REPORT

of

COMMITTEE ON THESIS

The undersigned, acting as a Committee of the Graduate School, have read the accompanying thesis submitted by James Arthur Buchanan, for the degree of Master of Science in Medicine. They approve it as a thesis meeting the requirements of the Graduate School of the University of Minnesota, and recommend that it be accepted in partial fulfillment of the requirements for the degree of Master of Science in Medicine.

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THE UNIVERSITY OF MINNESOTA

GRADUATE SCHOOL

Report

of

Committee on Examination

This is to certify that we the undersigned, as a committee of the Graduate School, have given James Arthur Buchanan final oral examination for the degree of Master of Science in Medicine / . We recommend that the degree of Master of Science in Medicine / be conferred upon the candidate.

Minneapolis, Minnesota

April 25, 1922

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THESIS

A CONSIDERATION OF THE LAWS OF HEREDITY AND THEIR APPLICATION TO SOME CONDITIONS IN MAN

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Submitted to the faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of Master of Science in Medicine.

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It is remarkable that a science so familiar as heredity, not only to physicians, but to all reading men, the principles of which are so easily gathered from the works of biologists, is so characterized by a lack of accuracy in its usage in medical literature.

The mechanism of heredity came into play with the appearance of bisexual life upon the surface of the earth. Its laws will continue to function until such life becomes extinct. The efforts, of ancient, of mediaeval, and of modern investigators, to unravel the workings of the mechanism of heredity, form an interesting chapter in the development of biologic knowledge. (5)

Heredity is a science devoted to the study of the phenomena of breeding.

The physico-biologic characters, which are transmitted to subsequent generations by means of the germ plasm, furnish the concrete evidences for studies in heredity. A biologic character signifies a type of physical and chemical composition possessed by individuals, and by which they may be differentiated. Characters are rendered physically immortal by heredity, and the study of heredity becomes in consequence an investigation of the mechanism of physical immortality. The vehicles upon which the transmission of the characters depends are the nuclear structures, chromosomes, in all germ cells, and in certain instances the cytoplasm of the germ cells. The hereditary substances in the chromosomes and cytoplastic substances together comprise the germ plasm. The germ cells or gametes in man are the ova and the spermatozoa.

Heredity never deals with the etiologic factors for disease. Any characters appearing in man that can be proven hereditary are normal, biologically speaking, regardless of how the characters may unfit their bearer for harmonious co-operation in the economic and social programs of civilization.

This conception becomes clear when it is remembered that characters are brought to their bearer as an integral part of the stuff from which he developed, and that there was no alteration from the normal course of life. The factor upon which the character depended was in the germ plasm. The character underwent development along a fairly fixed line, as a component part of the body in which it appeared. Hereditary characters in all plants and animals, and even in man in certain instances, are considered as expressions of normal features. The characters in man which embarrass his participation in all or certain parts of his duties and pleasures are looked upon as expressions of disease. A man with an untoward hereditary character could not be otherwise from a biologic and physiologic standpoint. The embarrassing characters are the physical expression of the type of stuff of which he was composed genetically, and not the expression of pathologic processes.

By heredity the quantitative and qualitative characters in all bisexual species are kept extant and limited. Under similar conditions of reproduction, the numerical expression of the transmission of these characters follows very closely, or is reducible to, a fairly definite ratio. A character once proven hereditary is always hereditary, and not hereditary on a percentage basis.

The science of heredity includes the study of the intermediate as well as of the mediate stage of certain features of the life cycle. The ova and spermatozoa form the intermediate stage of the life cycle in man. The rearrangement of chromosomes which occurs following their union furnishes the fundamental basis for the study of the method of production of the tangible evidences of heredity in the mediate stage of the life cycle.

Heredity as ordinarily used by medical authors means the presence of a like condition in parent and child. This occurrence is usually described

as one of the etiologic factors for the disease under consideration. The laws of heredity which have been established are at variance with this usage.

Kölreuter made the first systematic investigation of hybridization, which is the first stage resulting from the crossing of parents with different inheritable characters. By his experiments he established the fact that the hybrid offspring generally looked as closely like the male as the female parent.

Mendel carried the work of Kölreuter one step further by mating hybrid with hybrid. When the products of this mating were examined, he found that the parental characters which entered into the formation of the hybrid were separated out in a peculiarly striking manner, and that the hybrid reappeared in its identical form. To this phenomenon Mendel applied the name, "Segregation of Characters". This is now known as the first law of heredity. Mendel believed that in the offspring of a mating all characters were segregated independently, and that there was no interrelationship in the transmission of characters. This belief is usually spoken of as the "Independent Assortment of Characters", and is the second law of Mendel and of the science of heredity. This law has been found to be only partially true.

Since the time of Mendel four other laws have been derived from experiments carried out on plants and animals. They are known as (1) Linkage, and its corollary "Crossing Over", (2) Linear Order of Genes, (3) Interference, and (4) Limitation of the Linkage Groups. They have been carefully studied by Morgan. Linkage of characters has been found to occur in man. Its corollary and the other three laws have not yet been worked out in man.

The discovery of the spermatozoon in man by Leeuwenhoek, the ovum in man by Von Baer, the cell by Schleidin and Schwann, the chromosomes by van Beneden, the theory of cellular continuity by Virchow, the theory of germinal continuity by Nussbaum, furnished the material upon which Weismann evolved the theory of the germ plasm. This theory clearly isolated the ultimate

units upon which physico-bidlogic characters must depend. The units are located in the germ plasm, and in their finest division are known as "biophors"; aggregations of biophors are known as "determiners", and the latter when grouped together are known as "ids". Groups of ids are called "idants", which are identical with chromosomes. Determiners are the fundamental aggregation of hereditary units in the germ plasm. Weismann vivified the significance of the spermatozoon and ovum with their nuclear and cytoplastic structures as the medium for the transmission of the ultimate units for heredity.

The terminology used in studies in heredity is very simple. The parental generation, or the stock from which a series of studies have been made, is expressed by the symbol "P". The first product resulting from a mating of the parental generation in which unlike characters are crossed is known as the hybrid, and this stage is spoken of as the first filial generation. By mating members of the first filial generation, the second filial generation is obtained. This generation was the important one in the studies of Mendel. All generations, except the parental, are designated by the letter "F" and a subnumeral which indicates the generation under consideration. The term homozygote is used to designate individuals who are pure bred for a particular character. The homozygote always breeds true to the characters present when crossed with a homozygote with like characters. The term heterozygote refers to an individual who while possessing a certain character in his somatic cells has the ability because of certain properties in his germinal cells of transmitting not only a character present in the somatic cells but a character which is concealed or dormant in his germinal cells. The determiners for the dormant and evident characters are located in the germplasm.

The discovery of the heterozygous property of plants was one of the most fundamental discoveries made by Mendel. In man the heterozygous person

can only be determined by breeding, whereas in plants the knowledge of the nature of the parental generation furnishes information which enables an observer of plant breeding to determine by physical inspection the homozygous and heterozygous types.

The property of the hybrid in plants to conceal one character while another was evident led Mendel to introduce the words dominant and recessive. The character which is visibly represented in the hybrid is spoken of as dominant, while the other is spoken of as recessive. These words have been used in connection with the study of heredity in man, but erroneously so, as there is no direct way of determining which of the two characters will be dominant, because when two persons are mated together so as to produce a cross of different characters, instead of a hybrid generation resulting, there is an immediate progression to the segregation of the characters introduced in the cross, with the production of both homozygous and heterozygous individuals, just as occurs in plants and fowls in the second filial generation. The hybrid stage in man is absent. The terms 'dormant' and 'evident' are more expressive when speaking of hereditary characters in man.

Mendel left no graphic illustration of his work which was carried out on species and subspecies of the edible pea (Pisum sativium) and species of the hawkweed (Hieracium) but Correns, who discovered Mendel's work, confirmed and extended it, visualized in Figure 1 the parental generation, the first filial generation, and the second filial generation during which the segregation of characters took place. In this experiment the "four o'clock" was used. A red flower (Character "red") was crossed with a white flower, (Character "white"). The result was a pink hybrid. When two of the hybrids were mated together, their offspring consisted of a red, a white and two pink flowers. The separating out was the clearest possible example of what Mendel

meant by the expression - segregation of characters. The red and white if crossed with red and white respectively breed only red and white respectively, whereas if the pink flowers of the second filial generation are crossed with pink flowers the segregation of characters repeats itself.

By a statistical investigation of many crosses Mendel established the now famous 3 to 1 ratio. The 3 to 1 ratio is approximate and not absolute as shown by the investigations of Mendel. He found in experiment 1, a ratio of 2.96 to 1; in experiment 2, 3.01 to 1; in experiment 3, 3.15 to 1; in experiment 4, 2.95 to 1; in experiment 5, 2.82 to 1; in experiment 6, 3.14 to 1; and in experiment 7, 2.84 to 1. These figures show a rather narrow range of possibilities.

In the study of heredity in man the absence of the hybrid stage presents distinct obstacles to the direct application of the scheme used by Mendel in his investigations. The heterozygote in man is identical genetically with the hybrid of plants. Mendel demonstrated the segregation of characters by mating hybrids, which were the offspring of the same parents. The only similar biologic and genetic situation in man would be the crossing of sister and brother heterozygotes, provided their heterozygous nature could be proven beforehand. Such a cross in man is clearly impossible. Furthermore, it is quite impossible to say in advance of a mating, whether or not a cross is of heterozygotes, or of homozygotes and heterozygotes. The evident character is always discernible, but the dormant character in man exists without any tangible evidence. It is also often impossible to determine after studying the offspring resulting from a cross between two persons whether the parental generation was heterozygous or homozygous. The homozygous nature of both parents is demonstrated when all the children possess the same characters as the parents.

These difficulties make it impossible to derive mendelian ratios directly by tabulating the products of crosses in man. Through a long period of time, it may be possible to demonstrate which characters may appear in certain combinations only as evident or dormant characters. Hitherto no attempt has been made to prove this essential possibility in man, but by such an indirect procedure dominant and recessive characters can be determined. After the relationship in the heterozygote of the dormant and evident characters has been worked out, it will still be impossible to determine in advance of mating the homozygous or heterozygous nature of any particular person, unless his ancestors have been previously proven to be homozygous for the character under consideration. The accuracy of mendelian ratios in man will be lessened for a long time to come on account of these obstacles.

