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The Human Genome Project and its Social Implications

By

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Introduction

The title of this paper suggests that it is about the Human Genome Project. In a sense this is correct, for what I am trying to say has much to do with the science that constitutes this undertaking--the science that is unraveling the mysteries of genetics. In actuality, however, I am only using the Genome Project as a springboard for a broader discussion. What I am really addressing is the social nature of this science that deals with questions of human heredity. The Human Genome Project is concerned essentially with knowledge, and it is the social implications of this knowledge that I hope to explore.

In 1987 a project to sequence the entire human genome--the Human Genome Initiative or, as I refer to it, the Human Genome Project--was proposed.[1] p. 44 The next year, the Nobel laureate James Watson was asked by the director of the National Institutes of Health to coordinate this project, estimated to cost between $2 and 3 billion and take fifteen years. Based on size alone, this effort is deserving of scrutiny, particularly in terms of the human and financial resources it will require. For instance, it is estimated that sequencing the approximately 3 billion base pairs in the human genome could take up to 30,000 person-years. Proponents argue that this approach is more efficient and more egalitarian than

focussing resources in trying to locate individual genes for specific diseases.

As I have indicated, however, I do not intend to explore the details of the Human Genome Project, but instead discuss the implications of the genetic knowledge it will provide. To do this is to attempt to place genetic information in social context. The Human Genome Project will have great practical significance, as techniques for screening and manipulating genetic material have rapidly progressed--to the point, in fact, that forms of human gene therapy have already been proposed. Moreover, this information will have social significance because of the many possible agendas it could serve. As I view the issue, this is not just a matter of prognostication. Recombinant DNA technology has a short but nonetheless important history, while the history of the uses and abuses of genetic theories is much more extensive.

As a framework for my analysis of the social issues associated with genetic information and technology, I have attempted to illustrate in four chapters how what is taken to be scientific information in the field of human genetics has historically been appropriated; and how appreciating the social frame in which this knowledge develops provides insights into its potential uses. The first chapter of this paper looks at genetic information in the context of diagnostic testing. It describes how genetic information can be used as an instrument of control over individuals in the workplace and in the health care marketplace, based on economic and other incentives to discriminate.

The second chapter takes a more historical approach in exploring the social agendas behind the various uses of genetic information. Starting with the development of the eugenics movement in the 19th century, this chapter examines how genetic information has been politicized, based on contemporary social concerns. Several sources suggest that this model is as applicable--though sometimes less obviously so--to recent developments in the field of genetics as it is in its historical analysis.

The third chapter takes up the issues surrounding the potential uses of genetic information and technologies to treat human disease at the cellular level. The attempt is to delineate more precisely the kinds of concerns that are relevant to potential therapeutic modalities and to consider the strength of the positions taken up around the issue of gene therapy.

In the final chapter, I have attempted to frame the issues raised above in the context of the revolution taking place in the field of biotechnology. A new era of applied genetics is being driven along by economic incentives and therapeutic ambitions. Many have questioned where this revolution is going to take us, but this is a question that cannot be readily answered. However, this is not to say that genetic knowledge and its potential applications are developing in a vacuum. There are structures in place and standards already in practice that can inform the discussion of how we will adapt to the changing landscape of genetic technology.

In planning and executing this project, I was guided by a number of individuals, and I would like to gratefully acknowledge their assistance and criticism. My thesis committee chairman, Paul

Rabinow, met with me on numerous occasions and directed me towards many valuable references. I would also like to thank my other readers, Thomasine Kushner of the Health and Medical Sciences Department, and Troy Duster of the Sociology Department, for meeting with me, suggesting ways to attack the problem of genetic information and technology, and for reading my thesis and providing valuable criticism.

I would also like to thank Neal Halfon of the Health and Medical Sciences Department, for his assistance in the planning stages of this project. Also, Professor Evelyn Fox-Keller provided me with valuable unpublished materials when I consulted her.

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Chapter One: Genetics and Diagnostic Technology

One aspect of genetic information is that it is part of our growing fund of knowledge. The Human Genome Project, for example, will give us a valuable map of human genetic structure, and this information will be useful to many future inquiries, especially those that delve into the genetic bases of disease. However, another aspect of genetic information is that of its social significance and its social formation. We know from common experience that matters of inheritance are social as well as biological. The color of a man or woman's skin, for example, is be much more than a genetic reality. Elements of self-image, power and social control are intertwined with and to greater or lesser extent even comprise perceptions of race, health, disability and disease. What does it mean, for example, to tell an adopted child that her parents are not her *real* mother and father?

Regardless of what the general public understands about DNA *per se*, in certain sectors of our society, definitions about individuals are made based on hereditary considerations. Even ignoring the practices of other societies, it may be fine for a child in the United States to have her father's eyes, but, having his X-chromosome may

pose a whole host of issues and problems. This brings us to the issue of diagnostic testing. While people have not traditionally viewed one another literally in terms of their respective complements of chromosomes, issues are beginning to spring up around our ever-increasing understanding of human genetics. We will have to consider the importance of genetic findings not only in the doctor's office, but in the workplace and insurance sector as well. As Nelkin and Tancredi point out in Dangerous Diagnostics, information that may be quite helpful in one setting may be quite harmful in another--for instance, if it is used for purposes of discrimination.[1]

While diagnostic technologies offer much to the prospective patient in terms of health care and maintenance, they (their availability) also raise(s) important issues of privacy. Where a diagnostic finding is used as the basis of an employment or insurance decision, it has left the beneficent realm of the doctor-patient relationship. We might consider the case where a diagnostic test has no bearing on therapeutic benefit, yet unjustifiably causes a person to lose his or her job, or to have a job application rejected. An obvious example of this would involve applicant screening for the sickle-cell trait. In this context data reputed to be scientific may actually support other agendas. In other words, diagnostic tests originally designed for the patient's benefit are used as instruments of social control.[2]

Two major growth areas of diagnostic technology have been genetic testing and neurologic imaging.[3] The medical literature is full of references citing the role of genetic factors in disease. In addition, various techniques of neuroimaging have been explored for

their value in diagnosing and predicting disease. One characteristic these techniques have in common is the appearance of being value-neutral. They carry with them the aura of the impartiality of science and the supposed authority of fact. According to Nelkin and Tancredi, this is part of the "cultural appeal of testing."[4] To a degree, this reflects a tendency on the part of society to medicalize social problems. For example, there has been much discussion in the past of potential hereditary and physiological determinants of criminal behavior, a discussion based more on conjecture than on hard evidence. Furthermore, psychiatric testing is one of many examples of the role of medicine in defining the limits of "normal" behavior.

Another aspect of the appeal of testing is its conformation to actuarial principles. The actuarial mindset concerns itself with issues of potential risks and benefits.

> Actuarial thinking is designed to limit liability. It requires calculating the cost of future contingencies, taking into account expected losses, and selecting good risks while excluding bad ones. The individual must therefore be understood actuarially, that is, with reference to a statistical aggregate. In this context the information derived from tests becomes a valuable economic and political resource.[5]

We are all familiar with the recent trend in the gathering of personal information for various institutional purposes, ranging from whether a person is a good credit risk to whether or not they are a candidate for group health insurance to whether or not they have used illicit drugs, etc. This is not to say that the rationale behind all these

various uses of testing is wrong, but it raises the question of how certain types of personal information rapidly becoming available through testing will be put to use. Incentives for diagnostic testing outside the medical establishment often have to do with the vested interests of institutions as opposed to individuals. While even the medical use of tests for diagnostic purposes requires critical attention, it is apparent that the corporate use of tests is more likely to be skewed by concerns for efficiency, to the detriment of individual concerns. This is obviously a question of both motives and interpretation with regards to testing.

A similar observation pertaining to motives might be made of the actual practitioners of tests. As tests are often offshoots of the medical profession, which "professes" to act in the patient's best interests, the most experienced practitioners of these tests are often medical professionals in the employ of other agencies. This raises the possibility of conflicting loyalties on the part of the tester which may prove deleterious to a person in search of employment or insurance or to a child who is difficult to control in the classroom. As Nelkin and Tancredi observe, "The power of the test to enhance institutional conformity relies on active professional support."[6] Moreover, the ability to test reinforces belief in particular modes of judgement and decision-making, whose shortcomings may be overlooked.

