11,000 random donors of all ABO groups in the West of Scotland, but no other Cl(a+) was detected. However, by chance, a second example of the Cl^a antigen was encountered in a cord blood specimen. The cells of Baby Gil. were agglutinated by the routine anti-B grouping serum, but not by an anti-A + B (group O) serum. The infant was in fact group O and Cl(a+). It was established by cross-absorption and elution tests that the Caldwell and Gil. antigens were identical.

Evidence from two generations of the Caldwell family and from four generations of the Gil. family indicates that the Cl^a antigen is the regular expression of the heterozygous state of an autosomal allele. The Gil. *Cl^a* can by deduction be traced back for 6 generations to an Irish woman born in Ulster about 1830. She must have transmitted her *Cl^a* to the child of each of her two marriages, so that to-day 27 of her living descendants are known to be Cl(a+). As there is not complete linkage of *Cl^a* with the *ABO*, *Rh*, *P*, *Kell*, *Duffy* or *Secretor* loci, it can reasonably be taken that the new antigen is not controlled by any of them. However, when the Gil. family data are analysed with respect to *MNSs* and *Cl^a* it becomes apparent that there are no certain recombinants and 12 certain non-recombinants between *Ms* and *Cl^a*. That such a finding is due to chance has a probability of 1 in 2^{12}, that is, 1 in 4,000. In addition, the existence

of a further 30 almost certain non-recombinants confirms the closeness of this observed linkage. In the Gil. family the absence of a recombinant makes it impossible for us to decide whether *Cl*^{a} is part of, or linked to, the *MNSs* system. Cl^a must certainly now be considered as yet another of the rare antigens to be associated with the *MNSs* system in some manner.

Dr. T. E. Cleghorn has confirmed our findings or shown independently that the Cl^a antigen is not serologically identical with the following antigens which are known to belong to the MNSs complex—Hu, He (ref. 2), Mi^a, Vw (ref. 3), Mu(Murrell) (ref. 4), St^a(Stones), Ri^a(Ridley) (ref. 5), Vr (ref. 6), Mt^a (ref. 7) and Mg (ref. 8). The antigen does not appear to be similar to Mg; for example, there are no unexpected dosage effects observable in comparative titrations of Cl(a+) cells against anti-M, -N, -S, or -s sera. However, we have not yet encountered NN Cl(a+) or SS Cl(a+) bloods, and hence have not been able to test them for dosage. Such groupings would have been immediately indicative of recombination in the Gil. family.

Tests (again largely performed by Dr. T. E. Cleghorn) have also excluded identity of the Cl^a antigen with other rare or "private" antigens—C^w, C^x, E^w, V, VS, Bi, Be^a, Bp^a(Bishop) (ref. 9), Bu^a(Boisvert) (ref. 10), By, Donna, Good, Ho, Kp^a, Levay, P^k, Radin-Fleming (ref. 11), Stobo (ref. 12), Sw^a, Tr^a(Traversu) (ref. 9), Wb (ref. 13), Weil, Wr^a, Chr^a, Yahuda (ref. 9), Pritchard (ref. 9), Evans (ref. 14), Hunt (ref. 15), Kennedy (ref. 16) and Go^a (Gonzalez) (ref. 17). Three adult Cl(a+) persons have given normal adult I reactions, while 3 strong anti-Cl^a sera have contained no appreciable anti-i. Cl(a+) cells gave normal positive reactions with anti-Vel, -Ge, -U, -H, -Tj^a, with sera from 'Bombay' and D--/D-- persons, with potato lectin and with human 'D-like' antibody (ref. 18).

Though the Cl^a antigen is, at least in Baby Gil., well developed at birth, there is no evidence of it having been the cause of hæmolytic disease of the new-born in these two families under investigation. The 5 Cl(a−) mothers of Cl(a+) children have no detectable anti-Cl^a in their sera. Seventeen examples of saline-agglutinating anti-Cl^a were recognized in a series of 4,083 random donor sera of all ABO groups, that is, an incidence of 1 in 240 (0·42 per cent). Dr. T. E. Cleghorn found 7 examples of anti-Cl^a in 1,243 random South London donors.

Our anti-Cl^a sera have been apparently of natural origin. All had their optimal temperature of reaction at 4° C or at 12° C, none reacting at 37° C. In keeping with the findings of others[19] regarding the action of enzymes on antigen–antibody reactions within the *MNSs* system, the presence of bromelin, ficin, papain or trypsin was found to inhibit the Cl^a–anti-Cl^a reaction.

Finally, it is interesting to note that at an early stage of the investigation Cl(a+) cells were found positive with a South London anti-B serum, 'Easter', which Dr. I. Dunsford had shown to react with a Sheffield group O donor. Subsequent cross-absorption tests demonstrated that 'Easter' serum contains anti-Cl^a in addition to the antibody against the cells of the Sheffield donor.

We thank Dr. J. H. Renwick, Genetics Department, University of Glasgow, for collecting numerous blood samples for us, and for his guidance with the linkage studies. We also thank Dr. T. E. Cleghorn, South London Blood Transfusion Service, for performing many of the tests involving rare antigens and antibodies, and Dr. R. Sanger, Dr. I. Dunsford, Dr. M. C. Huth, Dr. M. Metaxas and Miss van der Hart for their co-operation.

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SCORING of BLOOD, SALIVA and SERUM GROUP LOCI

The following blood, saliva and serum groups have been established in the past (Race and Sanger, 1962) as showing regular autosomal inheritance : ABO, MNSs, P, Rhesus, Lutheran, Kell, Lewis, Duffy, Kidd, saliva ABH Secretor status and the serum Gm (Gamma-globulin) groups.

Whenever possible 20 ml. of venous blood were taken by Dr. J.H. Renwick from affected members and from their parents, sibs, spouses and children, 16 ml. being retained as clotted blood and 4 ml. being mixed with 1 ml. of sterile anti-coagulant (A.C.D.) solution containing 2% Sodium Acid Citrate and 3% Glucose, with 1 part in 10,000 of Thiomersal (Sodium ethyl mercuri-thiosalicylate) added to keep bacterial contamination to a minimum. This concentration of Thiomersal had been observed to have no effect on subsequent grouping tests of either fresh or stored cells.

Plasma and red cells from the citrated specimens were used in the red cell grouping tests, and serum from the clotted specimens in the serum typing tests. Surplus citrated red cells were stored for reference purposes at -20°C in an equal volume of a buffered Citrate-Glycerol mixture of pH 7.1. Excess serum was stored frozen at -20°C.

For some patients the grouping tests had to be performed/

performed on very small volumes of blood taken from finger-pricks into the anti-coagulant solution in small tubes.

Red Cell Grouping Tests

Standard serological techniques appropriate to the test antisera with regard to the suspending medium of the red cells and the optimum time and temperature of reaction of the antigen-antibody mixture were employed, as summarised in tables 3a and 3b.

Auto-agglutination control tests were included to confirm that a person's plasma did not agglutinate his own red cells in Saline Tube tests at room temperature (R.T.) or at 37^{o}C followed by Indirect Antiglobulin tests (I.A.G.T.), or in Enzyme Tube tests at 37^{o}C. Positive findings in these tests would have indicated that the red cell grouping results were probably false, and should be discarded.

Control tests of bloods of known positive and negative type were always grouped in parallel with specimens of the family material, in order to control the potency and specificity of the antisera and techniques beind used.

Saliva ABH Secretor Status

All specimens of saliva were boiled when fresh for 10 minutes in a water-bath, centrifuged and the clear supernatant fluid tested for the presence of water soluble ABH blood group substances by means of adequately controlled single/

single tube inhibition tests with suitably diluted anti-A, anti-B and anti-H sera (Race and Sanger, 1962). The anti-H was an extract prepared from Gorse (Ulex europaeus) seeds. Excess saliva was stored at -20°C.

There is a complex relationship between the red cell Lewis groups and the saliva ABH Secretor status (Race and Sanger, 1962). In practical terms it reduces to the fact that Le(a+) persons are ABH Non-secretors, while Le(a-) persons are usually, but not invariably, ABH Secretors. Each red cell Le^a result was, therefore, compared with its corresponding saliva ABH Secretor status, which was accepted without further investigation unless the cells were Le (a-) and the saliva apparently ABH Non-secretor. In such exceptional circumstances confirmatory tests were carried out by comparative titrations rather than by single tube tests.

Serum Grouping Tests

Gm Groups

The complexities of the Gm and Inv groups, serum gamma-globulin groups, have been steadily revealed since the original discovery by Grubb (1956) of the Gm^a factor and of its hereditary nature (Grubb and Laurell, 1956). Today there is knowledge of other factors of which the inheritance is apparently controlled from the Gm locus --- Gm^x (Harboe and Lundevall, 1959), Gm^b (Harboe, 1959a), Gm^r (Brandtzaeg, Fudenberg/

Fudenberg and Mohr, 1961), Gm^e (Roparts, Rivat and Rousseau, 1962) and Gm^c, formerly Gm-like, (Steinberg and Wilson, 1963).

It was possible in the present investigation to recognise technically the products of the $\underline{Gm}^a$, $\underline{Gm}^{ax}$ and $\underline{Gm}^b$ alleles.

From birth to the age of 8 - 12 months a child's Gm status is dependent on the state of his gamma-globulin development. The Gm group at birth is of maternal origin having crossed the placenta, and is only later superceded by the child's true hereditary Gm group (Linnet-Jepson, Galatius-Jensen and Hauge, 1958). Consequently the Gm groups of children under the age of 1 year are best omitted from genetical linkage studies.

The Inv system is genetically independent of Gm (Roparts, 1963), but as no anti-Inv sera were found by me, it could not be studied.

Gm Grouping Tests

Gm Grouping Tests

Search for my own anti-Gm reagents involved examination of rheumatoid arthritic sera for anti-Gm and anti-Inv specificities and the testing of a battery of anti-Rhesus sera for their ability to coat Rhesus-D(+) cells with specific Gm or Inv factors. To varying extents, over 40 incomplete anti-Rhesus sera provided by Dr. J. Wallace were examined,/

examined, but it was soon obvious that immediate attention should be concentrated on only 7 of them.

Sera from 158 rheumatoid arthritic patients were screened at a dilution of 1/10 with red cells coated as follows :

Gm^a	coating from serum 1386	sent by Dr. S.D. Lawler
Gm^b	" " " 2269	
Gm^b	" " " Ivan	sent by Dr. A.G. Steinberg
Gm^x, Inv^b	" " " Ham	
Inv^a	" " " Roehm	
?	" " " Dunc, Gall, How, Lai, McE, Som and Sha	sent by Dr. J. Wallace.

None of the rheumatoid sera reacted with the Gm^b coated cells, but 27 of them were tested further because of reactions to one or more of the other coated cells. Two-dimensional titrations with known Gm (a+x+), Gm(a+x-) and Gm (a-) sera, as recommended by Harboe (1959 b), revealed that they included 9 anti-Gm^a and 1 anti-Gm^x sufficiently potent to be used in Gm typing tests.

Dr. G. Roparts kindly confirmed that the complexes Ragg 147/Dunc, Ragg 144/Dunc and Ragg 144/Gall detected the Gm^a factor, while Ragg 97/Gall detected Gm^x. He also provided a comprehensive series of 40 sera of varying Gm and Inv type to serve as controls. Dr. A.G. Steinberg supplied antisera/

antisera for the complexes Bomb/Ivan and Taylor/Ham, together with instructions for their use.

Details of the complexes used to Gm-type the family material are summarised in table 4. The red cells from only one group O ccDEE donor were used throughout, the donor being bled (as before) into A.C.D. (acid citrate-dextrose) solution and the cells stored at +4°C for a maximum of 6 days. There were sufficient reagents to perform the Gm^a typing tests in triplicate with different complexes, but insufficient anti-Gm^b and anti-Gm^x.

In practice, Gm typing of the family material involved determining whether or not each serum inhibited agglutination by anti-Gm serum of red cells with appropriate Gm coating — presence of Gm substance caused inhibition of the reaction to give a negative reading, while absence of the substance from a non-inhibitory serum allowed agglutination to take place. Slide tests consisted of mixtures of 1 drop of diluted anti-Gm + 1 drop of diluted serum to be typed + 1 drop of Gm coated cells set up at room temperature for the times indicated (table 4).

Parallel saline control tests, in which 1 drop of saline was substituted for the anti-Gm serum, were also necessary to detect those family material sera containing an agglutinator for Gm-coated cells of natural or rheumatoid origin./

Such sera had to be typed, as recommended by Harboe (1960), by a combination of techniques e.g. the agglutinator was first destroyed by heat at 63°C for 15 minutes before the serum could be typed in the normal manner, or, alternatively, advantage was taken in carefully controlled and timed tests of the greater speed of reaction of a potent anti-Gm serum compared with that of the agglutinator.

The results of the blood, saliva and serum grouping tests on members of the Cal and Gil families were recorded in detail in tables 1 and 2, with the MNSs phenotypes noted on the pedigrees (figs. 14 and 15).

For the families Sau 1, 2 and 3 the ABO blood groups were noted on the appropriate pedigrees (figs. 2, 3 and 4).

The relevant Lutheran blood group and saliva ABH Secretor status results for sibships Bak, Bla, For, H-p H, McG, Oak and Sau 1 were recorded on figs. 5 - 13 inclusive.

PHENOTYPE FREQUENCIES of the BLOOD, SALIVA and SERUM GROUPS

The phenotype frequencies of the blood, saliva and serum groups have been calculated from a series of over 200 unrelated individuals, who married into all the families currently being investigated for genetical linkage relationship by Dr. J.H. Renwick and myself. Comparisons of these figures with those already published for the British population have proved of interest.

Pearson's χ^2 test was used to detect the significance of deviations from expected phenotype frequencies on a postulated null hypothesis that two series under comparison both represented random samples from the same population, and that any deviation between them in phenotypic proportions was due to chance alone. The formula used was

$$\chi^2 = \sum \frac{(a - nm)^2}{nm}$$, where a = number observed in a class,

m = proportion expected in a clas

n = total tested,

$\sum$ = summation over all classes,

(Mather, 1957).

Where it was necessary because of the small numbers involved to apply Yates' correction for continuity, the formula became

$$\text{corrected } \chi^2 = \sum \frac{(|a - nm| - \frac{1}{2})^2}{nm}$$

The/

The significance level, P, corresponding to the observed value of χ^2 with the given number of degrees of freedom, d.f., was taken from tables showing the distribution of χ^2. Mr. M.J. Davies of the Statistics Department kindly advised me on the topic of the relevant number of degrees of freedom, taking into consideration the number of phenotypic classes whose frequency could be assigned arbitrarily when calculating the expected numbers.

Racial heterogeneity in Britain was known to be reflected in the distribution of the ABO blood groups as an increasing incidence of the O and a decreasing incidence of the A allele, as one travels from the south of England to the north of Scotland (Mourant, 1954). It was not unreasonable to consider that a similar phenomenon might exist with the other blood group systems. The random series of persons who had married into the families was therefore divided into those of Scottish and into those of English origin. The analysis of the phenotype distribution by χ^2 tests therefore fell into two categories :

1) Between Series χ^2 tests for the concordance of each new national series with figures already published for the country.

2) Between Nations χ^2 tests for the recognition of statistically significant differences between the phenotype/

phenotype frequencies of the blood groups in Scotland and England.

1) Between Series X^2 Tests

Table 5 The ABO Blood Groups

The following X^2 values indicate there was no significant difference from published series (Mourant, Kopec and Domaniewska-Sobczak, 1958) in the distribution of the ABO groups in either the new Scottish or the new English series. The bulk of the Scottish families came from the Glasgow area, and the English families mainly from the Birmingham area. For both sets of X^2 tests the expectation of numbers in the AB class was less than 5, so this class was pooled with that of group B, the next smallest class.

New Scots/published Scots -- $X^2=0.16$, for 2 d.f., $0.95>P>0.90$

New English/published English -- $X^2=4.52$, for 2 d.f., $0.2>P>0.1$

Table 6 The MNSs Blood Groups

There was no significant difference in MNSs phenotype distributions between the new and published Scottish series (Mourant, 1954), or between the new and published English series (Cleghorn, 1960).

After combining the smallest classes of MsMs and MNS,

New Scots/published Scots -- $X^2 = 2.14$, for 4 d.f., $P \div 0.7$.

After combining the smallest classes of MSNS, NSNS and/

and NSNs,

New English/published English $\chi^2=6.00$, for 6 d.f., $0.5>P>0.3$.

Table 7 The P Blood Groups

The distributions of the P_1 phenotypes in the new Scottish and the new English series were not significantly different from those in published series (Mourant, 1954).

New Scots/published Scots — $\chi^2=2.64$, for 1 d.f., $0.2>P>0.1$

New English/published English — $\chi^2=0.38$, for 1 d.f., $0.7>P>0.5$

Table 8 The Rhesus Blood Groups

There was no significant difference in Rhesus phenotype distributions between the new and published Scottish series (Cameron and Izatt, 1962), or between the new and published English series (Race, Mourant, Lawler and Sanger, 1948).

All D^u positive bloods were scored as Rhesus -D(+), and classified according to their Cc and Ee status.

After combining the 4 smallest classes (ccDE, ccDee, Ccddee and ccddEe),

New Scots/published Scots — $\chi^2 = 1.64$, for 4 d.f., $P \doteqdot 0.8$

After combining the smallest classes (C^wCDEE, C^wcDee, C^wcDEe, ccDEE, ccDee, Ccddee, ccddEe and CCDEe),

New/

New English/published English $\chi^2=1.89$, for 5 d.f., $0.9>P>0.8$

Table 9. The Lutheran Blood Groups

There was no significant difference in Lutheran phenotype distributions between the new and published Scottish series (Mourant, 1954), or between the new and published English series (Race and Sanger, 1962).

New Scots/published Scots — corrected $\chi^2 = 0.51$, for 1 d.f., $0.5>P>0.3$.

New English/published English — $\chi^2 = 1.08$, for 1 d.f., $P \doteq 0.3$

Table 10 The Kell Blood Groups

There was no significant difference in Kell phenotype distributions between the new and published Scottish series (Mourant, 1954), or between the new and published English series (Race and Sanger, 1962).

New Scots/published Scots — $\chi^2 = 0.65$, for 1 d.f., $0.5>P>0.3$

New English/published English — corrected $\chi^2 = 1.69$, for 1 d.f., $0.2>P>0.1$

Table 11 The Rh(D) Blood Groups

Completion of comparative phenotype distributions was here complicated by the initial lack and subsequent scarcity/

scarcity of anti-Fy^b serum preventing the Fy^b testing of every Fy(a+) blood. The new Scottish series was composed of 23 Fy(a+ b-), 37 Fy(a+ b+), 38 Fy(a- b+) and 7 Fy(a+) which were not tested for the Fy^b antigen. These last 7 bloods were divided between the classes of Fy(a+ b-) and Fy(a+ b+) in proportions of 23/60 = 2.68 and 37/60 = 4.32 respectively, for there was no reason to suppose the distribution of Fy^b in them to be different from that in the other 60 Fy(a+) bloods --- failure to group them for Fy^b was solely due to lack of anti-Fy^b serum and to no other cause. The figures for the Duffy phenotype distributions in the new Scottish series thus became as shown in table 11.

Similarly, in the new English series 18 Fy(a+ b-), 52 Fy(a+ b+), 32 Fy(a- b+) and 4 Fy(a+) became redistributed as shown in table 11, by dividing the 4 Fy(a+) in the proportions of 18/70 = 1.03 and 52/70 = 2.97.

No significant difference was detected in Duffy phenotype distributions between the new Scottish series and an earlier Scottish series of random blood donors (Izatt, unpublished observations, 1953), or between the new and published English series (Race and Sanger, 1962).

New Scots/ donor Scots -- $\chi^2=0.84$, for 1 d.f., $0.5 > P > 0.3$,

New English/published English -- $\chi^2=0.61$, for 2 d.f.,

$0.8 > P > 0.7$.

The Kidd Blood Groups

Using the available anti-Jk sera many doubtful results were obtained. All too often a result was neither a clear-cut negative nor a definite positive of the same strength as the positive control. Accordingly it was decided to omit the Jk locus from the genetical linkage studies.

Table 12a — ABH Secretor Status

There was no significant difference in ABH Secretor phenotype frequencies between the new and published Scottish series (Wallace, Peebles Brown, Cook and Melrose, 1958), or between the new and published English series (Race and Sanger, 1962).

New Scots/published Scots — $\chi^2 = 2.57$, for 1 d.f., $0.2 > P > 0.$

New English/published English — $\chi^2 = 0.01$, for 1 d.f., $P \doteq 0.9$

Table 12b — Lewis (Le^a) Blood Groups

There was no significant difference in Le^a phenotype frequencies between the new and published Scottish series (Mourant, 1954), or between the new and published English series (Mourant, 1954).

New Scots/published Scots — $\chi^2 = 1.28$, for 1 d.f., $0.3 > P > 0.2$,

New English/published English — $\chi^2 = 0.04$, for 1 d.f., $0.9 > P > 0.8$,

Table 13a and c/

Tables 13a and c — The Gm Serum Groups

There were no known published reports of earlier work by others on the frequency of the Gm serum groups in the Scottish population. D. J. Wallace kindly supplied a random series of sera from 150 blood donors to the West of Scotland Regional Blood Transfusion Service for me to Gm^a type using the same reagents as typed the family material, from which the new Scottish and the new English series were abstracted. It will be seen that there was no significant variation in the Gm^a phenotype frequency between the two Scottish series (table 13a).

New Scottish/Donor Scottish — $\chi^2 = 0.007$, for 1 d.f.

$0.95 > P > 0.90$.

The frequency of the Gm^a phenotype was not significantly different in the new English series from that in the published English series, for which Dr. S.D. Lawler reported the allele frequencies (Lawler, 1961) and about which she supplied further information in a personal communication (1963) (table 13a).

New English/published English — $\chi^2 = 0.07$, for 1 d.f., $0.8 > P > 0.7$.

Likewise, there was no significant difference in Gm(Gm^a, Gm^b and Gm^{ax}) frequencies between the new English and the published English series (Lawler, 1961) (table 13c).

New English/published English — $\chi^2 = 1.70$, for 3 d.f., $0.7 > P > 0.5$.

None/

None of these χ^2 tests concerning the ABO, MNS, P, Rhesus, Lutheran, Kell, Duffy, Lewis, ABH Secretor and Gm groups of the new Scottish or the new English series of unrelated persons reached a significance level of 1/10. That is to say, the observed, or greater, differences in the blood group phenotype frequencies between the two Scottish or between the two English series could be expected to occur due to chance with one out of ten sets of samples. It is conventional in biological statistics to consider that the figures under comparison in a χ^2 test are not deviating significantly from each other due to influences other than chance till the significance level reaches 1/20.

Both new series of Scottish and English samples could therefore be considered as representative of the country of their origin. This finding was reassuring with regard to the accuracy of the chosen blood grouping techniques and reagents for the genetical linkage studies.

2) Between Nations χ^2 Tests

The object of these comparisons was to discover which, if any, of the blood group systems in addition to the ABO, showed a statistically significant racial heterogeneity of phenotype/

phenotype frequencies between the Scottish and English populations. Homogeneity between them having been established the corresponding new and published series were added together and the combined totals for the Scottish data compared in χ^2 tests with the combined totals for the English data.

For the following blood group systems there was no significant difference apparent in the phenotype frequencies in Scotland and England:-

MNSs -- Scottish data/English data - χ^2=6.53, for 5 d.f., 0.3 > P > 0.2, (table 6),

P -- Scottish data/English data - χ^2=0.001, for 1 d.f., 0.98 > P > 0.95, (table 7),

Kell -- Scottish data/English data - χ^2=0.31, for 1 d.f., 0.7 > P > 0.5, (table 10),

Duffy-- Scottish data/English data - χ^2=0.03, for 1 d.f., 0.9 > P > 0.8, (table 11).

On the other hand, the evidence was overwhelming for the known heterogeneity in the Scottish and English data on the ABO blood groups :-

ABO -- Scottish data/English data - χ^2= 31.4, for 3 d.f., P < 0.001, (table 5).

Considering the Rhesus system, after combining the classes of CcddEe, ccddEe and CCDDe (table 8),

Scottish/

Scottish data/English data - χ^2=15.77, for 7 d.f. $0.05 > P > 0.025$. This observed difference, significant at a level of 1/40, in Rhesus phenotype frequencies could well be the expression of heterogeneity between the two populations, but it could possibly be due to random sampling effects acting on the small numbers of the rare Rhesus phenotypes. It is informative to note that these three smallest classes (ddCee, ccddEe and ccddEE) contribute 10.13 towards the total χ^2 of 15.77.

The lowered incidence of Lu(a+), significant at a level of 1/40, in the Scottish series could indicate a genuinely lower frequency of the Lu^2 allele in Scotland. Lutheran — Scottish data/English data - χ^2 = 4.93, for 1 d.f., $P \doteq 0.025$, (table 9).