Certain requirements are necessary to determine if a character or condition in man is hereditary and to establish its relationship to another character. The character must be arbitrarily defined, and a contrasted character must be selected. When two such characters are crossed at least three, and preferably four, children must result in order to observe the segregation of the characters, and to establish their numerical relationships. A cross in man where only two characters are concerned needs investigation through but two generations. The evident characters will be discernible, but the recipients of the dormant characters cannot be distinguished. This fact must be borne constantly in mind, for a union of heterozygotes will reproduce their ancestors, and unless this faculty is recalled many conditions will be considered hereditary on a percentage basis or else not considered hereditary at all. The heterozygous principle has been responsible for immeasurable misunderstandings in the study of heredity in man. In cases where three or four characters are under investigation the four grandparents, the parents, and a final generation

of preferably four children must be studied. The sine qua non of an hereditary investigation is the knowledge of the characters represented in the germ plasm of the ancestors of the individuals under consideration.

The Inheritance of the Blood Group.

Study 1.

In 1900, Shattock observed that the serum of patients suffering from certain diseases agglutinated the red blood cells of healthy men. He also noted the persistence of the agglutinative phenomena during the convalescence from the diseases. In 1901, Landsteiner discovered that the red blood cells of healthy men, on account of certain agglutinative properties of the serum, could be classified into three groups. A fourth blood group, Group 1 of the Moss classification, was discovered by Decastello and Sturli, in 1902. In 1907, Jansky made observations which definitely established the existence of four blood groups. The same conclusion was arrived at by Moss independently in the United States in 1909. The four blood groups known today are arbitrarily designated as Group 1, Group II, Group III and Group IV. They have been classified by Jansky, and by Moss. Their classifications differ in that Jansky's Group I is the Group IV of Moss, and the reverse. The scheme of Moss has been concisely presented by Sandford (Figure 2). I have followed the Moss classification.

The mendelian transmission of blood group by the germ cells to subsequent generations has been suspected, some definite evidence has been presented, but certain difficulties remain. I have made this study in an attempt to obviate these difficulties.

The material used in this study was obtained in an unique way. In discussing my desire to add further data concerning the inheritance of blood group with Dr. W. A. Evans, he suggested that Figure 3 be inserted in his health column in the Chicago Tribune. It appeared on April 26, 1921. The same request

subsequently appeared in all the publications of the Tribune Syndicate. Through the kindness of the Eugenics Record Office, the interest of Mr. A. E. Wiggam was aroused, and a similar request appeared in the Physical Culture Magazine, August, 1921. The replies to these requests were mailed to me. Each member of the family was mailed a three cubic centimeter glass tube, which contained one to two cubic centimeters of two per cent sodium citrate solution. The tubes were well corked, packed in cotton in an ordinary mailing tube, and sent by first class mail to the family. At the same time, instructions were forwarded for collecting blood from the needle stab in the finger, and for labelling and remailing the tubes. The instructions were accompanied by a letter requesting the cooperation of the family in the work. Where the first letter failed, a follow-up letter was sent. One tube was broken; two times hemolysis of the red cells occurred, so that second specimens had to be obtained. I owe my thanks to Mr. Ed. C. Myers and Dr. J. I. Mershon, Mt. Carroll, Illinois, Dr. H. B. Cole and B. P. Flinn, Redwood Falls, Minnesota, Drs. R. A. Jacobson and C. F. Crow, Exira, Iowa, Dr. Greenleaf, Atlantic, Iowa and Dr. C. C. Bassett, Goodland, Indiana, for their assistance in the work. Families suitable for this study are very scarce. There is not such a family on record at the Eugenics Record Office, Cold Springs Harbor, New York.

The first suspicion that the blood group was heredi tary and transmitted to subsequent generations according to the laws of Mendel was held by Ottenberg[31] in 1908. In 1910, von Dungern and Hirschfeld reported 72 families, consisting of 348 persons. The grouping of the blood was carried through two generations. They concluded that blood group was hereditary and transmitted according to the mendelian rules. Their work was based on the hypothesis that the various blood groups depended upon the presence or absence of agglutinin, A and B. Ottenberg[32] in 1921 synthesized the data of von Dungern and Hirschfeld,

and established certain formulas which he considered to be representative of the blood groups. In this study, I have used the terms Group I, Group II, Group III and Group IV as expressive of a specific biologic property of the blood of man. The factor for blood group is considered as comparable to those unexplained factors upon which the unit characters height, shape, size, color and so forth, in plants and animals depend. The exact formulas of the ultimate units upon which these characters depend are unknown.

If the premise is assumed that blood group is expressive of an hereditary character dependent upon a unit factor comparable to that for color of flowers, height of plants, and so forth, it becomes necessary to present data to ascertain if blood group is transmitted between generations in a manner similar to what is known to occur in plants and flowers. The data presented in Fig. 4 consists of the crossing of blood group II with blood group IV through three generations. Comparison of this family with Figure I shows the absence of the hybrid stage or stage of the first filial generation. In the third generation one child in blood group IV and three children in blood group II appeared. The blood groups present in the previous generations appeared in the final generation. No other blood groups appeared. If the phenomena observed in the third generation of this family were considered as illustrative of the first law of Mendel, it might be assumed that two of the children were homozygous and two were heterozygous, as occurs in the mendelian segregation of characters. It was impossible to demonstrate this idea in this family, as it would have been necessary to group the progeny of all four children in the family, and their mates. The result would have been influenced by groups introduced by marriage, and the data obtained might or might not have been of any conclusive value.

The evidence that there are heterozygous individuals for blood group produced by the crossing of blood group II and blood group IV is

shown in Fig. 9. The parental generation on both sides of the family consisted of the union of blood group II with a blood group IV. Both families had a child in blood group 2. The mating of these children resulted in three children in blood group II and one child in blood group IV. If the blood group is hereditary the factor for the group IV must have been present in the germ plasm of either the male or the female parent, for there is no other mechanism in heredity by which it could have appeared in the final generation. The same situation is seen in Fig. 12.

The heterozygous property is again illustrated in Fig. 11. In the parental generation on the left, the cross consisted of presumably homozygous group II parents, and on the right a group IV was crossed with a group I. The result was a group II on the left and a group IV on the right. The final generation showed two children in group II, one in group I, and one in group IV. This happened because of the heterozygous nature of the parental group IV on the right. Fig. 11 is also a very clear demonstration that blood group is a distinct hereditary character, as all the characters concerned in the primary generation reappeared in the final generation. The same phenomenon is observed in Fig. 5, where group III and group IV appeared as the expression of the heterozygous principle.

The homozygous nature of blood group is illustrated in Fig. 7. In this family the parental crossings on both sides resulted in children in group II, which on being crossed produced four children in blood group II. The same situation is shown in Fig. 9 where group IV was the homozygous character. Ottenberg in 1908 demonstrated the homozygous nature of group III. He reported a father, mother, and four children all in group III. The homozygous nature of group I has not yet been demonstrated, but it seems reasonable to suppose from its behavior when crossed with other blood groups, that it could appear in the homozygous state as well as in the heterozygous state.(Figs. 12,12a and 18.)

The expressions dominant and recessive are frequently heard in discussing the inheritance of any character. Mendel described this usage by saying "Those characters which are transmitted entire, or almost unchanged in the hybridization, and therefore in themselves constitute the characters of the hybrid are termed the dominant, and those which become latent in the process, recessive. The expression "recessive" has been chosen because the characters thereby designated withdraw or entirely disappear in the hybrid, but nevertheless reappear unchanged in their progeny". The hybrid state is absent in all families studied by myself, as well as in all the families grouped by von Dungern and Hirschfeld; and all the families which I have found reported in the literature as representing an hereditary character in man have shown an absence of the hybrid stage. It is then improper to use the term dominant and recessive in connection with heredity in man until further studies are made. As the heterozygote in plants are identical physically and genetically with the plant hybrid, and as the heterozygote in man behaves in the same manner as the heterozygote in plants, it may be possible to work in a reverse manner to determine which blood groups in various combinations can appear only as the dormant and evident combinations. If there is no reversal in the relationship of the dormant and evident characters, dominance of one character to another may be spoken of in its true sense. If there is reversal, then the use of the expressions dominance and recessive will remain meaningless. The settlement of this point is however, not of vital importance in the study of heredity in man. It is more a matter of accuracy and correct usage of terminology. It could be, however, of importance in the use of the blood group in the adjudication of medico-legal disputes. Until it is proven which character may appear as dormant in certain unions, the use of blood group in medical legal affairs will be fraught with great danger, unless the blood grouping is carried in a definite scheme into the preceding generations.

Ottenberg has suggested that the child had to be in the same group as one of the asserted parents. A curious situation would exist in the family represented in Fig. 9, if this criterion were accepted. The twins were in different groups, and one was in a different group from either parent. The danger of drawing conclusions from two generation studies is shown in Figs.14, 15, 16, 17 and 18.

Alexander in 1921 made a study to see if Mendel's second law was fulfilled in the transmission of blood group. He came to the conclusion that in malignancy in particular,"that while persons belonging to all four groups are liable to malignant disease, those in groups I and III appear to be peculiarly susceptible, and the clinical type of disease is generally speaking more malignant". He probably presumed that cancer was hereditary and that linkage occurred between the factor for cancer and for blood group. The investigations of Higley and myself on material collected by Sanford in the Mayo Clinic showed this conclusion to be incorrect. We found in a study of 2,446 persons with a wide range of diseases that there were no evidences of linkage. There was no evidence that a person in a particular blood group was more susceptible to a particular disease. The reactions to disease were not different in persons of particular blood groups.

The percentage relationships of the blood groups did not vary in any way in the two sexes as shown by 2,176 groupings, which consisted of 1245 males and 931 females. The percentage distribution in the males was group I, 3.69 per cent; group II, 40.97 per cent; group III, 9.39 per cent, and group IV, 45.77 per cent; in the females, group I, 3.97 per cent; group II, 41.46 per cent; group III 8.69 per cent; and group IV, 45.85 per cent. The families represented in Figures 1 to 18 demonstrate the transmission of the blood group between males and females without regard to sex. There are no evidences of sex linkage in the transmission of the blood group.

The second law of Mendel, namely, the independent assortment of characters, so far as data at present are concerned, is fulfilled by the blood group.

Comment

The blood group is an expression of an hereditary character of man. There are four characters known at present, arbitrarily designated group I, group II, group III and group IV. The blood group is transmitted by the germ plasm according to the first and second laws of Mendel. The hybrid stage is absent.

There is no method available at this time by which a strict or presumptive delimitation can be made of the blood group possible in children resulting from the union of two persons. Careful investigation conducted into the ancestors of every generation must be carried out in order to ascertain the blood group possibilities in any family.

The blood group offers a concrete means for the study of heredity in man.

