GENES AND INTELLECT

EUGENICS AT THE TURN OF TWO CENTURIES

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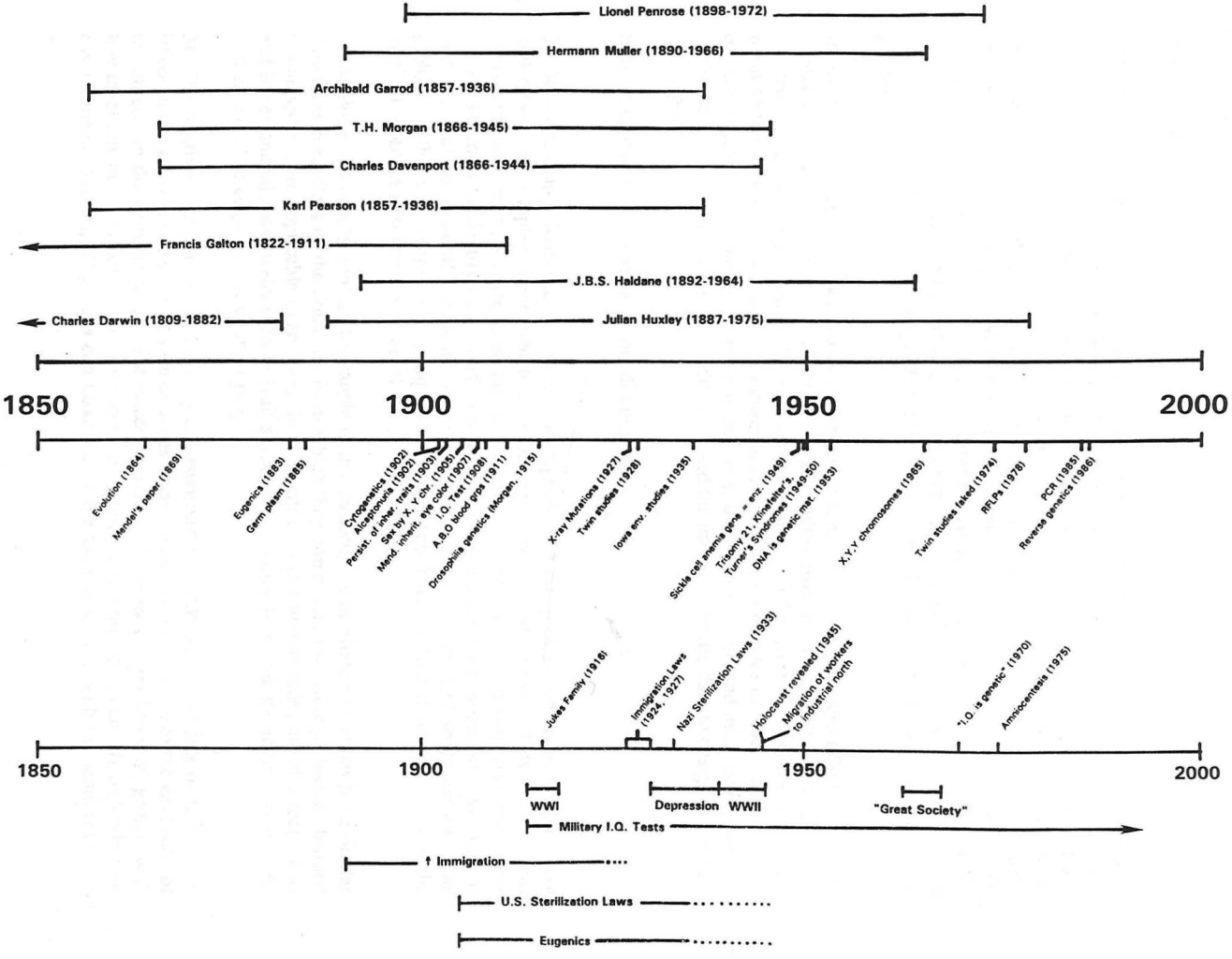

Lionel Penrose (1898-1972)
Hermann Muller (1890-1966)
Archibald Garrod (1857-1936)
T.H. Morgan (1866-1945)
Charles Davenport (1866-1944)
Karl Pearson (1857-1936)
Francis Galton (1822-1911)
J.B.S. Haldane (1892-1964)
Charles Darwin (1809-1882)
Julian Huxley (1887-1975)
1850
1900
1950
2000
Evolution (1864)
Mendel's paper (1869)
Eugenics (1883)
Germ plasm (1885)
Cytogenetics (1902)
Alcaptonuria (1902)
Persist. of other traits (1903)
Sex by X, Y chr. (1905)
Mend. inherit. eye color (1907)
I.Q. Test (1908)
A,B,O blood grps (1911)
Drosophila genetics (Morgan, 1915)
X-ray Mutations (1927)
Twin studies (1928)
Iowa env. studies (1935)
Sickle cell anemia gene = enz. (1949)
Trisomy 21, Klinefelter's,
Turner's Syndromes (1949-50)
DNA is genetic mat. (1953)
X,Y,Y chromosomes (1965)
Twin studies faked (1974)
RFLPs (1978)
PCR (1985)
Reverse genetics (1986)
Jukes Family (1916)
Immigration Laws
(1924, 1927)
Nazi Sterilization Laws (1933)
Holocaust revealed (1945)
Migration of workers
to industrial north
"I.Q. is genetic" (1970)
Amniocentesis (1975)
1850
1900
1950
2000
WWI
Depression
WWII
"Great Society"
Military I.Q. Tests
† Immigration
U.S. Sterilization Laws
Eugenics

Introduction.

The relationship between environmental and genetic factors in the determination of human intellectual function is complex, and poorly understood. Perhaps because intellectual function is one of the principal differences between us and animals, biologists have tried to understand its biologic basis. Since the early 1900s when inheritance began to receive scientific attention, the component of intellectual function that is due to heredity has been a subject of intense interest not only to biologists, but also to social scientists and government policy makers. the result of these events was the Eugenics movement. At various times in the twentieth century, the view as to the relative importance of environment and heredity has shaped social policy in the US and other nations in ways that have had profound effects on the welfare of various groups.

In presenting this subject, I will focus on the early twentieth century, the scientific data that was produced at that time and the social policies that resulted from it. I will then contrast turn-of-the-century science and social policy it to our current view of science as it relates the human brain and intellectual function. This subject is interesting on a number of levels, the evolution of neural science (and biologic science in general), the interpretation (and misinterpretation) of scientific data in light of prevailing "dogma", and the use of scientific data to design and justify social policy.

Several themes are important in this discussion.