Similarly, the Scottish and English data appear to show heterogeneity, which is significant at the level of 1/50, for the distribution of the ABH Secretor phenotypes, (table 12a) ABH Sec. — Scottish data/English data - χ^2 = 5.22, for 1 d.f., $0.025 > P > 0.02$.

Lewis (Le^a) phenotypes reflect mainly the genotype at the ABH Secretor locus. Thus the variation in the Le(a+) frequency in the Scottish and English series was almost certainly a consequence of the variation in the frequency of the ABH Secretor alleles. Comparing tables 12a and 12b it was noticeable that the increased number of ABH Non-secretors was paralleled by an increase in the numbers of Le(a+). As/

As was to be expected from the result of the χ^2 test comparing the Scottish and English data for heterogeneity of ABH Secretor phenotype frequencies, a corresponding χ^2 test comparing the Le(a+) distributions was statistically significant,

Lewis --- Scottish data/English data - $\chi^2=15.7$, for 1 d.f., $P<0.001$.

With regard to the Gm serum groups, it is suggested that the difference in the incidence of Gm(a+) in the Scottish and English data, though not quite significant at the arbitrarily selected level of significance of 1/20, is sufficiently large to be a reflection of a real difference in Gm frequencies in the two countries (table 13a),

Gm --- Scottish data/English data - $\chi^2=3.09$, for 1 d.f., $0.1>P>0.0$

Studies by many workers have confirmed that the frequency of the Gm^a factor increases with latitude in Europe, though the reason for this is as yet unknown. Table 13b was prepared from data summarised by Roparts, Rivat, Rousseau, Baitsch and van Loghem (1963). The relative positions, if confirmed, of the Scottish and English samples in the European series are thus of great interest.

Conclusions regarding the Phenotype Frequencies of the Blood, Saliva and Serum Groups

It was suggested that the racial heterogeneity between the Scottish and the English populations was manifest not only in different distributions of the ABO blood groups, but also in differing frequencies for the Lutheran, ABH Secretor, Gm and, perhaps, the Rhesus alleles. This conclusio if confirmed by future studies which are planned, is also directly relevant to those genetical linkage calculations of which the relative likelihoods of alternative blood group genotypes are integral parts. In future Scottish allele frequencies should ideally be used in linkage studies on families of Scottish origin.

ALLELE FREQUENCIES

Three methods of estimating allele frequencies will be described, and each illustrated by worked examples. Knowledge of the allele frequencies for each locus is essential, as a means of weighting alternative genotypes of untested or deceased parents, in the calculations of relevant likelihood/

likelihood ratios in genetical linkage studies.

1) It was possible by direct allele counting to obtain the maximum likelihood estimate of the allele frequencies in a two allele system, when the products of both alleles were detectable by observation of the phenotype. For example, in the new Scottish series of MNSs phenotypes (table 6):

allele frequency of M =(8 +5 +34 +19 +18 +25)/208 = 109/208
= 0.5240 = p,

" " " N = 1 - p = 1 - 0.5240 = 0.4760 = q.

Assuming the population to be in equilibrium under a system of random mating with Mendelian inheritance, these allele frequencies gave the expected numbers of the three genotypes in the new Scottish series of 104 persons as MM $= p^2 \times 104 = 28.56$, MN $= 2pq \times 104 = 51.88$ and NN $= q^2 \times 104 = 23.56$. A χ^2 test comparing these expectations with the observed numbers of MM = 30, MN = 49 and NN = 25 had a value, $\chi^2 = 0.32$, which for 1 d.f. had a significance level of $0.7 > P > 0.5$. Deviations due to chance as large as that observed would, therefore, be expected to occur in 5 - 7 series out of every 10, on the null hypothesis of conformation to random mating.

2) Maximum likelihood estimates of the Gm^a, Gm^{ax} and Gm^b allele frequencies in the new Scottish and new English series were/

were calculated from the observed phenotype frequencies by using Smith's (1957) counting method (table 13c, d). A direct count of the frequencies of the alleles $\underline{Gm}^{a}$ and $\underline{Gm}^{ax}$ was not possible, for no serological distinction could be made between the genotypes $\underline{Gm}^{a}\underline{Gm}^{ax}$ and $\underline{Gm}^{ax}\underline{Gm}^{ax}$, both being phenotypically Gm(a+ x+). However, the frequency of $\underline{Gm}^{b}$ could be calculated by direct allele counting to make the combined frequency of $\underline{Gm}^{a}$ + $\underline{Gm}^{ax}$ = 1 - (frequency of $\underline{Gm}^{b}$). The relative proportion of $\underline{Gm}^{a}/\underline{Gm}^{ax}$ in the English series of Lawler (1964) was then taken as a basis for the first rough estimation of the frequencies of $\underline{Gm}^{a}$ and $\underline{Gm}^{ax}$ in the series under discussion.

By applying these rough estimates it was possible to apportion Gm(a+ x+) persons between the classes of $\underline{Gm}^{a}\underline{Gm}^{ax}$ and $\underline{Gm}^{ax}\underline{Gm}^{ax}$, and to calculate the value of the ratio p(1) = no. of persons $\underline{Gm}^{a}\underline{Gm}^{ax}$/ no. of persons $\underline{Gm}^{ax}\underline{Gm}^{ax}$. Direct counting of the no. of each allele present/total no. of alleles present now yielded the first improved estimates of the allele frequencies. These estimates in their turn were used as provisional estimates to find the second improved estimates, together with an improved value for p = p(2).

Such an iterative process could be continued till an improved estimate of the allele frequencies was equal to its/

its provisional value to a sufficient degree of accuracy. In practice, after the third improved estimates were known, the application of acceleration formulae, as suggested by Smith (1957), speeded up calculations. The first acceleration formula established the next provisional value $y_o(est)$ of the ratio p.

$$y_o(est) = \frac{(y_1 x_2 - y_2 x_1)}{x_2 - x_1}$$, where $y_1 = p(1)$, $y_2 = p(2)$, $x_1 = p(1) - p(2)$, $x_2 = p(2) - p(3)$

A fourth set of improved estimates and the next ratio value, p(4), were obtained from this value of $y_o(est)$. Lastly the use of a second acceleration formula led to the final estimates of the allele frequencies of $\underline{Gm}^a$ and $\underline{Gm}^{ax}$.

$$y_o(final) = - \frac{y_1 x_2 x_3 (x_3 - x_2) + y_2 x_3 x_1 (x_1 - x_3) + y_3 x_1 x_2 (x_2 - x_1)}{(x_3 - x_2)(x_1 - x_3)(x_2 - x_1)}$$

in which

$y_1 = p(1)$, $y_2 = p(2)$, $y_3 = y_o(est)$, $x_1 = p(1) - p(2)$, $x_2 = p(2) - p(3)$, $x_3 = y_o(est) - p(4)$.

The estimated Gm allele frequencies (table 13d) for the new Scottish and new English series of unrelated person were :-

New Scottish series -- Gm^a(0.1855), Gm^b(0.6683) and Gm^{ax}(0.1462

New English series -- Gm^a(0.2213), Gm^b(0.6048) and Gm^{ax}(0.1739

Lawler (1961) found allele frequencies of Gm^a(0.270), Gm^b (0.615) and Gm^{ax}(0.115) in an English series of 100 persons.

Neither the new Scottish nor the new English series show significant deviation from random mating expectations (table 13e).

New Scottish series -- χ^2=0.31, for 1 d.f., $0.7 > P > 0.5$,

New English series -- χ^2=2.05, for 2 d.f., $0.5 > P > 0.3$.

3) In a two allele system (p and q), for which the product of only one allele, p, is detectable in the phenotype, the allele frequencies were calculated in the standard manner. For example, in the ABH Secretor status results of the new Scottish series (table 12a) both SeSe and Sese persons, by secreting water-soluble ABH substances in the saliva, were phenotypically Secretors, while sese persons are Non-secretors.

Frequency of sese (Non-secretor phenotype)= q^2 = 0.3398,

" " se allele = q = $\sqrt{0.3398}$ = 0.5829,

" " Se allele = p = 1 - q = 0.4171.

Similarly, in the new English series (table 12a) the frequency of the Se allele is 0.5275 with se being 0.4725, compared with figures of 0.5233 and 0.4767 for the published English series of Race and Sanger (1962).

SEGREGATION RATIOS

Genetical linkage analyses examine data for the independence of the segregation ratios of alleles at two loci. Therefore distortions of the primary ratio at either locus by influences such as incomplete penetrance of the factors or reduced viability of any class of progeny cause difficulties which demand a special approach (Mather, 1957). Fortunately, as will be shown, this was not necessary in the present investigation.

Nail-Patella syndrome and Ct^a(Caldwell) antigen

Both these rare conditions appear to be the regular expressions of autosomal alleles in the heterozygous state. In the pedigrees examined they have been regularly manifest in both sexes without skipping generations. It would appear that for both conditions all affected persons are heterozygotes. The extreme rarity of the conditions makes remote the possibility of there having been any marriages between affected persons. All matings have apparently been of a heterozygous affected x homozygous unaffected (a back-cross) from which we expect affected and unaffected children in the Mendelian ratio of 1 : 1.

The observed data were not inconsistent with this null hypothesis, as shown by the results of the following analysis :-

A/

A simple count was made of the observed numbers of affected and unaffected children in every sibship of the families, omitting the propositus (tables 14, 15). Each child for whom there was insufficient evidence for classification was shared equally between appropriate classes.

i) If it was not known which was the affected parent, the sharing was between the classes of Father Affected and Mother Affected.

ii) If the sex of a child was unknown, the sharing was between Males and Females.

iii) If classification with respect to the main condition was uncertain, the sharing was between Affected and Unaffected.

The expected numbers of males and females in each class was based on a Mendelian ratio of 1 affected : 1 unaffected, modified by a sex ratio at birth of 1.06 males to 1 female.

Nail-Patella syndrome --Total $\chi^2=6.42$, for 6 d.f., $0.5 > P > 0.3$,

Affected/Unaffected - $\chi^2=1.59$, for 1 d.f., $P \doteqdot 0.2$.

Gl^a(Caldwell) antigen --Total $\chi^2=0.80$, for 6 d.f., $P > 0.99$,

Affected/Unaffected $\chi^2=0.49$, for 1 d.f., $P \doteqdot 0.5$.

Blood, Saliva and Serum Groups

No special analysis was made of the segregation ratios/

ratios of these conditions. They have been sufficiently deeply studied in the past for it to be accepted that they show regular autosomal inheritance with complete penetrance, and, with three provisos, have segregation ratios as expected (Race and Sanger, 1962).

With the ABO blood group system there is selection in utero, different for the two sexes, against progeny whose ABO groups are incompatible with the mother's (Allan, 1955). This factor could, by virtue of the genetical linkage between the ABO and the Nail-Patella loci, influence the segregation ratio of the latter with respect to the two sexes.

There can be selection against Rhesus-D(+) children to cause miscarriage, stillbirth or haemolytic disease of the new born if a Rhesus-D(-) mother develops Rhesus antibodies in response to Rhesus incompatible pregnancies. All individuals comprising the family material were tested for the presence of an immune Rhesus antibody, but none showed such an antibody. In addition, no history was elicited from any of the mothers to indicate that she was sensitised to a blood group factor.

Apparently disturbed segregation ratios have been observed in families studied for the Jk blood group, using both anti-Jk^a and anti-Jk^b. As anti-Jk^b sera occur extremely rarely and are notoriously difficult to use technically,/

technically, it is not yet clear if the segregation ratios are truly disturbed, or if the effect is entirely due to misclassification. As already stated, in the present investigation it was decided to omit the Jk locus from the linkage studies, because the available antisera gave such unsatisfactory and often irreproducible results.

It was felt that, as the magnitude of these effects on the segregation ratios was slight, their secondary effects on linkage analyses could be ignored.

GENETICAL LINKAGE CALCULATIONS

The choice of suitable statistics for analysing data from human families for the presence of genetical linkages is more difficult than when dealing with organisms capable of being bred in the laboratory. Complications arise because of the small number of children in most families, uncertainty regarding parental genotypes (especially coupling phase), and the manner in which the family was first ascertained.

It is obvious from examination of the multiple generation pedigrees in the family material that much valuable information would be wasted were the results to be analysed by Penrose's Sib Pair technique, which is primarily for the testing of sibships of unspecified parentage for linkage (Penrose, 1935, 1953). Clearly material in pedigree form with many known parental groupings is more efficiently analysed by a method which takes into account this extra information.

One of the earliest procedures for the detection from two generation material of genetical linkage and the estimation of the recombination fraction, θ, between two loci in Man was that proposed by Bernstein in 1931. From it Fisher (1935), using the principles of maximum likelihood (Fisher, 1922), developed the statistics of u-scores, u being a function of $(1-\theta)$. Finney (1940) enlarged upon Fisher's/

Fisher's u-scores by utilising the extra information derived from the allele frequencies of test characters in the general population to determine the probability that the parents in a given cross were heterozygous. Previously all families lacking a child with recessive characteristics had to be rejected from a u-score analysis, for there was no way of knowing whether the parents were homozygous or heterozygous i.e. there was no way of knowing the probable mating type. These u-scores have the disadvantage that although efficient in the detection of linkage, they are less so in estimating the value of θ in linkages closer than 20% ($\theta < 0.2$). A more serious disadvantage is that there is no convenient method for combining data from families in which the coupling phase of the mating type is known with those in which it is not.

With many rare hereditary conditions the information for genetical linkage analysis may come from only one large ramifying pedigree, rather than from small two generation groups. For the efficient detection and estimation of linkage in large pedigrees a method was devised by Bell and Haldane (1937), developed further by Haldane and Smith (1947), by Morton (1955) and by Smith (1959). It was based on the theory that valid conclusions regarding the presence of linkage could be drawn from the likelihood of having actually observed/

observed the pedigree in the general population.

For the purposes of this thesis this "odds" approach to the problem of the detection of linkage and the estimation of the recombination fraction, θ, has been divided into 3 stages, each of which will be discussed and illustrated by appropriate calculations using the observed family material. The first two stages deal with the detection of linkage, and the third with the estimation of θ, if linkage has been shown to be present.

1. Obtaining a Likelihood /θ Curve
   a) Hand and computer calculation of lod scores.
   b) Lod scores from tables.
2. Probability of Linkage
   a) Derivation of the average likelihood from a likelihood/θ curve.
   b) Probability of linkage, $0 \leqslant \theta \leqslant 0.5$, between any pair of autosomal loci.
   c) Combination of probabilities of linkage relating to different pairs of loci.
   d) Probability of linkage closer than $\theta = 0.3$
3. Estimation of the Recombination Fraction, θ.
   a) Maximum likelihood estimate.
   b) Confidence limits of this estimate.

1./

1. Obtaining a Likelihood /θ Curve

Because of the greater ease of arithmetical manipulation, it was convenient to work with likelihood ratios in logarithmic form. By definition, a lod score, z (θ), is the logarithm to the base 10 of a likelihood ratio in which the likelihood of obtaining the family, F, (with its observed phenotypes) at a recombination fraction θ is compared with the likelihood if no linkage is present (when $\theta = 0.5$).

Lod score, $z(\theta) = \log_{10} \frac{P(F \mid \theta)}{P(F \mid 0.5)} = \log_{10} P(F \mid \theta) - \log_{10} P(F \mid 0.$

Likelihood ratio = antilog $_{10} z(\theta)$.

Hence at $\theta = 0.5$, the likelihood ratio = 1 and the lod = 0.

The combination of data from several families was a simple matter when lod scores were first calculated. Appropriate z (θ) scores were added and the antilog of the sum, $Z(\theta)$, gave the likelihood ratio for the combined data for that value of θ.

For example, to obtain the likelihood/θ curve for the data from the Sau 1, 2 and 3 families concerning linkage between the ABO and the Nail-Patella loci, a series of summed lod scores for θ in the range 0 to 0.5 was calculated, converted into likelihood ratios (antilods) by taking antilogs (table 18) and expressed graphically (fig. 16).

a)/

a) Hand and Computer Calculation of Lod Scores

By counting from inspection of the Sau 1 pedigree (fig. 2) the occurrence in the children of 31 instances of almost certain non-recombination between the A_1 and the Nail-Patella alleles, together with only 1 certain example of recombination, it was possible to estimate approximately the lod scores, as shown in table 16, on the basis that the likelihood of observing the family was $P(F|\theta) \propto \theta^1(1-\theta)^{31}$. These lod values compare reasonably with corresponding lods calculated by an electronic IBM 7094 computer, which extracted in this particular example only a small additional amount of information.

The computer was programmed to compute lod scores from large pedigrees of up to 9 generations using this same basic principle of calculating $P(F|\theta)$ (Renwick and Schulze, 1961). By incorporating information concerning relevant allele frequencies in the general population into calculations of the relative likelihoods of alternative genotypes of untested or deceased parents, the computer arrives at a much more exhaustive assessment of the family lod scores than is possible by hand calculation. It is also less liable to error and is much quicker.

Lod scores calculated by computer were used in the analyses of the Sau, Cal and Gil families, and were recorded as follows :

ABO/

ABO - Nail-Patella linkage — lods and antilods (table 18)
(Pedigrees Sen 1, 2 and 3) — likelihood/θ curve (fig. 16).

MNS - Cl(Caldwell) linkage — lods and antilods (table 19)
(Pedigrees Cal and Gil) — likelihood/θ curve (fig. 17),
— lod/θ curve (fig. 18).

MNSCl linkage to other blood group loci — lods and antilods (tables 20a,
(Pedigrees Cal and Gil) — likelihood/θ curves (figs. 19, 20).

It should be noted that in order to draw smooth likelihood/θ curves it was sometimes necessary to obtain intermediate antilod values via graphical interpolation from the appropriate lod/θ curve. For instance, in the preparation of the likelihood/θ curve for linkage between the MNS and Cl(Caldwell) loci (fig. 17) additional lod scores (marked with an asterisk * in table 19) were obtained by interpolation from the lod/θ graph (fig. 18), which had been drawn through points corresponding to the observed lod scores.

b) Lod Scores from Tables

Morton (1955) published in tabular form the lod scores for families of various mating types and size, together with/

with the applicable correction factors which have to be added, depending on the method of selection of the families. Morton's tables are useful in the analysis of two generation material consisting of parents and their children. Unfortunately extra information from the phenotypes of grandparents or grandchildren can only be incorporated easily if it leads to a precise specification of the genotypes of the parents or of their children. For example, the presence of a homozygous recessive grandparent indicates that the parent concerned must be heterozygous at least for that factor, and thus the coupling phase of the parental mating may be precisely defined.

Illustration of the use of lod tables

No family was selected and followed up solely for the purpose of further investigation into the known linkage between the Lutheran and the ABH Secretor loci. The finding of Lu(a-) persons in 9 sibships from families tested for other reasons was incidental, but advantage was taken of it to carry out the analysis summarised in table 17a.

Following Morton's precedent, the alleles Lu^a and Se in each parental mating were designated C or T according to the method of selection of the family, and the parental mating type and the phenotypes of the progeny expressed in terms of C and T. As each mating type had been assigned a number/

number by Morton, it became a simple matter to note this, and also the applicable z score. Consultation of the appropriate z score tables gave the lods when $\theta = 0.4$, 0.3, 0.2, 0.1 or 0.05. Lod scores for $\theta = 0$ were noted from an extension of the tables by Maynard-Smith, Penrose and Smith (1961). Depending on the method of selection of the family the lod scores were left uncorrected, or had added to them a suitable ascertainment correction (which was also obtainable from tables).

Ascertainment corrections, which were usually small, were necessary to counteract the bias introduced into the calculations when the families selected for the linkage study were not a random sample from the population. For instance, Sese x Sese matings, selected because of the presence of an Sese child, did not include those which by chance produced only SeSe or Sese children. If such selection had also occurred at the Lutheran locus, the succeeding calculations would have been biassed.

Family For VII 78 (fig. 8), being the double backcross $\frac{Sese Lu^a Lu^b}{}$ x $\frac{sese Lu^b Lu^b}{}$, corresponded to Morton's mating type 1 (GgTt x ggtt, Se = G, Lu^a = T) and was scored using z_1 scores.

z_1 /

$$z_1 = \log_{10} 2^{s-1} \left[\theta^{a+d}(1-\theta)^{b+c} + \theta^{b+c}(1-\theta)^{a+d} \right]$$, where

$s = a + b + c + d$, a = number of GT progeny, b = Gt, c = gT and d = gt.

This family was selected through the children for G(Se)(by the presence of a Non-Secretor (sese) child) and through the parents for T(Lu^a) by the mother being Lu(a+). This was equivalent to both characters being ascertained through the parents, so that no correction to the lod scores was required (Morton, 1955). There was no question of the selection for the Lutheran factor being influenced by the presence of the Lu(a-) child, VIII 71. Had both children in the sibship been Lu(a+) the family would still have been included in the study. The very rare anti-Lu^b serum would have been used in conjunction with the Lu^a tests to specify exactly the mother's genotype as Lu^aLu^a or Lu^aLu^b.

Similarly, both the single backcross families Sau 1 IV 6 (fig. 12) and Sau 1 IV 14 (fig. 13) of mating type 9 (GgTt x Ggtt, Se = G, Lu^a = T) were scored using uncorrected z_2 scores.

$$z_2 = \log_{10} \frac{2^{s-1}}{3^{a+c}} \left[(2-\theta)^a \theta^b (1+\theta)^c (1-\theta)^d + (1+\theta)^a (1-\theta)^b (2-\theta)^c \theta^d \right],$$

where $s = a + b + c + d$, a = GT, b = gT, c = Gt and d = gt.

Morton's/

Morton's tables do not include Z_2 scores for more than 5 children, so the lod scores for Saul IV 6 with 6 children had to be calculated by hand from the above formula.

Selection of families For VI 63 (fig.7) and N-p II (fig.9) was through Non-secretor children for G(Se) and an Lu(a+) parent for T(Lu^a), so that no ascertainment correction of lod scores was required. In both these families only one parent was tested, but examination of the pedigrees showed that the parental mating types were most probably 1 (GgTt x ggtt) or 9 (GgTt x Ggtt). It was highly improbable, considering the complete pedigrees of which these families are part, together with the rarity of the Lu^a allele, that the parental matings were the rare Lu^aLu^b x Lu^aLu^b (Tt x Tt)matings. Consequently, as recommended by Morton, the appropriate lod scores were compounded from the sum of the lod scores of possible mating types suitably adjusted, using population allele frequencies, for the prior likelihood of each possible mating type. Assuming random mating in the population, mating types 1 and 9 occur with relative frequency of g : 2g (frequency of se allele : 2 x frequency of Se allele). A further factor influencing the prior likelihood of each possible mating type was derived from the likelihood of having obtained the observed distribution/

distribution of children's phenotypes on the basis of independent Mendelian inheritance. An abstract in table 17b of the calculations for For VI 63 (fig. 7) demonstrates the application in practice of the above correction factors to the lod score calculations.

Scrutiny of the full Oak family pedigree led to the suspicion that the deceased III 12, as well as his wife III 13, could have been Lu(a+), so the very rare anti-Lu^b serum was used to type IV 5 and IV 8 (fig.11). The discovery that IV 5 was Lu(b-) and apparently homozygous $\underline{Lu^a}\underline{Lu^a}$ would confirm that $\underline{Lu^a}$ was carried by both her parents. Thus the two possible parental mating types to be considered in lod score calculations were 10 (GgTt x ggTt, G = $\underline{Se}$, $\underline{Lu^a}$ = T) and 13 (GgTt x GgTt, G= $\underline{Se}$, $\underline{Lu^a}$ = T). z_3 scores were used for the scoring of type 13.

$$z_3 = \log_{10}\frac{4^{s-1}}{9^{a_3}b+c}\left[(3-2\theta+\theta^2)^a\theta^{b+c}(2-\theta)^{b+c}(1-\theta)^{2d}\right.$$
$$+\ 2(2+\theta-\theta^2)^a(1-\theta+\theta^2)^{b+c}\theta^d$$
$$\left.\cdot(1-\theta)^d\ +\ (2+\theta^2)^a(1-\theta^2)^{b+c}\theta^{2d}\right]$$

where s = a + b + c + d, a = GT, b = Gt, c = gT and d = gt.

The three remaining families, Bak (fig.5), Bla (fig.6) and/

and MoG (fig.10) were treated in an identical manner. Neither parent had been tested, so selection of these families was entirely through the children. These sibships were ascertained through the Lu^a(G) factor, then tested for Se(T) and only included in the analysis because of the presence of a Non-secretor child. The possible mating types include 1 (GgTt x ggtt), 10 (GgTt x ggTt) and the uninformative mating of Ggtt x ggTt. In addition to adjusting the lod scores for the relative frequencies of each of the possible parental matings, further ascertainment corrections were incorporated.

