STUDY OF HEREDITY OF INSANITY IN THE LIGHT OF THE MENDELIAN THEORY pdf

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a study of heredity in insanity in the light of the mendelian theory. by a. j. rosanoff m. d.,, and florence i. orr b, s.., kings park state hospital, kings park, n. y.

Curiosity must first have been based on human family resemblances, such as similarity in body structure, voice, gait, and gestures. Such notions were instrumental in the establishment of family and royal dynasties. Early nomadic tribes were interested in the qualities of the animals that they herded and domesticated and, undoubtedly, bred selectively. The first human settlements that practiced farming appear to have selected crop plants with favourable qualities. Ancient tomb paintings show racehorse breeding pedigrees containing clear depictions of the inheritance of several distinct physical traits in the horses. Despite this interest, the first recorded speculations on heredity did not exist until the time of the ancient Greeks; some aspects of their ideas are still considered relevant today. Aristotle â€" bce emphasized the importance of blood in heredity. He thought that the blood supplied generative material for building all parts of the adult body, and he reasoned that blood was the basis for passing on this generative power to the next generation. These male and female contributions united in the womb to produce a baby. The blood contained some type of hereditary essences, but he believed that the baby would develop under the influence of these essences, rather than being built from the essences themselves. These single hereditary factors were identified as genes. Copies of genes are transmitted through sperm and egg and guide the development of the offspring. Genes are also responsible for reproducing the distinct features of both parents that are visible in their children. Preformation and natural selection In the two millennia between the lives of Aristotle and Mendel , few new ideas were recorded on the nature of heredity. In the 17th and 18th centuries the idea of preformation was introduced. Scientists using the newly developed microscope s imagined that they could see miniature replicas of human beings inside sperm heads. He lived at a time when the fixity of species was taken for granted, yet he maintained that this fixity was only found in a constant environment. He enunciated the law of use and disuse, which states that when certain organs become specially developed as a result of some environmental need, then that state of development is hereditary and can be passed on to progeny. He believed that in this way, over many generations, giraffe s could arise from deerlike animals that had to keep stretching their necks to reach high leaves on trees. British naturalist Alfred Russel Wallace originally postulated the theory of evolution by natural selection. The work of Mendel Before Gregor Mendel , theories for a hereditary mechanism were based largely on logic and speculation, not on experimentation. In his monastery garden, Mendel carried out a large number of cross-pollination experiments between variants of the garden pea , which he obtained as pure-breeding lines. He crossed peas with yellow seeds to those with green seeds and observed that the progeny seeds the first generation, F1 were all yellow. When the F1 individuals were self-pollinated or crossed among themselves, their progeny F2 showed a ratio of 3: He deduced that, since the F2 generation contained some green individuals, the determinants of greenness must have been present in the F1 generation, although they were not expressed because yellow is dominant over green. From the precise mathematical 3: Hence, the two original lines of pea plants were proposed to be YY yellow and yy green. The gametes from these were Y and y, thereby producing an F1 generation of Yy that were yellow in colour because of the dominance of Y. The forms of the pea colour genes, Y and y, are called alleles. Mendel also analyzed pure lines that differed in pairs of characters, such as seed colour yellow versus green and seed shape round versus wrinkled. The cross of yellow round seeds with green wrinkled seeds resulted in an F1 generation that were all yellow and round, revealing the dominance of the yellow and round traits. However, the F2 generation produced by self-pollination of F1 plants showed a ratio of 9: From this result and others like it, he deduced the independent assortment of separate gene pairs at gamete formation. He chose his experimental organism well and performed many controlled experiments to collect data. From his results, he developed brilliant explanatory hypotheses and went on to test these hypotheses experimentally. The 20th century saw