1) Reductionism. Reductionism is the description of a complex phenomenon which is not understood, in simpler terms which may be more easily understood. This practice has characterized Western science from the first dissections to understand human anatomy to our current attempts to identify the individual molecules responsible for a biologic process. Use of mathematical, mechanical, or animal models of diseases are examples of reductionism. The problem with reductionism is that important components may be missed or ignored, and the original problem misunderstood. (29a)

2) Analogy. Molecular biology has taught us that molecules with similar functions have similar structures regardless of the organism from which they come, and that biologic lessons learned in one species are applicable to another. In the context of this presentation, the idea that plants and lower animals pass traits such as fruit shape or hair color from one generation to the next was extended to cognitive function in people.

3) The relative contributions of heredity and environment. Although both sets of factors are important in a given outcome, at various times attention has focused on one to the exclusion of the other. In the extreme cases, if intellect is exclusively dependent on heredity, groups with low level function will not benefit from social programs, and if intellect is largely dependent on environmental factors, all groups can make use of the same resources with the same result.

4) Individual vs. Society. At times, social policy has reflected the belief that the interests of the society as a whole require sacrifices by the individual, and at others that the strength of the society is the individual and diversity.

5) Economics. The economic condition of a society affects its interpretation of scientific data. For example, when profits and tax revenue are down, problems in a society are more likely to be attributed to causes about which little can be done such as heredity, rather than to environmental causes the correction of which will cost a great deal of money.

The Origins of Human Genetics and Eugenics.

A number of sources trace the origin of human genetics to Archibald Garrod with his description of alcaptonuria in 1902, and the prediction that the unit of inheritance, or gene corresponds to an enzyme in a metabolic pathway. However, the study of inheritance in humans should more correctly be traced to Francis Galton in England in the late 1800s. This period was the first time that human heredity was studied systematically with the aim of manipulating it. Although Galton's concepts of heredity and their application to humanity are unrecognizable as human genetics by today's standards, Galton and his disciples shaped the field and the social policies that drew support from them in the first half of the twentieth century.

In the nineteenth century, natural science was concerned with identification and classification of natural phenomena such as plant and animal species and minerals, and so was descriptive rather than analytical or quantitative. Darwin's theory of evolution emphasized change, or adaptation of the organism to the environment. However, these changes appeared stable with time representing a paradox for Darwin and his theory. Classification lead to the observation in the scientific community (long known in agriculture) that "like tended to produce like". The concept of "germ plasm" or the continuity of character introduced in the 1880s, arose from repeated failure to induce inheritance of acquired characteristics. The germ plasm concept provided a physical mode of inheritance and a mechanism. Biologists became interested in the variability in their observations and began to quantify them with the aid of advances in mathematics, and the models provided by the physical sciences.

The neural sciences were similarly descriptive at the end of the nineteenth century. Detailed anatomic and histologic studies were carried out on many species including humans. The chemical composition of the blood, urine, and brains of patients in psychiatric and other institutions were carried out. These studies lead to the distinction between structural and functional diseases of the brain.

Technology, or the application of scientific developments to industry and society resulted in improved modes of travel and wider distribution of manufactured goods which translated into a higher standard of living. The development of an experimental approach to natural science and the effect of technology on society provided a rationale for intervention in human affairs. Science had new authority approaching that of religion. Consequently, scientific data were received by the public with little skepticism.

Galton essentially proposed that humanity could benefit from the application of biologic principles, most notably through the selection of good, and the elimination of bad genetic influences in society. In 1883, he coined the term "eugenics" to mean the science of improving humanity through the use of heredity. "Could not the race of men be improved? Could not the undesirables be got rid of, and the desirables multiplied?" In his book Hereditary Genius, published in 1869, he sought to identify the roots of "natural ability", or "those qualifications of intellect and disposition ... which lead to reputation, ... a leader of opinion, an originator" (17). Galton had found that "good qualities" tended to run in families as did "bad qualities" such as "feeble-mindedness", criminal behavior, and alcoholism. At this time, the "unit" of inheritance, or what constituted a heritable trait was not known, and our concepts of simple and complex traits were not imagined. Gregor Mendel's paper in 1865 describing "elements" of heredity and rules governing their expression was unnoticed for forty years.

The principal problem with Galton's approach to human genetics was that the traits which he used as unitary characteristics, such as "feeble-mindedness" were inadequately defined. For example, the feeble-minded group was defined largely by prejudices of the time and included people who were poor, uneducated, and those who primary language was not English, in addition to people with a variety of neurologic, psychiatric, chromosomal, and metabolic disorders which had not been differentiated at the time. Those whose reproduction should be encouraged were people like Galton himself, scientists, statesmen, artists, and authors. Galton completely ignored the contributions of environment to "feeblemindedness" or "genius" (17).

Galton used statistical analysis to derive his laws of human heredity. He used studies of sweet peas to define probabalistic laws of heredity which he could then apply to humans. In breeding experiments with seeds of different weights, he determined that the daughter seeds had weights that were distributed in a Gaussian (normal) distribution around a mean, that each group had the same statistical variability (deviation), and that in a population the mean weights of subgroups tended to regress towards the mean. Because a number of human characteristics which Galton had measured such as height or arm span also conformed to a Gaussian distribution, he concluded that plants and animals obeyed the same laws of nature, specifically heredity. Galton then studied the correlations between characteristics such as arm span and height, or height within a family, and derived formulas for correlation and the concept of the correlation coefficient. Galton named this school of biology Biometry. He subsequently applied correlation statistics to anthropomorphic characteristics, human intellectual function (poorly defined at that time), and families from different and socio-economic groups and backgrounds. Galton found an excellent correlation from generation to generation for "feeble-mindedness", which often simply meant illiteracy, as well as other characteristics. He assumed that correlation was equivalent to cause and effect, and that he had demonstrated the constancy of human characteristics through generations. At the time, Galton's approach to human heredity was accepted because it was quantitative. The fact that it was quantitative legitimized it as "scientific" to a large audience which included other scientists, politicians, artists and writers. With time, eugenics became a popular movement whose goal was to perfect humanity through careful breeding. The assumptions of eugenics generated controversy in many areas outside of science including marriage, birth control, women's rights, and public health, and politics. Many

of these controversies persist today in only slightly different terms.

One of Galton's followers, Karl Pearson was a gifted mathematician, and committed Eugenicist. Pearson's initial involvement with biology came from a collaboration with Walter Weldon, a zoologist who was interested in variability in species of crabs and how to classify them into groups based on physical characteristics. Pearson worked out a number of statistical methods for doing so, and made significant contributions to statistical analysis including the chi square test for regression analysis. He expanded the "statistical study of biological problems" working with statistical models and inheritance in a number of plant and animal species. In these systems, he demonstrated that physical characteristics were inherited in accordance with statistical laws, and further, that in humans, "psychical" characteristics were also inherited in the same fashion. Initially, Pearson used teachers' evaluations of students to assess their mental ability. In 1908, the advent of the IQ test in France allowed quantitation of intelligence which added to the objective appearance of Pearson's work. In order to eliminate the role of environment, Pearson correlated "intelligence" with traits which are unaffected by the environment such as eye or hair color (17,25).

