Abstract
Eugenics can be defined as the use of science applied to the qualitative and quantitative improvement of the human genome. The subject was initiated by Francis Galton with considerable support from Charles Darwin in the latter half of the 19th century. Its scope has increased enormously since the recent revolution in molecular genetics. Genetic files can be easily obtained for individuals either antenatally or at birth; somatic gene therapy has been introduced for some rare inborn errors of metabolism; and gene manipulation of human germ-line cells will no doubt occur in the near future to generate organs for transplantation.

The past history of eugenics has been appalling, with gross abuses in the USA between 1931 and 1945 when compulsory sterilization was practised; and in Germany between 1933 and 1945 when mass extermination and compulsory sterilization were performed. To prevent such abuses in the future statutory bodies, such as a genetics commission, should be established to provide guidance and rules of conduct for use of the new information and technologies as applied to the human genome.

Keywords: F Galton; eugenics; molecular genetics; genetic files; insurance abuses

Introduction
Francis Galton, (b 1822, d 1911) the founder of modern quantitative genetics, studied medicine (but never qualified) at Birmingham (1838) and King's College London (1839-40) and then read mathematics at Cambridge (1840-43) but did not obtain a degree. A major preoccupation of his later working life was in the field of eugenics. He invented and defined the term eugenics as “the science of improving inherited stock, not only by judicious matings, but by all the influences which give more suitable strains a better chance”. He wished to take account of all the inherited factors of intelligence, energy level and cognition “to give the more suitable races ... a better chance of prevailing speedily over the less suitable”. As with so many other ideas, eugenics can be directly traced back to Plato, who in The Republic and The Laws proposes many social measures to improve the quality of future generations.

Galton strongly believed, following on from Darwin's theories of evolution and natural selection, that “we should attempt to exert control over organic evolution in the same way as we exert control over the physical world and to direct it into channels of our own choosing”. This would provide practical applications for Darwin's theories and replace his idea of natural selection by a type of artificial selection. The publication of Darwin's Origin of Species in 1859 and the elaboration of his theory of evolution by natural selection provoked both bitter theological controversies with the creationist proponents of the animal world as well as spirited debates on its application to social progress and reform. In Victorian England many social reforms were being put in place including the Anti-slavery Bill, educational acts, institution of poor laws and workhouses, parliamentary reform, and plans for new hospital buildings. Struggle for existence, survival of the fittest, and natural selection were key Darwinian phrases which were used to support or attack the progress of such reforms. Francis Galton was a fervent disciple of Darwin and his evolutionary theories. It even led him to hold positions, such as the inheritance of acquired characteristics and Darwin's doctrine of pangenesis, in which he did not really believe. This has been attributed to his intense admiration for Darwin, which enforced an exaggerated respect for the authority of many of Darwin's opinions. He said in a speech to the Royal Society in 1886 that:

“I rarely approached his [Darwin's] general presence without an almost overwhelming sense of devotion and reverence and I valued his encouragement and approbation more perhaps than that of the whole world besides. This is the simple outline of my scientific history”. But it is of great significance that he valued Darwin's influence not so much for the insights it gave into the biological sciences but the "freedom Darwin gave us from theological bondage". By inference he was more concerned with the gains...
Table 1  Worth estimated either by class place or by scale value, modified after F Galton

1. Ministers of State, Heads of Departments, Bishops, Judges, Commanders and Admirals in Chief, Governors of Colonies and other appointments. Foreign Ambassadors, Ministers and other diplomats.
2. Choice out of many applicants as Secretary, Clerk, Civil Servant.
3. Choice of candidates for MP, Guardians and other municipal officers.
4. Choice of a Doctor, a Lawyer, an Agent, a Governess.
5. Selection of a Profession, a House, Investments, a Dress shape or colour, a book or any other purchase.
6. Classification by marks at school or college examinations, and competitions for Government services.