> Sophisticated biological tests are attractive to professionals who are faced with conflicting pressures, for tests can provide objective and therefore convincing data to back up difficult

> decisions. Such data can avoid social or ethical problems by redefining them in technical terms, but they do not resolve underlying questions of fairness or professional obligation....A test that defines a child as hyperactive can shift the physician's focus away from other influences on behavior, such as a disturbed teacher or an abusive home environment. In effect, biological data encourages the domination of physical over social ethical considerations.[7]

The motivation to test, as it relates to the actuarial mindset, translates into institutional pressure on the individual to conform to certain standards of behavior or acceptable risk.[8] These pressures abound in the workplace, in the schools, and in the legal system. They act, in a sense, as social sanctions in support of such values as efficiency and economy.

Nelkin and Tancredi cite many examples of the sorts of tendencies to which I have been referring. Health concerns are now corporate concerns, as companies scrutinize workers for the potential for future disease and implement policies based on possible health concerns as opposed to current job performance. Let us consider testing in the workplace as an illustrative model.

The modern company has a diverse set of roles and responsibilities. A company is obviously concerned with efficiency, productivity and profit. In relation to its employees, the company acts as employer, insurer, and often health care provider. Worker safety, absenteeism, and potential litigation are also important issues. Certain strategies have evolved, especially in the area of occupational exposure risks, that, in effect, shift a significant portion of these

burdens from the corporation to the individual employee. These are apparent in the case of American Cyanamid.[9]

In 1978, the company announced a policy to remove from its West Virginia plant all women of childbearing age who were working with certain toxic substances. Women who had already undergone sterilization procedures were exempt from this policy, and the company offered to provide for sterilizations for those women who wished to remain at their jobs. This occurred despite the fact that there is relatively little scientific evidence concerning the effects of occupational exposure to environmental chemicals on embryos/fetuses in early pregnancy. Furthermore, there was no offer by the company to provide alternative solutions--such as protection from exposure-- to women of childbearing age.[10]

Nelkin and Tancredi suggest that the American Cyanamid case illustrates several corporate strategies with respect to occupational health problems:

> 1) The tendency, even in the absence of definitive scientific evidence, to place responsibility for problems on the individual worker rather than on the conditions of the workplace.
> 2) The establishment of in-house medical services responsible for defining the health status of workers.
> 3) The effort to predict who may be prone to future illness.
> 4) The development of policies to exclude workers or to increase control over their private lives.[11]

These types of strategies meet the needs of companies in terms of efficiency and liability, but they also set the stage for more specific

tests, such as genetic tests that would reveal the susceptibilities of individual workers. For the time being, the problem of placing responsibility on the worker will continue with mostly racist and sexist overtones, as groups that can be more easily singled out for special "risks" (such as sickle-cell trait and pregnancy) will suffer the most discrimination.

The importance of genetic testing to labor and management can be seen in their respective viewpoints on the issues of chromosomal monitoring and genetic screening. In chromosomal monitoring, samples of blood and urine can be taken from workers in order to follow them prospectively for the appearance of chromosomal abnormalities--which may result from exposure to toxic chemicals. Labor supports this type of monitoring because of its potential implications for occupational safety. Companies, however, have been less enthusiastic about chromosomal monitoring because no studies have shown a definitive correlation between chromosomal damage and greater risk of disease. Besides the cost of such testing, indications of an exposure problem might create strong pressures for costly measures to reduce exposure risks.[12]

On the other hand, while labor has strongly opposed the use of genetic screening programs, companies have shown a great deal of interest in detecting genetic traits that might predispose workers to illness due to chemical exposure. Some of the concerns about genetic screening programs have been addressed by the Office of Technology Assessment of the United States Congress (OTA):

> According to the OTA, the data on the correlation between given genetic traits and risk for disease are simply not extensive enough to draw predictive conclusions. Nevertheless, the data are suggestive and employers are using genetic screening as part of pre-employment medical exams.[13]

Most disturbing of the trends toward genetic discrimination has been the targeting of ethnic groups presumed susceptible to certain chemical exposures. Of these groups blacks are the most frequently singled out for screening tests, based on the prevalence of the sickle-cell allele in the black population. While carriers of the sickle-cell gene can experience symptoms at sufficiently reduced blood oxygen levels, employers have commonly associated the trait with susceptibility to illness based on exposure to certain chemicals. Employers have used the test for sickle-cell trait to screen prospective employees, but there is little evidence of occupationally related illness in carriers.[14]

The pre-employment physical is now a standard feature in the American workplace, including tests for drug use, AIDS, and even personal habits and personality characteristics. It is also within reason to suggest that acceptance of these kinds of screening methods may decrease resistance to future types of testing.

Nelkin and Tancredi emphasize "...the potential for diagnostic fallacies in tests that rely on inferential evidence."[15] The tendency to rely on the objective, or factual, quality of tests (and to unquestioningly accept the role of physician-as-expert) creates a danger of overlooking the complexity in the etiology of most diseases--i.e. the interplay of biological, environmental and

behavioral factors in the causation of disease. Thus, increased accuracy in detecting certain genetic markers will not translate into an equivalent increase in the ability to predict degrees of future physical or mental disability.[16]

A review of the recent literature on depressive illness helps to illustrate these complexities in the search for markers for disease. An important issue in the study of major depressive illness has been the question of its heritability. Certain studies suggest that bipolar illness is inherited in an X-linked dominant manner. Twin studies show a 65 percent concordance for major depressive illness in monozygotic twins and only 14 percent in dizygotic twins. Other studies have demonstrated an increase in the incidence of unipolar illness in the first-degree relatives of patients with unipolar illness.[17] Risk rates exceed 25 percent if a sibling and one parent are affected. Moreover, the risk increases among first-degree relatives of patients with relatively early onset of depression (<40 years).[18]

Although the issue has received much attention, no definitive marker for major depression has yet been identified.[19] Despite some phenotypic linkage to the inheritance of bipolar illness in certain isolated populations, the use of restriction-fragment-length polymorphisms (RFLPs) has become the dominant tool in the search for the inheritance of specific genes for depression. One promising study recently found an association between two RFLPs on the short arm of chromosome 11 and the presence of the major affective illness in 19 of 81 Old Order Amish going back three generations. This group of individuals displayed bipolar, unipolar, and

schizoaffective disorders, suggesting a possible relationship between these disease entities. The incidence of major affective disorder in Amish persons with the two RFLPs described above was 63 percent, suggesting that the gene responsible is a dominant gene with incomplete penetrance.

Although this information provides the first convincing evidence of a genetic defect being involved in major affective disorder, the distance between the markers is on the order of 3 million base pairs so that the defect/defects could lie within this large area or to either side of it. One of the genes in this region codes for tyrosine hydroxylase, the rate limiting enzyme in the synthesis of catecholamines. Since some theories of affective disorder and antidepressant mechanisms involve the catecholamine, norepinephrine, the tyrosine hydoxylase gene should be the object of further investigation.

Studies of two other pedigrees (Icelandic and North American) found no association between major affective disorder and the two RFLPs in the Amish study. Still other pedigrees indicate an X-linked inheritance pattern. All of this suggests that there is a great deal of genetic heterogeneity in the major affective disorders. This information also leaves room for the importance of other etiologic factors in the development of depressive symptoms, and supports the view that an integrative approach to diagnosis will probably be required as the depressive illnesses are better understood.

The rate of progress in identifying possible genetic markers of disease is astounding. Glancing at a recent issue of the New England

Journal of Medicine, I see, "Genetic Analysis of an Inherited Predisposition to Colon Cancer in a Family with a Variable Number of Adenomatous Polyps."[20] This can be read as good news for the individual within the context of the doctor-patient relationship, because it may facilitate early detection of cancer in certain individuals. On the other hand, the issue of the availability of this information to insurance companies is more problematic.

As a final example, we might consider the case of Huntington's disease, as it raises some rather excruciating questions. This disease has been identified as a single-gene disorder with a dominant pattern of transmission. Based on family history, most individuals with one afflicted parent know that there is an approximate 50% chance of inheriting the abnormal gene. This alone is a weighty burden, and many individuals at risk have chosen not to have the genetic test. The implications in the insurance sector are that a negative test removes a person from a high-risk category, but this is not necessarily an adequate trade-off for someone facing the possibility of a positive test. There is also a question of fairness with regard to insurance. For example, a person with the appropriate genetic abnormality may not develop symptoms until the later decades of life. Furthermore, a person with a positive test for the abnormal gene may have difficulty finding insurance, yet that person may perish by an "act of God" before symptoms ever develop; and there are other painful scenarios.

