Papers on Genetics by M L Kothari et al

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An Epitaph for the Gene An Obituary for Genetics An Adieu for Heredity

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Abstract

Modern medicine has been researching on cancer cell, cancer, hypertension, heart attack and so on without once defining any of these clearly. It swears by these terms much like mankind swears by sunset and sunrise, which are just not there. It is possible that the pet hobbyhorses of modern times, namely, gene, genetics, and heredity may belong to the above mythical group-entities that are logically absent, but whose illogic is strong enough to sustain research and publication world over. Gene, genetics and heredity have outlived their utility and must be replaced in near future by new concepts and terms.

"Define your terms, Sir," used to be integral to any Aristotelian or Socratic dialogue. In absence of the

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intellectual precision that accompanies clarity of concepts and definitions, you could build an edifice Everest-high, except that the fundamental keystone may be missing. Modern medicine has been belabouring its research on immunity, infection, diabetes mellitus, hypertension, heart attack and so on without arriving at any definition for even once. The net result at the turn of millenium is that modern medicine knows that it knows nothing[1,2]. A perusal of texts[3,4,5,6] ordinary or advanced on genetics have everything except a semblance of exactness on the key terms gene, genetics, and heredity. If you are gifted with an interest in etymology, you realize with a sense of shock that gene enjoys no etymological locus standi[7,8] and what you call gene is a fractured portion of the term pangene. The term heredity is from heir[6] and is rooted in ownership of estate and the right over property and possessions and hence has nothing to do with transmission of characters.

Szent-Gyorgyi[9], the Nobel-laureate, while chairing a session on cancer was asked if he could define a cancer cell. And his considered reply was that he couldn't define it for he didn't know what is a normal cell in the first place. That is how a cancer cell is defined[10] circumlocutionally: a cancer cell is what it is, for it does what it does, and it does what it does, for it is what it is. As of today, this is how you will have to define a gene.

The cardinal fault of geneticist and cytologist has been nucleism[11]. They kept on investigating the easily accessible nucleus for they were forced to neglect the nebulous cytoplasm. Nuclear-transplantation[12] and Dolly-making have shown that the embryogenic blue print resides not in the zygotic nucleus but in its cytoplasm. And cytoplasm has not as yet obliged a Watson and Crick team with a double helix. On the other hand, the nuclear double helix has genes of binary code (AT, GC) that fills up the DNA tape without any demarcation of one gene from another. Gene, genetics, and heredity raise far more questions than answers and will have to be given up as concepts. Hans Eysenck[13], the noted British psychologist, waxes uncharitably eloquent over scientists: "Scientists, especially

when they leave the particular field in which they have specialized, are just as ordinary, pig-headed and unreasonable as anybody else, and their unusually high intelligence only makes their prejudices all the more dangerous." Geneticists, currently the blue-eyed babies of medical research, are no exception to Eysenckean estimate. The monstrously oversized edifice of oncology rested on the keystones of cancer-as-alien-non-self and cancer-cell-as-abnormal-cell. Alas, both the keystones have been missing[10], for they were, in the very first place, never there. The edifice, like a Mumbai building, has collapsed leaving behind a clear vindication of August Bier's generalisation[14] in the earlier part of this century: "All that we know about cancer can be written on a calling (visiting) card." Little wonder that James Watson[15] of The Double Helix Nobel-fame, summed up cancer research as intellectually bankrupt, therapeutically useless, and fiscally exsanguinating. If one could gather the invectives from an Eysenck, a Bier, a Watson and the like and hurl them at the promoters of gene, genetics and heredity, one could damn well be right.

Peter Medawar[16], an immunoNobelist, coined the term geneticism "to refer to a scheme of thought which extravagantly overestimates the explanatory power of genetical ideas. The pretended explanation on genetic lines of every aspect of human character and every nuance of personality, and the interpretation of the rise and fall of nations along genetic lines, may all be said to belong to geneticism, which has the ill effect of *bringing GENETICS into undeserved discredit*." The added italics in the foregoing are a confession by a *Dictionary of Modern Thought* that Genetics as a science stands discredited.

That the discredit is well-deserved can be gleaned from the plethora of apologetic terms and phrases that geneticists thrive upon to explain away whatever can't be genetically explained. Here is a sampling: Polygenic/multifactorial inheritance; incomplete penetrance; variable expressivity; forme fruste; phenocopy; genetic heterogeneity; pleiotropy; sex-limited/-influenced trait; delayed age of presentation; non-allelic interaction; spontaneous point mutation; chromosomal polymorphism including multiple fragile sites,

microdeletion, cryptic translocation; mosaicism; jumping/ overlapping/split genes; sporadic case; illegitimacy; and incorrect diagnosis. Having told some basic lies, geneticists had had to invent many more to acquit themselves.

An Epitaph for the Gene

The gene's epitaph is preordained in its definitionlessness. It comes as a surprise that modern medicine, as of today, has no exact definition for heart attack, stroke, diabetes mellitus, hypertension, cancer cell, cancer, normality, abnormality or infection. So anything, and everything, goes.

