The new genetics and ethics

Sixth Shri B. V. Narayana Reddy Memorial Lecture, Indian Institute of World Culture, Bangalore

H. Sarat Chandra

Introduction

I am honoured to have been invited to deliver this annual lecture in memory of Shri B. V. Narayana Reddy. My earliest recollection of Shri Narayana Reddy is of meeting him, almost forty years ago, with my father who had taken me to what everyone used to call 'Mysore Bank'. To my adolescent eyes, the two gentlemen looked very similar. Both dressed well, even immaculately with a dignity that came naturally. Both wore the Mysore turban with distinction, were widely read and, of course, were widely respected. They represented the finest traditions of old Mysore.

The topic of today's lecture would have evoked Shri Narayana Reddy's keen interest. I am sure of this because in an autobiographical sketch that he wrote a few years before his death, Shri Reddy mentioned that a classic he read more often than any other was *Meditations* by Marcus Aurelius Antoninus and he went on to speculate on the foundations of ethical life. It is a special pleasure for me to pay this tribute to the memory of Shri B. V. Narayana Reddy and the tradition he represented.

Studying our genes

An important goal of current research into human genetics is to identify genetic changes that lead to human disease so that effective interventions can be developed. Towards this goal, the molecular biology of human genes is being studied and there is an ambitious programme - the human genome project - to determine the DNA coding for the approximately 50,000 to 100,000 genes estimated to be present in each of our cells. Genes are also being mapped by classical genetic methods, which involve collecting detailed information on families. This approach, called pedigree analysis, permits localisation of particular genes on individual chromosomes, estimation of distances between genes on the same chromosome and also the chances that two genes present on a chromosome will be passed on together to a child. Such analyses permit the geneticist to correlate the presence or absence of particular marker genes with the chance of that embryo or child inheriting a disease that is determined by a gene located close to that marker.

The potential benefits of this new genetics are far reaching but there are also risks in terms of unanticipated consequences. The development of routine tests for detecting predispositions to disease and other human characteristics has serious implications for the practice of medicine, for the legal system, for insurance, for employment practices and for numerous other areas of society. This new knowledge combined with rapidly developing technologies in handling human gametes and embryos, will take us into highly complex and uncharted terrains. In this talk, I will touch upon a few of these issues as indicators of the type and range of problems that are emerging.

An early ethical dilemma

As early as 1965, long before the advent of the new genetics, there were indications of the type of ethical questions that would emerge as a result of advances of genetic technology. In that year, a paper based on a survey of Scottish prisoners was published in which it was observed that seven out of the one hundred and ninety seven prisoners with a history of violent crime that were studied had an extra Y chromosome in their cells. This seemed significant because an XYY child is born, on an average, once in every thousand male births. Subsequent provocative reports in the news media and scientific journals that men with an extra Y chromosome were destined to lives of criminality created demands for screening of individuals in jails and for prospective studies among new-born and school-going boys with the intention of following their behavioural development.

Partly as a result of intervention by the Boston-based Committee on Responsible Genetics, this survey, proposed by a few U.S. scientists, was stopped. The Committee on Responsible Genetics raised the following issues: if a survey of school-going children was conducted as planned, who would be privy to the information that particular boys were XYY? Should their parents be told? Should their teachers and school principal know? Might not such information lead to stigmatisation of such boys as 'abnormal'? The parents and siblings may, unconsciously or otherwise, begin to treat the XYY child differently from others. Special meaning may be attached by parents and teachers to childhood pranks when they involve XYY children. Who will ensure confidentiality of such information? How might insurance companies and employers react to such information about an applicant? In the face of stigmatisation and discrimination, the XYY individual might challenge society's norms resulting in what has been called a self-fulfillment of the prophecy.

Since about one in a thousand newborn children carries an extra Y chromosome, a few prospective studies were' eventually done and the development of such XYY children was followed into adolescence. The findings suggest that

H. Sarat Chandra, Centre for Genetic Engineering, Indian Institute of Science, Bangalore 560012

XYY children fall within the normal range, but with an array of relatively non-specific behavioural differences in attention, cognition, motor skills and personality. The only criminal history found was for minor offenses not characterised by violence or aggression. In other words, most male children with an additional Y chromosome grow up reasonably well-adjusted and but for prior knowledge of their chromosome constitution, little significance would probably be attached to behaviour that may be outside the normal range. Nevertheless, in the U.S., because of the publicity surrounding the XYY chromosome constitution, about 50% of parents have elected to terminate pregnancies for which prenatal diagnostic tests indicated the presence of an extra Y chromosome.