Inheritance of Migraine

Study II

The demonstration of the transmission of migraine between generations by means of the germ plasm transfers the condition from the category of a disease to that of a biologic character of man. The term migraine designates an unknown physiologic process which is recognized by periodic attacks of pain, usually in the head, either unilateral or bilateral, but occurring also in the abdomen, and in either location frequently associated with nausea, vomiting, mental depression, visual phenomena, and many vague somatic disturbances. One or all of the symptoms may occur in an attack, which lasts from a few to several hours or days. The first expression of the character appears

early in life, and as a rule it disappears during the fourth decade.

Studies instituted to prove migraine expressive of an hereditary character must investigate the parents and at least four children in families where the marriage consisted of the union of a person with migraine to a person without migraine, the marriage of known heterozygous individuals or the marriage of two persons with migraine. "Without migraine" is the contrasted character. Under like conditions, the segregation of the character will occur among the children in a fairly definite manner.

A study was made of 127 families of which one or more representatives were examined in the Mayo Clinic in 1919. Migraine followed the two laws of Mendel (Figs. 19, 20 and 21) The total number of children in the 127 families was 198 with migraine and 610 without migraine. At the time the study was reported a combined mendelian ratio was calculated for all the families studied. This ratio was incorrect, as the amalgamation of the crosses was contrary to the scheme of Mendel. The ratios were correct for the individual groups. The same difficulties exist in working out a mendelian ratio for migraine as for the blood group.

Like all hereditary characters migraine exists in either the homozygous or the heterozygous state. The heterozygous status which is illustrated in Fig. 22 has led many writers to say that migraine is hereditary in 90 per cent of instances and in various other percentages because it occurred in a varying number of families where it was not demonstrable in the parents. During the last two years many patients have been observed in the Mayo Clinic where migraine was not present in the parents, but present in the brothers or sisters if the family was sufficiently large, or known to be present in one or the other of the grandparents. Where patients have no knowledge of their parents and grandparents, the data derived from them is not usable as evidence against the mendelian transmission of migraine. Such information is valueless

on either side of the question. It is to be remembered that by means of the heterozygous status of certain persons a character may be transmitted through many generations of small families without any signs. The character appears in the first large family.

The homozygous status of migraine has been studied in three families where both parents had migraine. If migraine exists in a homozygous status in those individuals in which it occurs, all children resulting from such unions should have migraine. This occurred in the three families studied (Figs. 23, 24 and 25). Although this is an interesting observation, the data are too small to determine if the relationships of the dormant and evident phases of migraine are reversible. It may be that a person with migraine may become the parent of children without migraine, just as it has been shown that the relationships of the blood group in the heterozygote are reversible. This subject requires careful study.

One family has been studied (Fig. 26) in which twins presented in one migraine and in the other without migraine. This is interesting when compared with the appearance of different blood groups in twins (Fig 9)

In the description of the causal factors for a number of diseases various writers have given migraine as one of the etiologic factors. So far as known, the determiner in the germ plasm for migraine has nothing to do with the production or evolution of any character other than itself. The migraine determiner is as specific for itself as the determiner for the blood group is for a particular blood group. Any disease may occur in the person with migraine. It is an association and not an evidence of etiologic relationship.

Comment

Migraine is the expression of an hereditary character, but the physiologic processes which occur at the time of the manifestation of its phenomena are unknown. It is not possible to change the blood group by either

surgery or drugs, so it does not seem reasonable to expect that migraine which is a similarly derived character could be influenced by any of the procedures recommended. The patients with migraine who have been examined in the Mayo Clinic demonstrate the futility of all sorts of treatment. There has been no evidence accumulated to substantiate the belief that a tendency to migraine is inherited. A person either has or has not migraine, just as a person always belongs to a definite blood group.

Inheritance of Essential Epilepsy

Study III

There is no gross pathologic basis for the explanation of the seizures of essential epilepsy. Essential epilepsy is a condition in man characterized by periodic seizures in which there is loss of consciousness, preceded by more or less marked prodromal sensations, and followed by and associated with tonic or clonic spasms of the general musculature. The seizures last from a few minutes to an hour or more, and their frequency is very variable. A seizure in which there are severe convulsions and loss of consciousness is termed grand mal. A milder form in which vertiginous or momentary blank sensations replace the convulsions, is termed petit mal. Hippocrates believed that essential epilepsy began in utero, and as a consequence of this belief and the absence of a pathologic basis, many diseases as neurasthenia, hysteria, insanity, and the undefined group of diseases known as nervous disorders or neuropathies from time to time has been incriminated as the ancestral causal agents. St. Hildegard seems to have been one of the earliest writers to suspect that migraine and essential epilepsy were expressive of the same entity.

In order to obtain data on the relation of the various neuropathic influences to essential epilepsy two series of cases observed in the Mayo Clinic were analyzed. The results warranted the dismissal of all of the so called

nervous disorders as related factors as they occurred no more frequently in the ancestral history of persons with essential epilepsy than in the ancestral history of persons with diseases the etiology of which is known. Migraine is the only character which appeared with such frequency as to attract attention. In the first series of 127 cases, migraine occurred as an ancestral, sibling, or personal history in 53.9 per cent of the cases. The 127 cases comprising the second series had been carefully studied in the Department of Neurology, and of these cases 66.4 per cent gave an ancestral, sibling, or personal history of migraine. In the former series migraine was present before the onset of essential epilepsy and alternated with or continued with epilepsy in 14 per cent of the cases studied. In the latter series, this occurred in 10.5 per cent of the cases. The genetic relationship of migraine to essential epilepsy seemed to be quite striking.

If essential epilepsy were expressive of the same underlying biologic factor upon which migraine depended, its appearance in families would not disturb the relationship of persons with migraine to persons without migraine. It would simply replace or alternate with the migraine character in certain persons. The same laws and requirements that govern the transmission of the blood group or migraine alone would be followed and fulfilled.

Essential epilepsy on empirical ground was considered as simply another phase of the phenomena of the migraine character in a study of 47 families whose histories were complete for ancestral data. The contrasted character was 'without migraine-epilepsy', or what is commonly called the normal. The same segregation of characters was seen as when considering migraine alone (Figs. 27, 28 and 29). At a subsequent date 35 similar families were studied, and the data obtained in the first families were altered in no way. In a certain number of the patients studied, varying in all series from 10 to 14 per cent, migraine and epilepsy alternated in an irregular manner.

If essential epilepsy were expressive of the same phenomena as migraine, the marriage of an epileptic to a migrainous person would result in all of their children having migraine, or all or part having essential epilepsy. One family has been found to fulfill this condition, and all the children had migraine, and in one the migraine alternated irregularly with epileptic attacks, (Fig. 30).

If essential epilepsy depends upon the factor of migraine for its evolution, the marriage of homozygotes or heterozygotes for migraine should result in the production of a certain number of persons characterized by the seizures of essential epilepsy. The marriage of two persons with migraine is quite rare and as a consequence the opportunity to observe the frequency with which a person with essential epilepsy should result from such unions would be very infrequent. I have found but one family (Fig. 31)in the files of the Mayo Clinic which furnished any information on the subject. Many families (Figs. 32 & 33) have been found which demonstrate the heterozygous property of the normal to transmit migraine, essential epilepsy, or both to their children, because of the strain which had been introduced into their germ plasm by the grandparents.

Comment

Essential epilepsy and migraine are transmitted from generation to generation as the expression of the same underlying factor in the germ plasm. The mechanism for the production of the seizures is unknown. The organic factors capable of producing phenomena similar to those of essential epilepsy are so numerous that the classification of an individual in the essential epileptic class demands extreme caution.

A dimunution in the number of essential epileptics by segregation of those afflicted to colonies is not to be hoped for as the person with migraine is more likely to produce epileptic offspring than the epileptic himself.

The theory that essential epilepsy and migraine are the expression of a biologic character, and their mainfestations are, therefore, physiologic need offer no insurmountable obstacles in its acceptation. If it is possible for such striking characters as waltzing in a mouse, and tumbling in the pigeon to be hereditary, there is no reason why characters equally striking might not appear in man. The management of migraine and essential epilepsy as expressions of biologic characters will undoubtedly result in those individuals enjoying a greater degree of happiness and health than has hitherto been possible because of the unlimited and ever-varying type of operation and drug therapy which has been carried out in such patients without benefit.

Diabetes Mellitus

Study IV

From the very earliest period of the history of diabetes mellitus references have been made to the frequency of heredity as an explanation for the occurrence of a varying percentage of the cases of the disease. The reported families were compiled in 1912 by Foster who at the same time reported a family observed by himself. In practically all of the articles on the subject mention is made of the number of persons in the family who are afflicted, but no mention is made of those who are in good health. The three families reported by Long are noteworthy exceptions. Van Noorden, Naunyn, May and more recently Allen have called attention to the importance of heredity in diabetes. The latter author suggests that the subject should be studied by the methods used by biologists in determining hereditary characters, as no attempt has been made to study the condition in the light of the laws of heredity.

If diabetes mellitus is to be considered as representative of a unit character, it would be interpreted as a physiologic expression of a cycle in the life of certain persons, whereby they would lose the power to conduct

sugar metabolism, and as a consequence a portion or all of the sugar ingested, the stored carbohydrates, and a portion of the body proteins and ingested proteins are converted into sugar and excreted as such in the urine. At the same time the chemical changes which result in coma and death would be the final expression of this lethal cycle. The contrasted character would be what is called 'Normal', or a person whose carbohydrate metabolism is so constituted that the phenomena of diabetes mellitus do not appear. The families should be studied through two generations, and at least three and preferably four children should be present in the families used for study.

Diabetes mellitus, if hereditary, must conform to the known laws of heredity. To determine if such were the case, the progeny of persons with diabetes mellitus married to persons without diabetes mellitus have been studied. The data for the study was obtained largely through the kindness of R. M. Wilder, of the Mayo Clinic diabetic service. The material consisted of thirty-four families, seventeen of whom were studied through two generations and seventeen through three generations. The total number of diabetic offspring was sixty-five and 274 were without any evidence of diabetes mellitus at the time the data was collected. Sixty-five (16.08 per cent) children died in early life.

The results of unions (Figs. 34, 35, and 36) of diabetics (homozygotes) and non-diabetics in the cases studied by myself revealed no information to show that the condition was transmitted through the germ plasm. The occurrence in the children did not conform to the mendelian laws. Further investigation in these same families at a later date may reveal information of great value.