Herbert Spencer called genes as "physiological units," Charles Darwin called them "pan-genetic gemmules," August Weismann talked of "biophors" and "ids." None of the foregoing definitions[17] of the 19th century has been improved upon by the close-of-20th-century talking of "the basic unit of heredity, made of DNA." The reasoning is circular: wherever there is genesis, there ought to be a gene behind it, and vice versa. The reader of this article is requested to peruse all the latest western texts on genetics to look out for a satisfactory definition of gene, to realize the utter futility of such a search.

In 1963, David Smithers[18] of UK generalized that a cancer cell is NO structural entity, but only an organ of behaviour. That means that despite all the microscopic sophistication, a cancer cell as a structural entity is unlocatable for it was never there. From the time of Galen and Vesalius, students have been bored to death by the red and blue lines indicating the origins and insertions of muscles on bone. Now comes a realization[19] that those lines are pure figments of anatomic imagination for bone is attached to nothing, nothing is attached to bone.

Epitaph for Gene

Hic jacet (here lies) the GENE
Oversung, overwrung, overabused
We wish it were really there
Alas it never was nor will be.

An Obituary for Genetics

The two universal principles that militate against the idea of genes-governing-all-phenomena are individuation or uniquation and its balancing-opposite the TITE principle. The aforestated laws drive home an important point: Genes take orders to the extent that their very lay-out is determined by abstract noumenal powers that are superior to the genes themselves. The universality of uniquation is best illustrated by the SANA (Snowflakes Are Never Alike) principle. Each snowflake is made of at least 100 million million million water molecules, the arrangement of which, thanks to the TITE principle, is always unique.

The uniqueness of a person's Left Thumb Impression (LTI) is a result of that the thumb, while in its making, Totally Included all the other LTIs so that it could Totally Exclude them. The nascent science of Genetic/DNA Fingerprinting[20] has revealed the individualistic (individuation) and unique (uniquation) of the karyotype of a person. The noumenon provided by all the other karyotypes serves as the determinant of the uniqueness of a person's karyotype. If the very karyotype is determined by powers lying outside it, then the idea that the genes comprising the karyotype take rather than give orders becomes comprehensible.

Yet one more law that disproves the worth of geneticism is the principle of herdity. The very steady maintenance[21] of the incidence of various diseases - ALL 1 out of 33,000, cleft palate 1 out of 1000 births, overall cancer 1 out of 5, schizophrenia 1-2 out of 100, epilepsy 1-2 out of 100 - year after year, country after country and generations after generations goes to show that the manifestation of a disease phenomenon at the level of an individual is at the behest of the rest of the herd. It is herdity in action. Geneticists have missed to see the role of herdity which better explains the smaller-occurrence-and-the-much-greater-non-occurrence of any disease, malformation or malfunction. The escapist terms polygenic or multifactorial inheritance is neither here on the side of genetics nor there on the side of environment.

Beadle and Tatum were awarded the 1958 Nobel prize for their one gene-one enzyme hypothesis. The same was hurriedly replaced by the one gene-many enzymes-and-vice versa. This revision reduces the action of a gene to the level of speculation, thus leaving the fate of genetics as sub judice.

Obituary for Genetics

Died : Ms. Genetics who expired in the light of the discovery of the non-existence of gene and the acknowledgment of the laws of individuation, TITE and herdity.

An adieu for heredity

The reader should recall the song Dost dost naa rahaa from Raj Kapoor's Sangam, and then hum the following tune:

Sperm father naa rahaa
Ovum mother naa rahaa
Varsa hamein teraa
Etbaar naa rahaa
Etbaar naa rahaa …

The one cell in a male that is totally unlike him is the sperm, and ditto for ovum in a female. (That is how following vasectomy, the back-absorption of sperms excites immune response). This is because, during meiosis, the stage of crossing-over permits to the gametocyte a thorough riffle-shuffle of the paternal and maternal genetic cards, both sides merrily crossing the gender-divide. Nature in its infinite sense of fairness is not keen on foisting on the child either the virtues or the vices of the parents. Hence the stand-offishness of each gamete from its owner, and hence the few lines that you need to hum at the beginning of this Adieu.

If crossing-over effectively abolishes the dogma of heredity, the concept of reverse causality further accentuates the demolition. The TITE principle operates through the fact that a child's genotype is determined prior to the very birth of the parents. A marriage (made in Heaven or Hell as the case may turn out to be) is contrived by the child's genotype

whereby the parents meet and mate. Samuel Butler wrote 300 years ago: A hen is an egg's way of making another egg, A marriage is a child's way of making itself by forcing the parents into a sexual union.

> It is considered that the old Chinese Zen Masters saw everything in Nature as interrelated with everything else, and so did not regard some as good and others as bad, or some as superior or higher and others as inferior or lower. This is quite in agreement with modern science also, by which we can say that everything is what it is and where it is because of everything else - and itself.
>
> ***Earnest Wood***
> ***Zen Dictionary***

An immediate corollary of the aforequote is INNTOE which reads as In Nature No Terror of Error. A so-called congenital deformity, a so-called cancer or cancer-death, a moron on one side and mighty Einstein on the other are all integral parts of Herdity, being interconnected components of a normal distribution. The abnormality whatever lies in the eyes of the medical beholder.