Here is a situation in which seemingly normal male foetuses were aborted inspite of lack of a consensus among scientists about genetic predisposition of the XYY male to more violent, antisocial and criminal behaviour. These abortions were done on foetuses whose XYY chromosome constitution was unexpectedly diagnosed during prenatal diagnostic studies that were done on account of advanced maternal age or other reasons and not because there was prior interest on the part of the parents or the clinician to avoid the birth of an XYY child.

This case study illustrates how parents' perceptions (or misconceptions) of the relationship between genes and behaviour can determine decisions about continuation of pregnancy.

Prenatal determination of foetal sex in India

An ethical issue that has been widely discussed in our country is prenatal determination of sex by amniocentesis. This involves removal of a few cells from the amniotic fluid that surrounds the growing foetus, usually before the fourth month of pregnancy. From these cells, by appropriate analysis of chromosomes or DNA, the sex of the foetus can be readily told. This technique is useful to prevent the birth of male children carrying sex-linked genetic disorders in families with a history of such familial disease. Duchenne muscular dystrophy is an example. The procedure would involve not only the verification of the sex of the foetus but also the use of appropriate DNA probes to determine whether the foetus, if male, had inherited from the mother the defective gene that causes Duchenne muscular dystrophy.

When amniocentesis was first made available in this country at the All India Institute of Medical Sciences, New Delhi, the first hundred parents who requested this procedure had no obvious history of familial disease. All had two or three normal daughters and now wished to have a son. Apparently, no couple who had two or three sons and now wanted a daughter asked for such a diagnosis. Seeing this distortion, prenatal sex determination was discontinued in that institute.

As a result of criticism in the press and demonstrations, principally by womens' groups, the Government of Maharashtra enacted a law banning the determining of foetal sex when no genetic disease was involved. It is, however, common knowledge that such determination is done widely, especially in the states of Punjab, Maharashtra and the Union Territory of Delhi, often using highly unreliable methods.

A bill was being considered by Parliament and the Government of India to prevent the use of amniocentesis solely for the purpose of determining the sex of apparently normal foetuses. As often happens, this bill and the discussions relating to it have been made irrelevant by technological advances which have nothing to do with genetics. I refer to the non-invasive method of ultrasound imaging, which permits a trained observer to determine whether the growing foetus is male or female during the early stages of pregnancy.

Given the strong emotional and cultural underpinnings behind the parental desire to achieve a balance among the sex of their offspring, we may be eventually required to harmonise the parent's right to have a child of the desired sex and society's attempts to avoid discrimination based on sex. An ethically acceptable approach to this dilemma - and one that avoids termination of pregnancies of the 'wrong sex' - may become available if current attempts at separating male-determining (Y-bearing) and female-determining (X-bearing) human spermatozoa reach higher levels of reliability.

Yearning for children

Kathryn Allen Rabuzzi, writing in *The Encyclopaedia* ***of Religion,*** says that 'historically and cross-culturally, the family, in various forms, has (until the late twentieth century in post-industrialised nations) been so basic to human existence as to be a universal symbol of ultimacy.' It has also been said that 'the significance of the genetic connection between parent and child undoubtedly is part of what makes infertility a painful experience' and why adoption does not appear to satisfy 'the yearning to create a version of oneself unfold and develop.' (J. L. Hill 1992) It is therefore understandable that infertile couples often explore all possible avenues - from the religious to the biotechnological - to have a child of their own and raise a family.

Embryo and gamete technology have developed as rapidly as genetic technology and prenatal genetics is now a very active discipline. Methods of ***in vitro*** fertilisation and assisted reproduction have permitted many couples to overcome the pain of infertility. This has, however, led to novel family definitions and relationships: children with one biological father and two mothers, one genetic and the other gestational; children with two fathers, one known to the child and the other genetic, often unknown, who donated the sperm. There are also adoptive parents and adoptive children.