Occasional families have been observed (Fig. 37) which suggested the possibility that diabetes mellitus might be transmitted to a subsequent generation because of the heterozygous status of a parent. A study to throw

definite light on this subject was made in eighteen families, of whom eleven were studied through two generations, and seven through three generations. There were eighteen children with diabetes, and 126 without. Thirty-five (19.05 per cent) of the children died in early life. The impression that diabetes might be transmitted through the germ plasm on account of the heterozygous nature of a parent was not supported by the data obtained from the eighteen families studied. These families are typified in Fig. 38.

If diabetes mellitus were hereditary homozygous and heterozygous individuals would result from the crossing of the diabetic with the non-diabetic. The failure of the homozygous principle to be supported has been shown in the families of conjugal diabetes as reported by Crofton and others where it has been found that both parents may have diabetes mellitus without any of the children being afflicted. The lack of conformity to the laws of dominance and recessiveness in man, because of the absence of the hybrid stage, may explain certain discrepancies in the familial occurrence of diabetes, but even allowing for this possibility neither the homozygous nor heterozygous principles in heredity have been fulfilled by diabetes mellitus.

The methods as used today for collection of data in families where diabetes mellitus occurs are not such as will ever result in obtaining data of conclusive value. To prove diabetes mellitus hereditary, a cyclic nature of the disease would have to be postulated, that is, that the condition, if hereditary, would make its appearance at approximately the same age in a certain number of the members comprising the family, and have a definite progress. Therefore, data should be obtained in each family concerning the time of onset in the parents, the number of brothers and sisters of the parents, age of each, age of onset of diabetes mellitus in each, the number of children in the last generation, age at which the condition appeared in each child, and age of those at or beyond the age at which it appeared in the parents. The collection

of the data would necessitate a follow up system, and as the children arrived at the proper age they would have to be investigated. In no other way will it ever be possible to prove that conditions like diabetes mellitus should be transferred from the status of a disease to the list of conditions in man which are expressive of a biologic character that is transmissible through the germ plasm. The data presented in my study did not fulfill these requirements. So far as the data collected are reliable, there is not the slightest evidence to justify the statement that diabetes mellitus is at times hereditary. There is also insufficient evidence to say that the condition is not hereditray, but the evidence does point more toward the quantitative action of some causal factor rather than the expression of the segregative properties of the germ plasm upon which the science of heredity depends for study.

The high mortality in early life of children born of diabetic parentage is striking.

Essential Asthma

Study V.

In essential asthma, as in all conditions in man the etiology of which is obscure, the mechanism of heredity has been believed to play an etiologic role. Geddings reviewed the statistics of the earlier writers, and came to the conclusion that the tendency to essential asthma was hereditary. All of the earlier writers, with the exception of Drinkwater, reported a percentage of inheritance of essential asthma varying from 10 to 50 per cent. Drinkwater reported his families as expressive of the segregative power of the germ plasm. The more recent literature has been reviewed by Adkinson, who at the same time presented date obtained from a large number of cases. She found a family history of essential asthma in 48 per cent of the 400 cases studied, and came to the conclusion that asthma was hereditary in a varying percentage of the cases according to the group in which arranged. She also concluded that asthma appeared

at an earlier date in the children than in the parents. If asthma is an hereditary character it must have been present in man since his appearance on earth, as there is no way for hereditary characters to be kept extant except by breeding of those in whom the character is present. The known period of man on earth has been computed to be millions of years. Essential asthma was distinguished as a distinct clinical entity by Willis about 1600. If a character were present in primeval man, or even since 1600, and appeared at a perceptibly earlier age in the children of each generation, the cycle required for its appearance would eventually be brought down to a period earlier than the preformation of the embryo, or in the germ plasm, and after it had arrived at that state would of necessity either have to disappear, or else by some miraculous process again revert to appearing in old age. This claim is made for other conditions in man, but there is no evidence to support such an hypothesis in heredity.

An investigation to demonstrate the transmission of essential asthma to subsequent generations by the germ plasm must be conducted in the same manner as that for migraine. It would be transmitted in exactly the same manner, and follow the same rules of heredity. For this reason a small number of families would be sufficient to establish the hereditary character of the condition. The contrasted character would be "without asthma".

The families presented in Tables I and II are sufficient to justify a conclusion as to whether essential asthma is an hereditary character. The families used for the study were ones in which the children had reached the age at which the condition appeared in the parent. In the seventeen families in Table I there was evidence of asthma in parent and offspring. This does not warrant the conclusion that asthma is hereditary. The law for the segregation of characters is not followed to a degree in any way approximating the numerical ratio for hereditary characters. In Table II the data presented does not lead to the conclusion that asthma was transmitted in these families as a result of a heterozygous status of one or the other parent. If a

character or condition under consideration does not follow the course of either the homozygous or heterozygous type for hereditary characters it is safe to conclude that the condition is not hereditary. The study of a larger group of similar families would show the same figures.

Comment

Essential asthma in its familial appearance follows none of the known laws of heredity. It is not the expression of a specific hereditary biologic character of man.

Table I

Transmission in families where father or mother had asthma.

Father	Mother	No. of children with asthma.	No. of children without asthma.
-	*	1	14
*	-	0	5
-	*	2	7
-	*	1	4
-	*	1	3
-	*	1	8
-	*	0	6
*	-	0	4
*	-	0	4
-	*	0	3
*	-	0	5
-	*	0	8
-	*	0	9
*	-	0	5
-	*	2	6
*	-	0	7
*	-	0	4
		8	102

Total: 17 families

Table II

Transmission in families where neither father nor mother had asthma.

Group I		Group II		Group III	
No. of children		No. of children		No. of children	
with	without	with	without	with	without
1	7	1	5	1	12
1	7	1	7	2	3
1	3	1	6	1	4
1	3	1	5	1	5
1	7	1	9	2	3
1	4	1	4	1	5
2	3	1	6	1	5
1	3	3	4	1	6
1	3	2	12	1	5
1	12	1	6	1	5
1	6	1	7	1	7
1	3	1	8		
1	9	2	4		
1	9	1	4		

Total number of children with asthma 46
Total number of children without asthma.....226
Families studied..... 39

Protein Sensitivity

Study VI

Protein sensitivity has been attributed by Osler, Oppenheim, Gottlieb, Walker, Longcope, Barber, Cooke and others to the inheritance of a particular type of cells which are sensitive or react in a particular way when subjected to the influence of various protein substances. This belief permits of a very important investigation in man.

For many years "the inheritance of susceptibility to certain states" has been believed. If such be the case, the susceptibility must be transmitted in accordance with the laws which govern the inheritance of all characters. The mating of a person with protein sensitivity to a person without protein sensitivity, if the condition were dependent upon the transmission by the germ plasm of a particular type of cellular protoplasm, would result in the production of a certain number of children of this susceptible type, of whom

some would be heterozygous and others homozygous. When the children of such crosses were exposed to the same conditions for protein influence, and they would be so long as living under the same climatic and seasonal environments, those who inherited the peculiar type of somatic cells would react to the foreign substance in such numbers as to fulfill the mendelian law for the segregation of characters. The possibility of the inheritance of a type of cellular structure that is susceptible to certain influences could be demonstrated under no more propitious circumstances.

In order to investigate the possibility of inheritance of the susceptibility to foreign protein, I have studied a small number of families in which there was parental protein sensitivity, and a larger group in which there was no parental sensitivity to proteins.

The number of families studied in Table III is very small, but the segregative property of the germ plasm does not take until the hundredth family before showing its first evidences. The segregation will appear in the first family studied as well as in the last. There is no evidence in these families that the germ plasm carried any factor upon which the protein sensitivity depended.

The twenty-four families of Table IV consisted of twenty-eight children with and 126 children without protein sensitivity. The families might be considered as expressive of the transmission of the condition by a heterozygous parent. This assumption is disproved by the failure of protein sensitivity to reappear in the third generation of certain families of Tables III and IV. Hereditary characters are carried on forever otherwise the theory of germinal continuity would be false, and there is no obvious reason why an exception should be made in the case of protein sensitivity.

Comment.

A consideration of the families represented in Tables III and IV

leads me to the conclusion that protein sensitivity is not dependent upon the transmission through the germ plasm of a factor which is responsible for the appearance of the condition in man. Furthermore, the data presented are criteria against the continuation of the use of the expression, inheritance of susceptibility to disease. No evidence has been presented in the study of heredity to show that characters are susceptible of appearing or that there is a tendency for them to appear. They are either present or absent. There is no uncertainty.

Table III

The frequency of protein sensitization appearing in children when present in a parent.

Mother	Father	Number of children with	without.
*		1	3
*		0	6
*		1	11
*		0	4
*		0	4
	*	0	4
*		0	4
Total families: 7		2	36

Table IV

The frequency of protein sensitization appearing in children when absent in parents.

Group I No. of children with	without	Group II No. of children with	without	Group III No. of children with	without
1	5	1	6	1	7
1	4	1	6	1	5
1	9	1	3	1	5
2	2	2	5	1	4
1	4	2	2	1	3
1	3	1	3	1	6
1	5	1	6	1	5
1	9	1	7	1	6

Total number of children with 28
Total number of children without..... 126
Total number of families..... 24

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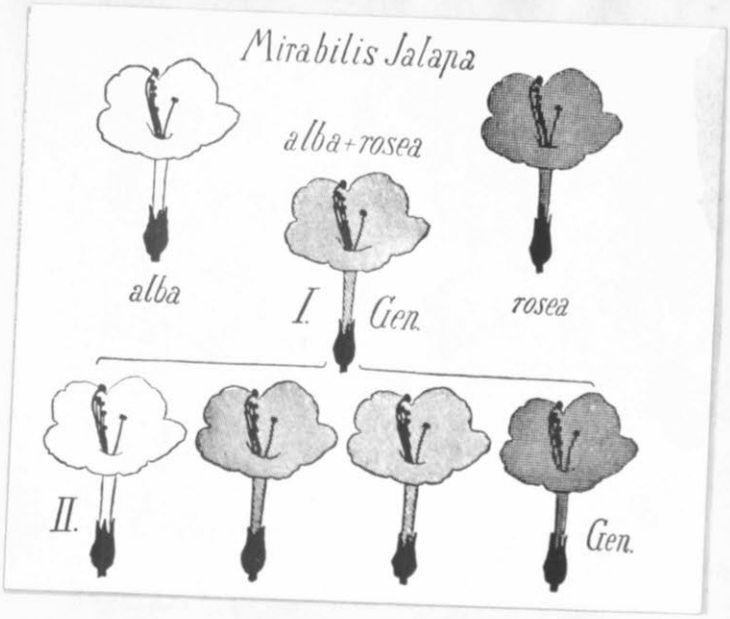


Fig. 1, A diagram to show inheritance of flower color in crosses of Mirabilis, the "four-o'clock". Alba, white parent; rosea, red parent; alba + rosea, the unfixable F_1 heterozygote, of intermediate color, pink, I. Gen. = F_1. II Gen. = F_2. (After Correns).