Explanation: “ the comparison of the merits of alternative objects is a familiar act and the classification of a large number of objects of like kind in order of merit is merely an application of this power. The selective process is gone through in renting a house, or buying an article of dress, wine, a horse, a pianoforte and, as a rule whenever a purchase has to be made. It is gone through with care in selecting an agent, a governor or other employees; Ministers of State, Heads of Departments, Bishops, Judges, Ambassadors etc. If we please to take the trouble we may arrange a class in order of any specified description of merit.”

for society and human progress that evolutionary theory might hold than the advances of scientific knowledge of animal evolution. And his eugenics hypothesis quickly became a creed, despite the fact that there was no new technology to underlie it, the ideas from Darwin’s writings on evolution appearing to be sufficient.

One area where Darwin and Galton disagreed in part was on the nature or mechanism of inheritance. Darwin firmly took the view of the blending nature of inheritance whereas Galton appeared to hold two independent views. He agreed on the nature of blending inheritance for characteristics such as skin colour; quoting the example of children from white or Negro marriages who show intermediate skin colours; but he also held the view of particulate inheritance for such characteristics as eye colour where children of light-eyed and dark-eyed parents tend more to take their own eye colours after one or other parent and rarely show intermediate or blended tints.

Conversely Darwin was not entirely in agreement with all of Galton’s theories, but came round to some of them after much discussion. Thus after reading Galton’s book on Hereditary Genius Darwin writes to Galton:

“You have made a convert of an opponent in one sense, for I have always maintained that excepting fools, men did not differ much in intellect, only in zeal and hard work...”.

Darwin now agrees in principle that intellectual ability can be inherited. However, Darwin was more sceptical of Galton’s ideas on eugenics. As one example, he writes to Galton in January 1873:

Table 2  A sample of Galton’s form to assess suitability for an Eugenics Certificate

<table>
<thead>
<tr>
<th>Register</th>
<th>Names or Initials in order of Birth</th>
<th>Sex M or F</th>
<th>Age of death</th>
<th>Cause of death</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Register</td>
<td>Initials</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Notable achievements of any brother or sister of the Mother of the Applicant that fall within the purview of this Certificate</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

We certify that to the best of our knowledge the above account is correct, also that with the exceptions mentioned below, no member of this Fraternity has ever suffered from Insanity, Epilepsy or other severe form of nervous disease.

Exceptions giving full particulars. If no exceptions write the word “None”

Signatures of the Applicant

“Though I see so much difficulty, the object seems a grand one and you have pointed out the sole feasible, yet I fear Utopian plan of procedure in improving the human race. I will make one or two criticisms ... the greatest difficulty I think would be in deciding who deserved to be on the [eugenics] register. How few are above mediocrity in health, strength, morals and intellect; and how difficult to judge on these latter heads. As far as I see within the same large superior families only a few of the children would deserve to be on the register....”

The value judgments as to who should be deemed more suitable, who less suitable to be on Galton’s eugenics register, and what constitutes an improvement in inherited stock were mainly left implicit in his definitions, but he did draw up a tentative scale of how to estimate “worth” (table 1), corresponding to the virtues and values of Victorian England. Despite this inadequacy, Galton’s eugenic methods were described in great detail. He proposed that family records should be kept (table 2) to estimate the average quality of offspring depending on their parents’ occupation and ancestry. Extensive genealogical work should be undertaken on families who should be...
classified as: (a) Gifted, (b) Capable (c) Average or (d) Degenerate. This information should be stored in a state eugenics record office. Early marriages for women of similar classes (a) and (b) should be encouraged and financial endowments made available to them for producing numerous offspring. These grants would be analogous to the use of grants for higher education for promising young adults.

Galton suggested that in competitive examinations for the civil services or other professional posts extra marks should be awarded for "family merit" if the youth came from a superior pedigree, as judged by the success of its members in their chosen profession. Rules of celibacy for Fellows at the older universities which were in place before 1870 should be abolished, to allow reputedly intelligent academics to have offspring. Eugenic certificates (see table 3) should become available for members of society and be kept in a eugenic records office. A eugenics research laboratory should be set up to gain more information on the inherited transmission of complex psychological traits such as intelligence, energy, and perceptual abilities. Finally, state institutions should take some sort of action against the feeble-minded, habitual criminals and the insane. They should be segregated and restricted from having offspring.