Like it or not, every single event / cell / organ/ individual is a phenomenal manifestation at noumenal behest. It is the Cosmos that controls whatever you see as a phenomenon or as chaos. The flag seems to flutter, but not by itself. The gene whatever seems to operate but the orders come not from the phenomenal gene but from the invisible, inviolable noumenal Cosmos. The so called genes do not give orders but they receive them and then transmit them. The jugglery of modern genetics and genetic engineering has rightly bred "romantic pessimism". If you see the very scholarly tome Gene IV and then the latest Gene VI, you can perceive the apologetic refrain in their unchanging epilogue.

Gene, genetics and Heredity will have to be replaced for they represent an isolatedness that is out of sync with

the seamless, timeless, spaceless and basically causefree universe. One of us way back in 1977 has had a long session with the biophilosopher Lewis Thomas, then the director of the famed Sloan-Katering Institute (SKI). His confession was that there was no headway made on cancer but "since we are politically so committed to the cure of cancer, we have no courage to tell the truth to the public." Thereafter there was lunch with Joseph Hixson[22] who wrote the biography of the greatest scientific scandal of the century perpetrated at the very SKI. When asked what he did before, he said he was PRO at the SKI for 19 cushy months but resigned for he got tired of telling lies to the public.

The much-hyped gene, genetics and heredity are plagued by the same dilemma: So much has been promised so how can the public be let down. If we give up, who will cure common cold and who will snub cancer! The show must go on.

It is time philosophy steps in. To those who pooh-pooh philosophy, let them know that dictionary[7] defines philosophy as Scientia scientiarum - the science of all sciences. A finer, cosmic analysis of human well being or suffering without the idea of exploiting any piece of knowledge in favour of arrogant mankind and medicalkind, may reveal truths that could be delights of the mind and soul.

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Non-identicality of Monozygous Twins

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Twinning (from twine = a double thread) is a universal human feature. The constancy of its incidence in an ethnic group makes it, like cancer or cleft-lip, a herd feature, a part of herdity. Its frequency varies from 1 in 30 births in Nigeria to 1 in 150 births in Japan. Roughly 1 out of 3 twin births are monozygous (MZ), arising from a single fertilized ovum and thus having "identical genotypes,"[23] as opposed to dizygous (DZ) twins that are "genetically quite distinct"[14] like "siblings of separate birth."[14]

That MZ twins are genetically identical is an idee fixe, a cliche enshrined in biology,[1,14] genetics,[12] and immunology.[11] The identicality, however, becomes questionable when MZ twins exhibit "frequent discordance" *vis-a-vis* various physiologic and pathologic features[15,16,19,21] e.g., "concordant cancer in identical twins is exceptional."[25]

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To explain away many a discordance between the supposedly genetically identical twins, recourse has been taken to environmental differences, cytoplasmic differences, equations of heritability versus variability, non-penetrance of the heritable mutant gene, gonadal mutation, and premutation.[19] The cul-de-sac nature of the above explanations compels flagrant violations of Occam's razor. To wit, the discordance exhibited by 58 per cent of MZ twins *vis-a-vis* congenital club-foot necessitates presupposing "special prenatal circumstances" involving "variations in the outer or the inner environment of the embryo" complicated by "a special genotype or genotypes necessary for the formation of club-foot".[21]

The over 100 centres for twin studies, in Europe, Japan, and the USA[4] nurse the common illusion that they are investigating "genetically identical human" pairs, with the further assumption that whatever the differences that are noted among such pairs are due to "environmental" factors. That the registry,[4] in a single country, of the health data of 50,000 pairs of MZ twins between 1870 and 1930, and, in another country of the medical histories of 23,000 living MZ pairs born between 1886 and 1973, and many such registries elsewhere have merely piled statistics upon statistics and theories upon theories, without throwing light on any single problem, bears testimony to the fundamental point that has been missed: MZ twins are highly similar, but not identical.

The recognition of the monozygotic or dizygotic origin of a given pair of twins - the most debated problem in twin studies[16]- is made by the means of similarity diagnosis using detailed comparison of the phenotypes: Great similarity is taken as evidence of monozygosity.[16,21] But to dub great similarity as identicality, and genetic one at that, is to miss the many ways in which MZ twins differ-"the within-pair differences of monozygotic twins are frequently found to have a wide and continuous range from near identity to great dissimilarity."[16] The nine-banded armadillo always delivers MZ quadruplets, without denying to each member of the quartet the right to assert its individuality, its urge to differ

from its fellow fetuses in particular and from other armadilloes in general. Siamese twins, bound in flesh and blood and indisputably MZ, are frequently less similar than twin pairs known to be dizygotic.[16]

Dubos[7] has glorified each individual as unprecedented, unparalleled and unrepeatable, an exaltation not denied to the members of MZ twin pairs. They form no exception to the generalization[26] that the only invariable law of nature is variation. GOD, the Generator Of Diversity,[11] does not fail even when it comes to two beings spawned off the same zygote. An analysis of the trump concordance - viz., the acid test[6,21] of intrapair tissue transplantability - allows us to settle the matter in favour of the concept advanced above.