For mating type 1 — applicable z score = z_1 + correction e_1.

For mating type 10 — applicable z score = z_2 + correction d_2.

$$e_1 = \log_{10} \frac{1 - (1/2)^s}{1 - \frac{1}{2}\theta^{s_1}(1-\theta)^{s_2} - \frac{1}{2}\theta^{s_2}(1-\theta)^{s_1}}$$

$$d_2 = \log_{10} \frac{2^s - (3/2)^s}{2^s - \frac{1}{2}(2-\theta)^{s_1}(1+\theta)^{s_2} - \frac{1}{2}(1+\theta)^{s_1}(2-\theta)^{s_2}}$$

where $s = s_1 + s_2$, s_1 = number of G children and s_2 = g.

2. Probability of Linkage

a) Derivation of Average Likelihood from Likelihood/θ Curve

The following description is given of the derivation/

derivation of the average likelihood, $\bar{P}_K$, from the likelihood/θ curve for linkage between the MNSC1 and the Kell loci (fig. 19). To arrive at the average likelihood, $\bar{P}_K$, the total area under the appropriate likelihood/θ curve had to be converted into a rectangle of equal area on the same base. The height of this rectangle then gave a measure of $\bar{P}_K$.

The perimeter of the area enclosed by the likelihood/θ curve was traced out by 0.755 revolutions of a planimeter wheel, for which 1 rev. = 63.86 sq. cms.. $\bar{P}_K$, expressed in cms. = total area under curve/ length of base, but the scales of the graph were such that the base of 0.5 units of recombination was 20 cms. long, and a likelihood of 1 had a height of 10 cms.

Hence $\bar{P}_K$ expressed as a likelihood = $\frac{0.755 \times 63.86}{20 \times 10} = 0.24$

All other average likelihood values quoted in this thesis were derived in a similar fashion, with due regard to the scales of the graphs involved.

b) Probability of Linkage, $0 \leq \theta < 0.5$, between any Pair of Loci

It has already been defined that the likelihood ratio is equal to the Prob $(F|\theta)$/Prob $(F|0.5)$ i.e. the likelihood ratio is a measure of the likelihood of observing the family data, F, when the recombination fraction between two autosomal loci is θ compared with the likelihood when $\theta = 0.5$. What we are really interested in deriving from/

from linkage data is the inverse of this, namely, the Prob(θ | F)/Prob(0.5 | F).

Smith (1959) has demonstrated that the postulates of the Theorem of Bayes (1763) could be applied to the problem, which resolved itself as follows, (provided two approximations are valid) :

i) The distribution of the likelihood ratios (antilods) could be interpreted as the distribution of the probability of θ, given the observed family data, F.

ii) For any pair of autosomal loci,
Probability of linkage, $0 \leqslant \theta \leqslant 0.5 = \bar{P}/(\bar{P}+a_1 P_{(0.5)})$,
where $\bar{P}$ = average likelihood and $P_{(0.5)}$ = likelihood at $\theta=0.5$ $=1$.

The two approximations, both of which Smith (1959) and others consider to be not grossly misleading are :

i) All human autosome pairs have an equal probability of carrying any particular autosomal locus. In Man there are 22 pairs of autosomes, so that initially in linkage calculations there is only an a priori probability of about 1/22 that any two autosomal genes chosen at random will lie on the same chromosome and have/

have a recombination fraction in the range $0 \leq \theta \leq 0.5$, but a probability of 21/22 that such genes will lie on different autosomal pairs and freely recombine ($\theta = 0.5$).

ii) For linked loci the recombination fractions are equally distributed throughout all parts of the range, $0 \leq \theta \leq 0.5$ (Morton, 1955).

Total lod scores and antilod values for linkage between the MNSGl and the ABO loci in the Gil family were recorded in tables 20a, 20b. From the resulting likelihood/θ curve fig. 19), the average likelihood, $\bar{P}_{ABO}$, was found to be 0.16 Thus the probability of linkage, $0 \leq \theta \leq 0.5$, between these two loci was 0.16/ (0.16 + 21) = 0.008, and the probability that they were unlinked was 0.992.

Similarly, the probability of autosomal linkage between the MNS and the Gl(Caldwell) loci was calculated, from an average likelihood of $\bar{P} = 0.1325 \times 10^{12}$, to be $1 - (1.6 \times 10^{-10})$ (Table 19, fig. 18). In other words, the probability that these two loci were unlinked was very remote -- only 1.6×10^{-10}.

c) Combination of probabilities of Linkage relating to Different Pairs of Loci

It has just been demonstrated that the MNS and Gl(Caldwell) loci were linked in the Cal and Gil families. In fact, the linkage was extremely close, no certain recombination/

recombination being observed between the Ms chromosomal arrangement and Cl^a. The presence of the Cl^a antigen on the red cells thus labelled most effectively in Cl(a+) persons the presence of a particular Ms chromosome, so increasing the efficiency of the MNS locus in linkage studies against the other 7 blood group loci. Tables 20a and 20b record the lod scores and antilod values respectively for linkage tests between the combined MNSCl locus and the loci of the blood, saliva and serum groups (ABO, P, Rh, K, Fy, Se and Gm). Corresponding likelihood/θ curves are shown in figs. 19 and 20.

If a locus is simultaneously tested for linkage with several loci, which are thought to be unlinked to one another, the finding of linkage with one locus decreases the probability of linkage to the others. Alternatively, strong evidence for "no linkage" with one locus increases the probability of linkage to the others, or to linkage groups on the unmarked chromosomes. Need has therefore to be paid to such non-independence wher calculating the probabilities of linkage of one condition to several others (Smith, in an appendix to Renwick and Lawler, 1963).

In the present instance, where the MNSCl locus was tested against 7 blood, saliva and serum group loci, which were believed to be unlinked to each other (Race and Sanger,/

Sanger, 1962), there were (22 - 7) = 15 unmarked linkage groups. By Smith's reasoning, the prior odds of 1:21 on the linkage, $0 \leqslant \theta \leqslant 0.5$, of the MNSC1 locus to each blood group locus, together with odds of (1/22) x 15 for linkage to the unmarked linkage groups, could be improved upon.

The new odds on linkage involving several loci are in the proportions of the individual average likelihoods, $\bar{P}$ (row (2) of table 21).

Determination of the respective probabilities of getting linkage, $0 \leqslant \theta \leqslant 0.5$, of the MNSC1 with the ABO, P, Rh, K, Fy, Se and Gm loci thus involved dividing the new odds on linkage each by the total odds (i.e. dividing the figures of row (2) of table 21 each by the total, 17.52, to obtain the final probabilities recorded in row (3) of table 21. These probabilities will be discussed at the end of section (d).

d) Probability of Linkage Closer than $\theta = 0.3$

In table 21 each probability of linkage, $0 \leqslant \theta \leqslant 0.5$, between the MNSC1 and a blood group locus could be regarded as the sum of two component probabilities -- that for θ in the range of $0 < \theta < 0.3$ plus that for θ in the range $0.3 < \theta < 0.5$.

$$\text{Prob}\left[\theta(0<\theta<0.5)\,\middle|\,\bar{P}\right] = \text{Prob}\left[\theta(0<\theta<0.3\,\middle|\,\bar{P}\right] + \text{Prob}\left[\theta(0.3<\theta<0.5\,\middle|\,\bar{P}\right]$$

A/

A measure of these component probabilities could be obtained by reference to the appropriate likelihood/θ curve (fig.19 and 20). (It has already been noted that the distribution of the likelihood ratios (antilods) for the family data, given θ, could be interpreted as the distribution of the probability of θ, given the family data). The proportion of the total probability of θ, for the full range of values $0 \leqslant \theta \leqslant 0.5$, which lay in the range $0 < \theta < 0.3$ was thus the same as the ratio, $r = a/A$, which could be determined by planimetry. A = total area under the likelihood/θ curve from $0 \leqslant \theta \leqslant 0.5$, and a = area under the likelihood /θ curve from $0 < \theta < 0.3$.

For example, in table 21, the probability of linkage $0 \leqslant \theta \leqslant 0.5$ between the MNSCl and the ABO loci could be subdivided (row 4) :

$$\text{Prob}\left[\theta\,(0<\theta<0.3)\,\middle|\,F\right] = r \times \text{Prob}\left[\theta\,(0\leqslant\theta\leqslant0.5)\,\middle|\,F\right] = 0.0078 \times 0.009 = 0.0001,$$

and $$\text{Prob}\left[\theta\,(0.3<\theta<0.5)\,\middle|\,F\right] = 0.009 - 0.0001 = 0.0089.$$

We are now, knowing the probabilities noted in row (4) of table 21, in a position to discuss the findings regarding the probabilities of genetical linkage between the/

the MNSGl and the 7 blood group loci (ABO, P, Rh, K, Fy, Se and Gm).

Firstly, it was shown when considering linkage between pairs of loci (section b) that the probability of linkage between the MNSGl and the ABO loci was 0.008 (1 in 125). It is now possible to see the effect of considering the linkage study as a whole by combining the probabilities of linkage relating to different pairs of loci (section c). When information concerning the probabilities of linkage of the MNSGl locus to the P, Rh, K, Fy, Se and Gm was incorporated the probability of linkage between the MNSGl and the ABO loci was increased slightly to 0.009 (1 in 110).

Secondly, it is usually very difficult to say, without extensive information, whether genes with an apparently high recombination fraction, say $\theta > 0.4$, are loosely linked on the same chromosome, or whether they segregate independently on different chromosomes. However, even when the total probability of linkage is still appreciable, it is sometimes possible to state that the probability of linkage closer than $\theta = 0.3$ is very small.

In the Cal and Gil families the evidence pointed towards the MNSGl locus being unlinked to the ABO, Rh, K, Fy or Gm loci. The probabilities of linkages over the full range of values $0 \leq \theta \leq 0.5$ were about 1 in 100, and linkages with/

with less than 30% recombination ($\theta < 0.3$) were even more unlikely (about 1 in 300 to 1 in 1,000). Similarly, it was unlikely that the MNSCl and the P loci were linked, though the probability was slightly greater (1 in 30 for linkage $\theta < 0.5$, but only 1 in 140 for linkage with $\theta < 0.3$). These findings are in keeping with those of others (Race and Sanger, 1962).

Considering the data concerning the MNSCl and the Se loci, the total probability of linkage, $\theta < 0.5$, was 0.063 (1 in 16), with component probabilities for $\theta < 0.3$ of 0.0275 (1 in 36) and for $\theta > 0.3$ of 0.0355 (1 in 28). These are very slightly greater than the prior probabilities, but no judgment concerning the presence or absence of autosomal linkage between these loci can be made till much of the other available information has been analysed.

3. Estimation of the Recombination Fraction, θ

The maximum likelihood estimate of the recombination fraction θ, is that value of θ which maximises the likelihood of the family material.

By direct counting of the number of certain recombinants and certain non-recombinants between the A_1 and the Nail-Patella alleles in the Seu 1 family (fig. 2), it was possible to obtain a maximum likelihood estimate of the recombination/

recombination fraction in this family as 1/32 = 0.03. However, when the lod scores for this family were calculated by computer, a small amount of additional information was incorporated by the computer and the maximum likelihood estimate of θ was raised to about 0.05. (In table 16, the maximum lod score by computer was obtained at θ = 0.05).

When the data from the three Sau families were combined, genetical linkage between the ABO and the Nail-Patella loci was confirmed, with the likelihood reaching its maximum at θ = 0.119, as estimated from inspection of the likelihood/θ curve (fig. 16). This observation of 11.9% recombination between this pair of alleles is consistent with the estimate of 10.4% by Renwick and Lawler (1955).

A linkage was shown to exist between the MNS and Gl(Caldwell) sites. In both the Cal and Gil families inspection of the pedigrees (fig.14, 15) indicated that coupling of the chromosomal arrangement Ms to Gl^a was unbroken, no certain recombination between them being observed. The maximum likelihood estimate of the recombination fraction was thus 0 (zero). Gl^a must certainly be regarded as yet another of the rare blood group antigens to be associated in some manner with the MNSs system (Wallace and Izatt, 1963).

b)/

b) Confidence Limits

Having obtained an estimate of the recombination fraction, θ, between a pair of linked loci in the sample of the population analysed (the family material), we would like to know its confidence limits. Confidence limits express with an appropriate probability our confidence that the true value of θ in the population as a whole lies within a certain range of values.

The 95% confidence limits for the estimate of $\theta = 0.119$ between the ABO and the Nail-Patella loci in the Sau 1, 2 and 3 families were determined by reference to the likelihood/θ curve (fig. 16). Areas corresponding to 2½% of the total area under the likelihood/θ curve were cut off from both the upper and lower tails of the curve.

In effect, the total area under this particular likelihood/θ curve (fig.16) was expressed by 1.054 revs. of a planimeter, so that 2½% of this area was traced out by 0.026 revs. By trial and error the value of θ limiting the lower 2½% was found at $\theta = 0.06$, while the upper 2½% was cut off at $\theta = 0.225$. The area between these upper and lower limits was thus a graphical representation of 95% of the total probability of θ. Hence we could say with 95% confidence that the true value of θ lay within the range of 6-22.5% recombination, with the maximum likelihood estimate/

estimate at 11.9%.

The linkage between MNS and Gl(Caldwell) sites in the Cal and Gil families was complete in the present data, with the maximum likelihood estimate of the recombination fraction being $\theta = 0$. To calculate a lower confidence limit in the conventional way would be misleading. Instead, the lower 95% confidence limit was set at $\theta = 0$, and the upper limit was found by cutting off from the likelihood/θ curve (fig. 17) 5% of its total area at the upper tail. Thus we could say with 95% confidence that the true value of the recombination fraction was less than 5.1%, with the maximum likelihood estimate at 0 (zero).

CONCLUSIONS.

The conclusions from this study, which was designed to search for genetical linkage relationships between the loci of selected autosomal characteristics in Man, can be summarised

1) By following Smith's (1959) method of interpreting likelihood ratio tests, involving the likelihood of the observed family pedigrees in the population, it was possible to assess simultaneously the probability of linkage and to estimate the value of the recombination fraction between pairs of autosomal loci.

2) Confirmation was obtained of the existence in the three families examined of an autosomal linkage between loci controlling the ABO blood groups and the Nail-Patella syndrome. The rate of recombination between these loci was estimated with 95% confidence to be in the range 6 - 22.5%, with the maximum likelihood estimate at 11.9%.

3) The existence of a new linkage relationship was established - that between the sites controlling the MNS and the Cl (Caldwell) blood groups, the probability of no linkage being only 1.6×10^{-10}. In the two families studied there was no certain recombination between the Ms chromosomal arrangement and Cl^a. The maximum likelihood estimate of the recombination fraction was 0(zero), and it could be stated with 95% confidence that the rate of recombination was less than 5.1%.

4) /

4) The available evidence indicated the probabilities of linkages of any degree between the MNSC1 locus and the ABO, P, Rh, K, Fy or Gm loci to be low (about 1 in 100), with the probabilities of linkages showing closer than 30% recombination being even less (1 in 300 to 1 in 1,000). These findings confirm that the MNS locus could be inferred to be unlinked to the ABO, P, Rh, K, Fy or Gm loci.

5) The evidence for linkage between the MNSC1 and the Se(ABH Secretor) loci was inconclusive in the two families tested.

6) A series of χ^2 calculations involving the phenotype frequencies of the various blood groups in new random series of unrelated persons (who had been grouped by the same techniques and reagents as were used for the rest of the family material) were reassuring with regard to the practical accuracy of the reported blood groups. The new random series of samples from persons of Scottish and English origin could be regarded as representative of their country of origin, when judged by the absence of statistically significant heterogeneity between them and previously published series.

7) It was suggested, because the racial heterogeneity between the Scottish and English populations appeared to be manifest not only in different distributions of the ABO blood groups, but also in differing frequencies for the Lutheran, Secretor, Gm and perhaps the Rhesus alleles that Scottish allele frequencies/

frequencies be used in linkage studies on families of Scottish origin in future. In the Scottish series investigated, the ABH Secretor alleles were estimated to have frequencies of Se = 0.4171 and se = 0.5829, while the Gm (serum gamma-globulin groups) alleles had frequencies of Gm^a = 0.1855, Gm^{ax} = 0.1462 and Gm^b = 0.6683.

8) Segregation ratios were consistent with the hypothesis that the Nail-Patella syndrome and the Cl^a (Caldwell) blood group antigen were the regular expressions of autosomal alleles in the heterozygous state.

Key to symbols used in Tables 1 and 2

Column 1 Pedigree number. * = Propositus.
2 Pedigree number of parents.
3 Sex.
4 Y. of b. = Year of birth.
5 L. or d. = Living (l.) or dead (d.), with date of death when known.

BLOOD GROUP SYSTEMS

6 Caldwell phenotype, Cl(a+) or Cl(a-).
7 ABO phenotype.
8 MNS phenotype. Tested with anti-M, anti-N, anti-S and anti-s sera.
9 P phenotype. Tested with anti-P_1 serum.
10 Rhesus phenotype. Tested with anti-C, anti-C^W, -c, -D, -E and -e sera.
11 Lutheran phenotype, Lu(a+) or Lu(a-).
12 Kell phenotype, K(+) or K(-).
13 Lewis phenotype, Le(a+) or Le(a-).
14 Duffy phenotype, Fy(a+) or Fy(a-): Fy(b+) or Fy(b-).
15 Kidd phenotype, Jk(a+) or Jk(a-): Jk(b+) or Jk(b-).
16 ABH secretion phenotype, + = Secretor, - = Non-secretor.
17 Gm phenotype, Gm(a+) or Gm(a-): Gm(b+) or Gm(b-): Gm(x+) or Gm(x-).

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
													Fy	Jk		Gm
No.	Parents	Sex	Y. of b.	L. or d.	O	ABO	MNS	P	Rh	Lu	K	Le	a b	a b	Sec	a b x
I 1	·	M	1842	d.	·	·	·	·	·	·	·	·	·	·	·	·
I 2	·	F	1842	d.	·	·	·	·	·	·	·	·	·	·	·	·
I 3	·	F	1853	d.1908	·	·	·	·	·	·	·	·	·	·	·	·
I 4	·	M	1840	d.1920	·	·	·	·	·	·	·	·	·	·	·	·
II 1	I 1,2	M	·	d.	·	·	·	·	·	·	·	·	·	·	·	·
II 2	·	F	·	d.	·	·	·	·	·	·	·	·	·	·	·	·
II 3	I 1,2	M	1865	d.	·	·	·	·	·	·	·	·	·	·	·	·
II 4	I 1,2	M	1867	d.	·	·	·	·	·	·	·	·	·	·	·	·
II 5	I 1,2	M	1869	d.1936	·	·	·	·	·	·	·	·	·	·	·	·
II 6	·	F	1875	d.1953	·	·	·	·	·	·	·	·	·	·	·	·
II 7	I 1,2	M	1871	d.	·	·	·	·	·	·	·	·	·	·	·	·
II 8	I 1,2	M	1875	d.1935	·	·	·	·	·	·	·	·	·	·	·	·
II 9	I 1,2	F	1878	d.1944	·	·	·	·	·	·	·	·	·	·	·	·
II 10	·	M	·	d.age 67	·	·	·	·	·	·	·	·	·	·	·	·
II 11	I 3,4	M	1876	d.	·	·	·	·	·	·	·	·	·	·	·	·
II 12	I 3,4	M	·	d.1945	·	·	·	·	·	·	·	·	·	·	·	·
II 13	·	F	1880	l.	·	·	·	·	·	·	·	·	·	·	·	·
II 14	I 3,4	M	1882	d.1935	·	·	·	·	·	·	·	·	·	·	·	·
II 15	·	F	·	l.	·	·	·	·	·	·	·	·	·	·	·	·
II 16	I 3,4	F	1884	l.	−	A_1	NsNs	−	CcDEe	−	−	+	+ +	+ ·	−	+ + −
II 17	I 3,4	M	1887	d.	·	·	·	·	·	·	·	·	·	·	·	·
II 18	I 3,4	F	1888	d.1959	·	·	·	·	·	·	·	·	·	·	·	·
II 19	·	M	·	l.	·	·	·	·	·	·	·	·	·	·	·	·
III 1	II 1,2	M	1901	d.1957	·	·	·	·	·	·	·	·	·	·	·	·
III 2	·	F	·	l.	·	·	·	·	·	·	·	·	·	·	·	·
III 3-6	II 4	·	·	1d.3l.	·	·	·	·	·	·	·	·	·	·	·	·
III 7	II 5,6	F	1896	d.1961	·	·	·	·	·	·	·	·	·	·	·	·
III 8	II 5,6	M	1902	l.	−	·	·	·	·	·	·	·	·	·	·	·
III 9	II 5,6	F	·	d.age 14	·	·	·	·	·	·	·	·	·	·	·	·
III 10	II 5,6	F	1905	l.	−	·	·	·	·	·	·	·	·	·	·	·
III 11	II 5,6	F	·	d.	·	·	·	·	·	·	·	·	·	·	·	·
III 12	II 5,6	F	1909	l.	−	·	·	·	·	·	·	·	·	·	·	·
III 13	II 5,6	M	·	s.b.	·	·	·	·	·	·	·	·	·	·	·	·
III 14	II 9,10	M	1906	l.	−	·	·	·	·	·	·	·	·	·	·	·
III 15	II 9,10	F	1908	l.	−	·	·	·	·	·	·	·	·	·	·	·
III 16	II 12,13	M	1918	l.	−	·	·	·	·	·	·	·	·	·	·	·

Table 1 (cont.) CALDWELL ANTIGEN Family Cal

1	2	3	4	5	6	7	8	9	10	11	12	13	14		15		16	17		
													Fy		JK			Gm		
No	Parents	Sex	Y. of b.	L. of d.	Q	ABO	MNS	P	Rh	Lu	K	Le	a	b	a	b	Sec	a	b	x
III 17	II 12,13	M	1923	l.	−	·	··	·	·	·	·	·	·		·		·		·	
III 18,19	II 14,15	·	·	l.	·	·	·	·	·	·	·	·	·		·		·		·	
III 20	II 14,15	M	1909	l.	−	A_1	·	·	·	·	·	·	·		·		·		·	
III 21	II 14,16	F	1912	l.	·	·	·	·	·	·	·	·	·		·		·		·	
III 22-24	II 16	·	·	l.	·	·	·	·	·	·	·	·	·		·		·		·	
III 25	II 18,19	M	1910	l.	+	0	MsNs	+	CcDee	−	−	−	−	+	+	+	+	+	+	−
III 26	·	F	1922	l.	−	A_1	NsNs	+	ccDEe	−	−	+	−	+	+	·	−	−	+	·
III 27*	II 18,19	M	1911	l.	+	0	MsNs	+	CcDEe	−	−	−	+	+	+	+	+	−	+	·
III 28	·	F	1926	l.	−	0	MSMs	+	CcDee	−	−	−	+	−	+	·	+	+	+	+
III 29	II 18,19	F	1913	l.	+	0	MsNs	+	ccDEe	−	−	−	−	+		·	+		·	
IV 1	III 1,2	F		l.	−	·	·	·	·	·	·	·	·		·		·		·	
IV 2	III 25,26	M	1951	l.	−	0	NsNs	+	ccddee	−	−	−	−	+	+	+	+	+	+	−
IV 3	III 27,28	F	1949	l.	+	0	MsMs	+	CcDEe	−	−	−	+	−		·	+	+	+	·