Pearson preferred to focus on biologic characteristics which could be observed and measured directly. For that reason, he resisted, and was in fact antagonistic towards Mendelian concepts of inheritance because they depended on unobservable "germ plasm" or genes. By the early 1900s, Mendelian genetics was gaining wide acceptance on a theoretical and experimental basis. Pearson found himself at odds with a number of scientists because many of his statistical models and correlations did not conform to Mendelian predictions. He founded his own journal, Biometrika, which was read more widely in North America than in England.

Pearson's influence extended beyond the scientific/intellectual community because with eugenics he was addressing issues of general concern to British and U.S. society. In both countries, concern existed that the "undesirable" elements of society, which included immigrants, illiterates, paupers, the "feeble-minded", alcoholics, criminals, and the "morally loose" were breeding faster than the "desirable" elements who were devsing, writing, making and enforcing social policy. The belief that both desirable and undesirable human characteristics were hereditary, had a number of implications for social policy. Charity or "alms" were felt to encourage breeding of "undesirables" and ways to discourage dysgenic and encourage eugenic mating were discussed.

Eugenics in the United States.

In the United States, the idea that heredity determined intellectual function met with a warm reception. A number of workers including charles Davenport and Henry Goddard began to collect and analyze data on various groups and families. Unlike Pearson in England, these workers generally believed in Mendelian principles of inheritance, but used many of Galton and Pearson's statistical methods with their theoretical framework. In the US, investigators developed data banks for the study of human genetics.

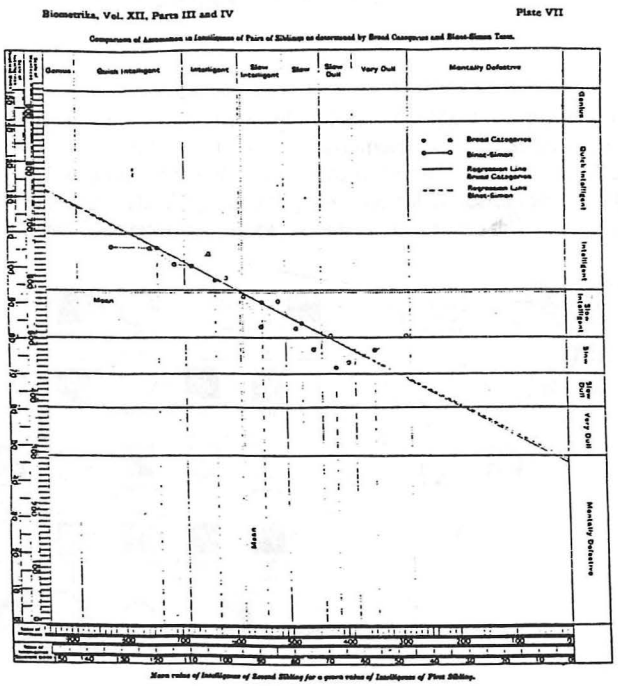
Charles Davenport became the director of the Cold Spring Harbor Laboratory in 1898, and raised considerable private money to establish a Station for Experimental Evolution and the Eugenics Record Office which he directed from 1904 to 1934. At Cold Spring Harbor, a great deal of high quality work on genetics was carried out. Davenport worked out the inheritance of hair and eye color. However, the data for the Eugenics Record Office was collected by inadequately trained personnel, and often inadequately - accepting subjective and unverified answers to questions about relatives. Davenport's studies found that feeblemindedness was hereditary. Like Galton and Pearson, he did not distinguish among the many possible forms of "feeblemindedness" (7,8,11,17). Furthermore, the analogy between inheritance of hair and eye color, and intellect was not appropriate.

Goddard brought the Binet-Simon IQ test to the US, and applied it at the Vineland, New Jersey Training School for Feeble-Minded Boys and Girls where he was the director of the laboratory for the study of mental deficiency. He studied his patients and their families in an effort to determine the causes of feeble-mindedness. Goddard developed a scale of feeblemindedness. Idiots had a mental age of less than two, imbeciles from three to seven, and morons from eight to twelve. Although Goddard found that feeblemindedness could be attributed to disease and trauma, heredity was the most common cause. He went on to conclude that feeblemindedness underlay a great deal of criminal behavior (11,17).

Another large body of data was generated by Robert Yerkes when a modified IQ test was given to US Army recruits during WW I. Intelligence could then be correlated with region, national origin, educational level, race, or economic status. Not surprisingly, immigrants, blacks, and people from lower socio-economic strata had lower IQs than educated white men (17).

During this period, eugenic data on intelligence met with some resistance. A fundamental question, the answer to which remained unknown for another twenty to thirty years, was what is the "unit" of inheritance? The eugenicists felt that intellect was inherited as a single unit, that a single gene controlled it, but their belief was not universally accepted. In many of the eugenicists studies of families, feeblemindedness occurred with too high a frequency to be explained by a Mendelian mechanism. Systems with truly Mendelian features such as the ABO blood groups were studied extensively beginning in 1911. Investigators such as Lionel Penrose in England and others in the US did high quality family studies with much more precise classification of the feebleminded. As a result, new syndromes and metabolic diseases were identified, some with faithful Mendelian patterns of inheritance. Investigators like JBS Haldane, Julian Huxley, Ronald Fisher, and Lancelot Hogben in England and Herbert Jennings in the US began to enter the field and perform careful genetic studies on humans and simpler systems incorporating cytology and chemistry in addition to statistical methods. Interest in environmental factors such as nutrition and health and intellectual stimulation began to erode an exclusively hereditary view of intelligence. In the 1930s in Iowa, children with low IQs were taken from the standard environment for the feebleminded, and placed in more stimulating environments with substantial improvements in their IQs. By the end of the 1930s, mainline biology was moving away from the initial oversimplified views of human heredity (17).

Despite growing sophistication in the subject, in the 1920s, the genetic nature of intelligence was generally accepted by the scientific and lay communities. The data from Davenport, Goddard, and others in the US, and Pearson in England all indicated that feeblemindedness was inherited. In many studies, feeblemindedness was found to be inherited in a Mendelian fashion, so it conformed to common sense and natural laws (11,17). The impact of feeblemindedness and its propagation through breeding was demonstrated by case studies such as that of the Jukes family in New York, in which feeblemindedness, criminal behavior, and loose morals could be traced to a common ancestor, Max Jukes (6,17). Because the Jukes family had propagated, they had cost the state of New York an enormous amount of money just like the other feebleminded families in the US. Since the cause of the problem was genetic, environmental intervention would not work, and other solutions had to be sought. The need for solutions was felt particularly because the feebleminded tended to breed faster than the more desirable members of society.



Figures 1. Figure from a paper in Biometrika by Pearson in 1918 showing the correlation if IQ scores between siblings. Statistical tests on other pages demonstrated the significance of the correlation. IQs are separated int genius, quick intelligent, slow intelligent, slow, slow dull, and very dull (25).