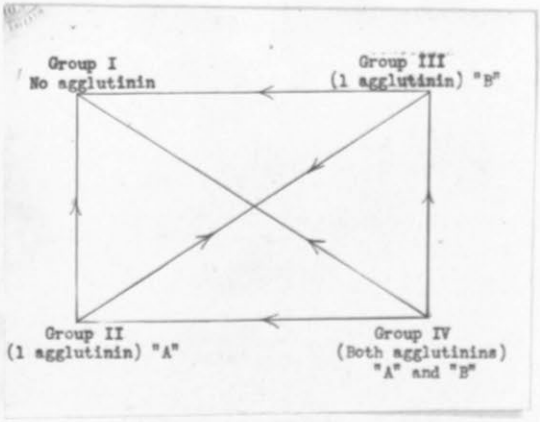


Fig. 2, The corpuscles of the various groups are agglutinated by the serums of the groups from which the arrows lead. (After Sanford)

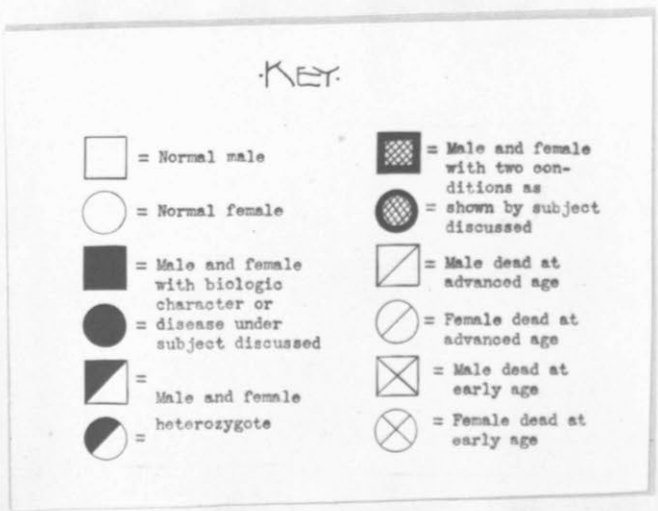
IT'S A BONA FIDE INQUIRY.

J.B. writes: "I would like to get the names and addresses of a few families in which four grandparents, both parents, and four or more children of the present generation are living and within reach. Will any one knowing of one or more such families write me the facts ? The promise is that no improper use of the information will be made. The object is to get light on a question of family resemblance."

DIFFICULT TO DIAGNOSE COMMENT.

I know the person inquiring and the object of the inquiry. If letters are sent to me I will see that they reach J.B. In violation of our rule we are keeping his name and address on file.

Fig. 3. Insert from Chicago Tribune, April 26, 1921. Kindness of Dr. W. A. Evans.



Key to Figs. 4 to 38.

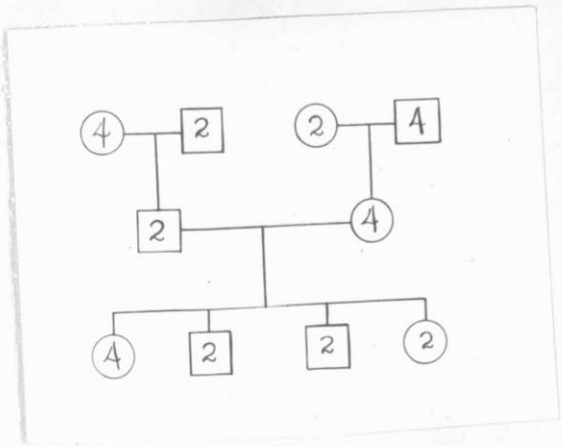


Fig. 4, Transmission of blood group IV and II through three generations.

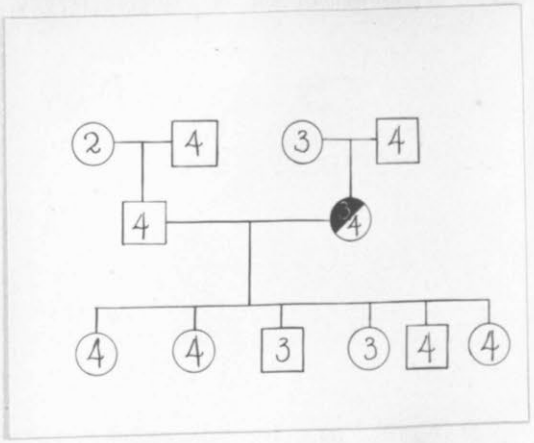


Fig. 5, Transmission of blood group IV and III through three generations by means of a heterozygous female in the second generation.

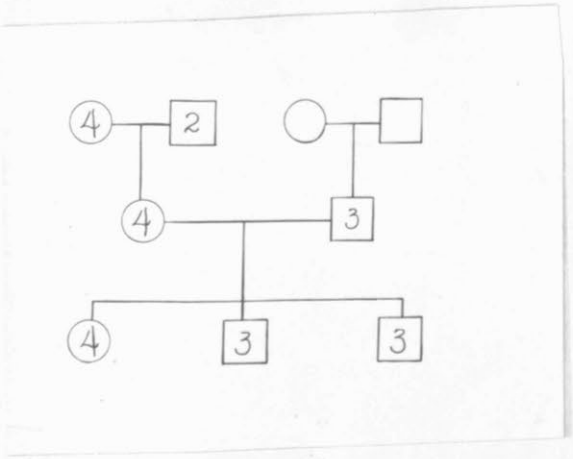


Fig. 6, Result of crossing pure group IV and pure group III through two generations.

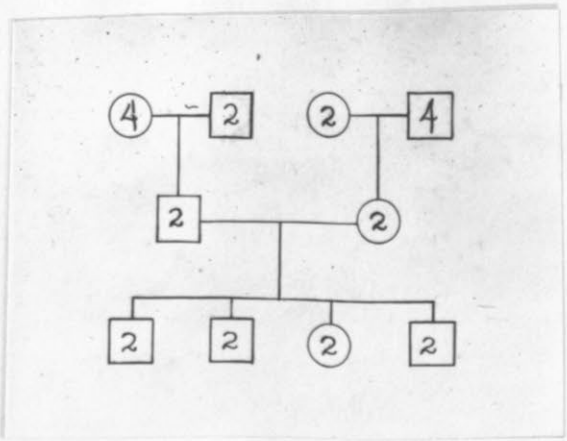


Fig. 7, Segregation of pure group II in the second generation as indicated by all the children of the third generation being in group II.

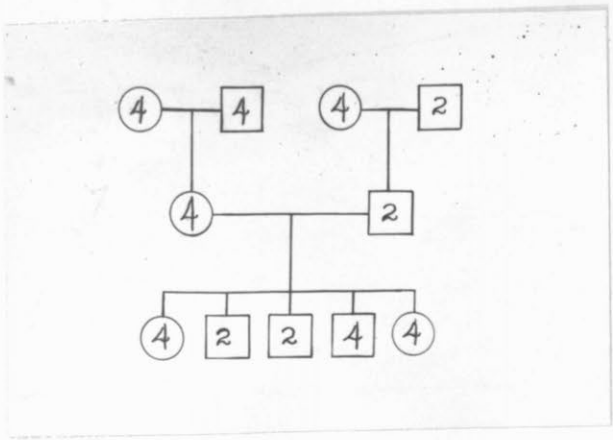


Fig. 8, Transmission of group IV and II through three generations.

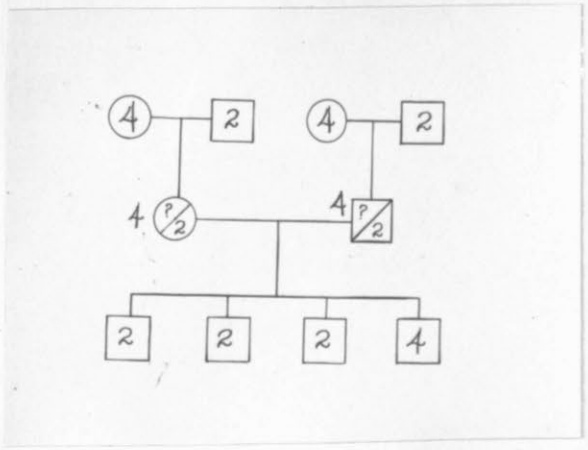


Fig. 9, Transmission of group IV and II to the third generation because of the heterozygous nature of one of the parents in the second generation.

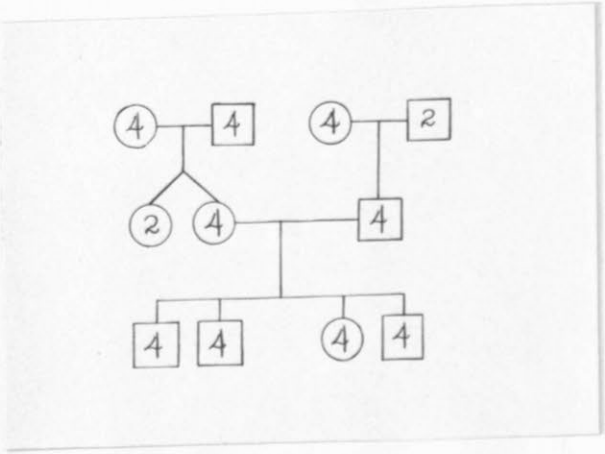


Fig. 10, Segregation of pure blood group IV from the parental generation as shown by all the children being in the same group. The twins are in different groups which demonstrates the heterozygous nature of one of the parents, and the peculiar segregative power of the germ plasm.

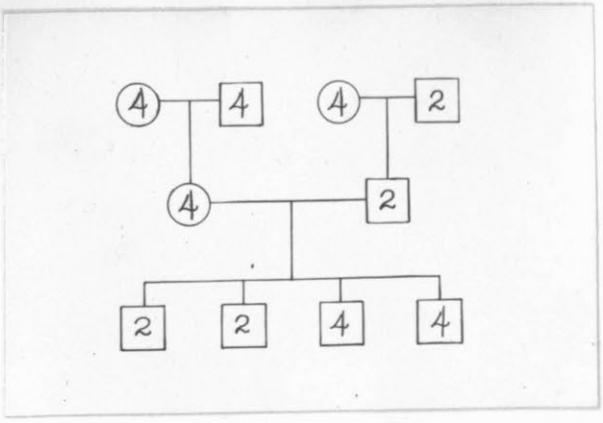


Fig. 11, Transmission of blood group II and IV through three generations. There is no method of demonstrating the homozygous or heterozygous staus of the male in the second generation.