Table 2

1 No.	2 Parents	3 Sex	4 Y. of b.	5 L. or d.	6 Qi	7 ABO	8 MNS	9 P	10 Rh	11 Lu	12 K	13 Le	14 Fy a b	15 Jk a b	16 Sec	17 Gm a b x
I 1	·	M	·	d.	·	·	·	·	·	·	·	·	·	·	·	·
I 2	·	F	·	d.	·	·	·	·	·	·	·	·	·	·	·	·
I 3	·	M	·	d.	·	·	·	·	·	·	·	·	·	·	·	·
I 4	·	F	·	d.	·	·	·	·	·	·	·	·	·	·	·	·
I 5	·	M	·	d.	·	·	·	·	·	·	·	·	·	·	·	·
II 1	I 1,2	F	1830	d. 1930	·	·	·	·	·	·	·	·	·	·	·	·
II 2	I 1,2	M	·	d.	·	·	·	·	·	·	·	·	·	·	·	·
II 3	I 1,2	F	·	d.	·	·	·	·	·	·	·	·	·	·	·	·
II 4	I 1,2	F	·	d.	·	·	·	·	·	·	·	·	·	·	·	·
II 5	·	M	·	d.	·	·	·	·	·	·	·	·	·	·	·	·
II 6	·	M	1855	d. 1915	·	·	·	·	·	·	·	·	·	·	·	·
II 7	I 1,2	F	1852	d. 1936	·	·	·	·	·	·	·	·	·	·	·	·
II 8	I 1,2	F	1852	d. 1918	·	·	·	·	·	·	·	·	·	·	·	·
II 9	·	M	·	d.	·	·	·	·	·	·	·	·	·	·	·	·
II 10	·	M	·	d.	·	·	·	·	·	·	·	·	·	·	·	·
II 11	·	M	·	d.	·	·	·	·	·	·	·	·	·	·	·	·
II 12	·	M	·	d.	·	·	·	·	·	·	·	·	·	·	·	·
II 13	I 1,2	F	1856	d. 1940	·	·	·	·	·	·	·	·	·	·	·	·
II 14	·	M	1874	d. 1948	·	·	·	·	·	·	·	·	·	·	·	·
II 15	I 1,2	F	·	·	·	·	·	·	·	·	·	·	·	·	·	·
II 16	I 1,2	M	1857	d. 1935	·	·	·	·	·	·	·	·	·	·	·	·
II 17	I 3,4	F	1858	d. 1931	·	·	·	·	·	·	·	·	·	·	·	·
II 18	I 3,4	F	·	d. age 28	·	·	·	·	·	·	·	·	·	·	·	·
II 19	I 4,5	M	1858	d. 1940	·	·	·	·	·	·	·	·	·	·	·	·
II 20	·	F	·	·	·	·	·	·	·	·	·	·	·	·	·	·
III 1	II 4,5	M	1879	d. 1959	·	·	·	·	·	·	·	·	·	·	·	·
III 2	·	F	1880	d. 1941	·	·	·	·	·	·	·	·	·	·	·	·
III 3	II 4,5	F	·	d.	·	·	·	·	·	·	·	·	·	·	·	·
III 4	II 4,5	F	·	d. 1956	·	·	·	·	·	·	·	·	·	·	·	·
III 5	II 6,7	M	·	d. 1960	·	·	·	·	·	·	·	·	·	·	·	·
III 6	·	F	·	d.	·	·	·	·	·	·	·	·	·	·	·	·
III 7	II 6,7	F	·	d.	·	·	·	·	·	·	·	·	·	·	·	·
III 8	II 6,7	F	·	·	·	·	·	·	·	·	·	·	·	·	·	·
III 9	II 6,7	M	1891	l.	–	A_2B	·	·	C^wcDee	·	–	·	·	·	·	·
III 10	II 6,7	M	1893	l.	–	A_1	·	·	ccDEe	·	–	·	·	·	·	·
III 11	II 6,7	F	·	d.	·	·	·	·	·	·	·	·	·	·	·	·

1	2	3	4	5	6	7	8	9	10	11	12	13	14		15		16	17		
No.	Parents	Sex	Y. of b.	L. or d.	Q	ABO	MNS	P	Rh	Lw	K	Le	Fy a	Fy b	Jk a	Jk b	Sec	Gy a	Gy b	X
III 12	II 6,7	F	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·		·	
III 13	II 6,7	F	1898	l.	−	B	·	·	C^wCeDee	·	+	·	·	·	·	·	·		·	
III 14	II 6,7	M	1900	l.	−	A_2B	·	·	ccDEe	·	+	·	·	·	·	·	·		·	
III 15	II 6,7	M	1902	l.	−	A_1	·	·	ccdee	·	−	·	·	·	·	·	·		·	
III 16	II 8,9	M	·	d.	·	·	·	·	·	·	·	·	·	·	·	·	·		·	
III 17	II 8,9	M	1881	d.1949	·	·	·	·	·	·	·	·	·	·	·	·	·		·	
III 18	·	F	1875	d.1927	·	·	·	·	·	·	·	·	·	·	·	·	·		·	
III 19	II 8,9	F	1882	l.	·	·	·	·	·	·	·	·	·	·	·	·	·		·	
III 20	II 8,9	M	·	d.	·	·	·	·	·	·	·	·	·	·	·	·	·		·	
III 21	II 8,9	F	·	d.	·	·	·	·	·	·	·	·	·	·	·	·	·		·	
III 22	II 8,9	F	·	l.	·	·	·	·	·	·	·	·	·	·	·	·	·		·	
III 23	II 8,9	F	1894	l.	·	·	·	·	·	·	·	·	·	·	·	·	·		·	
III 24	II 10,13	M	1878	d.1958	·	·	·	·	·	·	·	·	·	·	·	·	·		·	
III 25	II 10,13	M	1886	d.1959	·	·	·	·	·	·	·	·	·	·	·	·	·		·	
III 26	II 11,13	M	1887	l.	−	O	·	·	CCDee	·	−	·	·	·	·	·	·		·	
III 27	II 12,13	F	1889	l.	−	O	·	·	CcDee	·	−	·	·	·	·	·	·		·	
III 28	II 13,14	F	1894	d.1914	·	·	·	·	·	·	·	·	·	·	·	·	·		·	
III 29	II 13,14	M	1897	d.1959	·	·	·	·	·	·	·	·	·	·	·	·	·		·	
III 30	·	F	1895	d.1953	·	·	·	·	·	·	·	·	·	·	·	·	·		·	
III 31	II 13,14	M	1899	l.	−	B	·	·	CCDee	·	−	·	·	·	·	·	·	−	+	·
III 32	II 16,17	M	1879	l.	−	A_1	MSMs	−	CcDEe	−	−	−	+	+	+	·	+	−	+	−
III 33	II 16,17	F	1881	d.1955	·	·	·	·	·	·	·	·	·	·	·	·	·		·	
III 34	·	M	1879	d.1953	·	·	·	·	·	·	·	·	·	·	·	·	·		·	
III 35	II 16,17	M	·	d.1914	·	·	·	·	·	·	·	·	·	·	·	·	·		·	
III 36	II 16,17	M	1886	l.	+	A_1B	MSMs	−	C^wCeDEe	−	+	+	+	+	·	·	−	−	+	·
III 37	·	F	1882	d.1955	·	·	·	·	·	·	·	·	·	·	·	·	·		·	
III 38	II 16,17	M	·	d. INF.	·	·	·	·	·	·	·	·	·	·	·	·	·		·	
III 39	II 16,17	M	1890	l.	+	A_1B	MSMs	−	CcDee	−	−	−	+	+	+	·	−	−	+	·
III 40	·	F	1892	d.1955	·	·	·	·	·	·	·	·	·	·	·	·	·		·	
III 41	II 16,17	F	1891	d.1958	·	·	·	·	·	·	·	·	·	·	·	·	·		·	
III 42	·	M	1896	d.1939	·	·	·	·	·	·	·	·	·	·	·	·	·		·	
III 43	II 16,17	F	1894	l.	−	A_1B	MSMs	+	CcDee	−	−	+	−	·	−	·	−	−	+	·
III 44	II 16,17	F	1896	l.	−	A_1	MSMs	−	C^wCeDee	−	+	−	+	+	·	·	+	−	+	·
III 45	II 16,17	F	1896	d.1898	·	·	·	·	·	·	·	·	·	·	·	·	·		·	
III 46	II 16,17	M	1900	d. INF.	·	·	·	·	·	·	·	·	·	·	·	·	·		·	
III 47	II 16,17	F	1900	l.	−	A_1B	MSMS	−	C^wCeDEe	−	−	−	−	·	−	·	+	−	+	·

Table 2 (cont.) CALDWELL ANISOM

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
No.	Parents	Sex	Y. of b.	L. or d.	Cl	ABO	MNS	P	Rh	Lu	K	Le	Fy a b	Jk a b	Sec	Gm a b x
III 48	II 16,17	·	·	d. inf	·	·	·	·	·	·	·	·	·	·	·	·
III 49	II 16,17	·	·	d. inf.	·	·	·	·	·	·	·	·	·	·	·	·
III 50	II 16,17	·	·	d. inf	·	·	·	·	·	·	·	·	·	·	·	·
III 51	II 19,20	M	1876	d. 1960	·	·	·	·	·	·	·	·	·	·	·	·
III 52	II 19,20	M	1877	d. 1937	·	·	·	·	·	·	·	·	·	·	·	·
III 53	II 19,20	F	1880	l.	–	A_1	MsNs	–	ccDEe	–	–	+	– ·	+ ·	·	– + –
III 54	II 19,20	M	1881	d. 1920	·	·	·	·	·	·	·	·	·	·	·	·
III 55	·	F	1892	d. 1952	·	·	·	·	·	·	·	·	·	·	·	·
III 56	II 1920	F	1884	l.	–	A_1	NsNs	+	ccDEe	–	–	–	– ·	+ ·	·	– + ·
III 57	·	M	·	l.	·	·	·	·	·	·	·	·	·	·	·	·
III 58	II 19,20	M	1885	d. 1916	·	·	·	·	·	·	·	·	·	·	·	·
III 59	·	F	1888	l.	–	B	NsNs	+	CcDEe	–	–	+	– ·	+ ·	–	+ – +
IV 1	III 1,2	F	1900	l.	–	B	·	·	CcDee	·	–	·	·	·	·	·
IV 2-6	III 1,2	F	·	d.	·	·	·	·	·	·	·	·	·	·	·	·
IV 5	III 1,2	F	1903	l.	–	A_2B	·	·	CcDee	·	–	·	·	·	·	·
IV 6	III 1,2	F	1911	l.	–	A_2	·	·	CCDee	·	–	·	·	·	·	·
IV 7-11	III 1,2	·	·	d.	·	·	·	·	·	·	·	·	·	·	·	·
IV 12	III 1,2	M	1918	l.	–	B	·	·	ccDEe	·	–	·	·	·	·	·
IV 13	III 1,2	M	1923	l.	–	A_2	·	·	CcDee	·	–	·	·	·	·	·
IV 14	III 5,6	M	1915	l.	–	A_1	·	·	ccddee	·	–	·	·	·	·	·
IV 15	III 5,6	M	1916	l.	–	A_1	·	·	ccddee	·	–	·	·	·	·	·
IV 16	III 5,6	F	·	l.	·	·	·	·	·	·	·	·	·	·	·	·
IV 17	III 5,6	M	·	l.	·	·	·	·	·	·	·	·	·	·	·	·
IV 18	III 5,6	M	1925	l.	–	A_1	·	·	ccddee	·	–	·	·	·	·	·
IV 19	III 5,6	M	·	l.	·	·	·	·	·	·	·	·	·	·	·	·
IV 20	III 5,6	F	1927	l.	–	A_2	·	·	ccddee	·	–	·	·	·	·	·
IV 21	III 5,6	M	·	l.	·	·	·	·	·	·	·	·	·	·	·	·
IV 22	III 5,6	M	1932	l.	–	A_1	·	·	ccddee	·	–	·	·	·	·	·
IV 23,24	III 5,6	·	·	l.	·	·	·	·	·	·	·	·	·	·	·	·
IV 25	III 17,18	F	1904	l.	–	O	·	·	CCDee	·	–	·	·	·	·	– + ·
IV 26	III 17,18	F	1908	l.	–	O	·	·	CcDee	·	–	·	·	·	·	– + ·
IV 27	III 17,18	M	1912	l.	–	O	·	·	CcDee	·	–	·	·	·	·	– + ·
IV 28	III 29,30	M	1922	l.	–	A_2	·	·	ccddee	·	–	·	·	·	·	·
IV 29	III 29,30	F	1923	l.	–	B	·	·	C^wcDEe	·	–	·	·	·	·	– + ·
IV 30	III 29,30	M	·	l.	·	·	·	·	·	·	·	·	·	·	·	·
IV 31	III 29,30	M	1926	l.	–	B	·	·	ccddee	·	–	·	·	·	·	+ + –

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
No.	Parents	Sex	Year b.	L. or d.	Cl	ABO	MNS	P	Rh	Lu	K	Le	Fy^a Fy^b	Jk^a Jk^b	Sec	Gi^a Gi^b K
IV 32	III 29,30	M	·	l.	·	·	·	·	·	·	·	·	·	·	·	·
IV 33-36	III 32	·	·	2l.2d.	·	·	·	·	·	·	·	·	·	·	·	·
IV 37	III 33,34	M	1901	l.	−	A_1	MNSs	+	CcDee	−	+	−	− ·	·	+	− + ·
IV 38	III 33,34	F	1902	l.	+	A_1	MsNs	+	CCDee	−	+	−	− ·	·	+	− + ·
IV 39	·	M	1900	l.	−	A_1	NsNs	+	ccddee	−	−	−	+ ·	+ ·	+	+ + −
IV 40	III 33,34	M	1903	l.	+	A_1	MsNs	+	CcDee	−	+	−	− ·	·	+	+ + +
IV 41	III 33,34	F	1904	l.	+	A_1	MsNs	−	CCDee	−	−	−	− ·	+ ·	+	+ + +
IV 42	·	M	1908	d.1954	·	·	·	·	·	·	·	·	·	·	·	·
IV 43	III 33,34	M	1906	l.	+	A_1	MsNs	+	ccDee	−	−	−	− ·	+ ·	+	− + ·
IV 44	III 33,34	F	1909	l.	+	A_1	MsNs	−	CCDee	−	−	+	− ·	+ ·	−	− + ·
IV 45	·	M	1907	l.	−	O	MSMs	+	CcDEe	−	−	−	− ·	+ +	+	+ + −
IV 46	III 33,34	M	1911	l.	−	A_1	MNSs	+	CcDee	−	+	+	− ·	·	−	− + ·
IV 47	III 33,34	F	1913	l.	+	A_1	MsNs	−	CcDee	−	+	−	− ·	·	·	+ + +
IV 48	·	M	·	l.	−	B	MsNs	+	ccDEe	−	−	+	+ ·	+ ·	·	− + ·
IV 49-52	III 35	·	·	2l.2d.	·	·	·	·	·	·	·	·	·	·	·	·
IV 53	III 36,37	M	1908	l.	+	B	MsNs	+	C^wcDEe	−	+	−	+ +	·	+	− + −
IV 54	·	F	1906	l.	−	O	NSNS	+	CCDee	−	−	−	− ·	+ +	+	− + ·
IV 55	III 36,37	M	1910	d.1925	·	·	·	·	·	·	·	·	·	·	·	·
IV 56	III 36,37	F	1912	l.	+	A_1	MsNs	−	ccDEe	−	+	−	+ −	·	+	− + ·
IV 57	·	M	1913	l.	−	O	MSMs	−	CcDee	−	−	−	− ·	+ +	+	+ + ·
IV 58	III 36,37	F	1914	l.	−	B	MNSs	−	C^wcDEe	−	−	+	+ +	+ ·	−	+ + −
IV 59	III 39,40	F	1922	l.	+	A,B	MsNs	−	CcDee	−	−	−	+ +	+ ·	−	− + ·
IV 60	·	M	1921	l.	−	B	NSNs	−	CcDee	−	−	+	+ +	− ·	−	+ + −
IV 61	III 39,40	M	1925	l.	−	A,B	MNSs	−	C^wcDee	−	−	−	+ +	− ·	−	+ + −
IV 62	III 39,40	F	·	l.	·	·	·	·	·	·	·	·	·	·	·	·
IV 63	III 39,40	F	1933	l.	−	A_1	MSMs	−	CcDee	−	−	−	+ +	+ ·	+	+ + −
IV 64	III 39,40	F	·	l.	−	A,B	MSMs	−	C^wcDee	−	−	+	+ −	+ ·	·	+ + −
IV 65	·	M	·	l.	−	O	NsNs	−	ccddee	−	−	−	+ −	− ·	·	− + ·
IV 66	III 41,42	F	1917	d.1940	·	·	·	·	·	·	·	·	·	·	·	·
IV 67	III 41,42	M	1919	l.	+	A_1	MsNs	+	ccDee	−	−	+	− ·	− ·	−	+ + −
IV 68	·	F	1922	l.	−	B	MsNs	+	ccddEe	−	−	+	− ·	+ ·	−	− + ·
IV 69	III 41,42	M	1922	l.	+	A_1	MsMs	+	CcDee	−	−	+	− ·	+ ·	−	+ + +
IV 70	·	F	1921	l.	−	O	MSNS	+	CcDee	−	+	+	+ ·	+ +	−	− + ·
IV 71	III 41,42	M	1926	l.	−	A_1	MsMs	+	CcDee	−	−	+	− ·	− ·	−	+ + +
IV 72	III 41,42	F	1930	l	−	A_1	MsMs	+	ccDee	−	−	+	− ·	+ ·	−	+ + +
IV 73-80	III 43	·	·	4l.4d	·	·	·	·	·	·	·	·	·	·	·	·

1	2	3	4	5	6	7	8	9	10	11	12	13	14		15		16	17		
No.	Parents	Sex	Y. of b.	L. or d.	CL	ABO	MNS	P	Rh	Lu	K	Le	Fy a	Fy b	Jk a	Jk b	Sx	Cw a	Cw b	X
IV 81	III 54,55	M	·	d. INF.	·	·	·	·	·	·	·	·	·		·		·		·	
IV 82	III 54,55	F	1908	l.	+	O	MNSs	+	ccDEe	−	−	−	+	+	+	+	+	−	+	·
IV 83	·	M	·	l.	·	·	·	·	·	·	·	·	·		·		·		·	
IV 84	III 54,55	F	1910	l.	−	O	MNSs	+	cc Dee	−	−	−	+	+	+	·	·	−	+	·
IV 85	III 54,55	F	1912	d. 1921	·	·	·	·	·	·	·	·	·		·		·		·	
IV 86	III 54,55	M	1914	l.	−	O	MNSs	+	cc Dee	−	−	−	−	·	+	+	·	−	+	·
IV 87	III 54,55	M	1917	d. 1921	·	·	·	·	·	·	·	·	·		·		·		·	
IV 88	III 54,55	F	1918	l.	+	A_1	MNSs	+	cc Dee	−	−	+	−	·	−	·	·	−	+	·
IV 89	·	M	1908	l.	−	B	MsNs	+	CC Dee	−	−	−	+	·	−	·	+	+	+	−
IV 90-96	III 56,57	·	·	St. 2d.	·	·	·	·	·	·	·	·	·		·		·		·	
V 97	III 56,57	M	1920	l.	−	A_1	·	·	Cc Dee	·	−	·	·		·		·		·	
V 98,99	III 56,57	M	·	l.	·	·	·	·	·	·	·	·	·		·		·		·	
IV 100	III 58,59	F	1907	d. 1926	·	·	·	·	·	·	·	·	·		·		·		·	
IV 101	III 58,59	M	1910	l.	−	A_1B	NsNs	+	CcDee	−	−	+	−	·	+	·	·	+	+	−
IV 102	III 58,59	M	1912	l.	−	A_1B	NSNs	+	ccDEe	−	−	+	−	·	+	·	·	+	+	−
IV 103	III 58,59	F	·	d. INF	·	·	·	·	·	·	·	·	·		·		·		·	
V 1-5	IV 37	·	·	St. d.	·	·	·	·	·	·	·	·	·		·		·		·	
V 6	IV 38,39	M	1924	l.	−	O	NsNs	+	CcDee	−	+	−	+	·	+	+	+	−	+	·
V 7	IV 38,39	M	·	l.	·	·	·	·	·	·	·	·	·		·		·		·	
V 8	IV 38,39	F	1928	l.	−	A_1	NsNs	+	CcDee	−	−	+	+	·	+	·	−	−	+	·
V 9	IV 38,39	M	·	d. INF	·	·	·	·	·	·	·	·	·		·		·		·	
V 10	IV 38,39	F	1931	l.	+	A_1	MsNs	+	CcDee	−	−	−	+	·	+	·	+	+	+	−
V 11	·	M	1932	l.	−	A_2	MNSs	+	ccddee	−	−	−	−	·	·		+	−	+	·
V 12	IV 38,39	M	1934	l.	+	O	MsNs	+	CcDee	−	+	−	+	·	+	+	+	−	+	·
V 13	IV 38,39	M	1937	l.	−	O	NsNs	+	CcDee	−	−	+	+	·	+	+	−	+	+	−
V 14	IV 38,39	F	1940	l.	−	A_1	NsNs	+	CcDee	−	−	+	+	·	+	·	−	−	+	·
V 15	IV 41,42	M	1933	d. 1939	·	·	·	·	·	·	·	·	·		·		·		·	
V 16	IV 41,42	M	1937	l.	−	A_1	NsNs	+	CcDee	−	−	+	−	·	−	·	−	+	−	+
V 17	IV 41,42	F	1942	l.	−	A_1	NsNs	+	CC Dee	−	−	−	−	·	−	·	+	−	+	·
V 18	IV 44,45	M	1940	l.	+	A_1	MsMs	+	CcDEe	−	−	+	−	·		·	−	−	+	·
V 19	IV 44,45	F	1941	l.	−	A_1	MNSs	+	CCDee	−	−	+	−	·		·	−	−	+	·
V 20	IV 46	F	·	l.	·	·	·	·	·	·	·	·	·		·		·		·	
V 21	IV 47,48	F	1942	l.	−	A_1B	NsNs	−	ccDEe	−	−	+	−	·	+	·	·	−	+	−
V 22	IV 53,54	F	1936	l.	−	O	NSNs	+	CcDEe	−	+	−	−	·	+	−	+	−	+	·
V 23	IV 53,54	M	1940	l.	·	·	·	·	·	·	·	·	·		·		·		·	
V 24	IV 53,54	F	·	d. INF.	·	·	·	·	·	·	·	·	·		·		·		·	

Table 2 (cont.) CALDWELL ANTIGEN Family GH

1	2	3	4	5	6	7	8	9	10	11	12	13	14		15		16	17		
No.	Parents	Sex	Y. of b.	L. or d.	Cl	ABO	MNS	P	Rh	Le	K	Le	Fy a	Fy b	Jk a	Jk b	Sec	Gtv a	Gtv b	K
V 25	IV 53,54	M	1942	l.	−	B	NSNs	+	CcDee	−	−	+	+	·	+	·	−	−	+	·
V 26	IV 53,54	M	1943	l.	+	O	MNSs	+	CcDee	−	+	+	−	·	+	+	−	−	+	·
V 27	·	F	1943	l.	−	A1	MSMS	+	ccddee	−	−	+	+	·		·	−	+	+	−
V 28	IV 53,54	F	·	d. INF	·	·	·	·	·	·	·	·		·		·	·		·	
V 29	IV 53,54	M	1943	l.	+	O	MNSs	+	CcDee	−	+	+	+	+	+	+	−	−	+	·
V 30	IV 56,57	M	1935	l.	−	O	MsNs	−	CcDee	−	−	−	+	·	+	−	+	−	+	·
V 31	IV 56,57	M	1938	l.	−	A1	MsNs	−	CcDee	−	+	−	+	·	·		+	+	+	−
V 32	IV 56,57	M	1942	l.	+	O	MsMs	−	CcDEe	−	−	−	+	+	+	+	+	+	−	−
V 33	IV 56,57	M	1948	l.	−	A1	MNSs	−	ccDEe	−	+	−	+	·	·		+	+	+	−
V 34	IV 56,57	F	1953	l.	+	A1	MSMs	−	CcDee	−	−	−	+	+	+	·	+	−	+	·
V 35	IV 59,60	M	1948	l.	−	A1	NsNs	−	CCDee	−	−	+	+	+	−	·	−	+	+	−
V 36-39	IV 61	·	·	l.	·	·	·	·	·	·	·	·		·		·	·		·	
V 40	IV 63	·	·	l.	·	·	·	·	·	·	·	·		·		·	·		·	
V 41	IV 64,65	F	1954	l.	−	A1	MNSs	−	ccDee	−	−	+	+	−		·	·	+	+	−
V 42	IV 64,65	F	1954	d.	·	·	·	·	·	·	·	·		·		·	·		·	
V 43	IV 64,65	F	1957	l.	−	A1	MNSs	−	ccDee	−	−	−	+	−		·	·	+	+	−
V 44	IV 67,68	M	1943	l.	−	B	MsNs	+	ccDee	−	−	+	−	·	+	·	−	−	+	·
V 45	IV 67,68	M	1945	l.	−	B	MsNs	+	ccddEe	−	−	+	−	·	+	·	−	−	+	·
V 46	IV 67,68	F	1951	l.	−	B	MsNs	−	ccDee	−	−	+	−	·	+	·	−	−	+	·
V 47	IV 67,68	F	1958	l.	+	O	MsNs	−	ccDEe	−	−	+	−	·	+	+	−	+	+	−
V 48	IV 67,68	F	1960	l.	−	AB	MsNs	+	ccDEe	−	−	+	−	·	+	·	·	−	+	·
V 49	IV 69,70	M	1953	l.	−	O	MSMs	+	CcDee	−	+	+	+	·	+	+	−	+	+	+
V 50	IV 69,70	M	1956	l.	+	O	MNSs	+	CcDee	−	−	+	+	·	+	+	−	+	+	+
V 51	IV 69,70	M	1961	l.	+	A1	MSMs	−	ccDee	−	−	+	−	·	−	·	·	−	+	·
V 52-54	IV 71	M	·	l.	·	·	·	·	·	·	·	·		·		·	·		·	
V 55-59	IV 72	·	·	l.	·	·	·	·	·	·	·	·		·		·	·		·	
V 60	IV 82,83	·	·	s.b.	·	·	·	·	·	·	·	·		·		·	·		·	
V 61	IV 82,83	·	·	d. INF.	·	·	·	·	·	·	·	·		·		·	·		·	
V 62-69	IV 84	·	·	·	·	·	·	·	·	·	·	·		·		·	·		·	
V 70-76	IV 86	·	·	5l.2d	·	·	·	·	·	·	·	·		·		·	·		·	
V 77	IV 88,89	M	1937	d. INF.	·	·	·	·	·	·	·	·		·		·	·		·	
V 78	IV 88,89	F	1939	l.	+	B	MsNs	+	CcDee	−	−	+	+	·		·	−	−	+	·
V 79	·	M	1937	l.	−	O	MNSs	+	CcDEe	−	−	−	−	·	+	+	+	+	+	−
VI 1-3	V 6	·	·	·	·	·	·	·	·	·	·	·		·		·	·		·	
VI 4-9	V 7	·	·	·	·	·	·	·	·	·	·	·		·		·	·		·	
VI 10-13	V 8	·	·	·	·	·	·	·	·	·	·	·		·		·	·		·	

TABLE 2 (CONT.) CALDWELL ANTIGEN FAMILY CR

1	2	3	4	5	6	7	8	9	10	11	12	13	14		15		16	17		
													Fy		Jk					
No.	PARENTS	SEX	Y. of b.	L. or d.	Cl	ABO	MNS	P	Rh	Lu	K	Le	a	b	a	b	Lea	a	b	x
VI 14	V 10,11	·	·	d. INF.	·	·	·	·	·	·	·	·	·		·		·	·	·	
VI 15	V 10,11	M	1959	l.	−	A_1	NsNs	−	CcDee	−	−	−	−	·	·		+	−	+	·
VI 16	V 13	M	1954	l.	·	·	·	·	·	·	·	·	·		·		·		·	
VI 17	V 16	M	·	l.	·	·	·	·	·	·	·	·	·		·		·		·	
VI 18,11	V 23	·	·	l.	·	·	·	·	·	·	·	·	·		·		·		·	
VI 20*	V 26,27	M	1961	l.	+	O	MSMs	+	C^wCDee	−	−	+	+	·	·		−		·	
VI 21-23	V 30	·	·	l.	·	·	·	·	·	·	·	·	·		·		·		·	
VI 24	V 78,77	F	1961	l.	−	O	MNSs	+	CCDee	−	−	−	−	·	+	+	+	−	+	·
VI 25	V 78,77	F	1962	l.	−	O	NsNs	+	ccDEe	−	−	+	−	·	−	+	−		·	
VI 20a	V 26,27	M	1963	l.	−	A	MSNS	−	C^wCDee	−	+	·	+	·	·		·		·	

Table 3a. Techniques used in the Red Cell Grouping Tests.