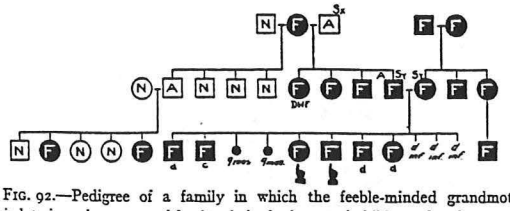


FIG. 92.—Pedigree of a family in which the feeble-minded grandmother married twice; by a normal husband she had normal children; but by an alcoholic, sex-offending (Sx), doubtless feeble-minded husband she had only feeble-minded children.—GODDARD.

From Davenport, C. Inheritance of physical and mental traits in Heredity and Eugenics, WE Castle et al Eds, 1912.

Figure 2. This pedigree from a family studied by Henry Goddard was presented at a symposium at the University of Chicago by Charles Davenport, and illustrates the heritability of feeblemindedness. F in a dark symbol corresponds to feebleminded, A, to alcoholic, Sx to sex offender, and N to normal. The finger pointing to a symbol indicates patients who were actually studied. The legend illustrates the spirit in which much of this data was collected and interpreted (7).

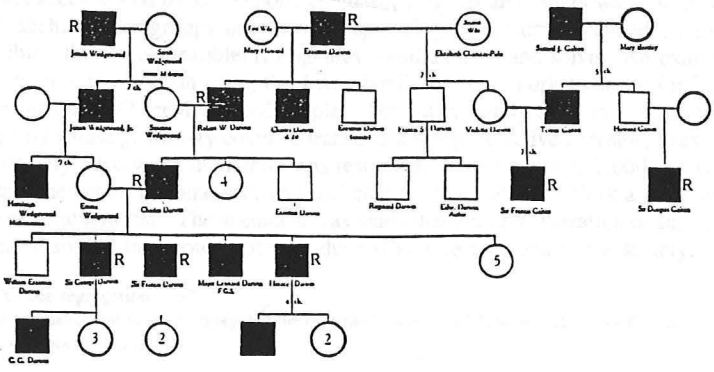


Figure 3. This is the pedigree of Francis Galton and Charles Darwin who were cousins. The dark symbols represent "a man of note", and the "R" next to a symbol indicates a member of the Royal Society. Women are not shown individually, but as circles with a number indicating the number of daughters. Analysis of this and similar genealogies was believed to demonstrate that "high quality" was heritable (11).

Type of mating	No. of matings	Total offspring	D. inf. and misc.	Undetermined mentality	Feeble-minded offspring		Normal offspring	
					Actual findings	Theoret. expectation	Actual findings	Theoret. expectation
FF FF	144	749	149	118	476	482.0	6	0.0
FF NF	122	689	161	166	193	185.5	178	185.5
FF NN	18	66	13	19	0	0.0	34	34.0
NF NF	33	212	39	27	39	36.5	107	109.5
NF NN	7	27	2	2	0	0.0	23	23.0
Totals.....	324	1,743	364	332	708	704.0	348	352.0

Figure 4. Table from a book edited by Charles Davenport demonstrating a recessive Mendelian inheritance pattern for feeblemindedness in a large number of people (8).

The scientific data accumulated by Davenport, Goddard, Pearson and others was not presented to the public as such. Other groups interested in spreading Eugenics distributed educational pamphlets describing the societal problems Eugenics could address and solve. An example of this sort of information is a section using the Jukes family of New York to argue for limiting the reproductive capability of feebleminded people. The Jukes family took on almost mythical character as a family whose genealogy could be traced to a single defective ancestor, Max Jukes, in the early 1800s. By 1916 when the family was restudied, there were over 2,000 descendants who were mentally defective in some way and had cost the State of New York a great deal of money in crime or incarceration. The argument was made that either sterilization or segregation of the feebleminded so that they could not reproduce would be a benefit to the society.

Q. How much does segregation cost?
A. It has been estimated that to have segregated the original "Jukes" for life would have cost the State of New York about $25,000.

Q. Is that a real saving?
A. Yes. It has been estimated that the State of New York up to 1916 spent over $2,000,000 on the descendants of these people.

Q. How much would it have cost to sterilize the original Jukes pair?
A. Less than $150.

A Eugenics Catechism Ca. 1920

US Laws Incorporating Eugenic Principles.

In the US in the early 1920s, the response to concern about the cost of the feebleminded in the context of increasing immigration and labor unrest was immigration barriers and forced sterilization laws in many states. The Changes in immigration laws were inspired by a number of factors in addition to eugenics including racism, post WWI unemployment, and fear of radicalism. Nevertheless, the rationale for restricting immigration to the US was frequently put in eugenic terms. In 1922, Vice President Calvin coolidge said, "America must be kept American. ... Biological laws show that Nordics deteriorate when mixed with other races". Lively testimony was presented to congressional committees by Harry Laughlin, the director of the Eugenics Record Office at cold Spring Harbor using data from that database, and by Robert Yerkes using data from US Army intelligence tests. Needless to say, these data demonstrated the genetic inferiority of immigrants. All of these factors resulted in strict laws in 1924 and 1927 restricting immigration to the US which passed Congress by large margins. At this time, England did not have a substantial immigration problem (17).

Although Eugenics was only a component of immigration policy, it was the moving force behind laws seeking to regulate reproduction through marriage and sterilization. Laws restricting marriage between 'idiots, the unfit, drunkards, and people with venereal disease' were enacted in many states. Some states forced a delay between marriage license application and granting the license in order to prevent hastily conceived marriages. From 1907 to 1935, 22 states enacted compulsory sterilization laws for people in state institutions who had varying forms of mental deficiency. These categories included 'habitual or confirmed criminals, conviction for specific crimes such as rape, epileptics, idiots, and the insane' in state institutions. These laws did not require informed consent of the person or a guardian, or the approval of a neutral body. By the mid 1930s, approximately 20,000 people had been sterilized in the US (17,20). German social policies of the 1930s drew considerable strength from the eugenic movement in the US. In fact, one of Davenport's assistants, Harry Laughlin was awarded an honorary degree by the University of Heidelberg in 1936 for his work in the Eugenics Records Office (17,23). In England no consensus existed for sterilization, but voluntary programs to alter human breeding practices and segregation of "mentally defective" people by sex were discussed extensively.

Biologic And Social Science In The Early 20th Century.