The universal assumption that intrapair histocompatibility of MZ twins is a function of the identicality of genotypes calls for a sea change in view of the fact that such a phenomenon of easy tissue-exchangeability also occurs in freemartin binovular, genetically different twin calves "which share a common placenta in utero and are consequently bathed in each other's blood before birth; they sometimes prove to be chimeras."[11] Starting with the observations made by Owen,[17] the foregoing was confirmed by Medawar and colleagues in cattle twins[3] and in man,[8] and such tolerance was induced in mice[2] by injecting into the embryo, in utero, living cell suspensions from an animal of an antigenically different strain. Swappability of tissues between members of a pair is a function not of the identicality of genotypes but of the transplantation tolerance through clonal elimination[20] induced by natural or artificial exposure to each other's cells at an appropriate time. The celebrated histocompatibility between MZ twins, whereby one twin can readily receive graft from the other and vice versa, is entirely dependent on their mutual chimerism consequent upon the placental connection, a chance occurrence not denied to binovular twins with patently distinct genotypes, yet a chance occurrence definitely denied to monozygous twins should they be dichorial in nature.

Of 3 sets of MZ twins in human beings 2 tend to be monochorial (monoplacental), and one dichorial (biplacental),[5,9] the former mediating chimerism, the latter denying it. Dichorial MZ twins treat each other as mutually histoincompatible, and graft rejection is as natural and rapid as between unrelated individuals. The time at which the monozygote splits to spawn twins determines the nature of their placentation. If the split occurs from the time of conception to the third day when trophoblast has not yet differentiated, the placenta tends to be dichorial and diamniotic. Between 3rd and 8th day (blastocyst stage), the placenta becomes monochorial but diamniotic. From 8th day to 13th day, the placenta remains monochorial and amnion also tends to be one. After 13th day, the monochorial and monoamniotic placenta may be associated with Siamese twins.

MZ twins, by their rather frequent monoplacentality, achieve the transplantation tolerance with ease to become chimeras that exhibit histocompatibility. The chimerism of MZ twins must be so subtle as to have escaped detection so far. Such chimerism, called point chimerism (of point mutation), is only waiting to be discovered by modern cytogenetics. It is a poorly emphasized fact[16,21] that DZ twins may share a placenta and MZ may fail to share one, a set of circumstances that may make DZ twins more histocompatible than MZ twins. Grafts between MZ twins do not always succeed,[11,16] and rather startlingly enough,[22] an acute graft-versus-host disease can occur following marrow transplant between "genetically identical" twins even when the recipient had been prepared with irradiation and cytotoxic drugs.[10,18] (Why should the recipient be prepared if the donor is genetically identical?) To hold[6,21] intrapair tissue transplantability as a *sine qua non* as also the cardinal test of monozygosity is to miss the role played by the placental connection.

Medawar[13] has described highly inbred animals as "pure line" organisms in whom the "genetic variation has been extinguished" to the point of their resembling each other "as closely as if they were identical twins." The implications here are clear: inbred animals with a single genetic strain are many

animals with a single genetic soul, and so are the members of a pair of MZ twins. Both assumptions are wrong.

Intrastrain grafts in highly inbred strains of animals are not exempt from rejection;[24] the same may happen in MZ twins.[11,16] The most we can say of inbred animals/MZ twins is that grossly they tend to be so similar that the finer points of variation - both phenotypic and genotypic - are not easily detectable and therefore tend to be glossed over.

The logic advanced herein to explain MZ twins' mutual histocompatibility or so-called identicality also accounts for the failure of transplantation between MZ twins as also its success among DZ twins. Such an approach divests MZ twins of their specialized identical status, allows them to be widely discordant, and reaffirms the infallibility of the force of variation or individuation. In due humility, all that we - medical men, biologists, geneticists - need to do is to accept individuality as Nature's unfailing gift, no matter what types of twins, triplets or quadruplets, or how they are derived.

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The Cloning Bandwagon

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Thanks to Keith Campbell[1], Dolly the wonder sheep has arrived in Scotland, at the modest price of $750,000. Mankind has been thus dragged yet nearer to the Huxleyean Brave New World. To an already contentious, consumerist and cruel world, the spectre of manufacturing Hitlers and Huns on a clonal scale is frightening. No wonder discerning journals - to wit, the July-Sept 1997 *Issues in Medical Ethics* - are full of debates on the ethicality of new genetic discoveries and applications thereof. The ethical bandwagon would make more sense if the geneticists and ethicists were to bear in mind some fundamental principles that govern the field of genetics. This done, our expectations - social, medical, financial - from genetic adventurism would be trimmed to size, and our fears from genetic misadventurism would be pruned as well.

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Set below are some incontrovertible data that could guide our genetic *weltanschauung* in the coming decades.