Before a genetic test for Huntington's disease was available, MacKay and Shea addressed the general ethical issues pertaining to research on this illness.[21] They recognized that research into the

biological causes of this disease should be accompanied by study of economic and psychosocial aspects as well.

> The desperate plight of the HD population makes them more vulnerable in certain respects than other disease groups: their numbers are small; their sufferings intense; their hopes fragile. Their special sets of needs require a range of basic health services and a strong form of advocacy and protection.[22]

In the context of the present discussion, these concerns are quite understandable.

In general, as diagnostic tests proliferate, their use and interpretation should be more closely evaluated. Standards for assessing the significance of diagnosed conditions should be brought into line with the interests of individuals as opposed to institutions. It has been suggested that the role of physicians should encompass the responsibility to inform patients of the social as well as the biological implications of testing, even if the best advice is not to be tested.[23] Also, the role of medical persons in nonclinical settings deserves more scrutiny, considering the institutional pressures they may face. Finally, the progress in diagnostic abilities should at least be matched by increased protection of individual privacy.

Chapter Two: Social Uses of Genetic Information

In an area as potentially controversial as genetic research and technology, it would seem particularly important to have a sense of the interplay of forces in the social practice of pure and applied science. What we commonly refer to as scientific progress is generally viewed as a process of building on previous knowledge and application. Less frequently do we take a critical look at the forces driving such endeavors. As a rule, we tend to treat science as a natural process without questioning its motives. Yet, just as in the case of diagnostic testing, there are both obvious and subtle rationales (agendas) behind scientific progress. A critical approach to this subject requires that we examine the systemic biases in areas of current research. Furthermore, we need to examine historically the interplay between scientific theories and social agendas. We need to look at both what kind of science we are doing and why we are doing it.

In the late19th century, when scholars were just beginning to have a sense that heredity could be conceptualized even at the level of whole populations, a movement by some of the leading scientists of the day was underway. Some biologists began to look at populations as aggregates of heritable traits whose frequencies could

be described statistically. Some of these same scientists felt that many of society's ills, such as crime, immorality, and low intelligence were factors passed on from generation to generation as individuals with these traits reproduced themselves. Therefore, these scientists reasoned that the quality of pairings and the rate at which various pairings occurred had profound implications for society. Their theories suggested that it might be possible to control the quality of society by encouraging pairings between individuals with positive traits and discouraging breeding in those with undesirable traits. Recommendations for this particular kind of social engineering were put forward under the banner of "eugenics."

What Francis Galton referred to as the "science" of eugenics was the concept that the hereditary quality of the human race could be improved by encouraging breeding between individuals with favorable qualities and discouraging breeding between those with unfavorable ones. The question of who was defining the qualities for "positive" and "negative" eugenic programs apparently did not occur to the early eugenicists, nor would it have been likely to have done so. As Troy Duster observes,

> In times of great social stress and upheaval scientists are made directly aware of the social frame of knowledge development. From 1936 to 1943, nuclear physicists in Germany, England, and the United States knew that their research was impelled along a particular "scientific" road by forces with a powerful impetus. In peace time these forces remain, but they are often sufficiently subtle to permit us to sometimes indulge the illusion of

> substantial scientific autonomy (i.e. autonomy from those forces).[1]

The goals of eugenics were faulty on scientific grounds alone, but they were based on the virtually unchallenged social assumptions of a very well-to-do class of people. The norms of these upper class social engineers were racist, sexist and elitist. Their tools, in the form of social policy masquerading as science, could be turned against groups such as immigrants, criminals, misfits, and the developmentally impaired.[2]

In the eugenic framework, a biological model explains an undesirable behavior or condition. Society then has the opportunity to improve itself by intervening in activities that perpetuate such undesirable traits, i.e. breeding. For example, an I.Q. test administered to children might diagnose hereditary dispositions to low intelligence which could be reduced in the general population by sterilizing individuals with very low test scores. This kind of program was a reality in this country for a number of years. In such programs postulated genetic traits become convenient models for explaining complicated conditions and act as additional burdens on the disadvantaged. In turn, these models require conformity as defined by an advantaged class, and their purpose is to perpetuate the values of this particular class. In the process they tend to obscure other competing sets of values and ideologies.

The founder of the eugenics movement was the English scientist, Francis Galton. Galton was the son of a wealthy banker and in his education had been steered toward the esteemed professions. Having switched from the study of medicine to mathematics, he took

a degree at Cambridge University. Although a large inheritance soon made him self-sufficient, this background was to prove central to the formation of his ideas about eugenics (from the Greek, meaning "good in birth" or "noble in Heredity").[3]

Galton's attitudes about society reflected his own social background.[4] As a man of status, he could picture himself near the top of Darwin's evolutionary ladder with the luxury of pondering how the rest of society might be raised to his level. Moreover, it has been suggested that the apparent infertility of his marriage may have contributed to his interest in eugenics and heredity: "Galton may well have diverted frustration over his own lack of children into an obsession with the propagation of Galton-like offspring."[5] His theories suggested that society could be improved by an increase in the fertility of its more gifted, successful individuals.

Galton's approach to hereditary problems was almost purely statistical, and in this he was a true pioneer. The science of statistics was new at this time. Thus, Galton's application of numbers theory to biological issues was a novel approach, and in fact it was numbers that most fascinated him. While the statistics of the time consisted mostly of the compilation of socially useful facts by the government, Galton in the 1860s came across the concept of the normal, or Gaussian, distribution. This formulation was developed by the German mathematician Carl Friedrich Gauss and was known at the time as "the law of error." It referred to the probability of error in the making of physical measurements and was represented by the bell curve, or normal distribution.[6]

Based on his observations of the distribution of various biological properties, Galton seized upon the idea of applying the law of error to the analysis of certain measurable characteristics in large, randomly selected groups of people. With it he proposed to study populations in terms of the frequencies with which characteristics deviated from the mean and exclaimed that there was "scarcely anything so apt to impress the imagination as the wonderful form of cosmic order expressed by the 'Law of Frequency of Error.'"[7]

Galton did not ultimately espouse state control of marriage and reproduction as a means to social betterment, in part because he realized how little was known about heredity at the time. He wrote,

> My attitude, which has usually been misrepresented, is to urge serious inquiry into specific matters which still require investigation in the well-justified hope that a material improvement in our British breed is not so Utopian an object as it may seem, but is quite feasible under the conditions just named.[8]

Instead, he envisioned eugenics as a kind of secular religion to be advanced on the strength of further research into the laws of inheritance. Knowledge about inheritance might then be used to guide reproductive decisions as gestures of faith in the eugenic creed.

Galton's followers in England represented one of two major branches of human genetic research, both of which derived most of their support from eugenic movements in England and the United States. Like Galton, most British students of genetics concentrated on the statistical study of biological traits. The "biometricians'" as they

were called, tended to look at the distribution of traits that showed continuous variation along a given scale of measurement, such as height or skull size. In America, the field of genetics was dominated by the Mendelian approach to heredity. Mendelian genetics developed as the study of discrete but related traits in individuals within a population, such as white versus red eyes in *Drosophila* or round versus wrinkled skin in peas. (The concept of dominant and recessive traits is derived from Mendelian studies). The Mendelians soon discovered that many human phenotypic characteristics, including certain diseases, were inherited in accordance with Mendel's laws. Similarly, the biometricians made important contributions--namely in the field of statistics, where they developed or found novel applications for such tools as coefficients of correlation and regression, the Gaussian curve and the chi-square test.[9]

The hereditary theory of the late nineteenth and early twentieth centuries was thus abstracted from a peculiar mix of scientific investigation and social thought. In his book No Other Gods Charles Rosenberg traces the evolution of what he calls "hereditarianism," beginning in the second half of the nineteenth century.[10] He analyzes the development of a kind of deterministic thought regarding heredity and disease which had been absent in the first part of the century.