In the early twentieth century, a number of discoveries anticipated the developments of the middle of the century, but were largely ignored because supporting biologic data were not available. Examples are the metabolic disease alcaptonuria, characterized by Archibald Garrod in the early 1900s. He correctly interpreted his findings to mean that the disease was the consequence of a mutation in one gene which was responsible for the loss of one enzyme in a metabolic pathway. In 1902, at Columbia, Walter Sutton identified chromosomes in dividing cells and demonstrated that they behaved in a way consistent with Mendelian inheritance - segregation and independent assortment. TH Morgan's work with Drosophila around WW I laid the foundations for genetic mapping. He and his group demonstrated that chromosomes carry

the information for inheritance, that they are held together in linkage groups, that independent assortment occurs in genes in different linkage groups, and finally, that an orderly interchange of information occurs through crossing over or recombination where the frequency of recombination was proportional to the distance between genes. In the 1920s, Morgan's student, Hermann Muller demonstrated that radiation could produce stable changes in genetic material. Consequently, by 1930, the mechanisms of inheritance as well as their limits were much better understood than they had been thirty years earlier. The idea that intelligence was a unitary heritable trait was questioned.

During the 1920s and 1930s, the data compiled by workers like Davenport and Galton was questioned in terms of its precision and reliability. In many cases, family studies relied on second or third hand information. Despite the data on intelligence in twins reared apart from Cyril Burt in England in 1927 indicating that intelligence was largely governed by heredity, interest in environmental determinants of intellect increased. Twin studies performed in the US demonstrated that environment had an important role in determining intelligence. In one study in Iowa, the IQ of patients in state institutions was profoundly affected by the level intellectual stimulation. The importance of factors such as diet and health care were recognized.

Consequently, by the late 1930s and early 1940s, the simplistic genetic view of intelligence as advanced by Davenport, Goddard, Pearson, and their followers could not be supported by biologic or social science. In 1945, when the consequences of German eugenic policy was known, such policies were untenable even for those who were not sophisticated scientifically (23).

Biologic Science in the Last Half of the 20th Century.

In the 1940s and 1950s, biochemistry and genetics were connected by solid scientific work. In the 1940s, studies of Beadle and Tatum in Neurospora demonstrated that the gene is the unit of inheritance, and corresponds to a metabolic step or enzyme. The atomic bomb attacks on Hiroshima and Nagasaki inspired a great deal of work on the relationship between radiation and genetic defects. The evidence that DNA is the genetic material was published in 1953 by Watson and Crick. The link between genetics and biochemistry was made in 1949 when Neel demonstrated the recessive genetic basis for sickle cell anemia, and Pauling demonstrated that sickle cell anemia results from an altered form of hemoglobin. By 1956, Ingram demonstrated that sickle hemoglobin was abnormal because of a single amino acid substitution. In 1949 and 1950, advances in cytology allowed the demonstration that chromosomal abnormalities were found in Klinefelter's syndrome, Turner's syndrome, and "Mongoloid idiocy" (17).

Scientists like JBS Haldane, Julian Huxley, and Hermann Muller remained committed to the basic concept of Eugenics, the perfection of humanity through breeding. However, they had the humility to claim ignorance as to what constituted perfection in humanity, and were aware of complexities in genetics and limitations of their knowledge. They did not believe that intellect or other desirable human qualities were inherited in unitary fashion, and were aware of environmental contributions to the phenotype. In the cases of known genetic diseases, the

difficulty in identifying multiple recessive alleles in a population was understood. The value of genetic complexity as opposed to selecting "pure bred" humans was discussed. Hermann Muller introduced the concept of "genetic load" by which he meant the accumulation of deleterious mutations in humanity through advances in medical science (17).

Molecular biologic and biochemical techniques subsequently allowed the isolation of individual genes and the identification of specific mutations in them. Restriction enzymes which cut DNA at unique sequences allowed the development of markers for genetic diseases and the localization of the markers to specific regions of chromosomes. Genetic markers can be followed through populations and family pedigrees. More recently, with a technique called reverse genetics, or positional cloning, a gene involved in a disease can be cloned and identified despite the fact that its precise function is not known. Examples include the genes involved in chronic granulomatous disease, cystic fibrosis and muscular dystrophy (2).

Current views of genetic diseases distinguish between monogenic and polygenic contributions to a disease "phenotype" and allow for important contributions of the environment in the production of an abnormal phenotype. Monogenic diseases are caused by abnormalities in a single gene. These diseases may be either dominant (osteogenesis imperfecta) or recessive (sickle cell anemia) depending on the particular gene affected, and may be autosomal or sex chromosome linked. Some monogenic diseases such as Tay Sachs disease are independent of the environment, while others such as glyceraldehyde-6-phosphate dehydrogenase deficiency require specific environmental factors for their expression.

Polygenic diseases or traits require the action of multiple genes in combination often in association with the environment to produce disease. Examples of these diseases include hypertension, coronary artery disease, Type I diabetes, and schizophrenia. These diseases are rarely seen in the presence of only one abnormal gene and require specific environmental factors for expression. Traits that are also polygenic include height, and intellectual capacity. A clue that a given characteristic is polygenic is provided the finding that the character fits a continuum. People do not have either high or low blood pressure, blood pressure falls into a range. Identification of the genes for this group of diseases is more difficult than for the monogenic disorders because the patterns of inheritance are more difficult to sort out. Either genes are identified by markers as with monogenic diseases, or candidate genes are tested based on known physiology, biochemistry or studies in animals.

In general, current genetic studies use families or groups of people who are genetically isolated in order to enrich the study population for an allele or genetic marker. The investigators are then able to follow the allele or marker it and correlate it with a trait of interest. Most successful investigators use traits that can be easily and objectively measured such as plasma LDL level, factor VII, or a metabolite. Ideally, the difference between the normal and mutant values is so great that no overlap of values exists. Since most of these studies rely on genetic markers which are at unknown distances from the mutation and do not actually identify it, some possibility exists that the marker which cosegregates with the trait does so on an artifactual or random basis. In order to minimize errors of this sort, complex statistical and computational

methods have been devised with specific criteria for significance. By these methods, the phenotype of the individual is correlated with their genotype (2).

In the last twenty five years, debate over the relative contributions of genes and environment to intellect and specific forms of behavior has continued. In contrast to the late 1800s and early 1900s, the emphasis has been on environment rather than heredity. This was the time of Lyndon Johnson's Great Society program, a program directed at environmental causes of social problems. In the late 1960s and early 1970s, researchers in England, Denmark and the US published reports indicating violent male criminals had a disproportionate number of XYY karyotypes. The possible role of an extra X chromosome was never defined. Initially, there was considerable excitement about the possibility of identifying criminals cytogenetically, but lack of formal proof of a cause and effect relationship and civil statutes prevented enactment of such policies.(17) At the same time, Arthur Jensen, Richard Herrenstein, and William Shockley published articles stating that IQ was primarily determined by genetic factors. A number of controls for environment were built into the studies. The early 1970s were a time of economic down-turn inthe US. The genetic point of view was challenged on scientific and political grounds, and policies that may have arisen from it were not developed.(13,17) In 1979, the twin studies by Cyril Burt relating IQ to heredity were found to be fabricated. The relative contributions of genetics and environment remain unresolved, but both appear to play an important role.