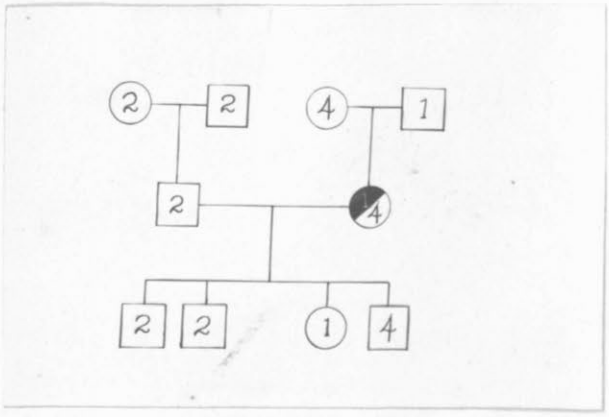


Fig. 12, Illustrates the segregation in the third generation of all the characters introduced by the ancestors. The female in the second generation was a heterozygote.

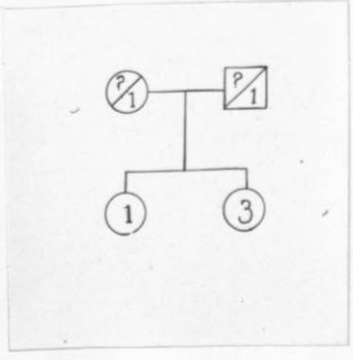


Fig. 12(a), Illustrates the value of the three generation study for determining the origin of blood group. The group III is explainable only by information obtained through families as in Fig. 12.

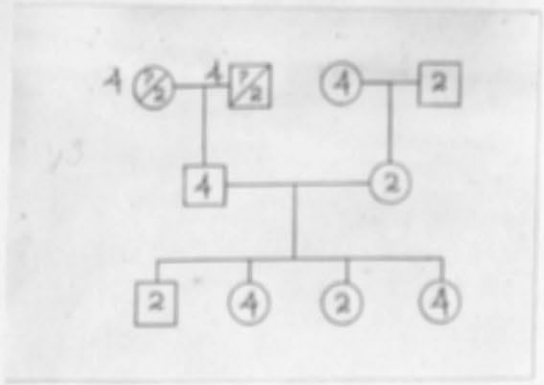


Fig. 13, Transmission of blood group II and IV through three generations. Demonstrates the heterozygous nature of one of the parents on the left in the parental generation.

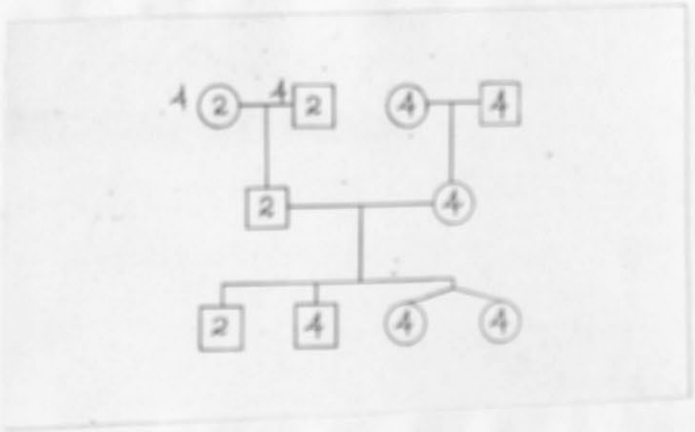


Fig. 14, Transmission of blood group II and IV through three generations and the occurrence of twins of the same blood group.

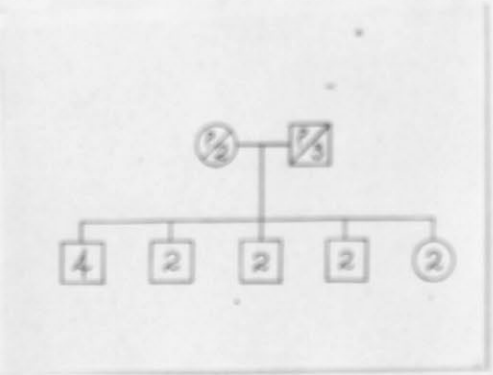


Fig. 15, Crossing of blood group II with group III. The result demonstrates the inability to state parentage from a two generation study of the blood group.

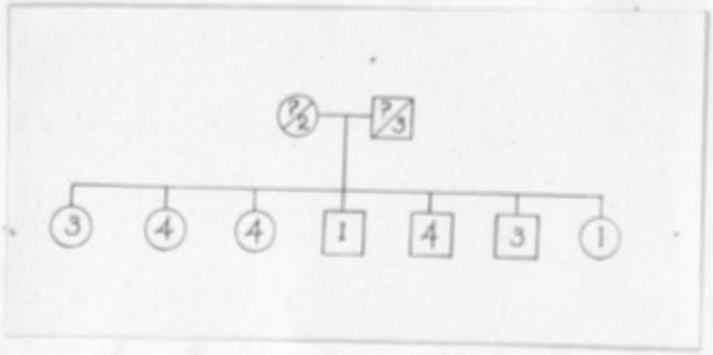


Fig. 16, The frequency of additional groups besides those represented in parents is due to scarcity of pure group III and the frequency of heterozygous group II.

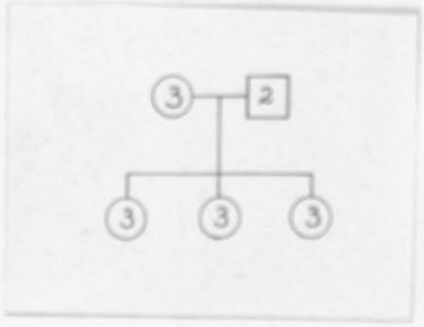


Fig. 17, Demonstrates the necessity for at least four children for the study of the segregation of characters.

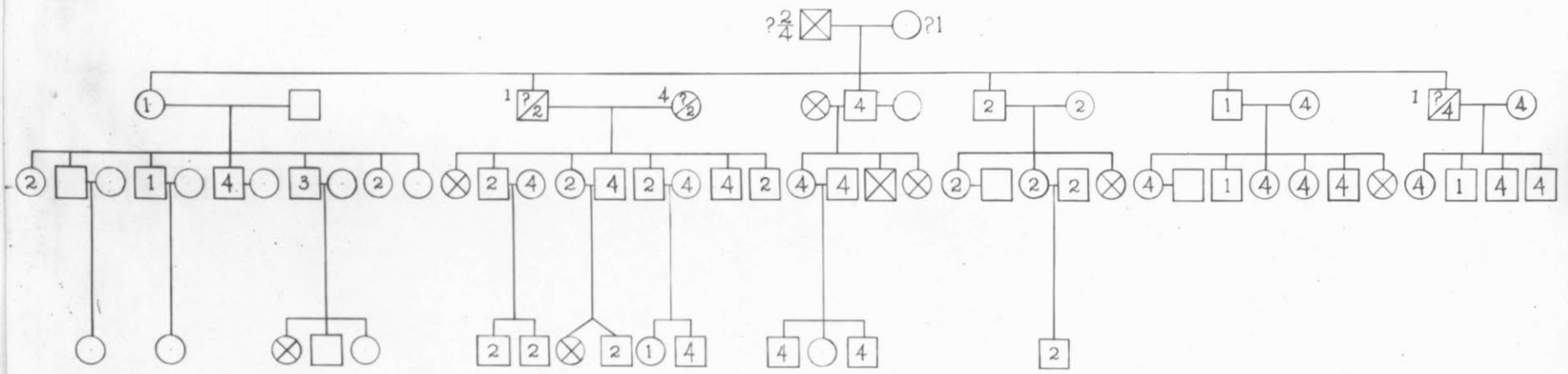


Fig. 18, Tink Family - (Information obtained through the courtesy of Mr. F. T. Jung, Sheboygan, Wisconsin) The parental generation can be presumed to be a heterozygous group II/IV male crossed by a homozygous group I female. The segregation of these characters in the first generation is striking. Additional undetermined groups are introduced into the second generation by marriage. If the heterozygous status of man for the blood group were not demonstrable the appearance of the group IV in the third generation of the second family, and the group I in the third generation of the sixth family and in the fourth generation in the third family would be inexplicable by ordinary means of the science of heredity. The difficulties in the medico-legal application of the blood group are sharply shown in this family and the inability to prove by the study of isolated small families the transmission of the blood group by the germ plasm.

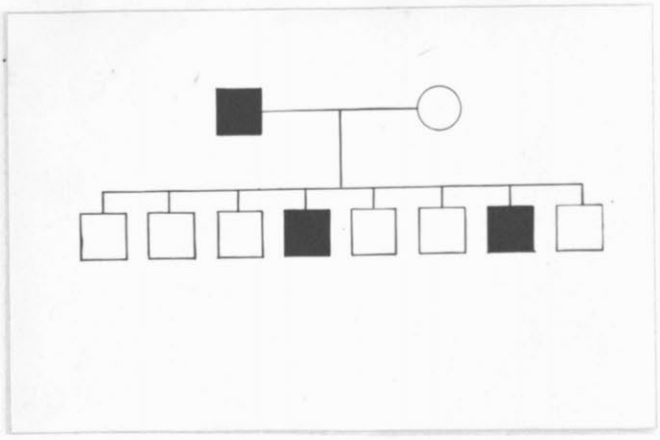


Fig. 19, Illustrates the segregation of the migraine character in families where the cross consists of a person with migraine and a person without migraine.

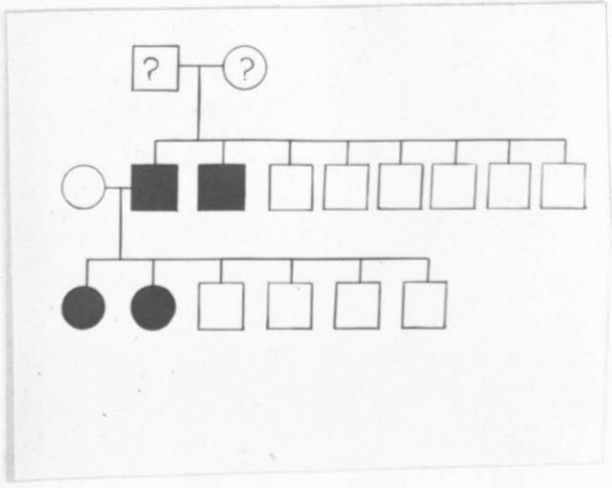


Fig. 20, Illustrates the value of searching for all the evidence available in a family where one member has migraine. It can be presumed that a parent in the first generation pictured here had migraine because of the distribution in the second generation. The segregation is carried into the third generation.