tremendous strides in the development of the understanding of the nature of gene s and how they function. Then there followed hundreds of papers showing Mendelian inheritance in a wide array of plants and animals, including humans. Many biologists noted that the inheritance of genes closely paralleled the inheritance of chromosome s during nuclear divisions, called meiosis , that occur in the cell divisions just prior to gamete formation. The discovery of linked genes It seemed that genes were parts of chromosomes. In this idea was strengthened through the demonstration of parallel inheritance of certain Drosophila a type of fruit fly genes on sex-determining chromosomes by American zoologist and geneticist Thomas Hunt Morgan. Morgan and one of his students, Alfred Henry Sturtevant , showed not only that certain genes seemed to be linked on the same chromosome but that the distance between genes on the same chromosome could be calculated by measuring the frequency at which new chromosomal combinations arose these were proposed to be caused by chromosomal breakage and reunion, also known as crossing over. In American botanist Harriet Creighton and American scientist Barbara McClintock demonstrated that new allelic combinations of linked genes were correlated with physically exchanged chromosome parts. Sex-linked inheritance of white eyes in Drosophila flies. Early molecular genetics In British physician Archibald Garrod proposed the important idea that the human disease alkaptonuria , and certain other hereditary diseases, were caused by inborn errors of metabolism , suggesting for the first time that linked genes had molecular action at the cell level. Molecular genetics did not begin in earnest until when American geneticist George Beadle and American biochemist Edward Tatum showed that the genes they were studying in the fungus Neurospora crassa acted by coding for catalytic proteins called enzymes. Subsequent studies in other organisms extended this idea to show that genes generally code for protein s. This model showed that DNA was capable of self-replication by separating its complementary strands and using them as templates for the synthesis of new DNA molecules. Each of the intertwined strands of DNA was proposed to be a chain of chemical groups called nucleotide s, of which there were known to be four types. Because proteins are strings of amino acid s, it was proposed that a specific nucleotide sequence of DNA could contain a code for an amino acid sequence and hence protein structure. In American molecular biologist Seymour Benzer , extending earlier studies in Drosophila , showed that the mutant sites within a gene could be mapped in relation to each other. His linear map indicated that the gene itself is a linear structure. In the strand-separation method for DNA replication called the semiconservative method was demonstrated experimentally for the first time by American molecular biologist Matthew Meselson and American geneticist Franklin W. In Crick and South African biologist Sydney Brenner showed that the genetic code must be read in triplets of nucleotides, called codons. American geneticist Charles Yanofsky showed that the positions of mutant sites within a gene matched perfectly the positions of altered amino acids in the amino acid sequence of the corresponding protein. In the complete genetic code of all 64 possible triplet coding units codons , and the specific amino acids they code for, was deduced by American biochemists Marshall Nirenberg and Har Gobind Khorana. Subsequent studies in many organisms showed that the double helical structure of DNA, the mode of its replication, and the genetic code are the same in virtually all organisms, including plant s, animal s, fungi , bacteria , and virus es. Recombinant DNA technology and the polymerase chain reaction Technical advances have played an important role in the advance of genetic understanding. In American microbiologists Daniel Nathans and Hamilton Othanel Smith discovered a specialized class of enzymes called restriction enzymes that cut DNA at specific nucleotide target sequences. That discovery allowed American biochemist Paul Berg in the early s to make the first artificial recombinant DNA molecule by isolating DNA molecules from different sources, cutting them, and joining them together in a test tube. Shortly thereafter, American biochemists Herbert W. Boyer and Stanley N. Cohen came up with methods to produce recombinant plasmids extragenomic circular DNA elements , which replicated naturally when inserted into bacterial cells. These advances allowed individual genes to be cloned amplified to a high copy number by splicing them into self-replicating DNA molecules, such as plasmids or viruses, and inserting these into living bacterial cells. From these methodologies arose the field of recombinant DNA technology that came to dominate molecular genetics. In two different methods were invented for determining the