Neural Science at the End of the 20th Century.

Because we began by talking about scientific treatment of intellect at the turn of the nineteenth century, I would now like to give several examples of how intellect is studied now, and what sort of information is derived from these studies. Again, reductionism and analogy are used. The studies I will present in Aplysia (the California sea slug), Drosophila, and humans follow the theme that the adenylyl cyclase is involved in intellectual function, if that term can be applied in all these cases. An important difference between these studies and those performed in the early part of the century are that the physiologic "readout" is more narrowly defined and therefore quantified more reliably, and biochemical and molecular genetic studies confirm that the groups being studied are uniform.

Over the last twenty years, Eric Kandel and his group at Columbia have tried to reduce learning and memory to their simplest cellular and molecular components. Kandel and associates chose Aplysia, the California sea slug because it has a simple nervous system with approximately 20,000 neurons which can be mapped, and is capable of a learning and "remembering" responses - such as sensitization and classical conditioning. I will describe facilitation of the gill and siphon withdrawal response to noxious stimuli because it is simpler than a conditioned response and it requires presynaptic facilitation, an essential component of classical conditioning. Facilitation means that input through an accessory sensory pathway to a motor neuron is synergistic with the direct input. This pathway demonstrates memory in that repetitive stimuli through both sensory pathways results in an enhanced response to the direct sensory pathway. In Aplysia, facilitation of the gill and siphon withdrawal response requires five neurons. The

sensory neuron of the siphon synapses directly with the motor neuron for the gill. These two neurons constitute the basic reflex arc. The sensory neuron from the tail synapses with a facilitatory interneuron that synapses with presynaptic regions of the sensory neuron from the siphon. Another interneuron synapses with the siphon sensory neuron and the motor neuron. Noxious stimuli are applied to the siphon and tail, and gill withdrawal is measured. In the simplest form of this system, electrical recordings are made from the various neurons allowing precise quantitation (5,14,22).

Interest in the biochemical events in facilitation centers on the presynaptic connection between the facilitatory interneuron and the primary sensory neuron. Stimulation of the primary sensory neuron leads to release of neurotransmitter by a mechanism dependent on increases in intracellular Ca which enters the cell through L-type Ca channels. Facilitation of the response occurs when the facilitatory neuron which synapses presynaptically on the primary sensory neuron releases serotonin (5-HT). 5-HT stimulates adenylyl cyclase through a classic G protein-dependent mechanism. The adenylyl cyclase is similar to the mammalian type I and drosophila adenylyl cyclases (Rutabaga - see below) in that it is synergistically activated by Ca-calmodulin and G_s. The Ca, calmodulin-sensitive adenylyl cyclase is a coincidence sensor in that it can receive and integrate signals from two sources, the increased intracellular Ca from nerve depolarization and G_s via 5-HT from the facilitatory interneuron. c-AMP activates c-AMP-dependent protein kinase (protein kinase A) which in turn phosphorylates the S-type K channel (or a regulatory protein), decreasing the K current. The decrease in the K current prolongs the action potential, allowing more Ca entry, and more neurotransmitter release. 5-HT has additional effects in that it also activates a second signalling pathway through a second G protein which results inactivation of protein kinase C. Together, protein kinases A and C increase the amount of neurotransmitter available for release at the synapse.(3,5,14,22)

With repeated episodes of sensitization, the enhanced response occurs with the primary stimulus alone and represents a memory of the sensitizing stimulus in the primary sensory neuron. This memory effect is dependent on c-AMP, and requires gene transcription and new protein synthesis. It consists of an increase in the activity of c-AMP-dependent protein kinase with decreased regulatory subunits relative to catalytic subunits, and a persistent c-AMP-dependent pattern of phosphoproteins. The morphology of the nerve terminal changes with increased numbers of postsynaptic terminals and active zones which are capable of releasing transmitter. Acute facilitation and chronic or long term facilitation occur through the same signalling pathways. The difference seems to be the amount and frequency of sensitization which determines the timing of c-AMP production and consequently the extent of new gene expression. The important points from these studies are first, that the molecular mechanism of memory is understood in a simple system and second, that environmental factors can modify biochemical factors including regulation of gene expression with consequent structural changes in the brain. (14,27,28)

A number of fundamental biologic processes have been identified in Drosophila through the study of mutations which affect functions such as development and eye color. Drosophila can be taught and remember responses such as flying towards or away from an odor through classic

conditioning, an example of associative learning. The response can be conditioned over a short period of time, and then "remembered". A number of Drosophila lines have been developed which are defective in learning and memory as defined by a classical conditioning test. These mutants have the entertaining names Dunce, Rutabaga, Turnip, Amnesiac, and Dopadecarboxylase. The molecular defects in two of these lines, Dunce and Rutabaga have been identified, and they both affect the adenylyl cyclase system. By biochemical and molecular genetic criteria, Dunce is a deletion of the c-AMP phosphodiesterase gene resulting in constitutively high levels of c-AMP, and Rutabaga is a point mutation leading to loss of function of a form of adenylyl cyclase which resembles the mammalian type I and aplysia cyclases (Ca-Calmodulin-sensitive adenylyl cyclase), which is concentrated in brain. Crossing these two lines produces flies with normal levels of c-AMP, but which are still learning-defective. This finding indicates that not only is the level of c-AMP important, but so is the ability to regulate it in the proper space and time. These studies demonstrate on a gross "whole animal" level that the adenylyl cyclase system is important in one model of learning and memory. (5,10,14,19)

From Drosophila and Aplysia we have learned that the c-AMP system is important for learning and memory in two organisms widely separated in evolution. My description of these learning and memory pathways is oversimplified. These pathways involve many other proteins and other signalling systems such as non receptor tyrosine kinases and Ca/calmodulin-sensitive protein kinases. Nevertheless, a Ca/Calmodulin-sensitive adenylyl cyclase is critical to both, and they establish precedents which appear to apply to higher organisms. More recent work has demonstrated that circuits similar to those found in Aplysia are present in the hippocampus (a region of the brain believed to be involved in learning and memory) of mammals. Preliminary studies using gene knockouts in transgenic animals demonstrate that both nonreceptor tyrosine kinases and Ca/calmodulin-dependent protein kinases are important for some forms of learning and memory.