> Heredity has always played some role in both medical and social thought. It was not until the second half of the nineteenth century, however, that it became a prominent component not only in

> accepted schemata of medical explanation, but of social analysis and rationalization as well.[11]

Rosenberg goes on to say that "while the formal content of scientific knowledge remained essentially unchanged, its social applications shifted markedly in scope and emphasis."[12] Examining this shift helps to illustrate how science can function as an element of social practice.

Rosenberg sees this shift in thinking as being embodied in the changing social applications of science. In the early part of the nineteenth century, the idea of diathetic or constitutional weakness served as a prominent model for explaining disease in individuals. For example, this model was particularly useful to physicians, because it helped to define the boundaries of medical practice.

> The physician's perspective is in many ways easiest to understand. Most important was his need to find explanations for the disease phenomena which made up his everyday routine, formulas at once flexible yet consistent with lay assumptions. Laymen, for example, recognized that most constitutional ills were generally unaffected by medical art; the physician's situation thus demanded an explanation which minimized the possible relevance of medical intervention.[13]

Rosenberg points out that it was the chronic diseases such as cancer, gout and tuberculosis which fit most readily into this framework. While these ills were seen as being largely hereditary, inheriting a predisposition was not observed to be the same thing as developing the disease. Physicians could utilize the role of advisor in advocating prophylaxis against such diseases, and thus confirm their basic

function of treating disease. They could be flexible in espousing models that "...served to underwrite the social effectiveness of the late-eighteenth- and early-nineteenth-century physician."[14] In this way the physician could provide counsel on the interaction of environment, diet, heredity and other factors in the etiology of diseases in which the role of these factors could not be precisely defined. Rosenberg goes on to argue that

> Doctors were, on the whole, little different from others of their class and time; and hereditary predispositions helped dramatize the need for temperance, for moderation in diet and sexual relations.[15]

Essentially, these conceptions of disease were both scientific and social constructions that served the needs of medical practice and acted as social sanctions.

The hereditarian thought of the latter half of the nineteenth century was characterized by a new activism. It reflected the belief that human characteristics should be modified by weeding out inherited weaknesses. In America a number of influences seem to have contributed to the development of hereditarian attitudes. Workers in the contemporary health reform movement brought a degree of religious fervor to their activism, adopting heredity as a mechanism by which they might attack social problems. Various opinions concerning heredity were also brought to bear on the issues of female autonomy and domesticity as related to childbearing and child-rearing.[16]

In Europe, hereditarian concepts enjoyed a growing popularity in academic circles.[17] The French psychiatrist Benedict Morel suggested that a "neuropathic constitution" might progressively degenerate from one generation to the next, resulting in a succession of individual psychological ills. A major focus of this "degeneration thesis" was on antisocial behavior. "The degeneration concept," writes Rosenberg, "was soon popularized outside the psychiatric community, most conspicuously in the study of criminal behavior."[18] In this model the criminal became a hereditary type, and more broadly, social problems--the increasingly crowded mental institutions, for example-- began to be viewed as a sort of genetic pathology.

The hereditarian thinking described above provided fertile ground for the development of eugenic movements. It seemed to offer an element of control over individual deviance and a precise rationale for enforcing certain social norms. It provided an emotional crutch, a support in coping with the profound social change of the period--i.e. the growth of secular and scientific modes of thought, urbanization and industrialization, and population growth. Ironically, though, bolstered as it was by the social logic of the day, this framework owed its viability to the imprecision of the very science (or "pseudoscience") upon which it was based.[19]

Regrettable as it was, the rhetoric of the eugenics movement was not nearly as tragic as was its application. Having popularized eugenics in the late nineteenth century, the proponents of this social engineering turned to legislation in the early years of the twentieth. Eugenic arguments were effective tools for racial discrimination and

for action against the mentally deficient. Immigration policy was a major focus of eugenic activism, and the development of the Binet test of intelligence also had a great impact in the context of rationales for sterilization. To understand the meaning of the eugenics movement, it is necessary to have some appreciation for what eugenics was in practice.

One of the earliest contributions of eugenic policy to national politics in America occurred in the area of immigration reform.[20] Eugenicists joined with other exclusionists to lobby for tighter immigration restrictions. These limits were directed mainly against the wave of Eastern and Southern Europeans immigrating in the early 1920s, and eugenic arguments took the form of expert testimony in hearings before committees of both houses of Congress.

> In 1923, the House Committee on Immigration and Naturalization began holding hearings on a permanent bill. Many witnesses argued that "biology" demanded the exclusion of most members of Eastern and Southern European "races."[21]

It was maintained by some, for example, that the intelligence of these peoples was inferior by American standards. In 1924, the Immigration Act was passed by Congress and signed into law. Based on strong restrictionist sentiments, it limited immigration, through 1927, from any European country to a fraction of the foreign-born Europeans in the U.S. at the time of the 1890 census--a time when their were proportionally much fewer Southern and Eastern Europeans in the country. In 1927, the law was revised, based on the 1920 census but it had the same discriminatory effect because it

involved a quota system based on the "distribution of national ancestries in the total population."[22]

If this analysis is correct, then the immigration policies described above clearly reflect elements of hereditarian thought, particularly the idea that intelligence is basically biological. The view that intelligence can therefore be biologically controlled is the next step in eugenic thought. This position provided part of the foundation for the U.S. sterilization laws, the first of which was passed in Indiana in 1907.[23]

While immigration policy was debated at the national level, the states took the lead in developing sterilization laws. By the end of the 1920s, there were sterilization laws in 24 states.[24] These laws were directed against a variety of groups, including habitual criminals, epileptics, sexual offenders, the insane and the mentally deficient. At a time when scientific authority was particularly influential in government reform, eugenicists were at the forefront of the sterilization movement.

> In many states the practice was modeled after the "Wisconsin Idea," advanced by the progressive governor Robert La Follette, of drawing upon experts in the state university for advice in complicated policy areas like taxes, agriculture, regulation, and public health. Eugenics experts aplenty were to be found in the biology, psychology, and sociology departments of universities or colleges, and among superintendents of state mental institutions.[25]

Kevles points out that politics and research were "symbiotically" linked in American eugenics.[26] For example, the most influential

training ground for eugenicists in the U.S. was the Eugenics Record Office of Charles Davenport in Cold Spring Harbor. These men and women were sent out across the country as field workers and took up positions in the staffs of mental institutions. Then, as "experts," they testified and lobbied for eugenic policies.[27]

According to eugenicists, mental deficiency could be explained on genetic grounds alone. Therefore, it made sense to argue that sterilization of the mentally deficient was the best remedy for the problem. Moreover, their position was also associated with certain biased attitudes about sexual behavior. For males, some asserted, there was excessive sex drive in the feebleminded. It was also suggested that retarded women were "easily yielding to lust," a point of view which did nothing to help the image of women in society at that time.[28]

The famous test of sterilization laws directed against the mentally deficient was the U.S. Supreme Court case *Buck* v. *Bell*.[29] This case involved a Virginia sterilization statute and a seventeen-year-old woman named Carrie Buck. Carrie Buck had a mental age of nine as determined by the Binet-Simon I.Q. test, her mother had been committed, and her young daughter was below average for a child her age, according to some experts. The majority opinion was written by Justice Oliver Wendell Holmes:

> We have seen more than once that the public welfare may call upon the best citizens for their lives. It would be strange if it could not call upon those who already sap the strength of the State for these lesser sacrifices...in order to prevent our being swamped with incompetence.... The principle that sustains

> compulsory vaccination is broad enough to cover cutting the fallopian tubes....Three generations of imbeciles are enough.[30]

Carrie Buck was sterilized soon after the court's decision, and there were sterilization laws in twenty-four states by the end of the 1920s. By the middle of the next decade, about twenty thousand legal sterilizations had been performed.[31]

The sterilization laws, the immigration policy, and various other political movements influenced by eugenics were part of a social framework where numerous discriminatory, restrictionist, generally middle-class biases combined with science and "pseudoscience" to effect political and moral reform. They can be best understood in the context of their particular social history. By the end of World War II, the eugenic movement had for the most part come to an end. The "science" of eugenics had been superseded by more accurate genetic theory, and the atrocities of Nazi eugenics threw a dark shadow over the entire enterprise. This is not to say that the racist and and sexist sentiments behind it no longer exist or that science is no longer constrained by its various ulterior motives. That is to say, the motives behind the eugenics movement have not vanished, but they serve other purposes in different guises.