nucleotide sequence of DNA: Such technologies made it possible to examine the structure of genes directly by nucleotide sequencing, resulting in the confirmation of many of the inferences about genes originally made indirectly. In the s Canadian biochemist Michael Smith revolutionized the art of redesigning genes by devising a method for inducing specifically tailored mutations at defined sites within a gene, creating a technique known as site-directed mutagenesis. In American biochemist Kary B. Mullis invented the polymerase chain reaction , a method for rapidly detecting and amplifying a specific DNA sequence without cloning it. In the last decade of the 20th century, progress in recombinant DNA technology and in the development of automated sequencing machines led to the elucidation of complete DNA sequences of several viruses, bacteria, plants, and animals. In the complete sequence of human DNA, approximately three billion nucleotide pairs, was made public. Time line of important milestones in the history of genetics A time line of important milestones in the history of genetics is provided in the table. Timeline of important milestones in the history of genetics year event Austrian botanist Gregor Mendel published the results of his experiments with pea plants. His work later provided the mathematical foundation of the science of genetics. Although he developed hypotheses explaining the role of nuclein in heredity , he ultimately concluded that one molecule alone could not provide the level of variation observed in nature within and between species. Creighton and Barbara McClintock published a paper demonstrating that new allelic combinations of linked genes are correlated with physically exchanged chromosome parts. Their findings suggested that chromosomes form the basis of genetics. Thus, the amount of adenine A is always equal to the amount of thymine T , and the amount of guanine G is always equal to the amount of cytosine C. The discovery, for which the three men shared the Nobel Prize for Physiology or Medicine, enabled scientists to manipulate genes by removing and inserting DNA sequences. Gilbert and Sanger shared the Nobel Prize for Chemistry for their work. Mullis invented the polymerase chain reaction PCR , a simple technique that allows a specific stretch of DNA to be copied billions of times in a few hours. Mullis received the Nobel Prize for Chemistry for his invention. By the time of its completion in , HGP researchers had successfully determined, stored, and rendered publicly available the sequences of almost all the genetic content of the human genome. By completion of Phase II of the project in , scientists had data on some 3. The project was completed in Areas of study Classical genetics Classical genetics, which remains the foundation for all other areas in genetics, is concerned primarily with the method by which genetic traitsâ€”classified as dominant always expressed , recessive subordinate to a dominant trait , intermediate partially expressed , or polygenic due to multiple genes â€”are transmitted in plants and animals. These traits may be sex-linked resulting from the action of a gene on the sex, or X, chromosome or autosomal resulting from the action of a gene on a chromosome other than a sex chromosome. Today a prime reason for performing classical genetics is for gene discoveryâ€”the finding and assembling of a set of genes that affects a biological property of interest. Punnett square; classical geneticsThis video uses a Punnett square to illustrate how Gregor Mendel determined the way traits are inherited. Cytogenetics Cytogenetics, the microscopic study of chromosomes, blends the skills of cytologists , who study the structure and activities of cell s, with those of geneticists, who study genes. Cytologists discovered chromosome s and the way in which they duplicate and separate during cell division at about the same time that geneticists began to understand the behaviour of genes at the cellular level. The close correlation between the two disciplines led to their combination. Plant cytogenetics early became an important subdivision of cytogenetics because, as a general rule, plant chromosomes are larger than those of animals. Animal cytogenetics became important after the development of the so-called squash technique, in which entire cells are pressed flat on a piece of glass and observed through a microscope ; the human chromosomes were numbered using this technique. Today there are multiple ways to attach molecular labels to specific genes and chromosomes, as well as to specific RNAs and proteins, that make these molecules easily discernible from other components of cells, thereby greatly facilitating cytogenetics research. Microbial genetics Microorganisms were generally ignored by the early geneticists because they are small in size and were thought to lack variable traits and the sexual reproduction necessary for a mixing of genes from different organisms. After it was discovered that microorganisms have

many different physical and physiological characteristics that are amenable to study, they became objects of great interest to geneticists because of their small size and the fact that they reproduce much more rapidly than larger organisms. Bacteria became important model organisms in genetic analysis, and many discoveries of general interest in genetics arose from their study. Bacterial genetics is the centre of cloning technology.