Given the importance of c-AMP in learning and memory in lower species, we would expect that it might also have similar importance in humans. Two human genetic diseases, pseudohypoparathyroidism type 1a (PHP) and McCune-Albright syndrome, represent experiments of nature, and may be analogous to the Drosophila Rutabaga and Dunce mutants. Unfortunately, they are not particularly informative in terms of the contribution of the adenylyl cyclase system to intellectual function in humans. PHP is an autosomal dominant disease in which one allele of α_s is lost or nonfunctional, and patients have a reduced c-AMP responses to hormones which activate adenylyl cyclase. Consequently, it is a c-AMP deficiency disease. The syndrome is characterized by short stature, metacarpal shortening, obesity, a characteristic osteodystrophy, hypocalcemia and hyperphosphatemia with elevated PTH levels and normal renal function, multiple hormone resistance (including PTH), and mental retardation. Ascribing the mental retardation to the reduced c-AMP production as a consequence of α_s deficiency is tempting in light of the data presented above, but most of these patients are hypothyroid, a known cause of mental retardation. To my knowledge, intellectual function has not been precisely characterized in this group of patients, nor has thyroid hormone been replaced since birth. (24,31)

The McCune-Albright syndrome is a disease of c-AMP excess. It is caused by a dominant somatic mutation early in embryogenesis which leads to a constitutively active allele of α_s in a mosaic distribution, or cells scattered around the body. The syndrome consists of polyostotic fibrous dysplasia, cafe au lait pigmentation of the skin, and multiple endocrinopathies including sexual precocity, hyperthyroidism, growth hormone-secreting pituitary adenomas, and focal adrenal hyperplasia. Despite pathology in varied organs, no mention was made of altered mentation or intellectual function. The mutation may not have been expressed in the appropriate cells in the CNS, or the levels of c-AMP produced may not have interfered with normal function. (32)

Elegant studies in simpler biologic systems, Aplysia and Drosophila, each the product of reductionist thinking, indicate that the adenylyl cyclase system is central to learning and memory. Unfortunately, in two human genetic diseases, PHP 1a and McCune-Albright, where the model could be tested, either it does not apply, or the "experiment of nature" cannot be interpreted. Our ability to develop and use models is not yet perfected.

Mental deficiency can now be related to a number of genetic diseases including metabolic diseases such as Tay-Sachs and phenylketonuria, familial Alzheimer's, Huntington's Chorea, and the fragile X syndrome. Other intellectual traits which have a sex bias, and therefore may be in part genetic include mathematic ability, stuttering, dyslexia, criminality, and homosexuality. Many of these conditions are sufficiently common that they bear study form a public health perspective. However, they are undoubtedly complex and will not be understood in terms of simple monogenic, Mendelian models.

Current studies of schizophrenia illustrate a number of the complexities of dealing with polygenic diseases with important environmental components. The disease itself has a number of subtypes which may or may not represent different biologic variants. Consequently, the study group may be heterogenous. The situation may not be as bad as feeblemindedness in the early 1900s, but greatly complicates genetic and biochemical studies. Schizophrenia appears to have a genetic component because of the increased frequency in relatives of schizophrenics. Approximately 1% of the general population suffers from some form of schizophrenia (chronic, latent, or schizoid personality), while siblings of patients have fifteen times, and monozygotic twins have fifty times the risk of unrelated people. The genetic component of schizophrenia has been pursued by two routes, polymorphisms for candidate genes, and looking for polymorphisms in families that segregate with the disease.

So far, the most promising candidate genes are the growing family of dopamine receptors because they are the targets of the antipsychotic drugs. The D_2 D_3, and D_4 isoforms are of particular interest because of their pharmacologic characteristics with respect to the antipsychotic drugs, and their localization in the brain. Additionally, increased concentrations of D_2 receptors have been reported in the caudate nucleus and striatum. D_2 receptors are coupled to inhibition of adenylyl cyclase, but the function of D_3 and D_4 is not known. To date, no polymorphisms linking any of the dopamine receptors to schizophrenia have been identified. (15)

The standard linkage analysis strategy has been problematic. In 1988, Sherrington et al reported linkage of schizophrenia in seven families from Iceland and two from England with markers on a region of chromosome 5q (5q11-13) (30). In the same issue of Nature, Kennedy et. al. reported failure to find linkage between schizophrenia and 5q11-13 in a Swedish family. Subsequently, other groups have also failed to find linkage between 5q and schizophrenia (16). In both studies, the patients studied were evaluated individually and rigorously so that the phenotype could be classified appropriately. These studies were reviewed and published in a high profile journal, and presumably have been done, analyzed, and interpreted appropriately given the complexity of the data. They probably indicate a number of things. In the Sherrington (positive) study, a number of subcategories of schizophrenia were associated with the same genetic polymorphism, suggesting that the current classifications may not reflect etiology, or at least the genetic component. The results also indicate that different genes are involved in the pathogenesis of schizophrenia in different kindreds.

Reviewing the Sherrington study with a member of the Molecular Genetics Division, the analysis and presentation of the data are not clear or entirely convincing. No marker appears to segregate reliably with schizophrenia or the related disorders. Apparently, the Sherrington study is currently in disrepute. The study population despite careful phenotypic classification, and the fact that it involved families whose genealogies can be defined, may be too complicated for the statistical models currently available. (H. Hobbs, pers. comm.) Consequently, at this point we cannot claim to have identified a "schizophrenia gene", and certainly have not established cause and effect as in the more simple genetic disorders such as sickle cell anemia. One solution to the problem of a heterogenous study group is to look for markers which are easier to define such as biochemical markers. For schizophrenia, such markers might be a person's response to amphetamines. (18)

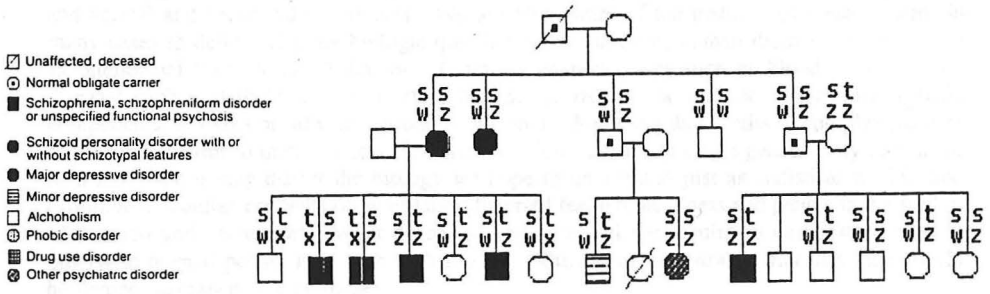


Figure 5. Pedigree from Sherrington paperdemonstrating linkage between schizophrenia and markers on chromosome 5q11. The marker which segregates with schizophrenia is Z, but does not result in a schizophrenic phenotype in all cases. In other pedigrees in this publication, the discrepancies are more marked including unaffected homozygotes and schizophrenic patients without the Z allele.

Summary.

Despite the fact that eugenics was discredited scientifically and aesthetically in the 1940s, many Eugenic concepts and practices remain with us. Amniocentesis with chromosomal and genetic studies and abortion allow us to dispose of genetically damaged progeny. In the New York Times on Labor Day, William Saphire celebrated the fact that Albert Einstein and his fiancee, Mileva Maric chose to have their child out of wedlock and put her up for adoption rather than abort the pregnancy because "the genes of genius were preserved" (26). The University of Maryland is organizing a conference on crime where the "crime gene" was to be discussed. Because of the racial implications and the belief that insufficient scientific data exists to support the concept, the NIH withdrew support (12).