A fifty-nine-year-old British woman gave birth to so-called test-tube twins in an Italian clinic and a sixty-two-year-old wcman became pregnant after implantation of a fertilised egg. These cases of reproduction assisted by gamete and embryo biotechnology and the birth of a white boy to a black mother by similar methods have renewed the debate over the ethical and moral dimensions of such reproductive choices. The controversy over the proposal of British scientists to use eggs recovered from aborted foetuses to help infertile couples and thus overcome the shortage of human eggs became heated. This technique would, in effect, lead to the birth of children whose mothers were never born!

In many Western societies, the concept of the traditional family had come under severe pressure even before embryo technology and genetic testing became available. With the advent of the first, and increasing availability of the second, perplexing ethical and legal questions have arisen. Courts in California - and subsequently courts the world over - have distinguished between the genetic parent (donor of the egg) or 'genetic progenitor' and the gestational parent (the woman in whose womb the foetus developed). In a landmark custody case in which a woman who had no uterus had her eggs fertilised by her husband's sperm and hired another woman to carry the pregnancy to term, the judges rules in favour of the genetic linkage and said that the couple whose gametes were used for the *in vitro* fertilisation were the "genetic, biological and natural parents' and were, therefore, entitled to retain custody of the child. In the U.S. the term 'natural' or 'biological' mother is now widely understood to mean the 'genetic' mother. However, it appears, this view that the gestational mother is no more than a foster parent, is prevalent only in the U.S. and Israel, whereas in several other countries including the United Kingdom, Germany, Switzerland and South Africa, the courts have held the view that the woman who gives birth is the child's mother.

Unwanted groups

In the past, in many societies, the poor, the unpopular and those perceived as disabled (whether or not the perceived disability was genetic in origin) have been targets of discriminatory policies and prompted eugenic measures such as sterilisation aimed at 'purifying the race'. Lancelot Hogben, a geneticist active in the 1930s and '40s, angrily reacted to such policies and, referring to the prevalence of haemophilia in the royal houses of Europe, reminded that no one has 'publicly proposed sterilisation as the remedy for defective kingship.'

The targeting of gypsies and Jews for elimination from Nazi Germany is well known. Less well known. perhaps, is the similar targeting of individuals and their families for carrying a specific genetic defect, Huntington's disease. The symptoms of Huntington's disease are rapid and progressive neurological and mental deterioration in adult life, leading to death within a few years of the onset of the disease. It is an autosomal dominant gene defect, meaning that a child has a fifty percent chance of inheriting the disease from an affected parent. Since the first symptoms appear when an individual is in his or her forties or fifties, the patient would have had children who, in turn, would not know whether they are carriers of the defective gene until they themselves reach middle age. The disease poses severe burdens on the individual and the family and pre-symptomatic detection of the defective gene has therefore been greatly desired. This gene has now been mapped and cloned and DNA probes are available for prenatal diagnosis as well as for pre-symptomatic diagnosis of children and adults.

Huntington's disease is one of several psychiatric disorders that were part of an extraordinary policy in Europe during the Second World War. In July 1933, an act was passed in Germany to enable compulsory sterilisation of anyone suspected to carry Huntington's disease and eight other categories of disorder. Professionals, including scientists, lawyers, doctors and others with specialist training in what was called racial hygiene, were co-opted for this purpose. A system of hereditary courts were set up and the state established primacy over reproduction. As a result of the facade of legality and expert opinion, appeals to higher courts were rejected (Weindling 1389). It is estimated that in this well-organised campaign, 350,000 to 400,000 individuals were sterilised, among whom there may have been 3000-4000 patients with Huntington's disease and their families and that over 100 patients with this disease may have been killed in one psychiatric clinic alone (Harper). I need hardly remind the audience of the incidents in Poona where a number of young women in an institute for the mentally handicapped were involuntarily subjected to hysterectomy.

It is perhaps for the potential for such misuse of genetic data that at a meeting of the European community on the human genome programme it was concluded that the most important problems arising from genome mapping are 'moral rather than practical and legislative'.

Breach ***of confidentiality***

The type of pedigree analysis and DNA research that led to the identification of the Huntington gene reveals information about the health status of individuals belonging to the family whether or not they have agreed to be investigated. Information about such individuals would become part of the records of the investigator and the institution conducting the study. Disclosure of such information, deliberately or inadvertently, can lead to complex legal and ethical problems. Should a member of the family, who was not part of the formal study, be told, for instance that he is a carrier of the disease? Who owns this information?