These suggestions were taken up by various countries and by 1931 sterilization laws had been enacted in 27 states in the USA. Most of these laws provided for the voluntary or compulsory sterilization of certain classes of people thought to be insane, feeble-minded or epileptic; some were extended to habitual criminals and moral perverts. In most states these extreme measures were not enforced - except in California where 9,931 persons had been sterilised by 1935, on the basis of eugenic principles.

It is also noteworthy that some of Galton's papers on eugenics were translated into German and published in the Archiv für Rassen und Gesellschafts-Biologie in 1906. By 1931, two years before Hitler came to power, the German Society of Rassenhygiene had added eugenics to its name. Many of the early evolutionary biologists such as Julian Huxley and Gaylord Simpson were appalled by the subsequent perverted and macabre abuse of eugenics in Germany during the period of 1935-44. Hitler did not justify his social policies on the basis of Darwinism or eugenics. No reference to such subjects can be found in his books, Mein Kampf or his Table-Talk. His social ideas appeared to derive more from the 19th-century German philosophers Schopenhauer, Hegel and particularly Nietzsche, who is quoted several times in Hitler's Table-Talk. The case is different with regard to the German biologists, anthropologists and geneticists of the period between 1933 and 1945. They actively invoked eugenic principles to justify the social policies of the Nazis. The consequences of these policies have been extensively documented elsewhere; suffice it to record that approximately 200,000 women were compulsorily sterilized and more than six million people belonging to "inferior races" suffered mass extermination.

Following the events of the second world war, overt eugenic ideas became unacceptable; but in the climate of Victorian England, Darwin eventually endorsed many of Galton's views, possibly seeing them as practical consequences of his own theory of evolution and natural selection. Although Galton's work is not quoted in Origin of Species it is mentioned on more than ten occasions in the Descent of Man. Darwin came round to Galton's opinion that "general intelligence, courage, bad and good temper are certainly transm-
ted in families, and on the other hand it is certain that insanity and deteriorated mental power tends to be inherited". He believed that “natural selection is affecting civilised nations, and the weak in body and mind are soon eliminated”. He goes on:

“We civilised men, on the other hand, do our utmost to check the process of elimination; we build asylums for the imbecile, the maimed, and the sick; we institute poor-laws; and our medical men exert their utmost skill to save the life of every one to the last moment. Thus the weak members of civilised societies propagate their kind. No one who has attended to the breeding of domestic animals will doubt this must be highly injurious to the race of man. We must therefore bear the undoubtedly bad effects of the weak surviving and propagating their kind".17 Darwin summarises his views in the concluding chapter of Descent of Man:

“The advancement of the welfare of mankind is a most intricate problem; all ought to refrain from marriage who cannot avoid abject poverty for their children; for poverty is not only a great evil, but tends to its own increase by leading to recklessness in marriage. On the other hand, as Mr Galton has remarked, if the prudent avoid marriage, whilst the reckless marry, the inferior members tend to supplant the better members of society. Man, like every other animal, has no doubt advanced to his present high condition through a struggle for existence consequent on his rapid multiplication; and if he is to advance still higher, it is to be feared that he must remain subject to severe struggle. Otherwise he would sink into idleness, and the more gifted men would not be more successful in the battle of life than the less gifted”.17