Technique	Reference	Page No.
Saline Slide	Race and Sanger(1958)	254
Saline Tube	Race and Sanger(1958)	244
Indirect Antiglobulin (I.A.G.T.)	Dunsford and Grant(1959)	-
2-Hour Albumin Tube	Race and Sanger(1958)	246
Albumin Replacement	Boorman and Dodd(1961)	42
Enzyme Tube (Ficin)	Race and Sanger(1958)	251
Capillary Tube	Chown (1962)	personal communication
Trypsin - I.A.G.T.	Race and Sanger (1958)	253

Table 3b. Red Cell Grouping Tests.

System	Typing Serum	Grouping Tests		Comments
		Temp	Technique	
ABO	Anti-A and anti-B	R.T.	Saline Tube	Check purposes and detection of chimeras - none found.
		R.T.	Saline Slide	
	anti-A+B (group O)	R.T.	Saline Tube	Detection of low sub-groups of A e.g. A_x - none found Check on anti-A and anti-B results.
	anti-A_1	+4°C	Saline Slide	Subtyping of group A and AB into A_1 and A_2.
	family mat. plasma	R.T.	Saline Tube Tests with A,B and O cells	Detection of natural anti-A &/or anti-B, and irregular antibodies e.g. anti-A_1 or anti-H.
MNSs	anti-M	R.T.	Saline Slide	
	anti-N	R.T.	Saline Slide	
	anti-S	37°C	Saline Tube	
	anti-s	37°C	2 Hour Alb.Tube or I.A.G.T.	To conserve rare sera only S(+)cells tested.
P	anti-P_1	+4°C	Saline Tube	
Rhesus	anti- C^w+C	37°C	Saline Tube	
	anti- C^w	37°C	Saline Tube	C+C^w (+) cells tested.
	anti-c	37°C	Saline Tube or Enzyme Tube	
	anti-D	37°C	Enzyme Tube & Alb Rep	Every blood tested with 2 anti-D sera
		37°C	Enzyme Tube & I.A.G.T.	D(-) cells tested for D^u with 2 further anti-D sera
	anti-E	37°C	Enzyme Tube	
	anti-e	37°C	Saline Tube	E(+) cells tested.

Table 3b (continued) Red Cell Grouping Tests.

System	Typing Serum	Grouping Tests		Comments
		Temp	Technique	
Lutheran	anti-Lu^a	+4°C	Saline Tube	
	anti-Lu^b	+4°C	I.A.G.T.	Very rare serum only used for special cases e.g. Fam Oak IV 5 and IV 8.
Kell	anti-K	37°C	I.A.G.T.	
Lewis	anti-Le^a	+4°C	Saline Tube	
Duffy	anti-Fy^a	37°C	I.A.G.T.	
	anti-Fy^b	37°C	I.A.G.T.	Suitable for testing bloods of all ABO groups.
			or	
		R.T.	Capillary Tube	Suitable for testing group A and O blood only.*
Kidd	anti-Jk^a	37°C	Trypsin-I.A.G.T.	Suitable for testing group O bloods only.*
			or	
		37°C	I.A.G.T.	Suitable for testing K(-) bloods of all ABO groups.**
	anti-Jk^b	37°C	Trypsin-I.A.G.T.	Suitable for testing group O bloods only.*

* These anti-sera contain anti-B ± anti-A in addition to the specific test anti serum.

** This anti-serum also contains anti-Kell.

Table 4. Serum Gm Grouping Tests

Gm Typing	Coating of red cells *	Gm Grouping Tests **		
	Dilns. of anti-Ra	Dilns. of anti-Gm	Dilns. of family material sera	Time
Gm^a	1/5 Dunc	1/20 Ragg 147	1/8 and 1/16	15-30 mins.
	1/5 Dunc	1/40 Ragg 144	1/8 and 1/16	15-30 mins.
	1/5 Gall	1/20 Ragg 144	1/8 and 1/16	1 hour
Gm^b	1/10 Ivan or 1/10 2269	1/64 Ragg Bomb	1/8 and 1/16	30min.
		1/64 Ragg Bomb	1/8 and 1/16	30 mins.
Gm^x	1/10 Hem or 1/2 Gall	1/32 Taylor	1/16 and 1/32	1 hour
		1/10 Ragg 97	1/16 and 1/32	45-60 mins.

* Group O ccDEE cells were sensitised at 37°C for 90 mins., and used in Gm grouping tests as a 1% suspension in saline.

** Gm grouping tests were carried out on slides at room temperature (R.T.)

Table 5. ABO Phenotype Frequencies

Series	New Scottish	Published * Scottish	New English	Published ** English
AB	3 (2.86%)	284 (3.06%)	2 (1.89%)	1,317 (3.12%)
A	33 (31.43%)	3,038(32.75%)	37 (34.91%)	17,815(42.24%)
B	11 (10.48%)	1,015(10.94%)	16 (15.09%)	3,415(8.10%)
O	58 (55.24%)	4,940(53.25%)	51 (48.11%)	19,632(46.54%)
Totals	105	9,277	106	42,179

* The counties of Dunbarton, Stirling, Renfrew, Ayr and Lanark.

** The S. part of the West Riding, Notts, Derby, Stafford, Salop, Worcester, Warwick, S. part of Northants and Bedford.

New Scots/published Scots - $\chi^2 = 0.16$, for 2 d.f., $0.95 > P > 0.90$,

New English/published English - $\chi^2 = 4.52$, for 2 d.f., $0.2 > P > 0.1$,

Scottish data/English data - $\chi^2 = 514$, for 3 d.f., $P < 0.001$.

Table 6 MNSs Phenotype Frequencies.

Series	New Scottish	Published Scottish	New English	Published English
MSMS	4 (3.85%)	105(19.92%)	7(6.73%)	57(5.7%)
MSMs	17 (16.35%)		11(10.58%)	140(14.0%)
MsMs	9 (8.65%)	37(7.02%)	9(8.65%)	101(10.1%)
MSNS	5 (4.81%)	139(26.38%)	4(3.85%)	39(3.9%)
MNSs	19 (18.27%)		26(25.0%)	224(22.4%)
MsNs	25 (24.04%)	145(27.51%)	32(30.77%)	226(22.6%)
NSNS	2 (1.92%)	22(4.17%)	1(0.96%)	3(0.3%)
NSNs	3 (2.88%)		2(1.92%)	54(5.4%)
NsNs	20 (19.23%)	79(14.99%)	12(11.54%)	156(15.6%)
Totals	104	527	104	1,000

New Scots/published Scots - $\chi^2 = 2.14$, for 4 d.f., $P \doteq 0.7$,

New English/published English - $\chi^2 = 6.00$, for 6 d.f., $0.5 > P > 0.3$,

Scottish data/English data - $\chi^2 = 6.53$, for 5 d.f., $0.3 > P > 0.2$.

Table 7 — P Phenotype Frequencies

Series	New Scottish	Published Scottish	New English	Published English
$P_1(+)$	87(82.86%)	398(75.52%)	84(79.25%)	893(76.59%)
$P_1(-)$	18(17.14%)	129(24.48%)	22(20.75%)	273(23.41%)
Totals	105	527	106	1,166

New Scots/published Scots - $\chi^2 = 2.64$, for 1 d.f., $0.2 > P > 0.1$,
New English/published English - $\chi^2 = 0.38$, for 1 d.f., $0.7 > P > 0.5$,
Scottish data/English data - $\chi^2 = 0.001$, for 1 d.f., $0.98 > P > 0.95$.

Table 8 — Rhesus Phenotype Frequencies

Series	New Scottish	Published Scottish	New English	Published English
CCDee	17(16.19%)	795(17.16%)	17(16.04%)	178(16.59%)
C^{V}CDee	2(1.90%)		1(0.94%)	12(1.12%)
CcDee	36(34.29%)	1,690(36.49%)	34(32.08%)	354(32.99%)
C^{V}cDee	-		1 (0.94%)	9(0.84%)
CcDEe	17(16.19%)	639(13.79%)	14(13.21%)	138(12.86%)
C^{V}cDEe	1(0.95%)		1(0.94%)	6(0.56%)
ccDEe	11(10.48%)	655(14.14%)	17(16.04%)	137(12.77%)
ccDEE	1(0.95%)		5(4.72%)	29(2.70%)
ccddee	18(17.14%)	752(16.23%)	13(12.26%)	170(15.84%)
ccDee	1(0.95%)	58(1.25%)	-	19(1.77%)
Ccddee	-	25(0.54%)	3(2.83%)	10(0.93%)
ccddEe	1(0.95%)	18(0.39%)	-	7(0.65%)
CCDEe	-	-	-	4(0.37%)
Totals	105	4,632	106	1,073

New Scots/published Scots - $\chi^2 = 1.64$, for 4 d.f., $P \doteq 0.8$,
New English/published English - $\chi^2 = 1.85$, for 5 d.f., $0.9 > P > 0.8$,
Scottish data/English data - $\chi^2 = 15.77$, for 7 d.f., $0.05 > P > 0.025$.

Table 9 Lutheran Phenotype Frequencies

Series	New Scottish	Published Scottish	New English	Published English
Lu (a+)	3(3.13%)	29(5.5%)	11(10.48%)	105(7.65%)
Lu (a-)	93(96.87%)	498(94.5%)	94(89.52%)	1,268(92.35%)
Totals	96	527	105	1,373

New Scots/Published Scots - corrected $\chi^2 = 0.51$, for 1 d.f., $0.5 > P > 0.3$,
New English/published English - $\chi^2 = 1.08$, for 1 d.f., $P \div 0.3$,
Scottish data/English data - $\chi^2 = 4.93$, for 1 d.f., $P \div 0.025$.

Table 10 Kell Phenotype Frequencies.

Series	New Scottish	Published Scottish	New English	Published English
Kell (+)	12(11.43%)	47(8.92%)	5(4.72%)	99(8.94%)
Kell (-)	93(88.57%)	480(91.08)	101(95.28%)	1,009(9.06%)
Totals	105	527	106	1,108

New Scots/published Scots - $\chi^2 = 0.65$, for 1 d.f., $0.5 > P > 0.3$,
New English/published English-corrected - $\chi^2 = 1.69$, for 1 d.f., $0.2 > P > 0.1$,
Scottish data/English data - $\chi^2 = 0.31$, for 1 d.f., $0.7 > P > 0.5$.

Table 11 Duffy Phenotype Frequencies

Series	New Scottish	Donor Scottish	New English	Published English
Fy(a+ b-)	25.68(24.46%)	123(69.1%)	19.03(17.95%)	178(19.58%)
Fy(a+ b+)	41.32(39.35%)		54.97(51.86%)	435(47.85%)
Fy(a- b+)	38 (36.19%)	55(30.9%)	32 (30.19%)	296(32.56%)
Totals	105	178	106	909

New Scots/donor Scots - χ^2 = 0.84, for 1 d.f., 0.5 > P > 0.3,
New English/published English - χ^2 = 0.61, for 2 d.f., 0.8 > P > 0.7,
Scottish data/English data - χ^2 = 0.03, for 1 d.f. 0.9 > P > 0.8.

Table 12a ABH Secretor Phenotype Frequencies.

Series	New Scottish	Published Scottish	New English	Published English
Secretor	68(66.02%)	371(73.76%)	80(77.67%)	864(77.28%)
Non-Sec	35(33.98%)	132(26.24%)	23(22.33%)	254(22.72%)
Totals	103	503	103	1,118

New Scots/published Scots - χ^2 = 2.57, for 1 d.f., 0.2 > P > 0.1,
New English/published English - χ^2 = 0.01, for 1 d.f., P = 0.9,
Scottish data/English data - χ^2 = 5.22, for 1 d.f., 0.025 > P > 0.02.

Table 12b Lewis (Le^2) Phenotype Frequencies.

Series	New Scottish	Published Scottish	New English	Published English
Le (a+)	36(33.96%)	150(28.46%)	23(21.90%)	246(21.1%)
Le (a-)	70(66.04%)	377(71.54%)	82(78.10%)	920(78.9%)
Totals	106	527	105	1,166

New Scots/published Scots - χ^2 = 1.28, for 1 d.f., 0.3 > P > 0.2,
New English/published English - χ^2 = 0.04, for 1 d.f., 0.9 > P > 0.8,
Scottish data/English data - χ^2 = 15.7, for 1 d.f., P < 0.001.

Table 15a — Gm (Gm^a) Phenotype Frequencies

Series	New Scottish	Donor Scottish	New English	Published English
Gm (a+)	56(55.45%)	84(56.0%)	68(64.76%)	63 (63%)
Gm (a-)	45(44.55%)	66(44.0%)	37(35.24%)	37(37%)
Totals	101	150	105	100

New Scottish/Donor Scottish $= \chi^2 = 0.007$, for 1 d.f., $0.95 > P > 0.90$,
New English/published English $= \chi^2 = 0.07$, for 1 d.f., $0.8 > P > 0.7$,
Scottish data/English data $= \chi^2 = 3.09$, for 1 d.f., $0.1 > P > 0.05$.

Table 15b — Frequency (%) of Gm(a+) Factor in Europe

Based on Roberts, Rivat, Rousseau, Daitsch and van Loghem (1963)

Series	Approx.[x] Lat.	No. Tested	Gm(a+)	Gm(a-)
Greece (Attica)	38°	178	37.64	62.36
Italy (Naples)	41°	84	40.5	59.5
France (Rouen)	49°	1,000	51.7	49.3
Denmark	56°	1,084	55.63	44.37
Scotland (Glasgow)	56°	251	55.78	44.22
Sweden	59°	560	59.7	40.3
Norway	60°	1,000	61.8	38.2
England	52°	205	63.9	36.1
Finland	60°	477	64.99	35.01

[x] Approximate latitude is that of capital city, unless otherwise indicated

Table 15c. — Gm (Gm^a, Gm^b, Gm^{ax}) Phenotype Frequencies.

Series		New Scottish	New English	Published English
Gm(a+b+x+)	$Gm^{ax}Gm^b$	18(17.82%)	25(23.81%)	17(17.0%)
Gm(a+b+x-)	Gm^aGm^b	27(26.73%)	28(26.67%)	32(32.0%)
Gm(a+b-x+)	$Gm^aGm^{ax}/Gm^{ax}Gm^{ax}$	8(7.92%)	8(7.62%)	8(8.0%)
Gm(a+b-x-)	Gm^aGm^a	3(2.97%)	7(6.67%)	6(6.0%)
Gm(a-b+x-)	Gm^bGm^b	45(44.55%)	37(35.24%)	37(37.0%)
Totals		101	105	100

New English/published English $= \chi^2 = 1.70$, for 3 d.f., $0.7 > P > 0.5$.

Table 15d Gm Allele Frequencies

Allele	Rough Estimate	Improved Estimates First	Second	Third	Fourth	Final Estimate	Populn.
Gm^a	0.2527	0.1912	0.18619	0.18598	0.18554	0.18552	Scottish
	0.2772	0.22672	0.22185	0.22158	0.22155	0.22133	English
Gm^b	0.6685	.	.	.	.	0.6683	Scottish
	0.6048	.	.	.	.	0.6048	English
Gm^x	0.0990	0.1405	0.14548	0.14608	0.14614	0.14617	Scottish
	0.1180	0.16052	0.17339	0.17385	0.17389	0.17391	English
Gm^aGm^{ax} /	p(1)	p'(2)	p'(3)	y_o(est)	p(4)	y_o(final)	
$Gm^{ax}Gm^{ax}$	2.35047	1.36089	1.27975	1.27248	1.26971	1.26920	Scottish
= p	2.34918	1.34541	1.27967	1.27506	1.27295	1.27273	English

Table 15e. Random Mating Expectations

Phenotype	New Scottish Series Observed	Expected	χ^2	New English Series Observed	Expected	χ^2
Gm(a+b+x+)	18	19.74	0.1554	25	22.09	0.3855
Gm(a+b+x-)	27	25.04	0.1534	28	28.11	0.0004
Gm(a+b-x+)	8	7.64		8	11.26	0.9438
Gm(a+b-x-)	3	3.48	11.12 0.0015	7	5.14	0.6731
Gm(a-b+x-)	45	45.11	0.0003	37	38.41	0.0518
Totals	101	101	0.3084	105	105	2.0524

New Scottish series - χ^2 = 0.31, for 1 d.f., 0.7 > P > 0.5,

New English series - χ^2 = 2.05, for 2 d.f., 0.5 > P > 0.3.

Table 14. Segregation ratio - Nail-Patella syndrome.

Family	Father Affected					Mother Affected				
	Males		Females		Total	Males		Females		Total
	Aff.	Unaff.	Aff.	Unaff.		Aff.	Unaff.	Aff.	Unaff.	
Sau	16.25	12.25	11.25	13.25	53	4	9	1	8	22
Sau 2	7.75	10.25	6	5	29	6.75	11.25	10.5	9.5	38
Sau 3	11	10.5	5.5	8	35	10.5	7	2.5	7	27
Obs.	35	33	22.75	26.25	117	21.25	27.25	14	24.5	87
Exp.	30.1	30.1	28.4	28.4	117	22.30	22.38	21.12	21.12	87

Total χ^2 = 6.42, for 6 d.f., 0.5>P>0.3

Affected/Unaffected - χ^2 = 1.59, for 1 d.f., P ≒ 0.2

Table 15 Segregation ratio - Gl^a(Caldwell) antigen.

Family	Father Affected					Mother Affected				
	Males		Females		Total	Males		Females		Total
Cal + Gil	Aff.	Unaff.	Aff.	Unaff.		Aff.	Unaff.	Aff.	Unaff.	
Obs.	9.5	12.	8.5	11	41	15.25	16.75	13.75	14.25	60
Exp.	10.55	10.55	9.95	9.95	41	15.44	15.44	14.56	14.56	60

Total χ^2 = 0.80, for 6 d.f., P>0.99

Affected/Unaffected - χ^2 = 0.49, for 1 d.f., P ≒ 0.5

Table 16 Hand calculation of lod scores

For detection of linkage between the ABO and Nail-Patella loci in family Sou 1.

θ	$P(F\|\theta)$*	$\log_{10}P(F\|\theta)$**	Lod Score*** by counting	Lod Score by computer
0.50	$.5^{1}\times .5^{31}$	-9.6320	0	0
0.40	$.4^{1}\times .6^{31}$	-7.2737	+ 2.3583	+ 2.0382
0.30	$.3^{1}\times .7^{31}$	-5.3248	+ 4.3072	+ 4.0652
0.20	$.2^{1}\times .8^{31}$	-3.7 029	+ 5.9291	+ 5.6587
0.10	$.1^{1}\times .9^{31}$	-2.4398	+ 7.1822	+ 6.7267
0.05	$.05^{1}\times .95^{31}$	-1.9923	+ 7.6397	+ 6.9622
0.03	$.03^{1}\times .97^{31}$	-1.9321	+ 7.6999	+ 6.9463

* $P(F|\theta) \propto \theta^{1}(1-\theta)^{31}$

** $\log_{10}P(F|\theta) = \log_{10}\theta + 31\log_{10}(1-\theta)$

*** Lod score $= \log_{10}P(F|\theta) - \log_{10}P(F|0.5)$

Table 17a Lod scores for linkage between the Lutheran and Secretor loci.

From Morton's (1955) tables.

Family	G	Mating Type	Lod Scores, $z(\theta)$						
			$\theta = 0$	0.05	0.1	0.2	0.3	0.4	0.5
Bak III 4	Lu^a	1 (z_1, e_1) 10 (z_2, e_2) uninformative	-.3824	-.2317	-.1451	-.0557	-.0181	-.0036	0
Bla II 1*	Lu^a	as for Bak	-.3807	-.3475	-.2913	-.1698	-.0747	-.0184	0
For VI 63	Se	1 (z_1),9(z_2)	+.3962	+.3323	+.2804	+.1792	+.0887	+.0240	0
For VII 78	Se	1 (z_1)	+.3010	+.2577	+.2148	+.1535	+.0645	+.0170	0
H II 11	Se	1 (z_1),9(z_2)	+.5312	+.5272	+.4957	+.3791	+.2218	+.0691	0
M^eG II 4^F	Lu^a	as for Bak	+.0207	+.0912	+.1229	+.1202	+.0734	+.0219	0
Oak III 12	Se	10 (z_2),13(z_3)	-.6789	-.3824	-.2383	-.0971	-.0350	-.0077	0
San 1 IV 6	Se	9 (z_2)	+.0738	-.6584	-.3917	-.1623	-.0609	-.0139	0
San 1 IV 14	Se	9 (z_2)	$-\infty$	-.7212	-.4437	-.1938	-.0757	-.0177	0
Total lod score = $\sum z(\theta) = Z(\theta)$			$-\infty$	-1.3326	-.3968	+.1333	+.1840	+.0707	0
Antilod			0	0.0737	0.4011	1.359	1.528	1.175	1

= Of Scottish origin. Hence Scottish Se/se allele frequencies used in calculations.

Scottish Se = 0.4171 and se = 0.5829

Table 17b Abstract from lod score calculations in Lu-Sec linkage tests in family For VI 63.

Possible mating types	(a) relative freq. of mating	(b) likelihood of progeny	(c)=(a)x(b) adjusted rel freq. of mating	z(θ)	(d) antilod z(θ)	(f)=(c)x(d) adjusted antilod	log(f)	LOD	θ
1 GgTt x ggtt	g 0.4767	$(\frac{1}{2})^1.(\frac{1}{2})^2.(\frac{1}{2})^2.(\frac{1}{2})^1$ 1	1	z_1 0	1	1.0000	.	.	
9 GgTt x Ggtt	2G 1.0456	$(\frac{1}{2})^1.(\frac{1}{2})^2.(\frac{1}{2})^2.(\frac{1}{2})^1$ 1.125	2.4699	z_2 0	1	2.4699	.	.	0.5
						3.4699 $= \Sigma(f)$	+.5403	0	
"	"	"	"	+.0492	1.200	1.1200	.	.	
"	"	"	"	+.0133	1.0310	2.5465	.	.	0.4
						3.6665	+.5643	+.0240	

G = Se = 0.5233, T = Lu^a = 0.0390)
g = se = 0.4767, t = Lu^b = 0.9610) for English families (Race and Sanger, 1962)

In Mating Type 1, a = GT = 0, b = Gt = 2, c = gT = 1, d = gt = 0.
In Mating Type 9, a = GT = 0, b = gT = 1, c = Gt = 2, d = gt = 0

Table 18 Lod scores for linkage between the ABO and Nail-Patella loci.