- The decisive cell in the making of Dolly was not the mammary cell that loaned the nucleus, but the cytoplasm of the ovum that played host to the nucleus. This has remained the rule[2] from the time Gurdon[3] transplanted a somatic nucleus from an intestinal cell to the enucleate cytoplasm of toad zygote. Subsequent experiments involving nuclear swapping even among somatic cells has shown that the cytoplasm calls the tune[4], the nucleus merely follows it.
- Dolly's avowed refusal to be called a member of a clone or to be cloned lies in the individuality or uniqueness of the ovum that spawned Dolly and the individualistic ova that Dolly will carry in her ovaries. Nature, in its inscrutable wisdom, insists on the Darwinian 'descent with variation'. Towards this end it sees to the fact that neither the parental virtues nor the vices are foisted on the progeny. To achieve this, it has the gametogenic process of meiosis[5], in which reduction and crossing over provide gametes (ova/sperms) not one of which is identical to the other in the very same testis or ovary. Hence the Dolly that is extant and the Dollys that will be begotten will never, can never, belong to a clone, for the fundamental ovum from which each of them comes is invariably variable, individualistic, unprecedented, unparalleled, unrepeatable; in short, unique. All that Dolly-making has shown is that the ovular/zygotic cytoplasm can make do with a somatic nucleus. Good as news; wrong as clonal news.
- The genetic *idee fixe*[6] that homozygous human twins share a common genotype is belied by the fact that such twins are more discordant than cordant. Even Siamese twins, united in flesh and blood, have dissimilar finger prints. The exchangeability of tissues amongst twins is a function of their sharing a placenta *in utero:* even if the twins are dizygous but monoplacental, they can exchange tissues; but if they are monozygous and yet if they do not share a

placenta (one-third of pairs do not) than they reject each other's tissues as avidly as unrelated individuals.[6]

- Montaigne intuitively aphorised that "*There never were in the world two opinions alike, no more than two hairs or two grains; the most universal quality is diversity*." This generalisation of the 16th century has been confirmed with devastating effect in the 20th century. A pendulum moving in two planes never exhibits the same orbit: "*Each swing of this chaotic oscillator is unique. The system never repeats itself, so that each cycle covers a new region of phase space*."[7]

  Chaos[8] is a buzzword of today. It is modern science's euphemism for its incurable ignorance *vis-a-vis* any cell, animal, person or event. Science knows that each of the foregoing will be assertively unique, but science can never predict what exactly it would be. Science is wiser about the uniqueness only after the event is a *fait accompli.* How and why?

- It is time to synthesise modern science and Vedic wisdom.

  No two LTIs - Left Thumb Impressions - have been the same. Each LTI, when in the making *in utero,* is asked to be, in the telling words of Rene Dubos, unprecedented, unparalleled, and unrepeatable. This comes to pass because of the TITE principle which reads: Total Inclusion allows Total Exclusion. Any LTI first knows - includes as it were - all the LTIs that were, are, or will be. Having so included them, it also effectively excludes them. So for the uniqueness of atom, gene, DNA pattern, cell, cancer cell, human gyri and sulci of the cerebral hemispheres, venous pattern on dorsum of foot and so on. Every manifest phenomenon, as it were, gets guided by the cosmic noumenon.

  Vedanta has it that whatsoever is is, Isvar or God who is described as *ekam evam, advityam, nityam* - one and only one, without a second, and eternal. Each swing executed by the pendulum described above manifests all the qualities listed for Isvar. The *nityam*or eternal part

is simple to understand. The LTI of Christ is eternal in the sense that it guided all human beings, that preceded Him, were contemporary to Him, and have followed Him. Science and Vedas thus allow us a sweeping generalisation: No matter how closely clonish are things/cells/beings produced by human ingenuity, the Cosmos will see to it that each one of them will be different from the other. The *Brave New World* will remain restricted to the book that Huxley wrote.

- The TITE principle could be reinforced a little differently. Wolfgang Pauli won a Nobel prize for the Pauli Exclusion Principle (PEP) that declared that no two fermions (read, any elementary particle) can be in identical quantum states. "*Thus no two electrons in an atom can be identical in all their quantum numbers*."[9] An electron is a particle/mass/event that being Isvar assumes uniqueness. So does any other phenomenon. Hence the revised reading of PEP - Phenomenal Exclusion Principle. No two phenomena can ever be identical. If uniqueness prevails at an elementary level, what to talk of Dollys and humans. Let us breathe a sigh of relief that Genghis Khans will not be duplicated, much less cloned. Let us be reassured that even if there were, like Ravana, a Siamese twin with ten heads, all the ten heads will have dissimilar gyral-sulcal patterns as also distinctive lip-prints.

  Proponents of positive eugenics may argue that entire genetic advances may allow us, one day, to make a genius or a great man by order. But it needs to be understood that if a farmer's wife can beget Spinoza and a grocer's wife can spawn Gandhi, why should we hanker for a lab-manufactured superman?

- Modern science, with regard to the medical field has remained awfully long on promises and lamentably short on performance. It has pretended to research on all major diseases - coronary artery disease, stroke, cancer, hypertension, diabetes mellitus, arthritis - for none of which has if any precise, workable definition. No wonder that about the cause, course, and the cure of each of these

it has drawn a blank[10,11]. All the aforesaid maladies have remained not only trans-science but trans-technique as well[12,13].