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From the earliest times physicians have recorded observations of the transmission of nervous diseases by heredity. In modern times the accumulation of large amounts of material in the shape of clinical statistics published by hospitals has established beyond question the fact that heredity plays an essential part in the etiology of certain neuropathic conditions. Table I shows some statistical figures selected at random. Figures such as these are for all forms of insanity, including those which occur on a basis of exogenous causes; yet even as they are, their significance becomes quite apparent when they arc compared with figures representing the frequency of a neuropathic family history among normal subjects: In other words, there 1 Cited by Kraepelin, Psychiatric, 7th ed. December 31, 1ST Special mention may be made of color of eyes, 3 color of hair, 4 form of hair, 6 brachydactyly, 6 some forms of cataract, 7 and retinitis pigmentosa 8, as human traits which have been shown to be transmitted from generation to generation in accordance with the Mendelian theory. As regards insanity and allied neuropathic conditions, the facts to which we have already referred, namely, the facts of atavistic and collateral heredity, direct heredity, and the frequent failure of transmission seem to point plainly to alternative inheritance. This suggests the likelihood of a mechanism of inheritance according with the Mendelian theory, and the present study has been undertaken with a view to determining whether indeed the neuropathic constitution is transmitted in the manner of a Mendelian trait. The total inheritance of an individual is divisible into unit characters, each of which is, as a general rule, inherited independently of all other characters and may therefore be studied without reference to them. Jour of Nerv and Ment. ORR The inheritance of any such character is believed to be dependent upon the presence in the germ plasm of a unit of substance called a determiner. With reference to any given character the condition in an individual may be dominant or recessive: The dominant and recessive conditions of a character are designated by the symbols D and R respectively. Thus in the case of eye color the brown color is the dominant condition and the blue color is the recessive condition. In other words, the inheritance of brown eyes is due to the presence in the germ plasm of a determiner upon which the formation of brown pigment in the anterior layers of the irides depends, while the inheritance of blue eyes is due to the lack of determiner for brown pigment in the germ plasm, for the blue color of eyes is due merely to the absence of brown pigment, the effect of blue being produced by the choroid coat shining through the opalescent but pigment-free anterior layers of the irides in such cases. It is obvious that as regards any character an individual may inherit from both parentsâ€”duplex inheritance, designated by the symbol D, â€”or from one parent onlyâ€”simplex inheritance, designated by the symbol DR, â€”or he may fail to inherit from either parentâ€”nulliplcx inheritance, designated by the symbol R; in the last case the individual will exhibit the recessive condition. We are now in a position to estimate the relative number of each type of offspring according to theoretical expectation in the case of any combination of mates. There are but six theoretically possible combinations of mates. Continuing to make use of eye color as an instance of a Mendelian character, let us consider in turn each theoretical possibility. Both parents blue-eyed nulliplex: One parent brown-eyed and simplex that is to say inheriting the determiner for brown-eye pigment from one grandparent only , the other blue-eyed: One parent brown-eyed and duplex, the other blue-eyed: Both parents brown-eyed and simplex: Both parents brown-eyed, one duplex the other simplex: Both parents brown-eyed and duplex: It will be seen from these formulae that in attempting to predict the various types of offspring that may result from a given mating it is necessary to know not only whether the character is in each parent dominant or recessive, but in the case of the dominant condition also whether it is duplex or simplex. Turning again to the example of eye color, a blue-eyed individual we know to be nulliplex, as he has no brown pigment in his eyes and therefore could not have inherited the determiner for brown-eye pigment from either parent. But how are we to judge in the case of a brown-eyed person whether he has inherited the determiner for that character from both parents or only from one? We can judge this only