Commentary

Galton’s views on eugenics have naturally fallen into opprobrium and sullied his subsequent reputation as a scientist and the founding father of quantitative genetics. He and Darwin held, no doubt, the views of many eminent Victorians and it is a salutary lesson that they could not foresee or even give hints of the possible gross abuse of such ideas by politicians only 20 years after Galton’s death in 1911. However, covert eugenic practices that affect reproductive choices are widespread and are likely to predominate as our knowledge of the human genome increases. Selective abortion, mass sterilisation programmes for population control, artificial insemination of women with donor sperm are all contemporary issues. Moreover, very powerful eugenic techniques have recently been made available with the revolution in molecular genetics. Genetic markers and files can now be easily obtained for every individual, either antenatally or from birth with the availability of a multitude of microsatellite markers. These genetic markers are currently being used for polygenic disease as adjuncts to diagnosis (for example, HLA B27 and ankylosing spondylitis; apoipoprotein E2 homozygosity for Type 11 hyperlipidaemia); or for prognosis (for example, the mutation site of the low-density lipoprotein (LDL) receptor and the expected severity of the atherosclerotic complications) and soon will be available for risk prediction to provide the individual’s risk profile to develop deleterious medical and/or social characteristics such as those found in the early dementias, other neurodegenerative conditions or other polygenic disorders such as premature atherosclerosis. For example, there are more than 230 different mutations reported for the LDL-receptor that can cause variable degrees of hypercholesterolaemia due to differential effects on receptor function. This in turn can lead to a variable development of premature coronary atherosclerosis, depending on the exact position of the mutation with, in some cases, a >20-fold higher relative risk. Detection of such mutations therefore allows an unambiguous distinction of homo - from heterozygotes - improves prognosis for the development of the severity of the atherosclerosis; and unambiguously identifies affected first-degree relatives, including children who due to their age may be unable to give “informed consent” for the test. The major ethical problems arising from such a screening procedure are these: who should have access to the information - only the patient; or his first degree relatives if they are likely to be affected; or should first degree relatives be contacted “out of the blue” to be given the option of genetic testing? Should children not be tested until they are of an age when they can give informed consent? If the sudden onset of coronary heart disease at their place of work could endanger the lives of others should such tests be made compulsory? Why patients decline to have genetic tests, not for health reasons, but to reduce their premiums for life or health assurance (see below)?

Table 4 presents a list of other common polygenic disorders where genetic markers are/soon will be available to predict risks, and similar ethical issues arise. A recent ruling by the Association of British Insurers19 requires the reporting of any such genetic tests undertaken by people seeking all types of life cover, including endowments and personal pensions. Insurers define a genetic
test to mean “an examination of the DNA pattern to find out if it differs from normal. In the insurance context a genetic test is one which is regarded as predictive in an asymptomatic individual”.19 This is probably too restrictive a definition in that many phenotypic tests such as the Ishihara chart to diagnose colour blindness rests on a genetic basis. Life insurance in connection with mortgages for house purchase is a particularly sensitive area since it is a eugenic means of exerting control over the future gene pool by affecting reproductive decisions of families. For life insurance up to a total of £100,000 which is directly linked to a new mortgage for a private dwelling, the results of genetic tests must be declared but may not be taken into account by the insurance company even if they are to the detriment of the applicant. It is implied that for sums greater than £100,000 such genetic tests will be taken into account. The justification for this policy is that insurers are professional risk-takers and must make sure that the charged premiums equate to future risks. It is not possible for any insurance company to subsidise one type of policy holder (who may withhold information on genetic tests that may affect future life expectations) by charging the rest of the policy-holders more than the correct premiums. Otherwise people who have had genetic tests that reveal them to be at high risk may then over-insure themselves at the expense of other policy holders.

There is an evident conflict here between social justice which should make no discrimination on the basis of genetics and actuarial fairness which uses genetic discrimination to adjust premiums. One way to reconcile this discrepancy is to distinguish the situation of a “citizen” from that of a “consumer”. The former is entitled to social justice from government not to be discriminated against by virtue of his or her genetic constitution; whereas the latter can be considered as a purchaser of a commodity, ie life assurance, and is restricted in the choice by a variety of factors such as wealth, family relationships, employment etc, and now to include his genetic constitution. However, the alternative argument is equally cogent: that an individual should not be penalized for the chance inheritance of unfavourable genotypes over which he or she has no control, and that, if anything, health insurance, as an instrument of social policy, should be made cheaper not more expensive for the person. To resolve this clearly requires a political decision.