The spinelessness of definitionlessness equally plagues the field of genetics, Genes, genetics and heredity, in texts large and small, go abegging for definition. The most advanced texts and articles are replete with apologetic terms that explain away problem by buts, howevers, althoughs and ifs. Many a hypothesis in medicine smacks of a truth that cannot be verified nor a lie that can be nailed. The current obsession about oncogenes is guided more by market forces than any science: "*Francis Collins of the US National Institutes of Health, and director of the Human Genome Project, says the effort to market the genetic tests is alarming, entering territory that is still research and should not yet be commercialised. Ethicists and cancer specialists say that it is currently premature to test adults and children and label them cancer-prone when we are not at the stage of being able to do much about it.*"[14] As a review[15] of an American book on AIDS reveals, "*truth becomes a casualty of competing interests: commercial, political and scienfic,*" a pathetic play from which such luminaries as Robert Gallo, Jonas Salk and Henry Heinlich are not exempt. Dolly has made Wall Street busy with calls for investors who see a future in human and animal organs[1]. The ploy is scare-mongering, promise-mongering, dollar-spinning. Hippocrates, Osler, Susruta and Charaka are turning in their graves.

- The much-vaunted and much-costly HUGO[16] - Human Genome Organization - project promises to map all the 50,000 to 100,000 genes that makes the human genotype. The abysmal disparity between the gene number that each.of us have and the million-fold work that each gene would have to do makes it clear to us that the geneticists have been demanding too much out of a single, as-yet-undefined, human gene.

  "*The human genome (the sum total of the genes in our chromosomes) does not specify the entire structure of the brain.*

There are not enough genes available to determine the precise structure and place of everything in our organisms, least of all in the brain, where billions of neurons form their synaptic contacts. The disproportion is not subtle: we probably carry about 50,000-1,00,000 genes, but we have more than a trillion synapses in our brains."[17] Each human being comprises 1,00,000 billion cells which are in far excess of the approximately 3,000,000,000 base pairs that constitute the 100,000 genes. This takes us straight to the conclusion that any single gene must control a myriad of cells and processes. So the gene that supposedly controls/decontrols cancer must, of necessity control 1,000 other things in the body. In the name of preventing/treating cancer you tamper with particular gene , and invite in the bargain 1,000-fold disturbances. Let it be understood that the HUGO project is not going to provide geneticists a tinkerers' paradise.

Most common human afflictions are governed by polygenic or multifactorial inheritance[16,18], which is another way of saying that it is not the genes of an individual that decide the presence or absence, staticness or progress of a disease, but the abstract relationship that the individual bears to the whole herd. It is *herdity* at work, and not *heredity***.** Frazer Roberts[18] is quite candid about the genetic basis of disease: "*A single gene is certainly the simplest and most economical hypothesis; but it is the least likely*."

With due respect to the HUGO project, and a 12 million dollar gift[19] to it by billionaire William Gates III of Microsoft fame, it must be concluded that the gene-hunt for discovering the basis of the cause and the cure of diseases is like the search for the Holy Grail. It surely amounts to asking a blind man to go into a dark room to find a black hat which is not there.

- Genetic science, like all other sciences, rests on experiments. It is significant that the terms experience, experiment, experimental, expert, expertise are rooted in Latin ***experientia*** from ***experiri*** meaning try, trial, observation,

peril, and more importantly, fear. (An expert, by etymology, is most fearful and fearsome.) Experimental science, then, is observational exercise depending on what the senses of the experiencer perceives. And here, indeed, lies the rub.

The lay and the learned are subject to APDOR: Anthropo Psychic Distortion Of Reality. A good 500 years after Copernicus, we are still stuck with sunset and sunrise, for try as we may, the earth seems stationary and the sun revolving. On a moonlit night with clouds around, it is the moon which seems to move and hide behind the clouds. We say 'we take breath', when in reality it is not something we can take, for the active role is played by the air rushing in under its positive pressure. The healthy do not necessarily survive, the diseased do not necessarily die - death and disease are not related, the former being a function of time, the latter a function of the body. Yet the institution of the cause of death thrives. Smithers[20] declared long ago that there is nothing like a cancer cell, and yet the Himalayan edifice of cancer research has been built on the keystone that is missing. Sir Wilfred Trotter was amused by the mysterious viability of the false, a state we all can merrily share. Heisenberg, the father of the Uncertainty Principle, summed it up pithily: The very act of observation alters its reality.

Like the temporal second, minute, hours and year which in reality exist not, so may be the case with what passes as gene. It is time to revise our thinking: The gene is a point of convergence of cosmic noumenon from which it receives orders. The gene is operative but not decisive. What the gene or genes would be is predetermined before the gene or the genes come into being. As the TITE principle renders it clear, the uniqueness of a person precedes, accompanies and outlives the person. Hence the person's genetic constitution, DNA fingerprints, chromosomal constitution are predetermined by cosmic forces well beyond the nose of the geneticist. Gene/ genes/ chromosomes/genome are resultant events that take orders to merely execute them. With regard to the

never-fulfilled promise of gene-therapy of this disease or that, the geneticists are surely tilting quixotically at windmills.