This paper is about the social implications of genetic knowledge. More specifically, it is about the meaning of genetic knowledge in the context of our own society and our own time. In line with the theme of this chapter, we should consider asking how biases affect our present day science and policy that might be

relevant in the context of genetic information. Are we even aware of them?

Troy Duster suggests that "social concerns frame the path to knowledge, and sort the kinds of biological questions that get raised."[32] These are substantive issues that depend very much on the particular society in question. For example, in the Unites States, a great amount of our medical research and treatment is possible only because our society has decided to invest in technological medicine. At the same time, there are many individuals who could benefit from affordable preventive medicine but who do not have adequate access to it. Part of this has to do with our society's prioritization of health care goals and needs.

Economic forces are, of course, another issue, and this will be seen in greater detail in the next chapter. But to quote from Edward Yoxen's The Gene Business,

> The economic forces that have led to the constitution of a certain kind of medicine operate continuously on medical biotechnology. It is their latest offspring, their project, their hope for the future. It is a route into new markets, selling a kind of health care that has proved efficacious and profitable, appealing and costly.[33]

Economics has thus become a driving force in the new biology.

In his article, "Constructing Genetic Diseases," Yoxen also examines the field of genetic counseling and its evolution. In it he makes the following "linked claims."

1. The conceptualization of certain states as genetic diseases, or potentialities as hereditary predispositions to disease, depended on the formation of a basic model that the inheritance of a specific, transmissible, causative factor (a gene) leads to a specific disease.

2. The assimilation of particular conditions to this model and their reinterpretation in its terms was and continues to be the result of technical development *and* cultural change.

3. The use of such genetic insight in medicine is constrained by its structures of specialization and competition.

4. What counts as an appropriate medical response to genetic disease is culturally defined and a political issue which may be debated as such.

5. The most common behavior by counselors in this position is to control the counseling agenda and the display of knowledge, so as to protect their notion of their expertise.[34]

Whereas medical response was once the sterilization of certain individuals on the basis of "genetic" criteria, techniques such as amniocentesis and ultrasound together with counseling are directed at genetic diseases. This is a new medical approach within a new cultural context. Yoxen suggests that this model lends itself to a focus on diagnosis and sometimes a neglect of complex personal and societal issues as a manifestation of the power of control deriving from expertise.

Chapter Three: Controlling the Human Genome

As the events of recent decades have demonstrated, the progress of science has challenged our abilities to evaluate and govern the use and potential abuse of our new technologies. The obvious corollary to this assertion is that knowledge and wisdom do not always go hand-in-hand, as, perhaps, our experience with splitting the atom may illustrate. This, indeed, appears to be the case in the incipient field of fetal therapy, where some of the most troubling questions are raised by the prospects of therapeutic access to the human genome. Some go so far as to say that in this new field the control of human nature is at stake.

Recent advances in the understanding of hereditary mechanisms in humans and lab animals have fostered a burgeoning research effort into potential manipulations of these mechanisms at a molecular level. Efforts are already underway to map the entire human genome. These and other efforts may eventually open the way to highly specific permanent alterations in specific sequences of human DNA. Not surprisingly, these advances raise important questions for our national society and for the international community. Before going on to an examination of the issues raised by these developments, however, it will be useful to discuss the state of

advancement in genetic manipulations today and the prospects for clinical application.

The starting point for this discussion is the concept that genetic markers can be used to identify potential disease states in individuals and carrier gene states in prospective parents. In particular, two techniques constitute most of the molecular diagnosis that is currently possible.[1] In both techniques, enzymatic "probes" cleave DNA at particular points to generate fragments of varying length. Depending on their size and charge, these fragments will migrate at different rates through a gel when the gel is exposed to an electric field. This process generates patterns which are particular to different DNA sequences cleaved by the probe. Thus, when these patterns can be found to be statistically associated with certain conditions, they can be said to be genetic markers for these conditions. This can take the form of "linkage analysis," where an individual's pattern is compared to those of his or her affected and unaffected family members, or "direct analysis," where no reference to the markers of family members is necessary to establish a diagnosis.

With the rapid development of marker analysis, the potential for diagnosis of disorders at the genetic level has increased dramatically. In diseases such as beta thalassemia (a hemoglobin disorder), clinical or biochemical abnormalities may be non-diagnostic, while gene probes are useful. Markers have also been developed to identify silent genes in carriers for cystic fibrosis and Duchenne muscular dystrophy. Furthermore, markers may be used to predict the later development of disease in any tested individual.[2]

The techniques described above are useful in that they augment the diagnostic repertoire of the physician, and they may represent the foundation for important decisions for individuals and for reproductive partners. Moreover, they represent another step in our understanding of the genetic bases of disease. This, in turn, raises the possibility of therapy at the most fundamental of levels -- that of the human genetic code.

The prerequisite for gene therapy is the ability to introduce DNA into cells in a manner which allows for its appropriate expression. The introduction of new genetic material into cells is not an entirely novel idea. For example, it has been known for some time that certain viruses insert their genetic material into the DNA of infected bacterial cells. Similarly, the AIDS virus introduces DNA into the chromosomes of infected human cells. From their position inside the cell, viral nucleic acids can take advantage of cellular machinery to control their own replication. Needless, to say, the effects of this process can be quite detrimental to the infected cell.

More recently, however, scientists have been experimenting with ways in which to introduce useful genetic material into cells with the hope of one day transforming defective cells into functional ones. One technique again involves viruses. It rests on the principle that in some cases a virus may pick up genetic material from one cell and then transfer this material to the next cell it infects. This "injected" material may then be incorporated into the new cell's DNA and be expressed along with the other native products of DNA translation, while at the same time the harmful effects of the virus are neutralized. The infected cell might then be transformed in some

recognizable way, such as secreting a new hormone or producing a new enzyme. Experimentally, it has been possible to recreate this phenomenon with various genes of interest.

Another technique involves cellular uptake of DNA from the culture medium and subsequent integration and expression of the foreign genetic material. Similarly, DNA can be introduced directly into cells by a process called microinjection, and this may possibly effect a transformation. The problem with these and other techniques is that, in general, they do not allow for the creation of specific genetic changes in appropriate places in the cellular DNA. The incorporation of the foreign DNA into the cellular genome is essentially random. Furthermore, its insertion may interrupt the normal sequence of important cellular genes or activate certain deleterious genes by disrupting their normal genetic repressors. These difficulties in "gene targeting" represent one of the greatest obstacles to the development of reliable methods of gene therapy.

Recently, however, in a gene transplantation experiment, scientists at the University of Utah devised an elaborate procedure which allowed them to select out of a mass of embryonic cells those that had undergone targeted change.[3] Investigation along these lines is likely to open up new possibilities for genetic repair and modification not only in individual cells, but in tissues and whole organisms as well. The ultimate goal of gene therapy, then, is to take this knowledge and apply it to humans.

In assessing the implications of this last proposal, it is important to first characterize the general forms that genetic engineering procedures could take.[4] There are basically four. The

first of these is *somatic cell gene therapy*. This could involve correction of genetic defects in any number of somatic (body) cells, but it would not affect the germ line cells, and, hence, the changes would not be passed on to the patient's progeny. Secondly, the reproductive cells of an individual could be modified in such a way that the changes would be passed on to her or his offspring. This is known as *germ line gene therapy*, a concept morally troubling to many, for it entails permanent changes in genetic lines. A third approach is known as *enhancement genetics*, and would involve the insertion of a gene to enhance a genetic characteristic, such as height (if tall offspring were desired). Finally, it might also be possible to develop the capacity for *eugenic genetic engineering* . Here an attempt would be made to "improve" certain complex human traits -- such as personality or intelligence -- which may be only partially determined by genetics. These last three approaches have been and will continue to be the most controversial.

The preliminary models for gene therapy involve primarily bone marrow cells, for reasons having to do with ease of manipulation. Furthermore, bone marrow is the site of large numbers of primordial or stem cells which give rise to important components of human blood.[5] In theory, genetic repair of a defective stem cell should produce a functional cell line descending from the repaired stem cell. At present, there is a great deal of optimism that serious diseases such as sickle cell anemia and a number of the thalassemias -- whose treatment now is only palliative -- might be cured by repairing the defective globin genes in stem cells that are responsible for red blood cell dysfunction.