As with many other local interest groups (see below, the UK Alzheimer’s Disease Genetics Consortium the Association of British Insurers has set up a code of practice for insurance companies to safeguard their financial position. However, such codes might not take into account all the wider implications of genetic testing and eugenics. Insurance companies will quickly build up files of genetic data for large numbers of the population and this could be used for other purposes. For example, it may not be long before employers can (or indeed ought) to demand access to such information, either from the individual concerned or from other sources. If the employment of the individual puts at hazard the lives of others by his genetic defect then the employer should have the right to know this and disqualify him from the job. For example, many unexplained road accidents are due to narcolepsy which can be predicted by the genetic marker HLA DR2 and such carriers (with the other associated features) perhaps

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Frequency*</th>
<th>Genetic markers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes Type I</td>
<td>1:500</td>
<td>HLA-DR3/4; INS.vntr</td>
</tr>
<tr>
<td>Diabetes Type II</td>
<td>1–7%</td>
<td>INS-r; GLU-r; GK</td>
</tr>
<tr>
<td>Hypertriglyceridaemia</td>
<td>5–10%</td>
<td>A1/CII/AlIV cluster, LPL.</td>
</tr>
<tr>
<td>Hypercholesterolaemia</td>
<td>1–5%</td>
<td>LDL-r; apo B</td>
</tr>
<tr>
<td>Premature CAD</td>
<td>1:5 male adults</td>
<td>Apo E, and others</td>
</tr>
<tr>
<td>Hypertension</td>
<td>15–20%</td>
<td>ACE; angiotensinogen</td>
</tr>
<tr>
<td>Cancer</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breast</td>
<td>–25,000 new cases pa</td>
<td>BRCA1, BRCA2</td>
</tr>
<tr>
<td>Polyposis coli. (FAP)</td>
<td>–1:8,000</td>
<td>APC, K-ras, p53</td>
</tr>
<tr>
<td>Colorectal (HNPC)</td>
<td>–20,000 deaths pa</td>
<td>PMS1, PMS2, MLH1, MSH2.</td>
</tr>
<tr>
<td>Neurology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alzheimer’s</td>
<td>–10% of over 65s</td>
<td>Apo E4, APP,S1,S2</td>
</tr>
<tr>
<td>Others</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ankylosing spondylitis</td>
<td>0.5%</td>
<td>HLA-B27</td>
</tr>
<tr>
<td>Venous thromboembolism</td>
<td>0.1–1%</td>
<td>Factor 5 Leiden</td>
</tr>
</tbody>
</table>

INS=insulin gene; vntr=variable number of tandem repeats; INS-r=insulin receptor; GLU-r=glucose transporter; GK=glucokinase; LDL-r=low density lipoprotein receptor; ApoE=apolipoprotein E; ACE=angiotensin converting enzyme; BRCA=breast cancer gene; p53=p53 tumour suppressor gene; APP=amyloid precursor protein; LPL=lipoprotein lipase; A1,C111,AlIV=apolipoproteins A1,C111,AlIV. PMS1/2, MLH1=mismatch repair genes; S1,S2=presenilin genes; K-ras= oncogene. Frequency refers to either incidence, prevalence or frequency depending on population studied.
should be prohibited from occupations such as those of coach driver or airline pilot.