- Smithers[20] of England, and Nobelist Burnet[21] of Australia have lamented the amazing lack of "biological scholarship" that permeates the lives and works of medical practitioners and researchers. "*For it is necessary to insist upon this extraordinary but undeniable fact: experimental science has progressed thanks in great part to the work of men astoundingly mediocre, and even less than mediocre.*"[22] In continuity with this sweeping generalisation by Ortega Y Gasset, read Eysenck: "*Scientists, especially when they leave the particular field in which they have specialised, are just as ordinary, pig-headed and unreasonable as anybody else, and their unusually high intelligence only makes their prejudices all the more dangerous...*"[23]
- Watson[24] of *The Double Helix* fame, described cancer research as "scientifically bankrupt, therapeutically ineffective, and wasteful." The same words could be used for the whole field of gene, genetics and heredity in its attempts to alter the cause, course and cure of human suffering.

The essential burden of this essay is to make explicit the built-in impotency of the whole science of genetics and cloning, and to put our minds to rest *vis-a-vis* the ethical issues arising therefrom. The oft raised discussions on ethical issues give to genetic research the importance and attention that it inherently does not deserve. Till we realise that, ethical discussions will re-main a good intellectual pastime, adequate filler material for lay and learned publications, and enough excuse for international safaris and conferences.

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8
Cloning

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The Mythology

Genetics, with all the hype and hoopla over Dolly-and-after, has of late been at a low ebb. The sixty-sixth Ciba Foundation Symposium titled "Human Genetics: Possibilities and Realities", held in 1979, concluded with the frank comment of its chairman, Sydney Brenner: "Scientists should not promise society too much... Our promises have been made too easily... we are nearly always wrong... our symposium will be a landmark even if it only records our confused perception of the future of genetics and human biology." Benjamin Levin's huge tome *Genes IV* (Oxford University Press, 1990) concludes with Nobelist Salvador E. Luria's 1986 "attitude of romantic pessimism", a note unchanged in the epilogue to the sixth edition of *Genes* (Oxford, 1997). Dolly-making arrived in 1997 without, alas, providing any reasons for changing the

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pessimistic note into an optimistic one, notwithstanding the media blitz on the Human Genome Project and its sequel, the Human Proteame Project.

Aldous Huxley set his *Brave New World* in the seventh century AF (After Ford). The Dolly-device seems to have achieved a time contraction, raising the BNW spectre barely fifty years AF. Yet, there are saving graces. Soon after Dolly, *Time* (10 March 1997), scarcely the most enlightened expression of opinion, commented: "But on the more profound question of what, exactly, a human clone would be, doubters and believers are unanimous. A human clone might resemble, superficially, the individual from whom it was made. But it would differ dramatically in the traits that define an individual-personality and character, intelligence and talents." "Here's the rule," says psychologist Jerome Kagan of Harvard, "You will never get 100 percent identity - never - because of chance factors and because environments are never exactly the same." As if to underscore the aforementioned came rapid disclaimers from the Roslin Institute that spawned Dolly. The *Times of India* of 6 January 2000 ran a headline imported from the UK: "Human cloning hits a natural barrier". The report read: "The cloning technology that produced Dolly the sheep will never be able to produce identical humans, research has shown." Professor Keith Campbell, who directed the creation of a clone of four rams at the Roslin Institute, declared that "physically and mentally the rams were progressively diverging from each other". Campbell's concluding remarks are oxymoronic: "The only real clones are identical twins and anyone who really knows twins understands that even they have different features and personalities."

Nature Negatived Cloning Long Ago

The nine-banded armadillo, as a rule, delivers a litter of eight offsprings, all of which develop from a single zygote, and yet each differs from the other. As if to match the armadillo, Oliva Dionne, a Canadian woman, had her ovum most naturally impregnated in 1933 by Elzire Dionne, the single zygote splitting into six, one getting aborted at three months

and the other five being prematurely delivered but growing up fully, "everyone of them developing into a consummate woman by 1950" (see Murchie 1978). Regarding the Dionne quintuplets, the *Encyclopaedia Britannica* poses a question and then answers it as well: "How alike and how different can five adults become, who began genetically as one person... the question is a reasonable one, since differences commonly occur even between the right and left side of a person's face or body." Geneticists nurse many a dogma, which has been dubbed *geneticism* by Peter Medawar, this being "a scheme of thought which extravagantly overestimates the power of genetical ideas... which has the ill effect of bringing GENETICS into undeserved discredit."

Identicality of Monozygous Twins Does Not Exist

Despite the averred identicality of the human twin pairs derived from a single ovum and single sperm, one-third of such pairs exhibit tissue incompatibility to reject grafts from each other as vigorously as "non-identical" animals or humans. On the other hand, all dizygous, manifestly non-identical, cattle twins exhibit tissue compatibility, despite differing genetic constitutions. The secret of compatibility (or incompatibility) resides in the twins having had shared a common placenta. Two-thirds of "identical" human twins and all cattle non-identical twins share a placenta and hence are able to swap tissues and organs, along the theoretical and experimental lines established by the acclaimed work of Medawar and MacFarlane Burnet.

Conception versus Cloning: The 2n Game

Circa 1894, August Weismann intuited that the germ cells - ovum, sperm - ought to have n number of chromosomes, just half of the 2n number characteristic of body cells. He proved to be right, allowing biologists to classify gametes as haploid (single) and somatic cells as diploid (double). At fertilization, leading to conception, the n-nucleus of the sperm fuses with the n-nucleus of the ovum to beget a cell called a zygote that has the 2n number of chromosomes, a characteristic of all body cells. Embryological development

starts with the formation of the zygote, which could be seen as the first body cell that will clone itself to form the 100,000 billion cells that comprise a human being. The fertilization of an ovum by a sperm is usually achieved coitally, in the genital passages of the female. When such an act is achieved outside the body, in a petri dish, it is called in vitro (in glass) fertilization or IVF.