Attempts to genetically alter bone marrow target cells have also been directed at diseases caused by "inborn errors of metabolism." In these disorders, defective genes have led to the absence of certain enzymes that are essential for healthy physiologic functioning. In the Lesch-Nyhan syndrome, for example, males are deficient in an enzyme found in all somatic cells, whose lack results in a disorder clinically classified by mental retardation and self-mutilation behavior.[6] Laboratory experiments in mice have successfully used viral vectors to transplant the functional gene into bone marrow cells in mice. Investigations into how to apply these techniques to other tissues would logically be the next step.

Along with the Lesch-Nyhan syndrome, it is hoped that diseases such as sickle cell anemia, Tay-Sachs, hemophilia, cystic fibrosis and muscular dystrophy may be amenable to gene therapy techniques in the not-too-distant future. They share the common characteristic of representing disease due to a defect in a single gene. But here a constellation of legal and social issues surrounds the question of gene therapy, because the methods of gene therapy become intertwined with the issues of screening and genetic counseling. Methods of detecting genetic defects are developing at a rapid pace, but not without certain risks and thorny questions. For example, the implications of genetic screening for the insurance industry as we know it have yet to be sorted out. A second but related set of issues has to do with the control of information, particularly with respect to individual rights to confidentiality. Thirdly, while issues of informed consent and parental decision-making remain paramount, continuing questions about the status of

the fetus perpetuate the possibility of conflicts between mother and fetus and between parents and the state. Another level of complexity is added, consequently, when the option of gene therapy becomes a reality and no firm guidelines have been established. The questions arise how we will evaluate the risks and benefits of new genetic technologies, who will have access, and how our tampering with heredity will affect us as a species.

Focussing specifically on the subject of gene therapy, the first major consideration is its highly experimental nature. The distinction between somatic and germ line therapy has been mentioned, and there is already a growing consensus that somatic therapy can and should be attempted. However, no specific set of stipulations has yet been adopted or promulgated. According to one set of authors, such guidelines might take the following form:

> a. Only a disease that drastically reduces the quality or duration of life should be a candidate for somatic gene therapy.
>
> b. A clinical trial should be conducted only if there is no alternative established therapy that is likely to yield as good or better results.
>
> c. Investigators should be able to identify the nature of the selected genetic defect as well as the course of events leading to symptoms.
>
> d. There should be evidence that the planned procedure for modifying the specific genetic defect is regularly safe and efficacious in comparable animal studies. This should include a demonstration that the new gene has been inserted in proper target cells; that it remains there; that it is expressed appropriately (in other words, produces proper

> quantities of its product); and that it does no harm to target cells or, inadvertently, to nontarget cells.
>
> e. All established procedures for the ethical conduct of human clinical trials should be followed.
>
> f. The protocol should be so planned that even if therapy is not achieved its subsequent success will be more likely, i.e. "shots in the dark" should not be attempted.[7]

These guidelines reflect an appreciation of the novelty of the techniques of gene therapy and a concern with the uncertainties of its effects on the human genome. Nevertheless, no specific laws currently govern the clinical application of gene therapy.[8]

The issue of germ line therapy is attended by considerably more controversy than that surrounding somatic cell techniques. Because germ line therapy could potentially create permanent modifications in individual genomes, there is talk of *Brave New World* implications for humanity as a whole. It is feared that genetic manipulation could be used by some as a means of social control or discrimination. There is also added concern about the dehumanizing potential of attempts to "improve" complex human traits such as intelligence or personality. According to Jeremy Rifkin,

> Once we decide to begin the process of human genetic engineering, there is really no logical place to stop. If diabetes, sickle cell anemia, and cancer are to be cured by altering the genetic makeup of an individual why not proceed to other "disorders": myopia, color blindness, left-handedness? Indeed, what is to preclude a society from deciding that a certain skin color is a disorder.[9]

On the other side of the fence, Joseph Fletcher argues,

> Should we leave the fruits of human reproduction to take shape at random, keeping our children dependent on the accidents of romance and genetic endowment, of sexual lottery or what one physician calls "the meiotic roulette of his parents' chromosomes"? Or should we be responsible about it, that is exercise our rational and human choice, no longer submissively trusting to the blind worship of raw nature. [10]

The useful distinction that must be made in this type of dispute is between positive modifications and the elimination of defects. According to Peter Singer,

> In time we might come to accept the desirability of positive modifications. One reason for accepting this is that looking around us, there is reason to think that natural selection has left ample room for improvement.[11]

Yet, while some envision positive modifications as a useful extension of genetic therapy techniques, others view their application as a dehumanizing process.

At least three strands of thought are relevant to the above discussion. The first of these has to do with the definition of a disorder. As in other aspects of medicine, there has evolved an ideal of the weighing of risks and benefits within the framework of informed consent. In this sense, gene therapy might only differ from other medical procedures in terms of risk. This would be the case if therapy could be directed towards some obvious genetic defect.

There would have to be some reasonable assessment of the risks of the technique as opposed to the severity of the disorder. Yet, what limits, if any, should we attach to such decisions? Given the great uncertainties in ever fully controlling such intricate molecular processes as cellular genetics, it would seem that compelling arguments would be required to justify the potential hazards of gene therapy for our potential offspring.

Assuming that risks could be reduced to a relatively low level, then another consideration would involve the issue of parental control over reproduction. According to Lori Andrews, any limits to germ line therapy for childrens' characteristics are likely to reflect the influence of parents' constitutional right to privacy:

> The parents' right includes the right to control their offsprings' characteristics. That right may be infringed upon only to the extent necessary to further a compelling state interest in the least restrictive manner possible.[12]

This approach might also be affected by considerations having to do with the best interests of the offspring, as well as society.

The third consideration is in part a historical one. Reference is made to "the historical legacy of eugenics" in early twentieth century America.[13] It was thought at the time that human traits such as feeblemindedness, criminality, and pauperism were attributable to single gene defects. Control of reproduction was considered to be the optimal strategy for reforming society, since it could eliminate these defects from the general population. It was not until the 1960s and 1970s that compulsory sterilization laws and prohibitions against

interracial marriages were repealed and immigration policy was reformed. Today some critics of genetic engineering are particularly aware of this legacy:

> Jan Beckwith warns that the social conditions in the United States which led to the eugenics movement in the early part of this century (a movement which many leading scientists supported and advanced) exist today and that a new eugenics movement applying genetic technology to the germ line could occur. Such a movement would invariably discriminate against minorities, the poor, and those considered "deviant" in the eyes of the dominant class.[14]

This is an extreme view, particularly given our poor understanding of most human traits at the genetic level. Nevertheless, it is important to be cognizant of the potential for discrimination inherent in our new technologies. It should be in society's best interests to be just and fair in distributing resources that can clearly prevent suffering, but this is not always the actual outcome. It pays to be wary of new technologies that give us selective power over the characteristics of our progeny. On the one hand, as in sex selection, we may allow intolerable levels of discrimination; and on the other, we may be tampering with the healthy diversity which makes up our society.

Because germ line therapy will focus on the earliest stages of life, it has important implications for issues that have been emerging in the broader field of reproductive technologies. While *Roe v. Wade* has strongly supported maternal choice with respect to abortion,

cases such as *Raleigh Fitkin* and *In Re A.C.* suggest that certain maternal rights, particularly with respect to penumbral privacy considerations, may be subordinated to the interests of the fetus. Suits for wrongful birth, furthermore, have provided strong incentives to prevent poor infant outcomes due to fetal defects or fetal harm. In addition, medical technology is pushing fetal "viability" to earlier and earlier gestational age. In all this, the "personhood" of the fetus has ben the subject of growing debate, and the fetus has clearly emerged as in some sense a patient in its own right.