In families Sau 1, 2 and 3.

θ	Lod scores, $z(\theta)$			Total lod $z(\theta)$	Antilod
	Sau 1	Sau 2	Sau 3		
0.03	+ 6.9463	+ 0.8678	-1.7525	+ 6.0616	0.115×10^7
0.05	+ 6.9622	+ 1.0217	-0.9570	+ 7.0269	1.064×10^7
0.07	+ 6.9621	+ 1.0986	-0.4739	+ 7.5288	3.379×10^7
0.09	+ 6.7948	+ 1.1371	-0.1412	+ 7.7907	6.176×10^7
0.11	+ 6.6503	+ 1.1522	+ 0.0959	+ 7.8984	7.914×10^7
0.13	+ 6.4744	+ 1.1513	+ 0.2694	+ 7.8951	7.854×10^7
0.15	+ 6.2709	+ 1.1383	+ 0.3967	+ 7.8059	6.396×10^7
0.17	+ 6.0428	+ 1.1159	+ 0.4885	+ 7.6472	4.438×10^7
0.20	+ 5.6587	+ 1.0682	+ 0.5750	+ 7.3019	2.004×10^7
0.25	+ 4.9188	+ 0.9584	+ 0.6187	+ 6.4959	0.313×10^7
0.30	+ 4.0652	+ 0.8180	+ 0.5731	+ 5.4563	0.029×10^7
0.40	+ 2.0382	+ 0.4591	+ 0.3203	+ 2.8176	0.657×10^3
0.50	0	0	0	0	1

Table 19. Lod scores for linkage between the MNS and Cl(Caldwell) loci.

In Families Cal and Gil

θ	Lod scores, z(θ)		Total lod Z(θ)	Antilod
	Cal	Gil		
0	-	-	+ 12.57*	3.715×10^{12}
0.001	+ 0.7070	+ 11.771	+ 12.478	3.006×10^{12} **
0.005	-	-	+ 12.45 *	2.818×10^{12}
0.01	-	-	+ 12.35 *	2.239×10^{12}
0.02	-	-	+ 12.10 *	1.259×10^{12}
0.03	-	-	+ 11.80 *	0.631×10^{12}
0.04	-	-	+ 11.55 *	0.355×10^{12}
0.05	+ 0.5987	+ 10.719	+ 11.3177	0.208×10^{12}
0.08	-	-	+ 10.55 *	0.035×10^{12}
0.10	+ 0.4912	+ 9.6012	+ 10.0924	0.012×10^{12}
0.11	-	-	+ 9.80 *	0.006×10^{12}
0.12	-	-	+ 9.55 *	0.004×10^{12}
0.20	+ 0.2936	+ 7.2705	+ 7.5641	0.004×10^{10}
0.50	0	0	0	1

* By interpolation from the lod/θ graph (fig. 18)

** This value may be subject to slight error due to computer underflow.

Average likelihood = $\bar{P}$ = 0.1325×10^{12}

Probability of linkage between MNS and Cl = $1 - (1.6 \times 10^{-10})$

Probability of NO linkage between MNS and Cl = 1.6×10^{-10}

Table 20a. Lod scores for linkage between the MNSCl and 7 blood group loci.

In families Cal and Gil.

θ	ABO**	P	Rh	K**	Fy	Se***	Gm
0.50	0	0	0	0	0	0	0
0.45	-.1786	.	.	-.0439	.	.	-.2586
0.40	-.4441	+.0098	-.2566	-.2215	-.5023	+.1482	-.5387
0.35	-.8384	.	.	-.5487	.	.	-.8664
0.30	-1.4046	-.1536	-1.4660	-1.0503	-1.5157	+.3451	-1.2734
0.20	-3.2738	-.5988	-4.1331	-2.7534	-3.3595	+.0934	-2.4806
0.10	-7.3625	-1.7129	-10.0747	-6.1984	-6.9695	-1.4221	-4.7894
0.05	-11.2868	-3.0572	-16.8226	.	-10.8444	-3.5333	-7.2169
0	$-\infty$	$-\infty$	$-\infty$	$-\infty$	$-\infty$	$-\infty$	$-\infty$

** Family Gil only, family Cal gives no information.

*** Families Cal and Gil give no information regarding Lutheran-Secreton linkage, or Lutheran-MNSCl linkage.

Table 20b Likelihood ratio (antilod)values for linkage between the MNSCl and 7 blood group loci.

θ	ABO	P	Rh	K	Fy	Se	Gm
0.50	1	1	1	1	1	1	1
0.45	.663	.	.	.904	.	.	.551
0.40	.360	1.023	.554	.601	.315	1.407	.289
0.35	.145	.	.	.283	.	.	.136
0.30	0.39	.702	.034	.09	.031	2.214	.053
0.20	.001	.252	$.7 \times 10^{-4}$	.002	.001	1.240	.003
0.10	$.4 \times 10^{-7}$	.019	$.8 \times 10^{-10}$	$.6 \times 10^{-6}$	$.1 \times 10^{-6}$	.038	$.2 \times 10^{-4}$
0.05	$.5 \times 10^{-11}$	.001	$.7 \times 10^{-16}$	.	$.1 \times 10^{-10}$	$.3 \times 10^{-3}$	$.6 \times 10^{-7}$
0	0	0	0	0	0	0	0

Ie 21 Probabilities of linkage between the MNSOI and 7 blood group loci

Loci	ABO	P	Rh	K	Fy	Se	Gm	15 unmarked linkage gps.	Total
(1) $r = a/A$	.0078	.2445	.0044	.0238	.0083	.4360	.0215	...	...
(2) New odds on linkage, $\theta < .5$ $\bar{P}_{ABO} : \bar{P}_{P} : \bar{P}_{Rh}$ etc.	.16 :	.50 :	.22 :	.24 :	.15 :	1.10 :	.35 :	1(x 15)	17.52^{P}
(3) Probability of linkage, $\theta < .5$	.009	.029	.013	.014	.009	.063	.009	.057(x 15)	1.000
(4) Probability of linkage	.0001	.007	.0002	.0003	.0001	.027	.0002	.057(x 15)	1.000
$\theta < .3$ / $\theta > .3$	.0089	.022	.0129	.0137	.0089	.036	.0088		

(1) $r = a/A$, where a = area under likelihood/θ curve from $0 < \theta < 0.3$,

A = total area under likelihood/θ curve from $0 < \theta < 0.5$,

(2) $\bar{P}$ = average likelihood,

(3) Probability of linkage = (2) / T,

(4) Probability of linkage, $\theta < 0.3 = r \times (3)$,

$\theta > 0.3 = (3) - r \times (3)$.

After Bailey (1961)

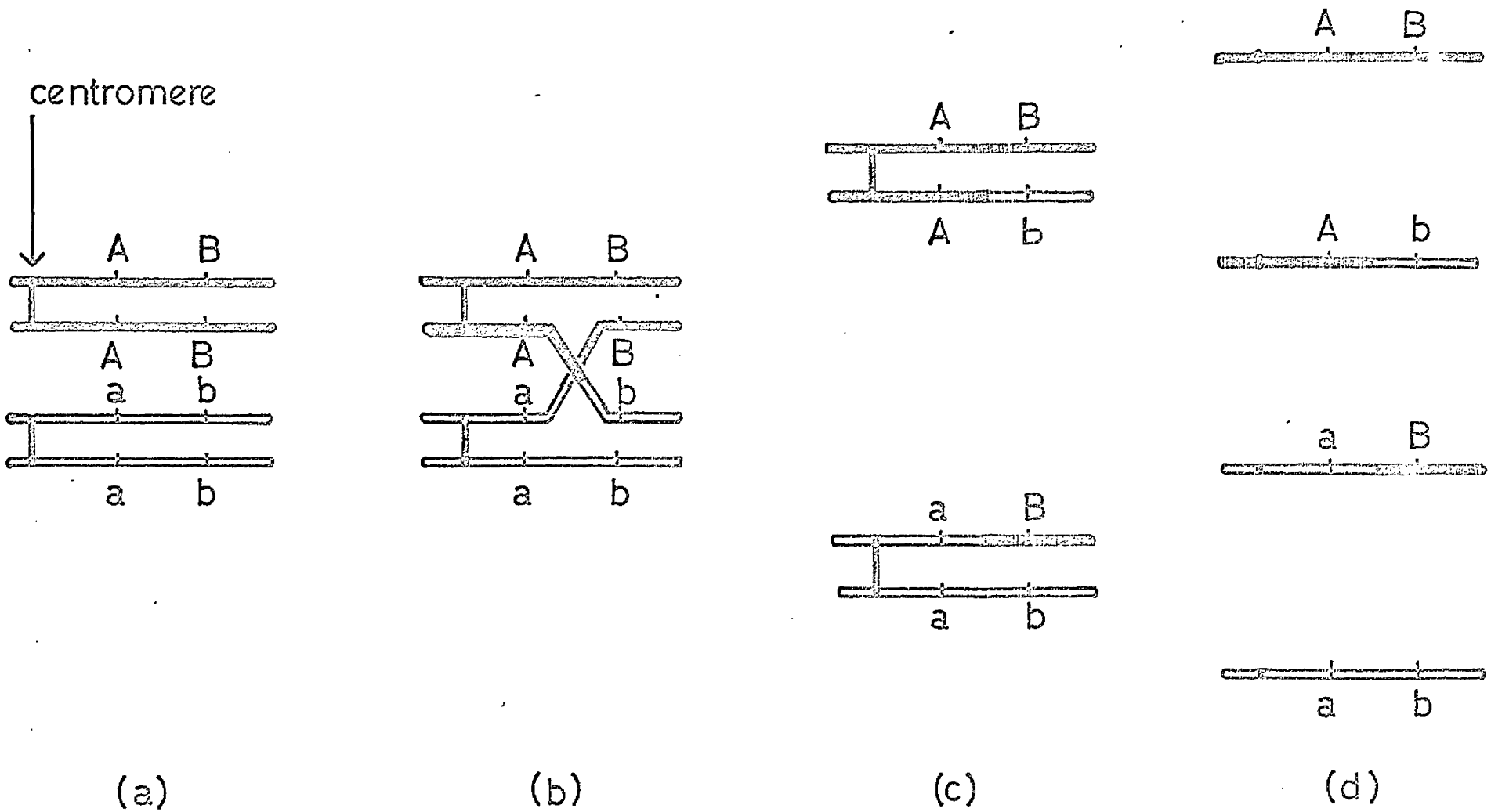


Fig. 1 Crossing-over between Linked Loci

Key to symbols used in Figs. 2 - 4

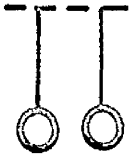

Nail - Patella syndrome present.

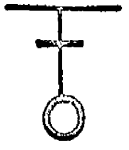

Nail - Patella syndrome absent.


Insufficient evidence on Nail-Patella syndrome.


Stillbirth or death in infancy.

Miscarriage.


Exact birth order of sibs not known.


Blood groups indicate extra-marital offspring.


Propositus.

ABO phenotypes recorded where known.

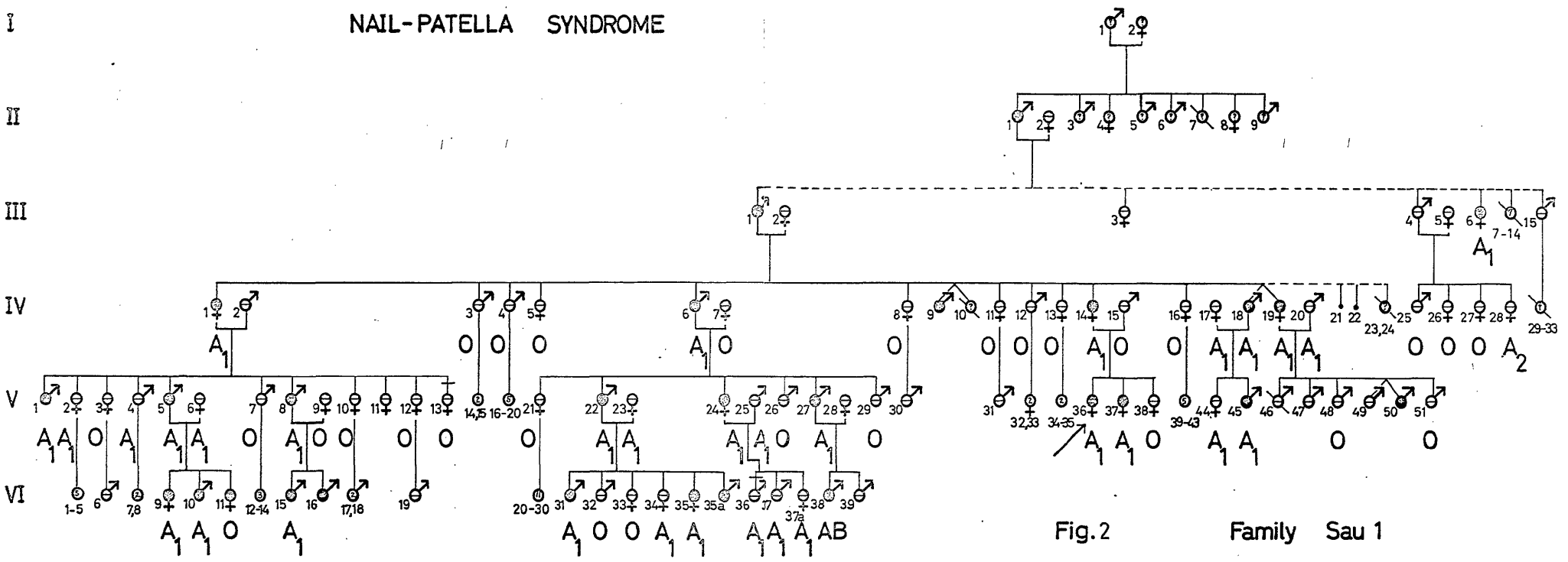


Fig. 2 Family Sau 1

NAIL-PATELLA SYNDROME

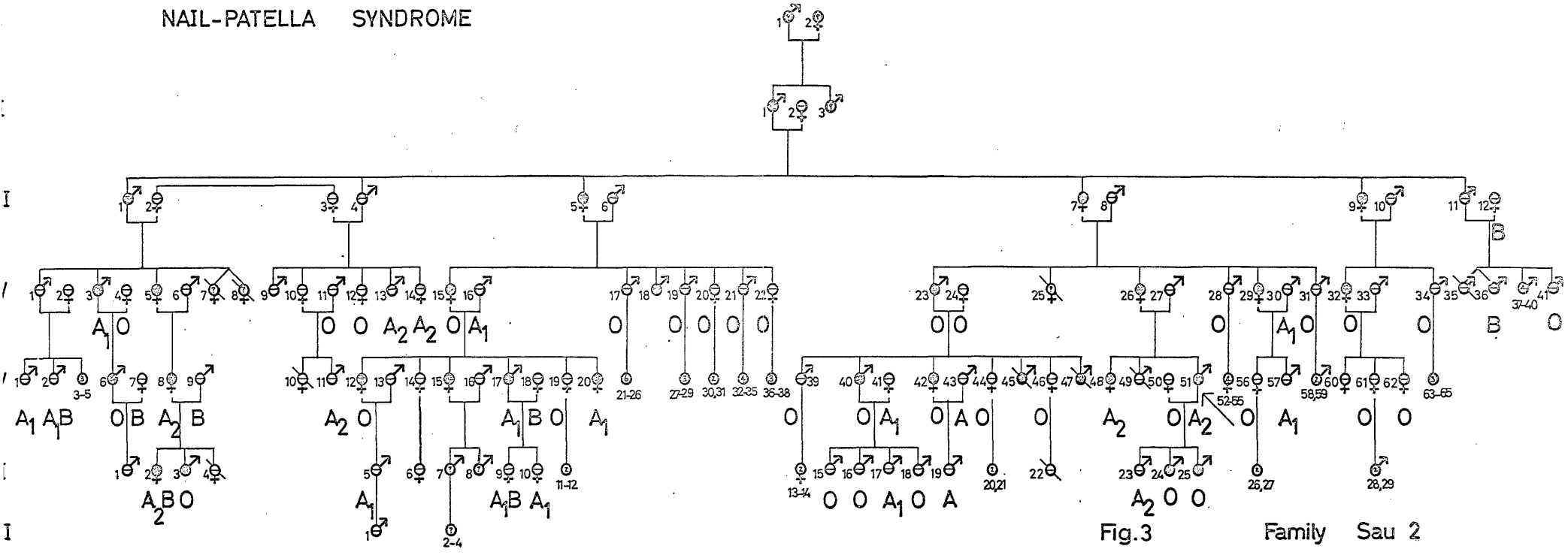


Fig.3 Family Sau 2

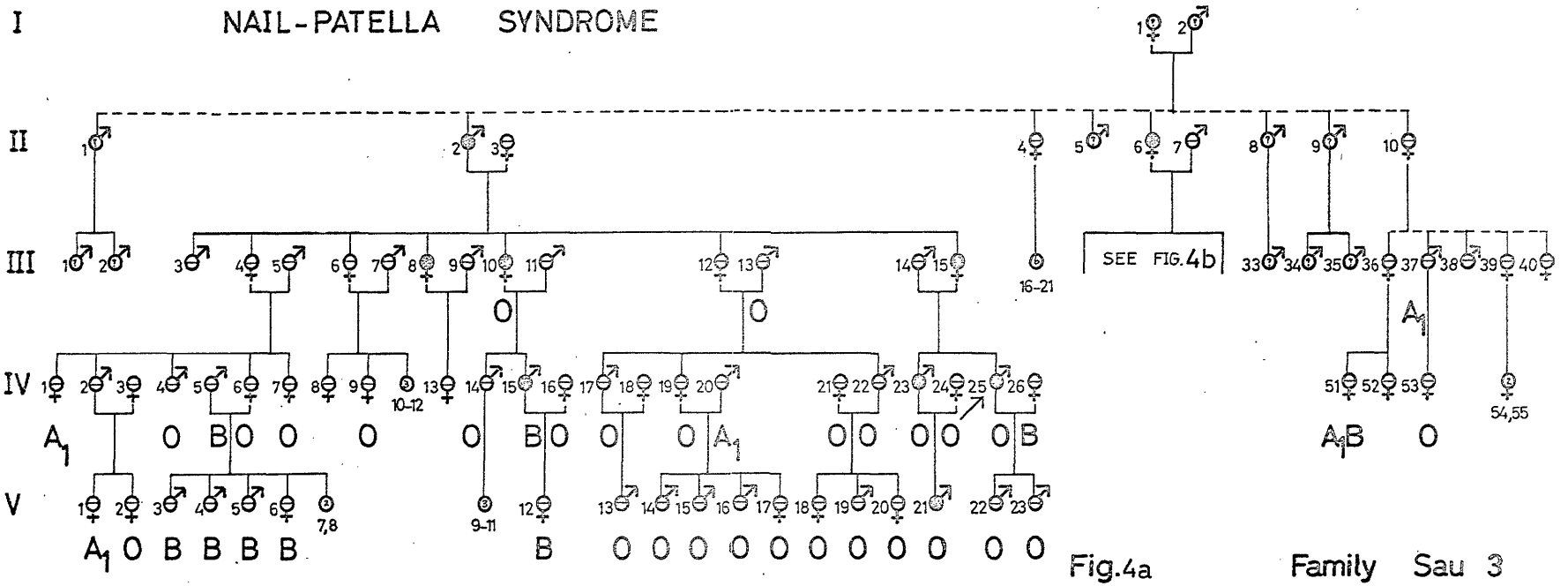


Fig.4a Family Sau 3

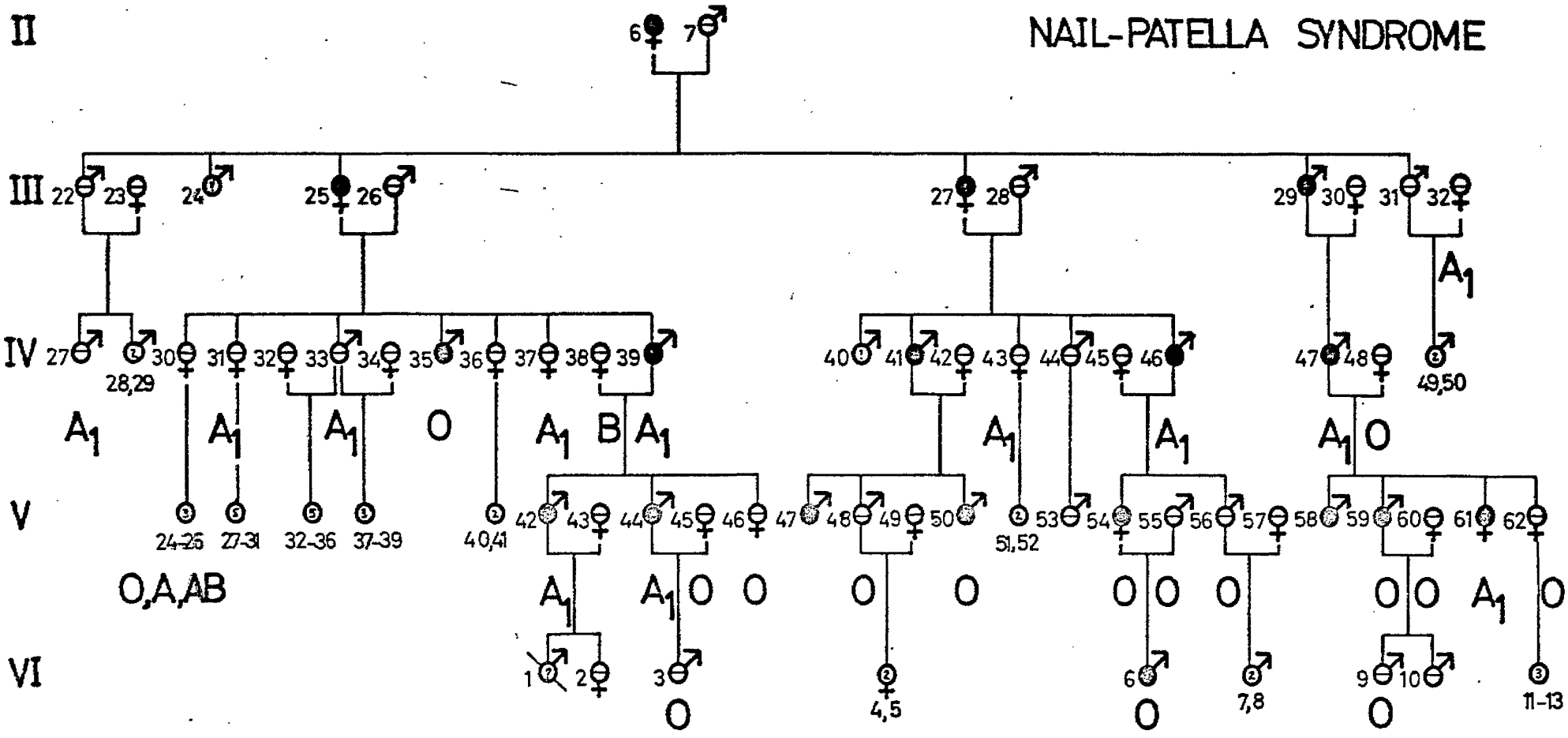


Fig. 4b

Family Sau 3

Key to symbols used in Figs. 5-13

◍	Blood grouped. Found to be Lu(a+).
⊙	Blood not grouped. Inferred to be Lu(a+).
⊖	Blood grouped. Found to be Lu(a-).
○	Blood not grouped.
Sec	Secretor of ABH substances in saliva.
Non	Non-secretor of ABH substances in saliva.