Cloning is conception by devious means. J.B. Gurdon in 1969 excised the haploid nucleus of a frog ovum and replaced it by a 2n nucleus of a body cell, and a frog was eventually formed. It should be clear to the reader that Gurdon created a zygotic cell - the first body cell - without the intervention of the sperm. This little experiment proves that the sperm is utilized by Nature primarily to diploidize the haploid nucleus of the ovum. Paternality rides piggyback on the sperm's haploidy. So does maternality. The cytoplasm of the ovum does not seem to bother whether its diploidy comes from the sperm or the ovum, or a body cell. All it wants is a 2n nucleus. Occasionally, an animal ovum that by itself has remained 2n or diploid, begets an offspring, a process called parthenogenesis (from the Greek *parthenos*, virgin, implying a virgin birth). Dolly-making, or Wakayama's cloning of mice, by "impregnating" the cytoplasm of mice-ova by the nuclei of body cells, is merely mimicking the diploidy that the zygote had had to start with. The clonologists forget that any somatic cell is nothing but the clonal progeny of the zygotic cell and hence genetically no different from it.

The sine qua non in this genetic manipulation is the cytoplasm of the ovum or the female gamete, which carries within it the entire blueprint of embryo-making. All that it needs is nuclear diploidy that replaces the unipolatity (n) of an ovum by the 2n bipolarity. No two ova, even from the same ovary, are ever alike. The total possible number of chromosome arrangements due to reassortment in meiosis (gamete formation) alone is 2^{23}, which is more than 8×10^6. Further rearrangement takes place because of crossing over, so it is not surprising that the individual zygotes from the same parents are never alike genetically. Hence, no matter what nucleus and from where,

it is the irrepressible individuality of the ovum-cytoplasm that begets an invariably variable progeny. As Robert Ardrey puts it, despite all the knowledge we have on gravity, the apple refuses to fall upwards. Despite all the experimental ingenuity, the individuality of the ovum and the uniqueness of the offspring it begets have the last laugh, rendering the past, the present and the future of cloning into a farce. An article in *Science*, 6 July 2001, has inspired media headlines: "Healthy clones can carry genetic abnotmalities". Reading between the lines, one gleans the double folly of claiming cloning when it just does not exist and willy-nilly admitting that Nature's forethought inherent in ovum/sperm-making had better not be dispensed with.

Cloning Smacks of Male Chauvinism

The synonymy of sperm with a seed, and of diploidization with fertilization betrays the age-old obsession that the female and her egg merely provide soil through which the sperm spawns a progeny. "Your wives are a tilth unto you. So come into your tilth when and how you will" (*Quran*: 2.223). In fact, the theory of preformation, popular long before the microscopy of cells came into its own, assumed that the fully formed human lies coiled up in the head of the sperm, and that landing into the ovum it merely grows to a large size during pregnancy. David Rorvik's infamous book had to have the title *In His Image*, betraying an obsession that the sperm rules the roost. Here too, male chauvinism was beaten to the post by the pioneering of Dolly in her image, as it were.

Cloning Is Mythology

The whole fallacy of cloning may seem to reside in the idea that in a cell, the nucleus is the boss, and cytoplasm the obedient servant. Hence, if a series of ova can be impregnated with the nuclei of the body cells of a person, all the resulting progeny should be identical. The idea has bitten the dust on the clear realization that the cytoplasm of the ovum calls the developmental shots, and all that the sperm, or body nuclei,

do is to provide a nuclear bipolarity characteristic of all body cells. The cloning idea could well be called the greatest misconception of the second millennium, deserving a decent abortion at the very start of the third millennium. In any case, since the so-called cloning is a dead-end exercise, so that a Dolly can't re-Dolly itself, the mythopoetic term cloning can be dropped forever from biological and medical lexicons. This despite *Time*'s cover story (26 February 2001) declaring that "Human cloning is closer than you think".

Cloning is conception by asexual, non-spermal means, a third millennial version of the immaculate conception. Clonology is out to square a circle. When no two atoms, leaves, fingerprints or homozygous twins have ever been identical, clonologists promise to create identical copies of sheep, mice, pigs and, quite soon, human beings. Their "proton pseudo" or the basic mistake is their calculated ignorance of the self-evident fact that it is not the nucleus of the zygote but the maternal ovular cytoplasm that has the entire mechanism of embryogenesis encoded into it. No two ova have ever been, are, or would be, alike. Likewise, no two "cloned" individuals will ever be clonal to each other. Thank God, Huxley's *Brave New World* will never come to pass. Cloning shall, forever, remain a dream not because of inadequate money, technology, intellect or will or ingenuity but because of the boon of uniqueness or individuation that St Thomas Aquinas clearly enunciated in the thirteenth century. It is a universal principle that no clonologist dare deny.

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