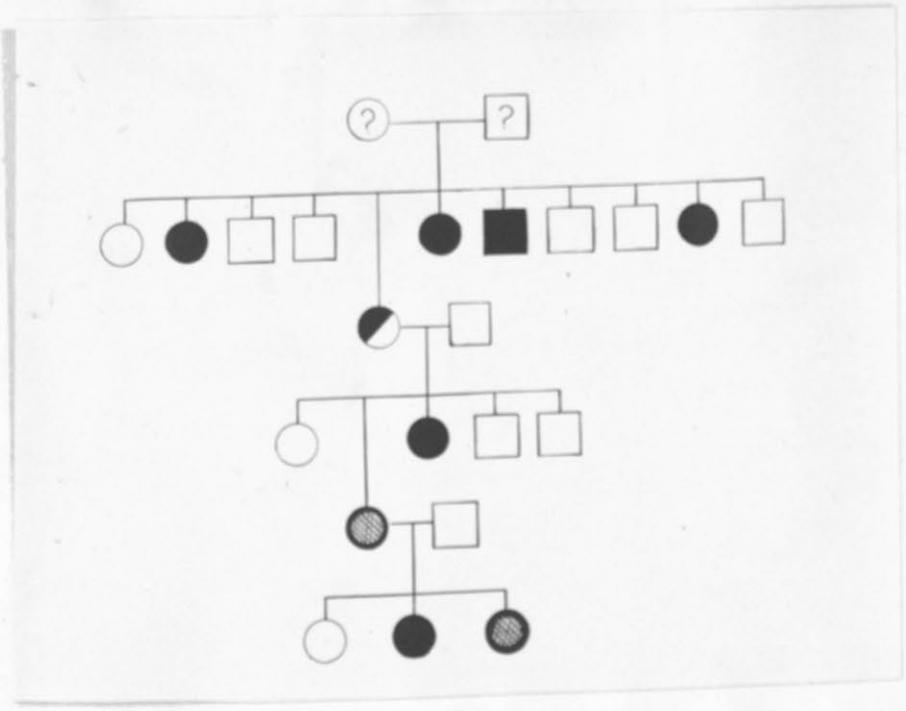


Fig. 21, Transmission of migraine with abdominal crises.

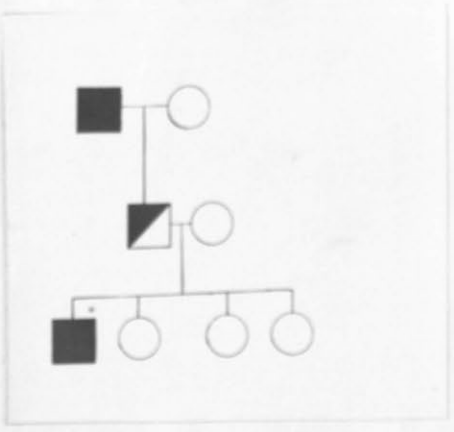


Fig. 22, Illustrating the heterozygous status of male of second generation as shown in the reappearance of the character in the final generation.

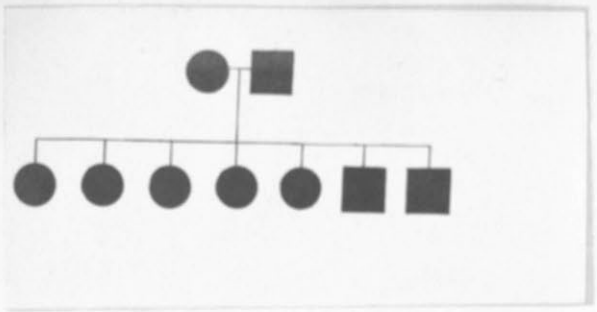


Fig. 23, Illustrates a cross of persons with the pure migraine character.

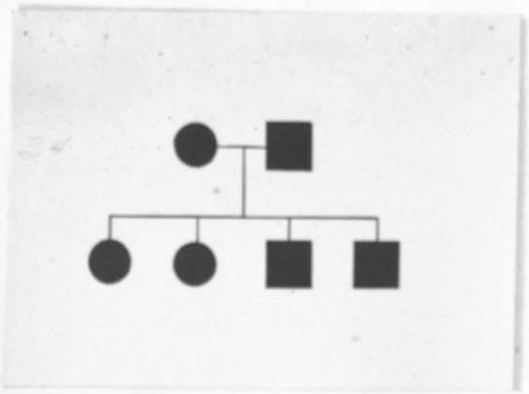
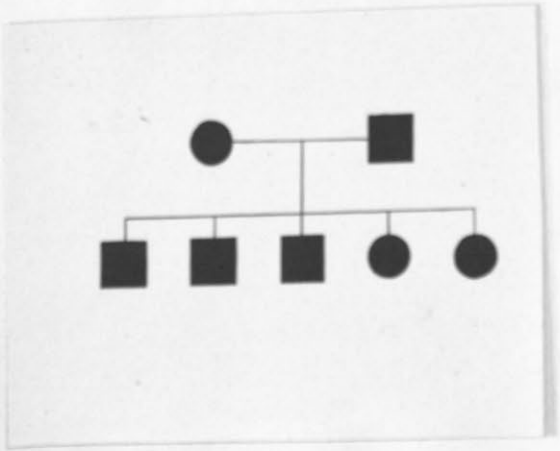


Fig. 24, The union of homozygotes results in all offspring having the same character.



is
Fig. 25, If migraine/heterozygous, for without migraine individuals without the character should be segregated in families of four or more children. The absence of such segregation is illustrated in this family.

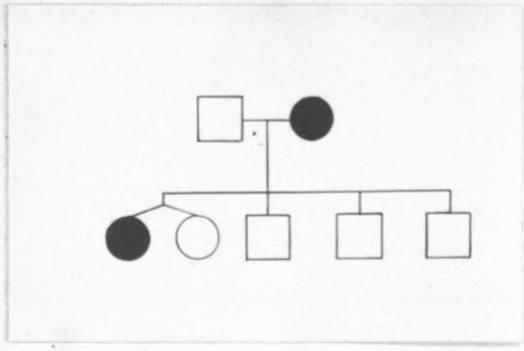


Fig. 26, Illustrates the segregative power of the germ plasm. One twin had migraine, the other was without migraine.

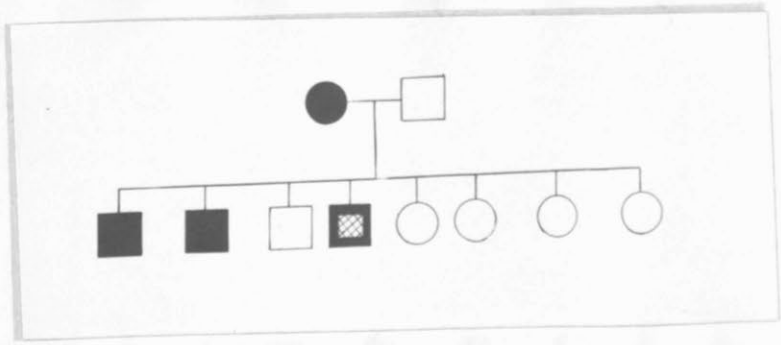


Fig. 27, Illustrates the failure of essential epilepsy to disturb the numerical relationship of normal to those with the inherited character. Essential epilepsy is superimposed on an individual with the migraine character.

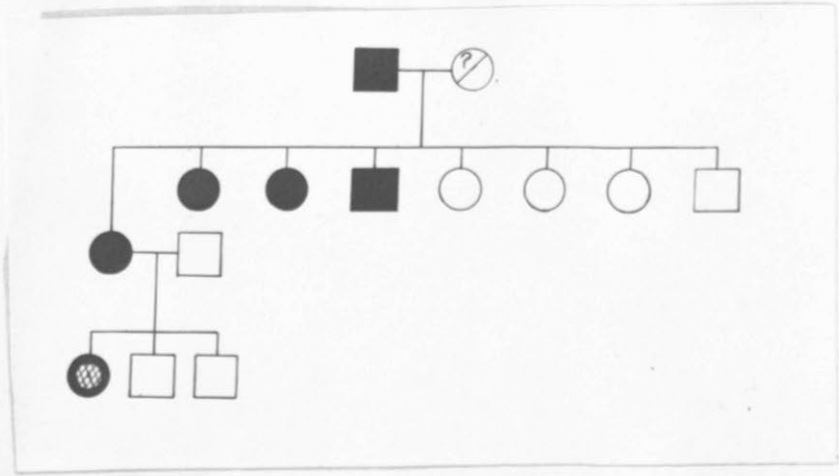


Fig. 28, The number of persons in the second generation with migraine is greater than to be expected from a cross of a pure migraine with a pure normal. This has been observed in several families and is considered due to the heterozygous, although unproven, status of the apparently normal parent. The character appears as essential epilepsy in the final generation.

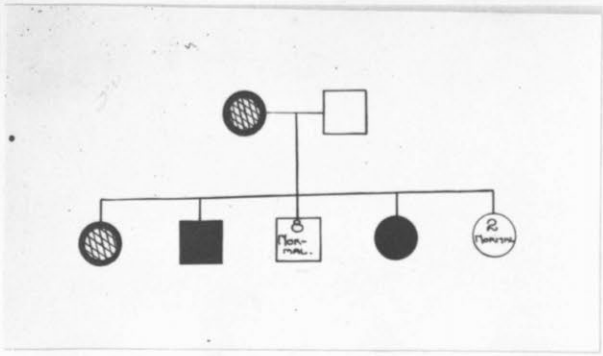


Fig. 29, The mother had epilepsy in early life, replaced by migraine. The same segregation of the characters occurred as if the mother had always presented migraine.

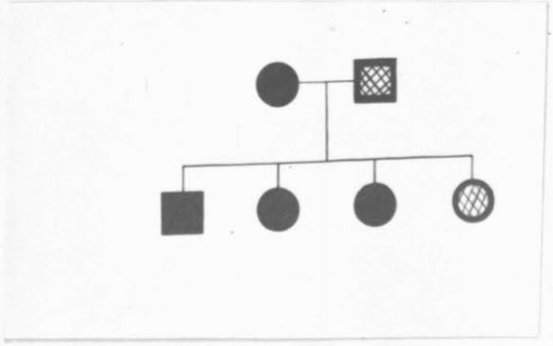


Fig. 30, Illustrates the crossing of a migraine person with an essential epileptic. The epileptic character behaves as does the migraine character.