Genetic files are already forming imperceptibly, and even by accident, with the multitude of studies being conducted on genetic variants that relate to disease. A good example of a coincidental discovery involves the genetic variants of apolipoprotein E that relate to a rare dyslipidaemia (type 111 hyperlipoproteinaemia). There are three common genetic variants, E2, E3, and E4 and it has been subsequently found that the apo-E 4 allele is associated with the common late onset and sporadic forms of Alzheimer's disease. Risk for Alzheimer's disease increased from 20% to 90% and mean age of onset decreased from 84 to 68 years with increasing number of apo-E 4 alleles inherited in the 42 families that were studied. Homozygosity for apo-E 4 was virtuall sufficient to cause Alzheimer's disease by the age of 80 years. A consensus statement on apolipoprotein-E genotyping in Alzheimer's disease was published by the National Institute on Ageing/Alzheimer's Association Working Group, in which it is suggested that physicians may use apo-E genotyping as adjunctive information for establishing the diagnosis of Alzheimer's disease in patients with dementia. The UK Alzheimer's Disease Genetics Consortium has drawn up guidelines for what it considers to be best possible practice which conflict with the rules drawn up by the Association of British Insurers. The Alzheimer's consortium proposes: (1) informed consent for genetic testing as part of a clinical trial protocol from either the patient and/or carer; (2) genetic data should not be transferred back to the patient, carer or treating physician except in the most exceptional circumstances, and then only with appropriate counselling; and (3) genotyping should only be undertaken at relevant loci to the primary condition. However, the problem of leaving such ethical decisions involving genetic research to locally interested consortia is that wider issues may be overlooked.

For example, apo-E genotyping has been in use as an important diagnostic aid for lipid disorders in lipid clinics worldwide for the last 20 years. However, this information, available in case notes and medical reports, may eventually be used to predict the occurrence or diagnosis of Alzheimer's dementia in some of the patients who were tested. There is no clear guidance or formulation on how these records should be used, and on who should have access to the information; the individuals were initially tested with a different condition in view. When genetic screening is performed by the biotechnology industry more problems can arise. For example, in one study where testing for familial adenomatous polyposis was performed by a commercial laboratory screening for mutations of the APC gene located on chromosome 5q21, only 19% of the patients received proper genetic counselling before the test; and in 32% of the cases the physician misinterpreted the test results. Of particular concern was that some patients at risk for familial adenomatous polyposis would have been given a false negative result.

The techniques for somatic cell gene therapy have been used to treat several of the rare inherited diseases such as homozgyous familial hypercholesterolaemia and adenosine deaminase deficiency. Some of these techniques can also be used for germ-line manipulation and cloning, with the use of adult nuclei to provide, for example, a potential supply of organs for transplantation surgery. When used to eliminate or reduce the burden of inherited disease in the population such as cystic fibrosis, Duchenne muscular dystrophy or homozgyous familial hypercholesterolaemia, no serious ethical issues appear to arise apart from the difficult choices for the patient or closest relatives. However, the real problem arises in the "grey area" between a disease phenotype and the natural aging process. For example, conditions with trinucleotide repeats have variable phenotypes that range from severe (intellectual impairment, muscular atrophy, severe respiratory muscle weakness) to mild (cataracts, or frontal baldness) and the intellectual and physical defects can resemble those seen in individuals of a normally aging population. Eugenic measures being taken for subjects, for example, with a predisposition to Huntington's disease, where the symptoms can be of early onset, might be proposed for use in the "normal" population. The use of genetic techniques, such as up-regulating a gene locus that is repressed or modulating a gene locus that is over-transcribing, in order to attempt to influence such factors as memory, cognition, volition or perception in subjects with no proven clinical diagnosis are highly controversial and must remain extremely suspect. Who, for example, draws up the ethical and aesthetic standards of value to decide which psychological characteristics to improve by gene therapy? Would attempts by somatic gene therapy to improve the antisocial behaviour and liability to deafness, for example, in a Beethoven, also improve his ability to compose music? How are such different characteristics to be evaluated?

To reiterate Darwin: "The advancement of the welfare of mankind is a most intricate problem".
standing of all the facets of how societies and populations evolve.

However, while molecular genetics is now firmly established and is likely to bring certain benefits to human welfare, like all great innovations it is open to abuse. Provided we foresee the possibility of abuse we may be able to avoid it or at least reduce it. If we are to learn anything from the past history of this important subject, from the monstrous scale of past abuses, it is that the new information derived from molecular genetics should be stringently safeguarded by the establishment of statutory bodies, such as a genetics commission, to provide a comprehensive and consistent set of rules along the possible lines presented in table 5. Also, appropriate licensing powers in the widest setting should be in place for the use of the information and the new techniques and methods that have, and will, become available.

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