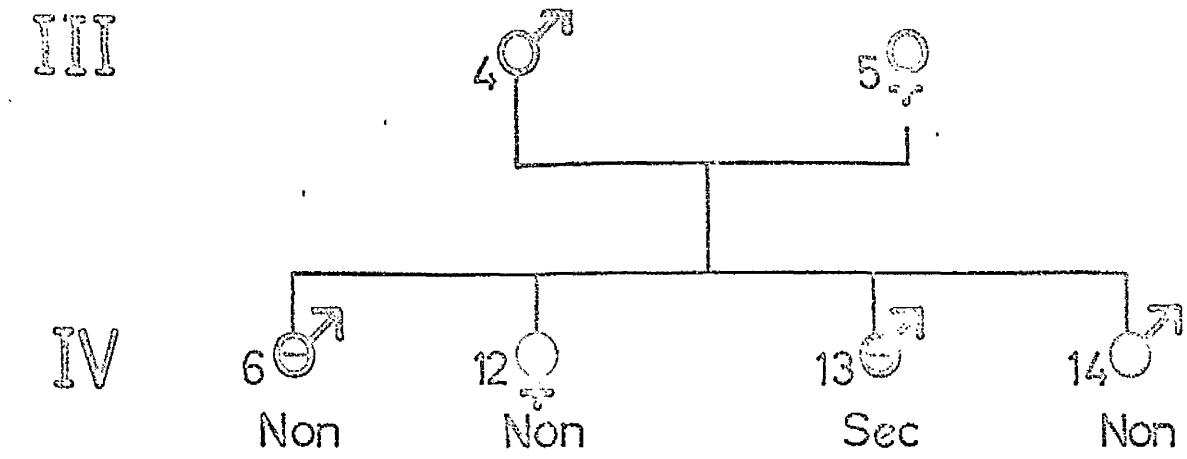


Fig.5 Family Bak

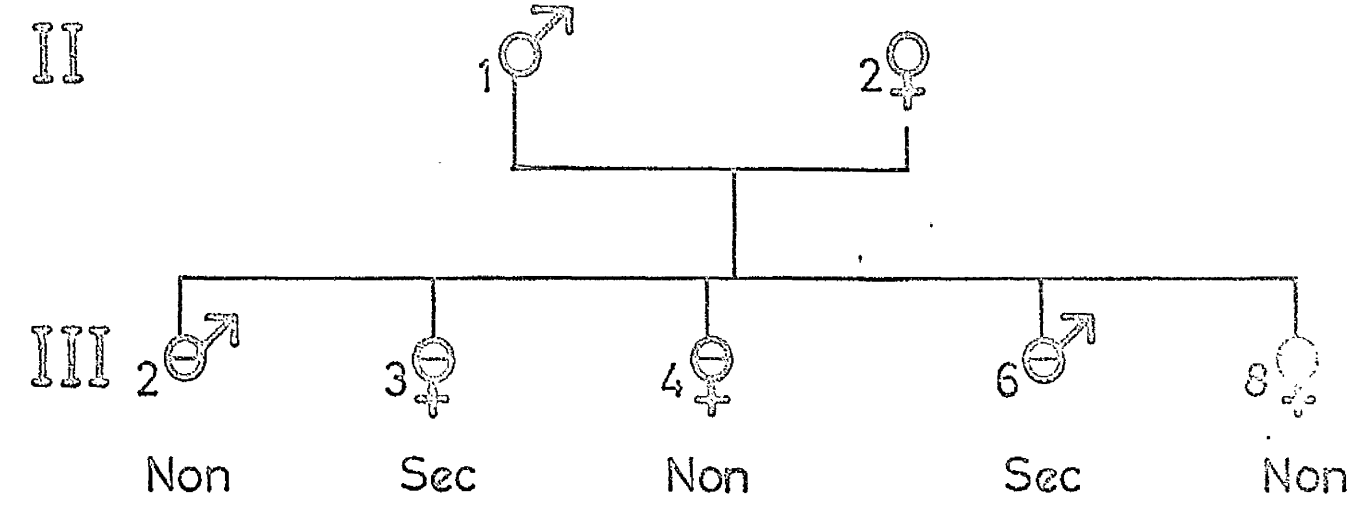


Fig.6 Family Bla

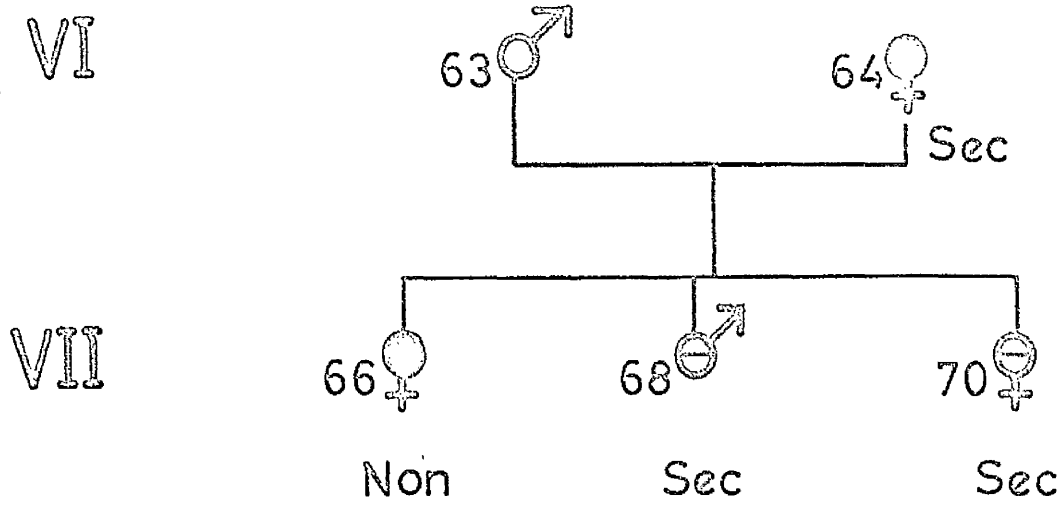


Fig.7 Family For

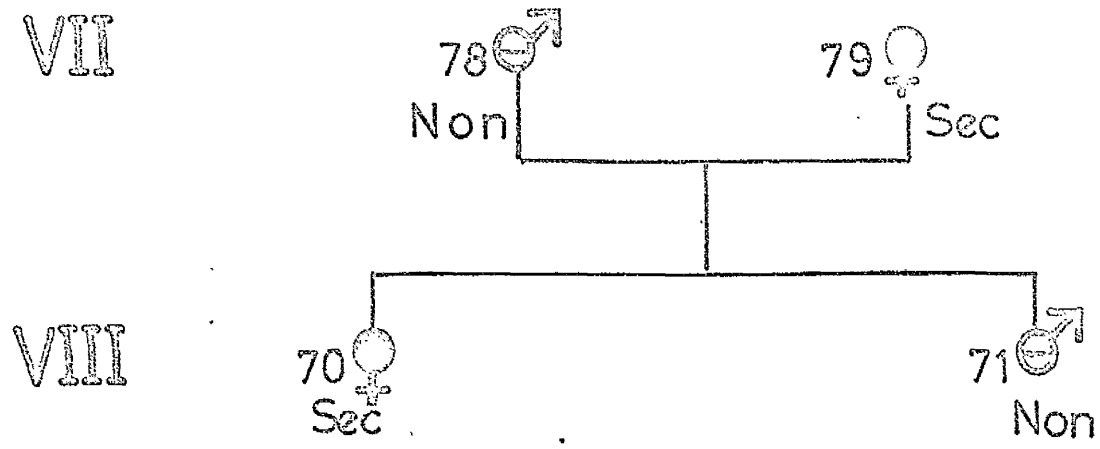


Fig.8 Family For

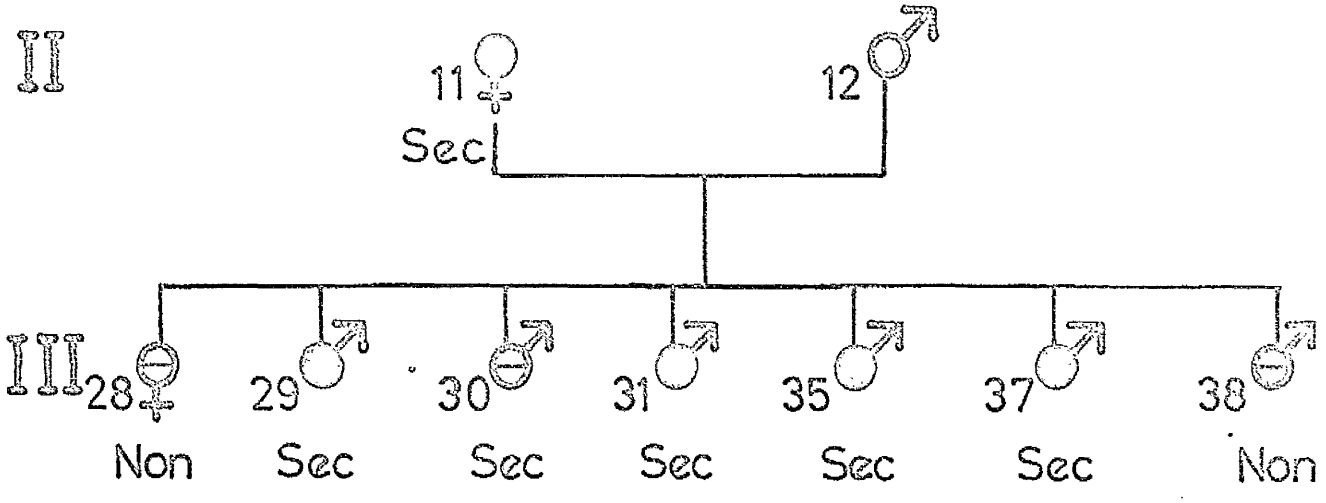


Fig.9 Family N-p H

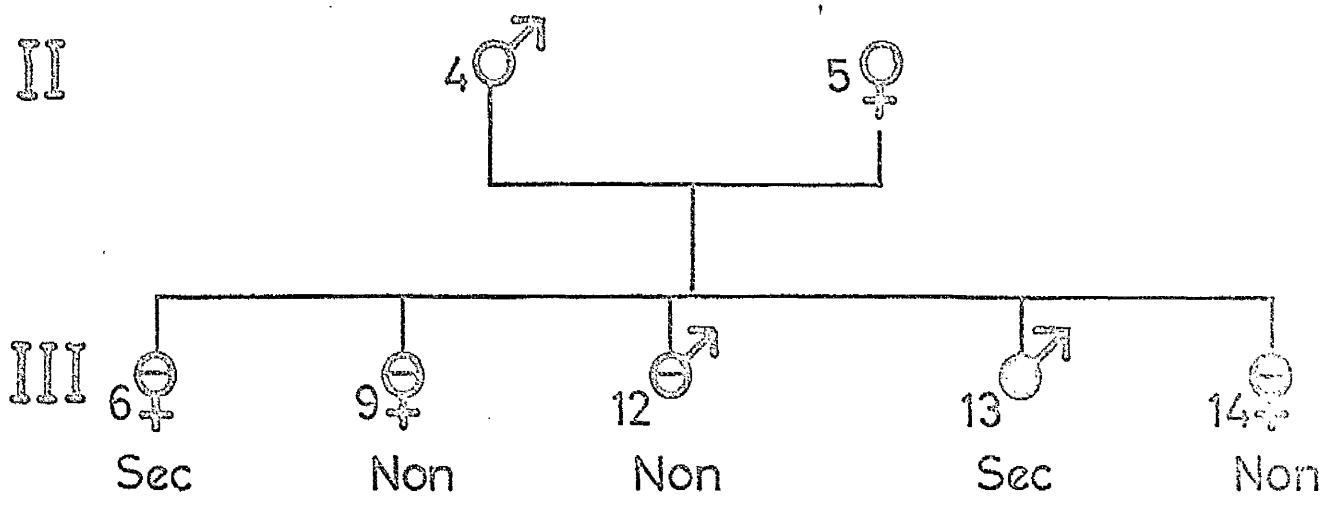


Fig.10 Family McG

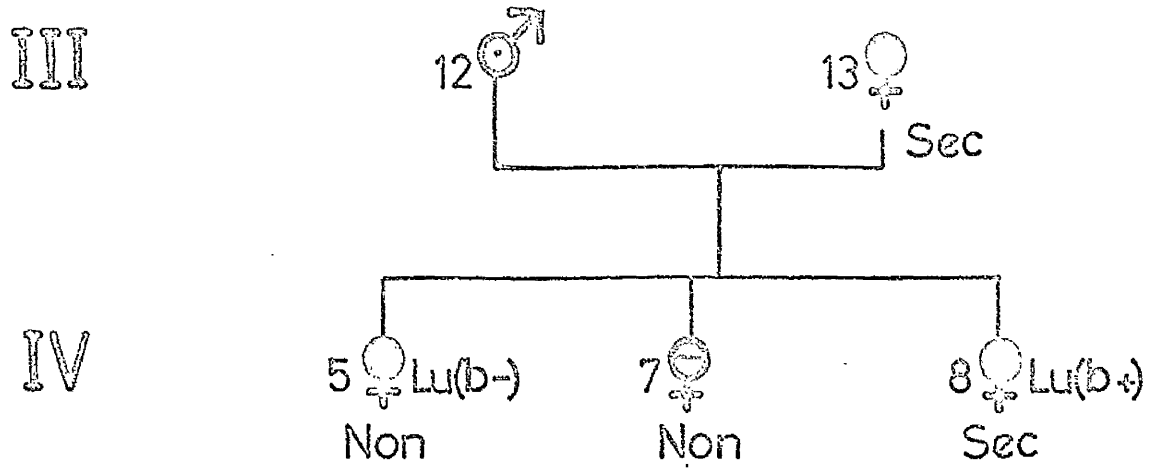


Fig.11 Family Oak

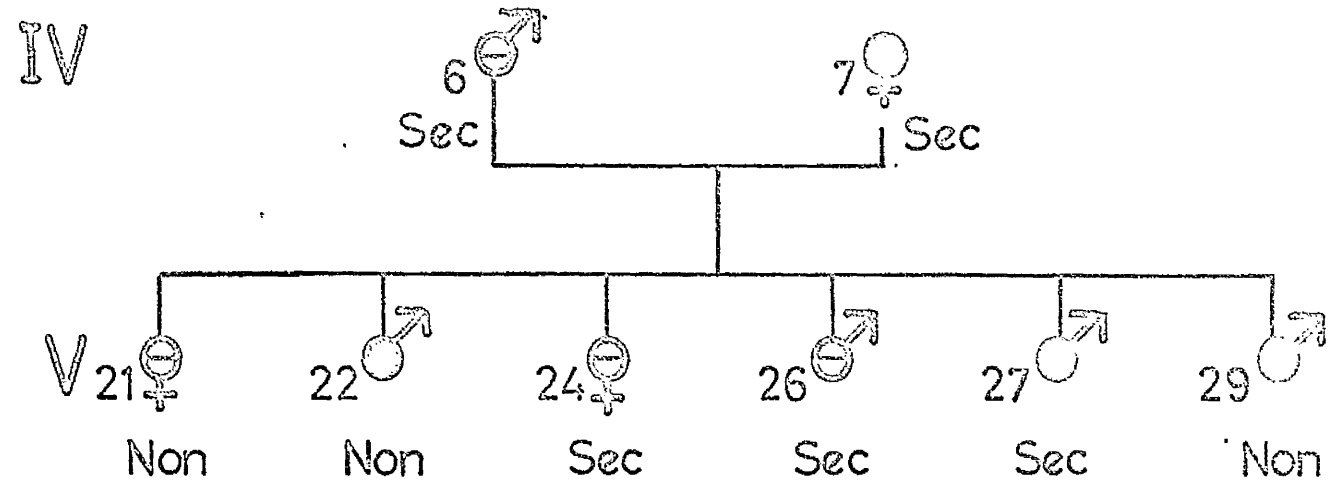


Fig.12 Family Sau 1

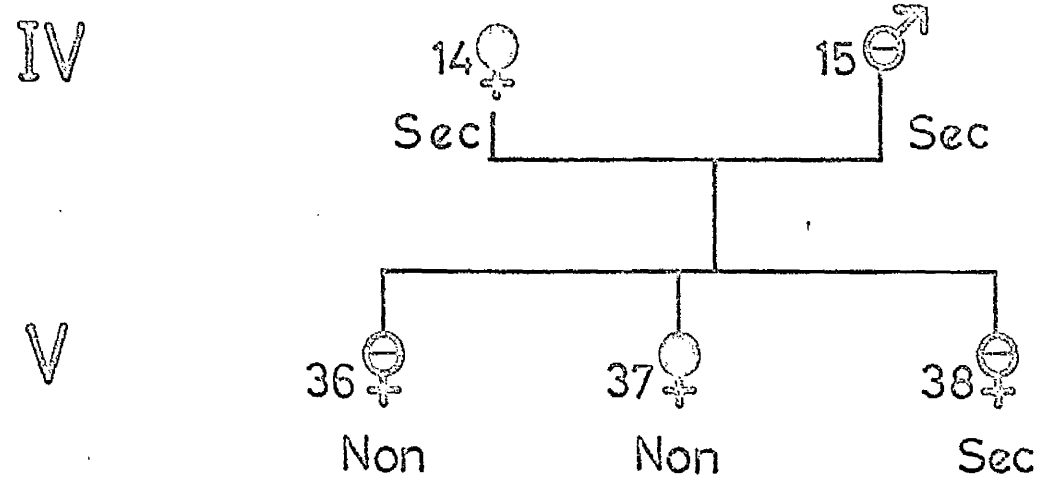


Fig.13 Family Sau 1

Key to symbols used in Figs.14 and 15

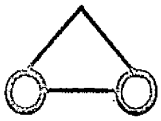

Blood grouped. Found to be Cl(a+).

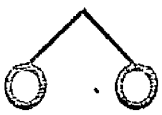

Blood not grouped. Inferred to be Cl(a+).

Blood grouped. Found to be Cl(a-).

Blood not grouped.


Stillbirth or death in infancy.


Identical twins.


Fraternal twins.


Propositus.

MNS phenotypes recorded where known, with the inferred genotype of an MNSs phenotype shown in brackets.