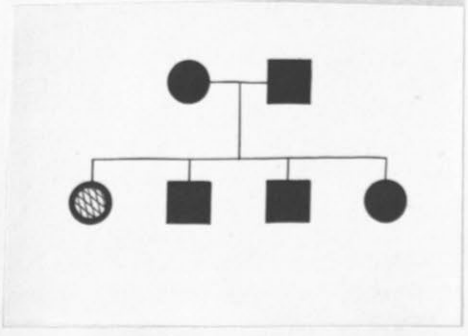


Fig. 31, The results of crossing two persons with migraine.

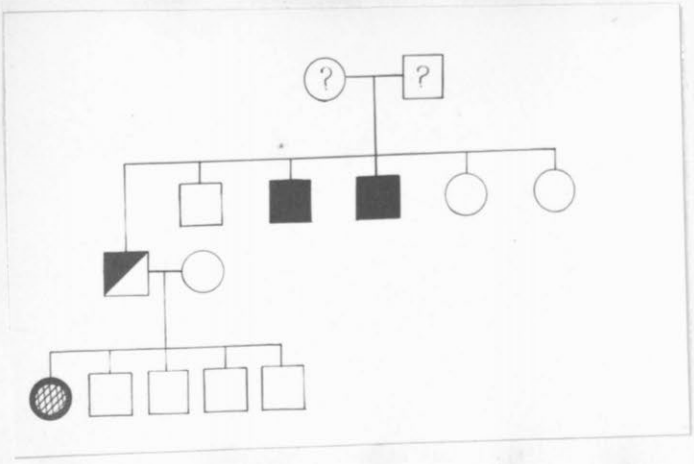


Fig. 32, Illustrates the transmission of the migraine-epilepsy character because of the heterozygous status of the male parent.

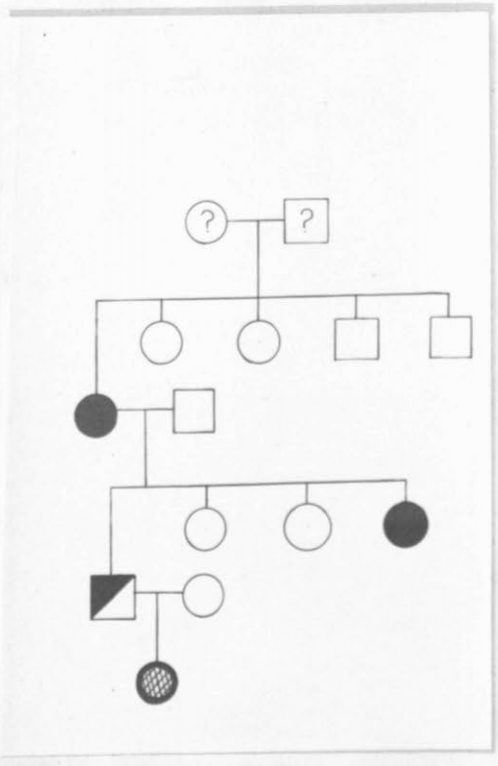


Fig. 33, Illustrates the heterozygous status of the germ plasm and its segregative power. The final generation studied would have no value if considered by itself without information obtained from other families.

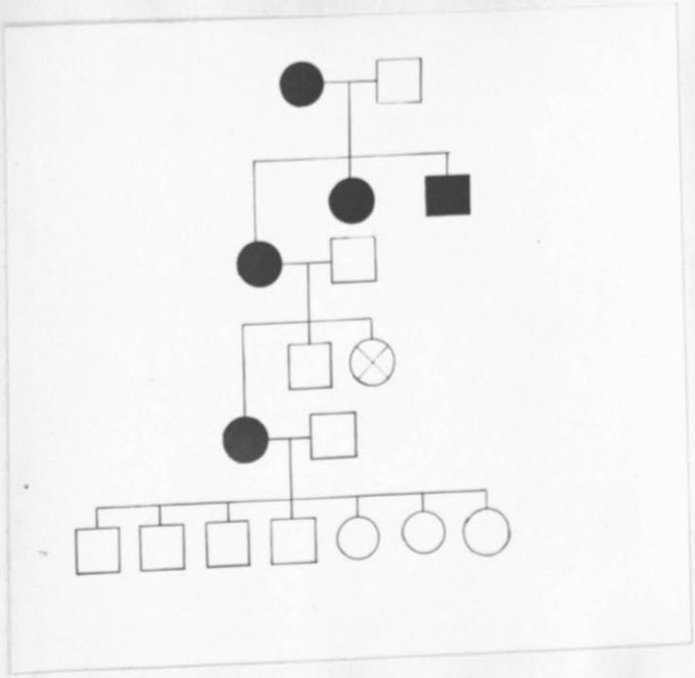


Fig. 34, Illustrates a family in which diabetes mellitus has occurred for three generations. It appeared in the mother of the last generation at the thirty-third year. None of the children was affected at the time the patient was investigated.

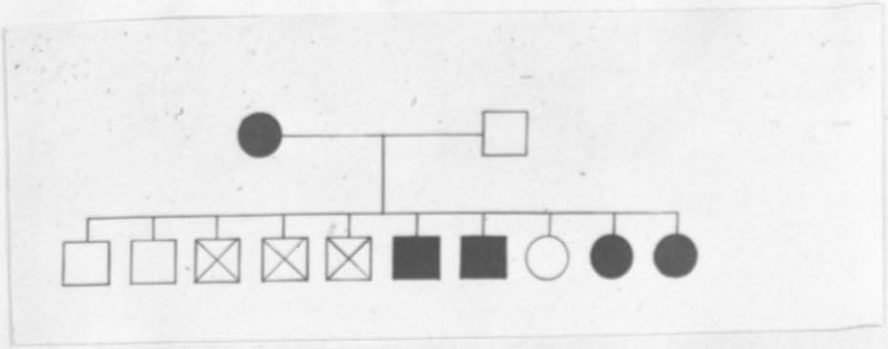


Fig. 35, Illustrates the results of crossing the diabetic and non-diabetic. The number of diabetic offspring is too large as the father's family was free of diabetes. Three children died in early life, presumably free of diabetes mellitus.

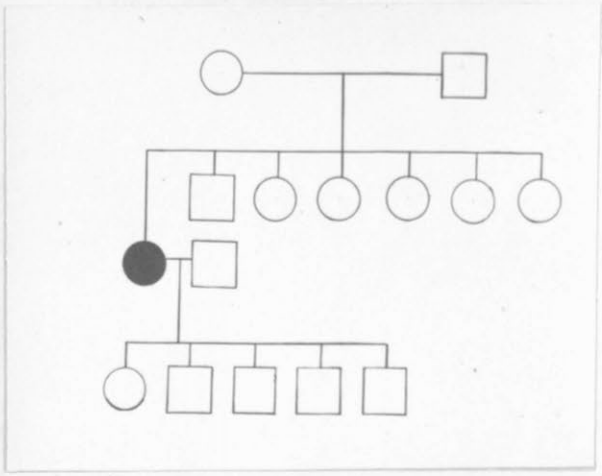


Fig. 36, The failure to conform to known laws of heredity are shown in this family. Diabetes if hereditary would have appeared at sixty-two or thereabouts in at least two children in the second generation.

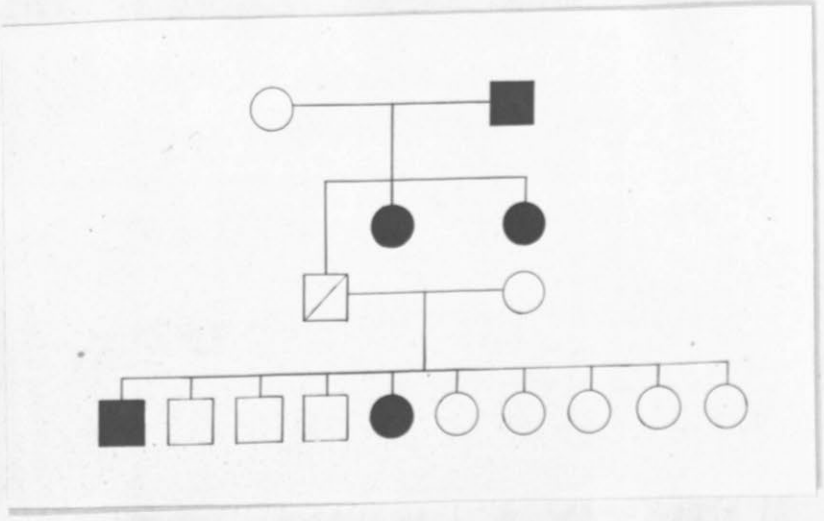


Fig. 37, Suggests that diabetes mellitus might be transmitted through the germ plasm because of the heterozygous nature of the male parent of the second generation.

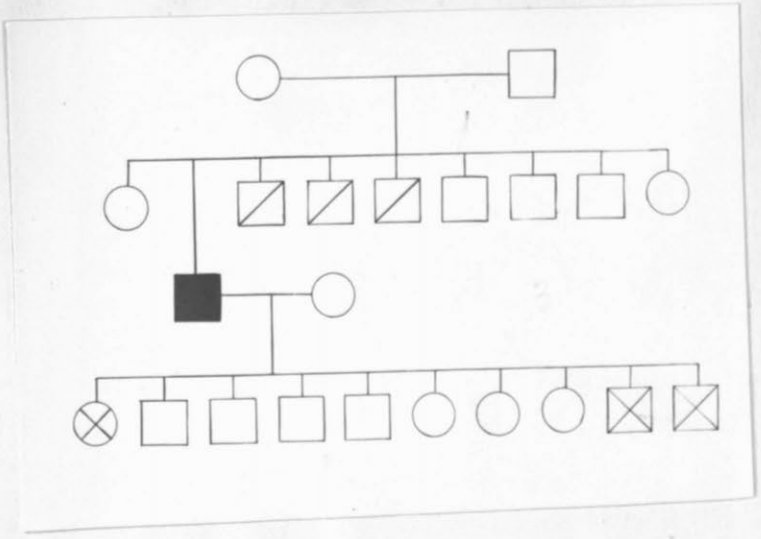


Fig. 38, A family illustrating the families studied to determine if diabetes mellitus is transmitted by a heterozygote.

Case No. 50096. A malpighian corpuscle with a great amount of fibrosis about it. The central artery is cut obliquely.