Heredity is an important component of all of our characteristics, and interacts in complex ways with the environment to determine our phenotype. The basic problem with the Eugenics movement at the turn of the nineteenth century was that a complex biologic phenomenon, intellectual function, was reduced to statistical formulations and other forms of scientific notation. Unsophistocated reductionism resulted in an over-simplified view, or caricature of humanity which found a large market in the lay public and with politicians and public policy makers who used it for their own purposes such as self justification and cost of welfare. At the time that many Eugenic regulations were enacted in the US and Germany, biologists understood that scientific data did not support publicly held views and policies, but the over-simplified public perception allowed their enactment.

At the turn of the twentieth century, we have learned a great deal about biology and consequently about ourselves through reductionist thinking - biochemistry, molecular genetics, and animal and tissue culture models. We are also aware of the inability of these systems in many cases to define fully the biologic question of real interest, human diseases or traits such as intellectual function and behavior. Certainly characteristics such as blood pressure, and diseases such as diabetes coronary artery disease, schizophrenia, and alcoholism have genetic components, but are not fully understood at this point. Reducing these traits or complex patterns of human behavior to mathematical formulation, a few neurons, a single genetic polymorphism, or a LOD score may distort the biology we hope to understand just as statistical models and primitive mendelian concepts of inheritance distorted feeblemindedness and genius in the studies of Pearson and Davenport. What degree of certainty will we require to demonstrate that an otherwise normal person is at such high risk for a disease or undesirable trait that they should be denied insurance or employment?

REFERENCES.

1. Ashby B. Dopamine and schizophrenia. Nature 348:493, 1990.

2. Beaudet AL, Scriver CR, Sly WS (eds). Genetics and biochemistry of variant human phenotypes in The Metabolic Basis of Inherited Disease. Scriver, CR, Beaudet, AL, Sly, WS, et al (eds). New York: McGraw-Hill Information Services Co., 1989.

3. Brunet JF, Shapiro E, Foster SA, et al. Identification of a peptide specific for Aplysia sensory neurones by PCR-based differential screening. Science 252:856-859, 1991.

4. Byerley WF. Genetic linkage revisited. Nature 340:340, 1989.

5. Carew TH, Sahley CL. Invertebrate learning and memory: From behavior to molecules. Ann Rev Neurosci 9:435-487, 1986.

6. Carlson EA. R.L. Dugdale and the Jukes family: A historical injustice corrected. Bioscience 30:535-359.

7. Castle WE, Coulter JM, Davenport CB, et al (eds). Heredity and Eugenics. Chicago: U Chicago, 1912.

8. Dana CL, Davis TK, Jelliffe SE (eds). Heredity in Nervous and Mental Disease. P.B. Hoeber, Inc., 1923.

9. Dash PK, Hochner B, Kandel ER. Injection of the cAMP-responsive element into the nucleus of Aplysia sensory neurons blocks long-term facilitation. Nature 345:718-721, 1990.

10. Davis RL, Dauwalder B. The drosophila dunce locus: learning and memory genes in the fly. Trends In Genetics 7:224-229, 1991.

11. Goddard HH (eds). Feeble-mindedness Its Causes and Consequences. New York: The MacMillan Co., 1926.

12. Hilts, PJ, Agency rejects study linking genes to crime. New York Times. p.1, September 5, 1992.

13. Jensen AK. How much can we boost IQ and scholastic achievement? In: Environment, Heredity, and Intelligence. Cambridge: Harvard Educational

Review, 1971.

14. Kandel ER. Cellular mechanisms of learning and the biological basis of individuality In: Principles of Neural Science. Kandel ER, Schwartz JH, Jessell TM (eds). New York: Elsevier, 1991.

15. Kandel ER. Disorders of thought: Schizophrenia In: Principles of Neural Science. Kandel ER, Schwartz JH, Jessell TM (eds). New York: Elsevier, 1991.

16. Kennedy JL, Giuffra, Moises HW, et al. Evidence against linkage of schizophrenia to markers on chromosome 5 in a northern Swedish pedigree. Nature 336:167-170, 1988.

17. Kevles DJ (eds). In the Name of Eugenics - Genetics and the Uses of Human Heredity. Berkeley: University of California Press, 1985.

18. Lander ES. Splitting schizophrenia. Nature 336:105-106, 1988.

19. Levin LR, Han P-L, Hwang PM, et al. The drosophila learning and memory gene rutabaga encodes a Ca^{2+}/calmodulin-responsive adenylyl cyclase. Cell 68:479-489, 1992

20. MacDonald MG, Meyer KC, Essig B. Sterilization in: Health Care Law: A Practical Guide. New York: Matthew Bender, 1991.

21. McHugh PR, McKusick, VA (eds). Genes, Brain, and Behavior. New York: Raven Press, 1991.

22. Morris RGM, Kandel ER, Squire LR. The neuroscience of learning and memory: cells, neural circuits and behavior. TINS 11:125-135, 1988.

23. Müller-Hill B. Genetics after Auschwitz. Holocaust and Genocide Studies 2:3-20, 1987.

24. Patten JL, Johns, DR, Valle D, et al. Mutation in the gene encoding the stimulatory G protein of adenylate cyclase in albright's hereditary osteodystrophy. N Engl J Med 322:1412-1462, 1990.

25. Pearson K. Miscellanea. Inheritance of Psychical Characters. Biometrika. XII, 1919.

26. Schacher S, Castellucci VF, Kandel ER. c-AMP evokes long-term facilitation in Aplysia sensory neurones that requires new protein synthesis. Science 240:1667-

1669, 1988.

27. Scholz KP, Bryne JH. Intracellular injection of c-AMP induces a long-term reduction of neuronal K^+ currents. Science 240:1664-1666, 1988.

28. Safire W. Essay New York Times. September 7, 1992.

29. Seldin DW. Presidential Address. Some reflections on the role of basic research and service in clinical departments. J Clin Invest 45:976-979, 1966.

29a Seldin DW, Presidential Address. The boundaries of medicine. transactions of the Association of American Physicians xciv: lxxv-lxxxvi, 1981.

30. Sherrington R, Brynjolfsson J, Petursson H, et al. Localization of a susceptibility locus for schizophrenia on chromosome 5. Nature 336:164-167, 1988.

31. Speigel, A. Pseudohypoparathyroidism in The Metabolic Basis of Inherited Disease. Scriver, CR, Beaudet, AL, Sly, WS, et al (eds). New York: McGraw-Hill Information Services Co., 1989.

32. Weinstein, LS, Shenker A, Gejman PV, et al. Activating mutations of the stimulatory G protein in the McCune-Albright syndrome. N Engl J Med 325:1688-1740, 1991.