CALDWELL ANTIGEN

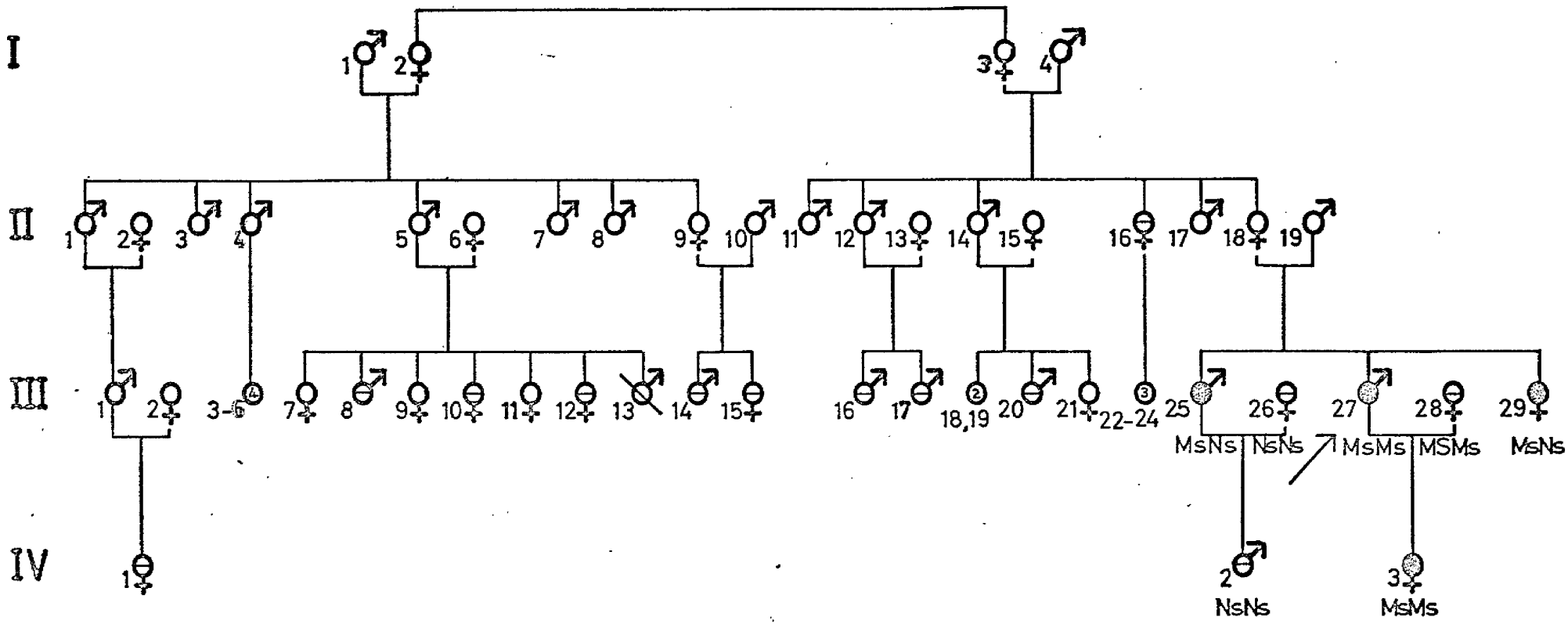


Fig.14 Family Cal

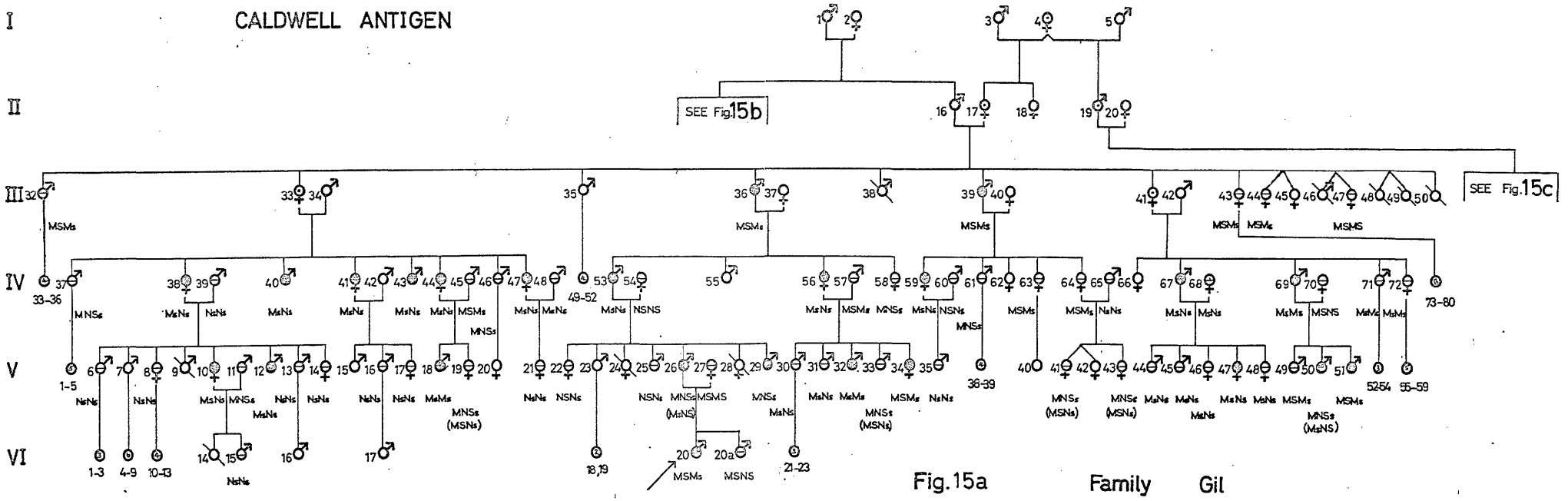


Fig.15a Family Gil

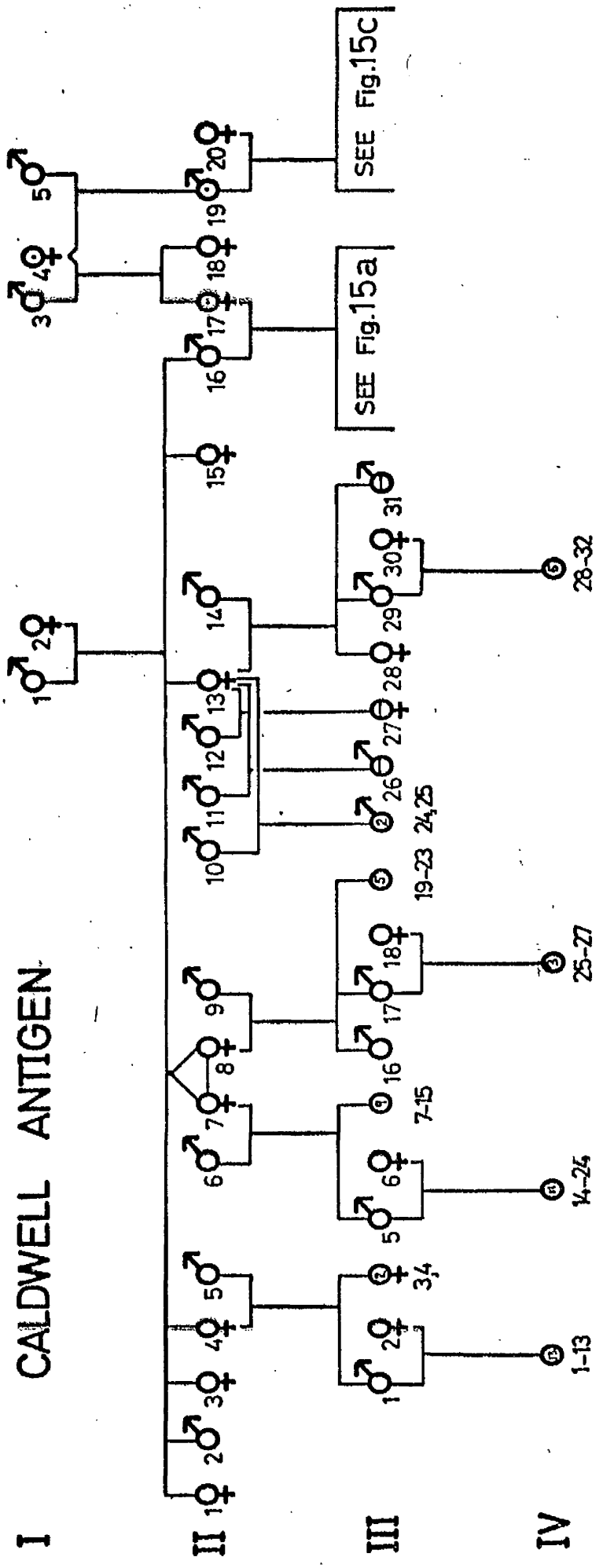


Fig. 15 b

Family Gil

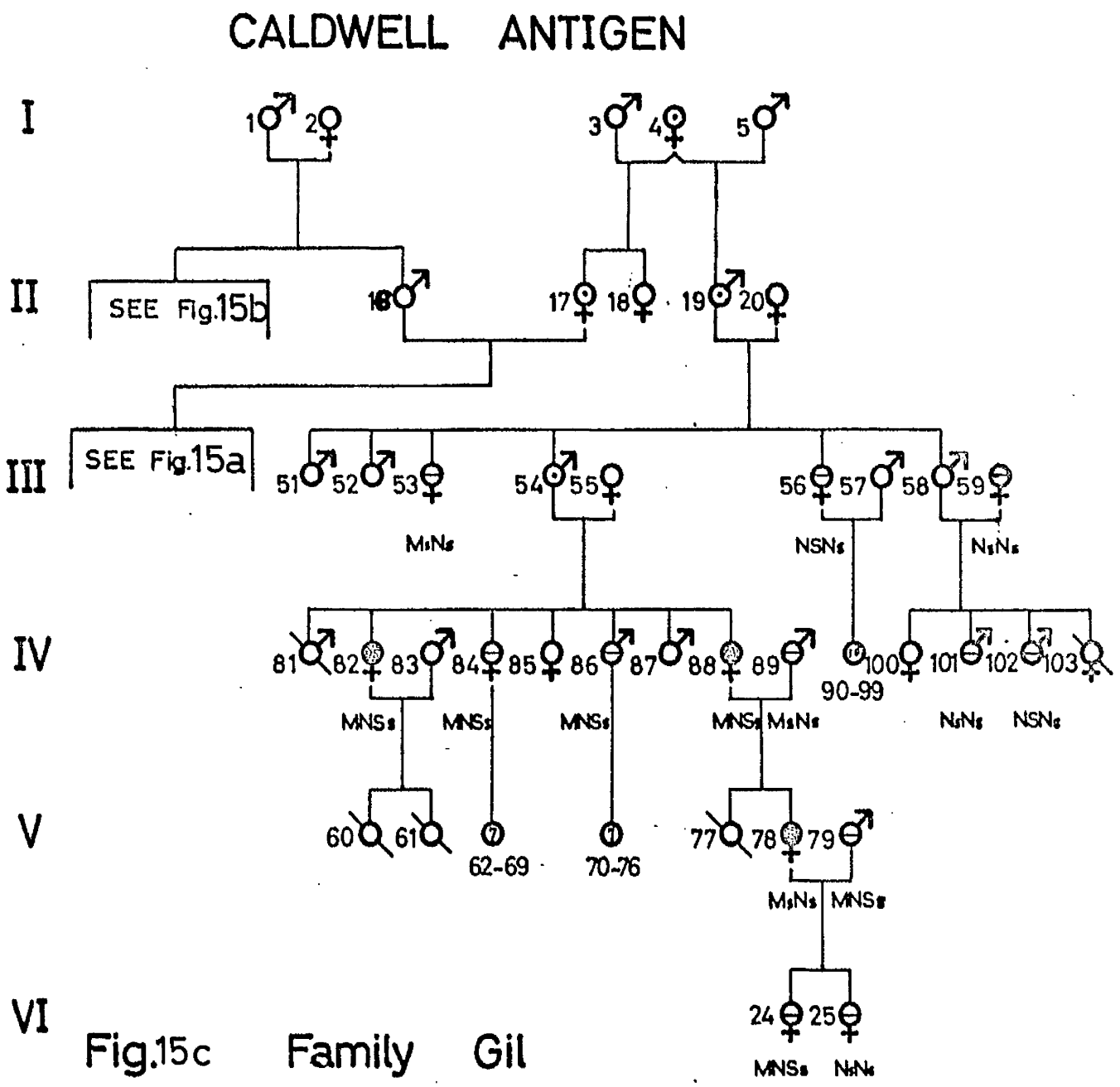


Fig.15c Family Gil

Fig. 16 For Linkage between the ABO and Nail-Patella Loci

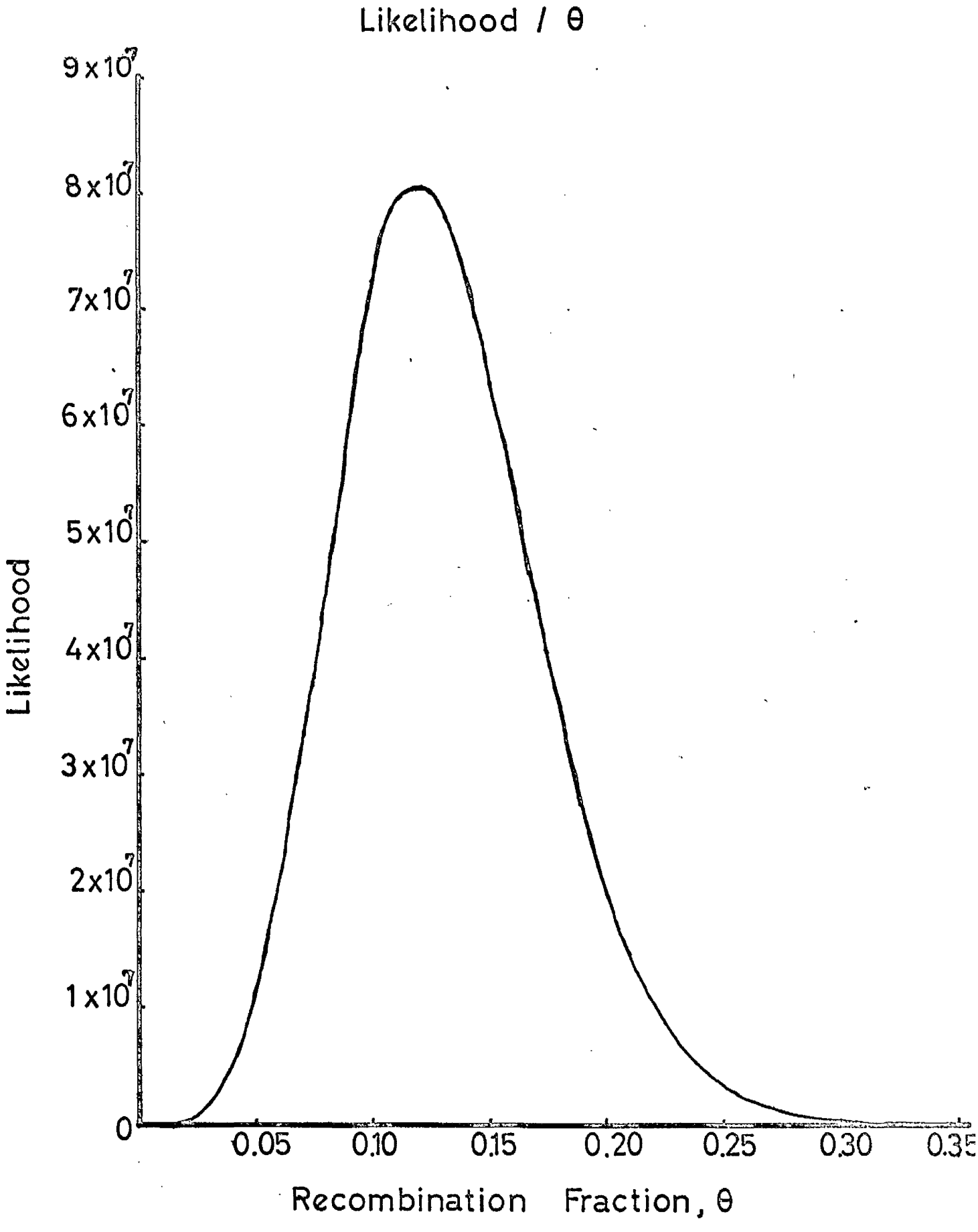
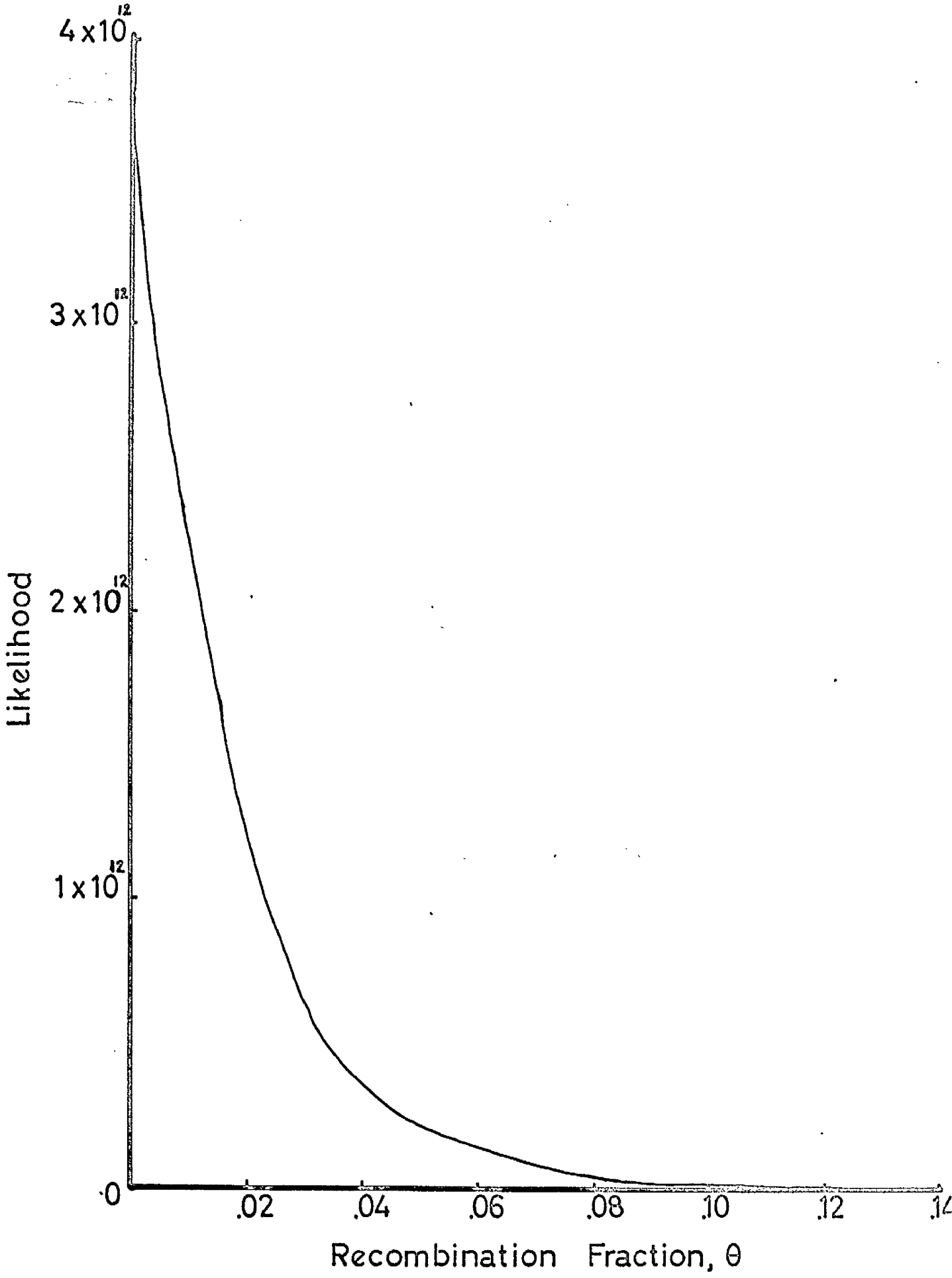


Fig.17 For Linkage between the MNS and Ct Loci



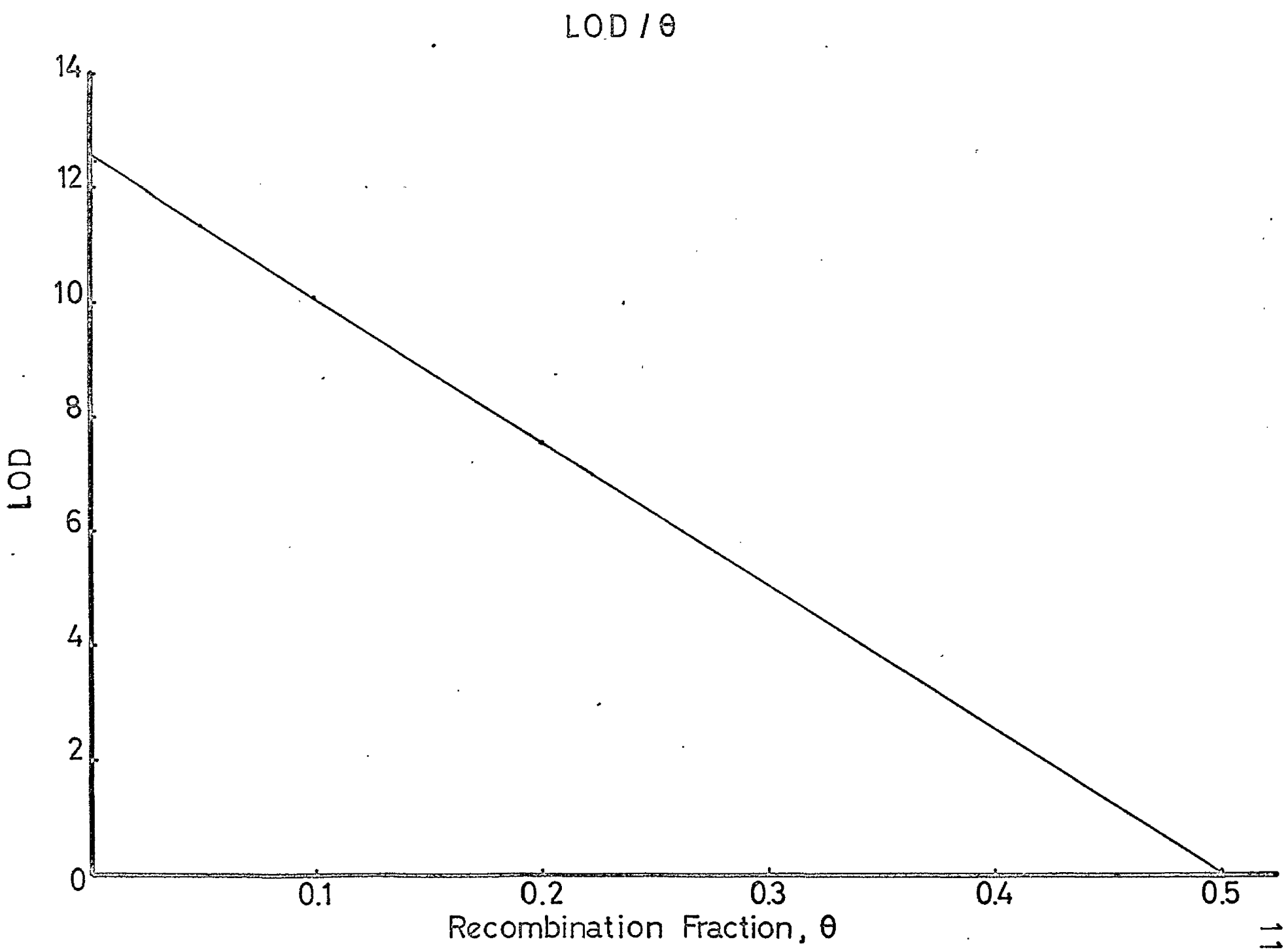

LOD / θ
14
12
10
8
6
4
2
0
LOD
0.1
0.2
0.3
0.4
0.5
Recombination Fraction, θ

Fig.19 For Linkage between the MNSCI and ABO, P, Rh, K, Fy or Gm Loci

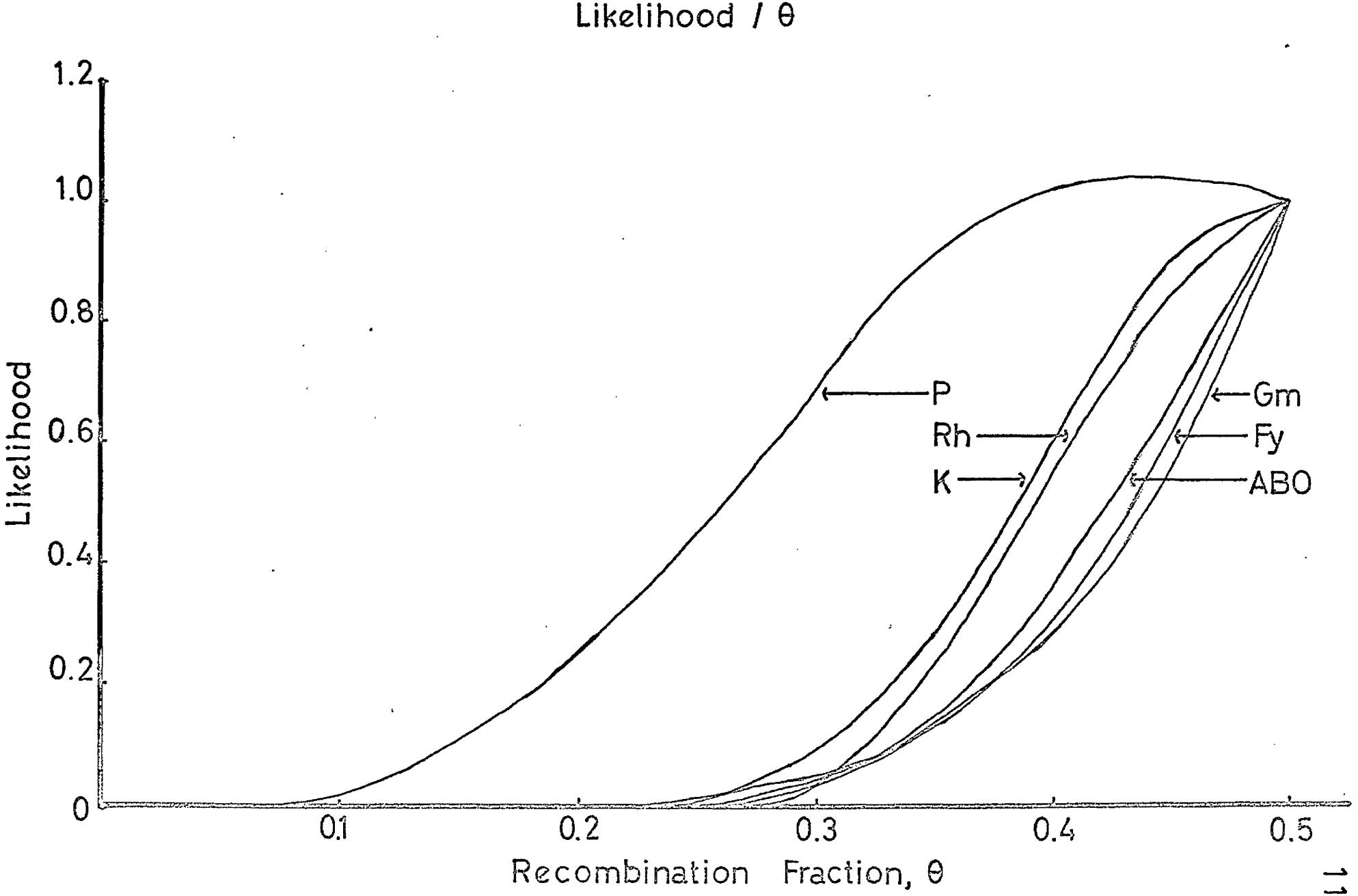
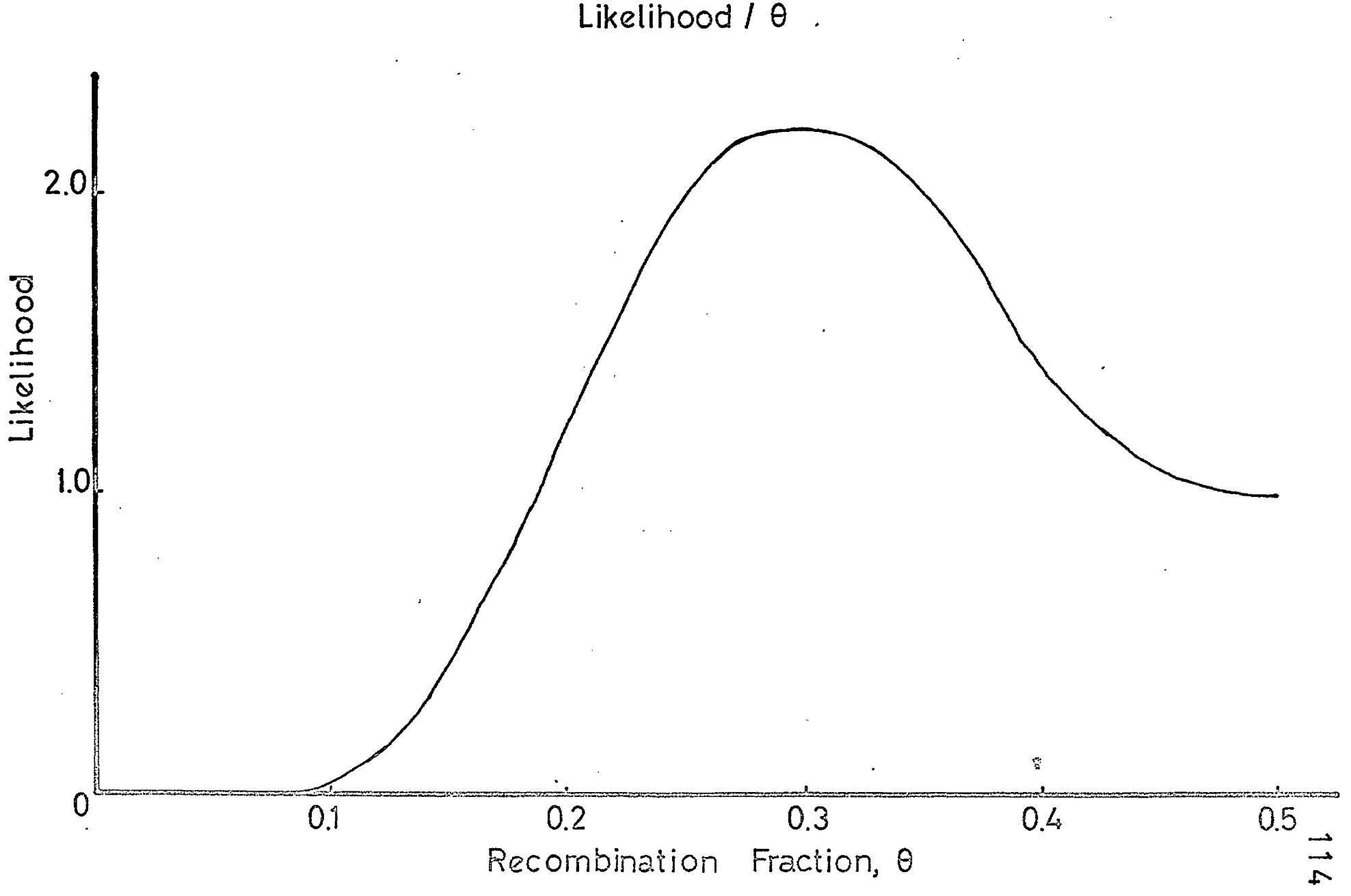


Fig. 20 For Linkage between the MNSCl and Se Loci



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