With respect to germ line therapy, the question of mandatory fetal treatment preceded, perhaps, by mandatory genetic screening may become a serious legal and social issue. It is easy to see, however, that this will be an old problem in a new guise. Our problem is not merely to recognize this but to reflect at length upon the original question. We are again dealing with one aspect of the question of reproductive privacy and the issue of maternal-fetal conflict. This is a fruitful area for philosophical debate, as a discussion of fetal therapy by Alan Fleischman and Ruth Macklin indicates. Their discussion centers around the merits of a rights-based ethical analysis versus a consequentialist, utilitarian approach to the issue of maternal-fetal conflict. They argue that "in struggling with the ethical issues surrounding fetal therapy, it is not a helpful tactic to ascribe rights to the fetus and then try to effect a balancing act with the rights of the mother."[15] Their approach relies in part on an analysis in terms of risks and benefits for both parties concerned. Fundamentally, the "risks to both parties should not be minimized in the eagerness to describe the potential benefits to one."[16] The

implications of this type of reasoning are that procedures such as Caesarian sections might not be justified merely on the grounds of being necessary for the fetus. Likewise, in the case of gene therapy, a judgement that a treatment is "necessary" for a fetus may not justify a therapeutic intervention. Instead of appointing a fetal advocate in such cases, it might be helpful to refer the matter to an institutional ethics committee.

In concluding, it seems that an important theme informing much of the discussion concerning gene therapy has been that of "medical necessity."[17] This idea relates to both the experimental nature of potential gene therapies and the further question of how far we go with our expanding abilities to manipulate the human genome. However, some argue that "medical necessity" does not provide a sufficient grounding. Lawrence Tribe, for example, has discussed the need for a broader understanding of the relationship between man and his machines with a view that the two can no longer be viewed as totally separate. Instead, each has a role in helping to define the other.[18]

Similarly, Clifford Grobstein argues for a search for broader principles that might define policy guidelines. Such principles as the following might serve as the basis for informed discussion and long-term oversight by an appropriately constituted advisory body:

> 1. No genetic intervention shall be attempted on any human being with the intention or reasonable expectation that it will reduce either somatic or germ line potential (intended to prevent gene transfer from becoming a tool for government tyranny).

2. Any human genetic modification that is intended or may reasonably be expected to alter germ line cells shall not be attempted without special review and sanction by a body suitably constituted to evaluate not only technical risks of effects on the human gene pool but political, social, and moral aspects as well (this affirms the special problem raised by germ line modification).

3. Except as demonstrably required under principles 1 and 2, no restriction shall be placed on research intended to increase understanding of human heredity and its expression (a freedom to research principle).

4. Principles regarding human genetic therapy should be incorporated into both national policy and international covenants, since the human gene pool knows no geographical boundaries within the species.[19]

In the long run, an advisory mechanism involved with these issues might anticipate new developments in genetic technology in such a way that they might be adequately prepared for, and it could perhaps provide the general public with the tools for discourse and education.[20]

Chapter Four: The Social Frame of Biological Knowledge

In previous chapters discussion has centered around the kinds of issues that are brought to mind when we consider the rapid advances being made in the field of human genetics. The starting point for this discussion has been the Human Genome Project financed by the U.S. Government. The point of this paper has been to suggest that it is not just the scale of the project that deserves consideration. This in itself is an issue, because the project requires massive amounts of financing and manpower. However, it has been my further contention that the knowledge we will obtain from this endeavor to sequence the entire human genetic code is not neutral information.

The preceding discussion suggests that genetic theories have historically served various purposes. They have served the needs of social reformers as well as evolutionists and sociobiologists. They have been used by scientists and doctors as tools of research and as powerful models of disease. Genetic information and technology have had an impact in the workplace as well as on Wall Street, not to mention on the individual and the family.

Discounting textbooks and scientific reports, there is nonetheless a vast and ever-expanding literature on genetic information and technology. There is much food for thought even in

the titles of recent works: Invisible Frontiers; Dangerous Diagnostics; and In the Name of Eugenics: Genetics and the Uses of Human Heredity are all intriguing. Few other fields have raised as much concern and prompted so much debate before they reached a stage of significant application. Yet criticism of the genetic revolution in biology has been widespread, and caution has been the *modus operandi*.

Many individuals and groups have expressed concerns about the possible dangers of recombinant DNA technology. For example, there have been fears that genetically engineered microorganisms could escape from biologists' laboratories and cause as yet undescribed diseases. Others have expressed concern about releasing genetically altered bacteria and plants into the environment to increase agricultural productivity. There are worries about the possibility that these organisms might genetically recombine with endemic organisms--with untold consequences.

One of the overriding concerns expressed in recent discussions of genetic technology has been that the ability to apply recombinant DNA techniques to human beings will be realized and will be subject to misuse. This future-oriented discussion has attempted to predict how genetic engineering techniques will be used on humans once they are available. There have been calls for federal legislation and international agreements to establish limits on acceptable applications of these techniques, and there have been rejoinders critical of this restrictive attitude. Such arguments tend to be based on philosophical and ethical positions with respect to human nature

and moral standing, as well as fears about who will be manning the genetic controls.

Some of the issues raised have been addressed in the previous chapters of this thesis. There are fears of a new eugenics based on human gene therapy. There are also concerns about how the genetic model of disease may provide a rationale for certain kinds of discrimination when new markers are associated with human diseases and susceptibilities. There have been extremist positions on both sides of the debate, such as Rifkin and Fletcher. Some suggest that research directed at any form of human gene therapy be halted because it will put us on a "slippery slope" towards positive eugenics. In other words, once we are on a path which could lead to enhancement genetics, it will be very difficult to draw the line between the acceptable and the unacceptable. On the other hand, some see human reproduction as a sort of genetic "roulette" and suggest that we can do better than nature through manipulation of the genetic code.

It is my position that many of the concerns raised have been valid ones and have been eloquently expressed by some critics. But with genetic science still in its relative infancy, is there anything further to say? A further philosophical analysis of the positions is not within the scope of this paper. Nor do I feel qualified at this point to offer any better elaboration of how events in the field of genetics will unfold, even though I have my own apprehensions about *laissez-faire* policies. Nevertheless, I would suggest that it is now time to elaborate on the field of genetics as it exists today. To

have a better sense of what genetic technology means to us, we must view it in an appropriate context.

This kind of approach, which some authors have begun to take, does not say, "This is what genetics can do, and this is why we should be concerned." Instead, it evaluates advances in the genetic field as an emerging technology. It describes what has been accomplished and by whom. It examines the recent history of genetic inquiry in terms of who has been involved --i.e. who the players are--and how they have behaved. This approach takes account of regulatory policies as well as economic incentives. It also considers the political and social context. This is essential for the following reason: to advance from the realm of speculation to that of informed analysis of genetic advances, it is necessary to have some coherent model describing the path this evolving field has taken.

For those who correctly suggest that it is now time for an informed discussion of the issues, we must address the issues of our time. We can learn, for example, many lessons from the eugenics movement, but it is not a suitable model for understanding our current situation. We should instead look at the relationship of scientists to industry and the relationship of regulatory bodies to science. We should consider the incentives of the insurance industry, practices in the workplace, and the situation of medicine. And we must recognize the characteristics of our own society and its issues.

Medicine appears to be entering a new era where disease properties are more and more associated with molecular markers and the prospects for treatment are ever better. Genetic information will play a significant role in this revolution. As mentioned before,

on March 7, 1990, a proposal for the first approved treatment of a human disease by gene implant therapy cleared its initial regulatory hurdle.[1] Future applications seem to be just around the corner, and there has been tremendous enthusiasm in some quarters for their development.

The new genetics is situated in a novel setting. It is part of a profound transformation affecting the biological sciences--the development of a new industry. Genetics has moved out of the lab and into the marketplace with the founding of such biotech companies as Genentech, Biogen and Genetic Systems. The history of this transformation makes for fascinating reading and suggests that there has been an evolution in the practice of genetic science. The idealized model of the disinterested pursuit of knowledge by the geneticist has gone the way of much other science, as new rewards and incentives have come into play.

In the 1970s investors flocked to support the intellectual capital developing in the genetic sciences. Interestingly, there was very little application for techniques such as genetic recombination outside the lab, but the tools were being quickly assembled for such uses. Investors were sold not on products but on potential goods, such as bacterial hormone factories and genetically produced vaccines that should soon be available through the application of genetic technology. Robert Teitelman describes this phenomenon in his discussion of the biotech company Genetic Systems, which was founded in 1980.