There have been cases in which particular members of a large family wanted all information for themselves, their spouses and their children deleted from records. If, at some future date, it develops that the only means of linking an individual to [illegible] through DNA data collected as part

of a scientific study in which the individual had unwittingly participated, is such evidence admissible? Is it ethical to disclose such information?

Gene therapy

A brief reference to gene therapy may be in order. By mid-1992, there were over 15 diseases for which gene therapy attempts were being made. In one case - adenosine deaminase (ADA) deficiency - its correction through gene therapy has led to dramatic improvement in the health of affected children. There is support from ethicists for such applications of gene therapy to somatic cells.

Controversy continues to surround the extension of such methods to the germ line which might enable the individual with the gene defect to bear children inheriting the inserted normal copy of the gene in place of the defective gene. Dr. French Anderson, who carried out the first somatic cell gene therapy' for ADA deficiency stated: "Besides the medical arguments, there are a number of philosophical, ethical and theological concerns. For instance, do infants have the right to inherit an un-manipulated genome? Does the capacity of informed consent have any validity for patients who do not yet exist? At what point do we cross the line into 'playing God' ?"

The feeling of many observers is that the germline gene therapy should not be considered until much more is learned from somatic line therapy, until animal studies demonstrate the safety and reliability of any proposed procedure and until the public has been educated on the implications of the procedure.

Genes and behaviour

Many, perhaps most, human geneticists believe that there is a significant genetic component to behaviour and that not all behaviour is equally influenced by the physical, biological and psychological components of the environment. This does not mean that heredity can be equated with inevitability because genes do not determine 'destiny' in a predictable manner. V. Elvong Anderson noted: "Few, if any, behaviours are completely without genetic influence and few behaviours are completely without environmental influence."

The question has been posed whether, if the genes plus environment equation explains all behaviour, there is room left for individual freedom and moral responsibility. This question, if pursued properly, necessarily takes us into the realms of moral beliefs and religion. Prudence suggests that I leave this discussion incomplete.

Instead, I will end with a hopeful statement by a theologian, Ronald Cole Porter. He asked the unusual question whether there is a genetic basis for the moral agency within us. He concluded his enquiry thus: "Genes appear to some to lock us into a vast web of biological determinism that deprives us of what distinguishes us from the rest of nature and so removes what we once thought was essentially human. By contrast, it has been argued that far from posing an ominous threat to humanity, behaviour genetics and related fields of research offer to illumine more precisely the moral nature of the human situation."

I end this talk by quoting Roger Shinn, Reinhold Neibhur Professor Emeritus of Social Ethics at the Union Theological Seminary in New York: "To the perilous leaps in power associated with war and ecology, we must now add genetic knowledge. Past genetic theories, usually infected with prejudice, have brought the world much sorrow. An ethical imagination, this time around, might do better. The historical record gives us no assurance of that heightened insight, but it allows us to hope."

Acknowledgements

In preparing this text I have made extensive use of *The genetic frontier: ethics, law and policy* and *Ethical and legal issues in pedigree research* (both edited by M. S. Frankel and A. H. Teich and published by the American Association for the Advancement of Science, Washington, D.C.) and the papers by Peter J. Harper on Huntington's disease.

I thank Sreeganga S. Chandra for making these and other documents available to me at short notice and Mustafa Saifi for assistance in other ways.

(The reader is also referred to the report on the Bachhawat Symposium on genome research on pages 84-88. Editor)

Why we must insist on informed consent...

The very fact of exclusion from participation is a subtle form of suppression. It gives individuals no opportunity to reflect and decide upon what is good for them. Others who are supposed to be wiser and who, in any case, have more power decide the question for them... This form of coercion and suppression is more subtle and more effective than is overt intimidation and restraint. When it is habitual and embodied in social institutions, it seems the normal and natural state of affairs.

-John Dewey (1859- ***1952)***

The core idea of personal autonomy is... personal rule of the self while remaining free frpm both controlling influences by others and personal limitations, such as inadequate understanding, that prevent meaningful choice.

— Tom L. Beauchamp and James F. Childress