by considering the ancestry and offspring of the individual. To put the whole matter in a nutshell, the essential difference between the dominant and the recessive conditions of a character lies in the fact that in a case of simplex inheritance the dominant condition is plainly manifest, while the recessive condition is not apparent and can be known to exist only through a study of ancestry and offspring. ORR This is important because it constitutes the criterion which enables us to determine whether any given inherited peculiarity or abnormality is, as compared with the average or normal condition, dominant or recessive. The total amount of psychiatric material which is available at this hospital is very large. We found, however, that for various reasons, to be spoken of presently, the greater part of the material could not be utilized in our study. In selecting cases our aim has been to exclude all those forms of insanity in the causation of which exogenous factors, such as traumata, alcoholism, and syphilis, are known to play an essential part; and we have also systematically excluded psychoses which occur upon a basis of organic cerebral affections, such as tumors, arteriosclerosis, apoplexy, and the like. We are not inclined to dispute the possible influence of heredity in these conditions; we have excluded them merely for the purpose of simplifying our problem by avoiding the necessity of dealing with a complicating factor in the shape of an essential exogenous cause. Moreover there seemed to be reason to believe that the so-called functional psychoses and neuroses are more closely related to each other than to the conditions which we have sought to exclude; and since our material had to be largely massed together for statistical treatment it was important that it should be as homogeneous as possible. More than half the patients at this hospital are either themselves foreign born or the children of foreign-born parents; and among those who were born in this country of American parents there are many whose homes are in distant states; thus but a small proportion remained whose families had for two or three generations resided in this country and were accessible to investigation. Other difficulties in obtaining our data were due to the ignorance of some of our informants or to their reluctance or refusal to co-operate in the investigation; and in many cases the investigation had to be discontinued and the data already collected had to be discarded owing to incompleteness. Such diagnosis often enough presents great difficulty when there is opportunity for direct observation, but when it has to be based upon observations of untrained informants related from memory the difficulty is, of course, greatly increased and with it the chance of error. We have endeavored to reduce the amount of error from this source by interviewing personally as many as possible of the nearest relatives of the patients whose pedigrees were being investigated, and by the practice of tracing almost all the families not farther than to the generation of grandparents, for the farther back our inquiries extended the more scant and more vague was the information which we were able to obtain. To the difficulty of diagnosis is added the further difficulty which results from the impossibility in the present state of psychiatry of precisely delimiting the conception of the neuropathic constitution. To this matter we shall have occasion to revert in subsequent sections. In the analysis of data it was often necessary in the case of a normal subject to determine whether the case was one of duplex or of simplex inheritance, it having appeared early in the course of our study that the normal condition was dominant over the neuropathic condition. The fact of simplex inheritance we were able in some cases to establish on the basis of the existence of neuropathic manifestations in the ancestors or collateral relatives of the subject; in other cases this evidence was lacking as our information did not extend to the more remote generations, so that it was necessary to assume the fact of simplex inheritance on the basis of the existence of neuropathic offspring: On the other hand, the fact of duplex inheritance was in every case based upon the absence of neuropathic manifestations in ancestors and collateral relatives, as far as known, as well as in the offspring; but inasmuch as in scarcely any case was the family history traced farther back than the third generation it is clear that the possibility of simplex inheritance was in no case positively excluded; we have here, therefore, another source of error which, fortunately, is slight, and affects the least important part of our mate- A. ORR rial, namely, the cases of matings from which no neuropathic offspring have resulted. On the whole, no pretension is made here of total elimination of error; but we believe that whatever errors remain they are not sufficient to invalidate the material as a basis for our study. In the Preliminary Report, to which we have already referred and which was based upon an analysis of the pedigrees of twelve families, it was

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shown that the neuropathic constitution is transmitted by heredity probably in the manner of a trait which is, in the Mendelian sense, recessive to the normal condition. Sixty other families have since been investigated; the entire material now includes the pedigrees of seventy-two families, representing two hundred and six different matings, with a total of one thousand and ninety-seven offspring. In Table I this mass of data has been arranged so as to show the proportions of normal and neuropathic offspring which resulted from the various types of mating alongside of figures representing theoretical expectation according to the Mendelian theory. Some of the data represented in the table require special explanation. Among the offspring which resulted from matings of the first type, R x R, ten are recorded as being normal, although Types of mating. Actua l find ings. Theoretica l expectation Neuropathic Normal offoffspring, spring. Of these ten one died at the age of thirty-eight years in an accident, during life suffered from asthma, had a son who died in convulsions; another is described as being easy going, is somewhat odd and possibly abnormal in make-up, is twenty-nine years of age; the rest are from eight to twenty-two years of age. In other words, in two of the ten subjects the neuropathic constitution is not positively excluded and the remaining eight have not reached the age of incidence. Parte 1 de 5.

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