> In essence the founders, in this case the Blechs [Isaac and David, two Wall Street investors], created an abstraction existing only on paper, and named it. The Blechs simply made up, or registered, a number of shares, which they sold, at varying prices, to investors. The Blechs created 30 million shares within a shell they called Genetic Systems.[2]

Investors were sold on the glowing predictions of the biotechnology field. They were led to expect medical breakthroughs just around the corner that would magically open up huge markets. The problem is that these dreams cannot always rapidly materialize, and it is a fact that has made the biotech market extremely volatile.

The first stage in the development of biotechnology was essentially a massive buildup of capital and staff (an exceedingly high number of these being involved in research). Competition at this point consisted of all-out races to secure the rights to certain products and new techniques for manufacturing them. Companies such as Genentech focussed on genetically engineered pharmaceuticals, such as human insulin, and established large research and development departments together with state-of-the-art production facilities. Other companies, such as Chiron, emphasized the usefulness of monoclonal antibodies in clinical testing and blood supply screening--i.e. for hepatitis antigens. In the early stages, biotech companies were faced with the problem of finding markets for their products and securing healthy incomes to offset large debts. Early on, these companies often raised money by entering into joint-venture agreements with large pharmaceutical companies.

More recently, the survivors have faced new management issues in a fiercely competitive environment where advantages over the competition may be transient. A January article in the New York Times profiled the San Francisco-based biotech company Genentech and its chief executive Robert Swanson.[3] Swanson is characterized as a "corporate cheerleader" who brilliantly built a full-fledged pharmaceutical company on the basis of optimistic expectations. He now faces the difficult task of managing the company at a time when other firms are introducing competing products.

> The company will not have any significant new products on the market for at least two or three years, which means that to spur sales Genentech must coax more growth out of its existing products--TPA [tissue plasminogen activator], which helps dissolve blood clots following heart attacks, and human growth, for treating children with pituitary dwarfism. That task will undoubtedly be difficult because of Smithkline Beecham's introduction of Eminase, a blood-clot dissolver.[4]

A further development in the Genentech story was the announcement on February 2, 1990 that controlling stock in the company had been purchased by the pharmaceutical giant Hoffmann La Roche.[5] This may illustrate a further stage in the biotechnology business as the industry goes through a period of consolidation by corporate merger.[6]

The biotech companies that capitalized best on the speculative frenzy in genetics were able to raise huge sums of money. Cetus, for example, assembled $120 million and Genentech raised $30 million in a short amount of time, although it was years before any real

profits were recorded.[7] These business ventures, of course, depended on talented scientists for labor and ideas. In fact, for scientists there were huge fortunes to be made in the new industry. This presented quite a different picture from the days when laboratory chiefs' biggest concern was the availability of grant money. Some of the leading scientists in the field of genetics--men such as Gilbert of Harvard and Boyer of UCSF--either left their university positions to head new companies or spent increasing amounts of time consulting on these business ventures. The incentives were obvious: wealth and attention. But this also raised questions, concerning such issues as the free exchange of information in the scientific community and the utilization of patent protection for new lab techniques and even living organisms.

Stephen S. Hall gives a fascinating account of the atmosphere of genetic research in the 1970s in his book, Invisible Frontiers: the Race to Synthesize a Human Gene.[8] Though the effort to make bacteria manufacture the human insulin protein did not have the element of public concern that helped to drive the search for the cause of AIDS in the early 1980s, the project was not conducted with any less urgency. For over two years, from May 1976 to August 1978, three research teams, comprising some of the world's best molecular biologists, struggled to outpace the other two. Each group faced substantial technological challenges and equally formidable regulatory hurdles--recombinant DNA had become a political hot potato. In some cases the obstacles led to feelings of outright persecution among these scientists.[9]

The insulin race occupied leading scientists in an effort to win notoriety and, in some cases, wealth. It was fiercely competitive, and the new economic incentives gave the discoveries a proprietary significance. Companies such as Genentech and Biogen were founded in the neighborhoods of major research universities--i.e. UCSF and Harvard--in the hope that they could exploit the new technology to produce synthetic insulin and later other pharmaceuticals.

The relationship between industry and academics in the field of biotechnology raises concerns about possible conflicts of interest as well as questions about who should rightfully benefit financially from the application of federally funded research. For example, research institutions and some scientists now have substantial ties to the biotech industry. It has been suggested that such relationships may become an impediment to disinterested research. However, it seems to be the rule, at least in the present American economy, that competitive technologies are invaluable national commodities. Economic competition from Japan and Western Europe has created an atmosphere very supportive of emerging technical industries.

Krimsky notes that recent precedents in patent law illustrate this trend very clearly.[10] University and biotech techniques in genetic engineering have depended on numerous discoveries in federally funded research, but patents have been allowed in order to foster the growth of industry, and this trend may continue and gain momentum for the foreseeable future. Patent controversies are more likely to take the form of internal disputes within the industry, as illustrated by a 1988 decision by the U.S. Court of Appeals for the Federal Circuit.[11] The case involved the rejection of a patent claim

by the University of California based on the use of genetically engineered bacteria to produce certain chemicals. Part of the litigation involved a U.C. challenge of a similar patent issued to Genentech the next year. The challenge was later dropped, but the 1988 ruling has been interpreted by some as leaving open the possibility for further challenges of the very broad Genentech patent for a method of making recombinant proteins in bacteria. (The New York Times reports that, "Genentech's patent is so broad that, in theory, almost every company trying to make drugs through recombinant DNA technology needs a license from Genentech").[12] It is difficult to predict how such controversies will eventually be resolved, but the biotech industry will have to adapt to whatever decisions are made.

The economic forces described above will most likely determine the general pattern of biotechnological development. Companies are motivated by profit and will continue to protect the competitive edge whenever possible. Even if this strategy is a slight impediment to open communication within the scientific community, it is not really a new development. This does not necessarily mean that all biotechnology companies are powerful and sinister figures who must be watched with eagle eyes. We must appreciate what other factors are important in the context of genetic information and technology.

Medical practice is perhaps foremost among these. Genetic technology holds great promise for the treatment of certain diseases, and gene therapy will soon be another element in the doctor's regimen. As previously described, there has been considerable

apprehension about the possibility of applying recombinant DNA techniques to humans. There are fears that individuals will one day select the characteristics of their offspring by choosing desired sex, height and I.Q.. However, I would maintain that the medical model could be interpreted so as to prevent such application, based on the principle of the definition of disease and the obligation to forego unnecessary risk.

The ethical issues raised by the development of specific gene therapy procedures will be primarily ones of beneficence and justice, the latter residing outside the practice of medicine *per se*. (Issues of justice are best addressed in a discussion of access to scarce health care resources and relate to the structural problems of modern health care systems). Beneficence requires that the treatment be in the patient's best interests and that it cause no harm. A philosophical argument could be made that the question of whether enhancement genetics would be in the best interests of the recipient will not be resolved--at least in the near future--to a degree that would legitimate the risks involved in manipulating the human genome. Thus, it would not be the physician's prerogative to offer genetic "improvements." Even in today's climate of strong support for reproductive rights (the courts are likely to continue to affirm Roe v. Wade, and medical interventions during pregnancy against the mother's wishes are being severely restricted), arguments for autonomy in reproductive decisions do not clearly imply that physicians should be able to offer gene therapy for anything other than conditions that would alleviate human suffering.

Certain regulatory measures have already been put into place.[13] The FDA and EPA have attempted to clarify their roles in overseeing the regulation of genetically engineered products. The NIH now conducts public reviews of gene therapy proposals, and the success of this model has obviated the need for premature legislative restrictions. Institutional review boards will have a role in this process in the future. They will discuss individual cases based on the ethical principles described above, following guidelines that can be worked out in advance.

Public discussion of genetic technology will be the ultimate and most important forum for the issues described in this paper. An uninformed public depends entirely upon experts for guidance, but the issues can be framed in terms familiar to most. Certainly, individuals should be concerned about the implications of genetic discoveries for medical insurance and for testing in the marketplace. Furthermore, there will need to be a mobilization of public concern on issues of justice and fairness that safeguard individuals from discrimination by the powerful and give access to health care to the greatest possible number. This can only be achieved through greater awareness and continued attention to the unfolding of events in this revolutionary time.

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