The cloning bandwagon : a hysterical outburst

The same article on cloning evoked a different response from **SK Bhattacharya**

In his lecture *Science and Authority*, first published in 1946, Michael Polanyi (1) said,'Unless it is somehow assured that professional teachers and research workers will not lack scientific qualifications of a certain grade, the whole system of endowed scientific institution is bound to dissolve in chaos and corruption. The experience of undeveloped countries, where scientific opinion is imperfectly organised, teaches us that even a comparative slight weakening of scientific control can have marked deleterious effects on the integrity of scientific activities.' .

After more than half a century, we continue to 'teach the West what should not be encouraged to keep creativity in science and technology thriving. The near hysterical opposition to the emerging cloning technology, published in this journal (2) is symptomatic of a deeper malaise.

Lost scientific control

The authors in their outburst against the possibility of human cloning have not only lost what Polanyi referred to as scientific control, but have deviated from raising the pertinent issues. It is easier to pick a few holes, real or imaginary, in the technicalities of a subject than to enter into the more complex ethical issues of an emerging technology. The authors attack cloning technology by blaming the science of genetics for its defects as perceived by them. Their perceptions are produced by a flawed understanding of the development of scientific ideas, an inability to distinguish between basic science and technology, and, most importantly, a prominent streak of mysticism.

'The essential burden of this essay is to make explicit the built-in impotence of the whole science of genetics and cloning and to put our minds to rest vis-a-vis the ethical issues arising therefrom...'

This statement can easily confuse and mislead. Therefore the arguments need to be critically examined. Without going into the question of ethics of cloning as a technology, I shall discuss only a few of the ideas raised by Kothari and Mehta, questioning whether their arguments are sufficient to claim the impotency of the 'science of genetics'. First, citing their own work (3), they claim that 'cytoplasm calls the tune, the nucleus merely follows it.' This gives the impression of a master-slave relation and projects cytoplasm as the master. This conclusion undermines the role of the nucleus in determining the composition of the cytoplasm -- something which, presumably, the authors cannot deny. A given cytoplasm can support only a narrow range of nuclei for the growth or development of the cell. It can be easily demonstrated in bacterial systems that if a gene transfer is carried out to replace a functional gene with an appropriate mutant gene the cytoplasm does not support the growth, and such cells are non-viable in a specific environment. However, in most cases it can be shown that it requires another genetic alteration called a suppressor mutation, within or outside the gene without the alteration of the original defect, to make the cell viable in the same environment (4). Similarly, a cytoplasm cannot support the normal development of an embryonic cell if both the copies of a gene carry identical lethal mutations (homozygous for recessive lethal allele). However, if one copy is normal, in many cases the development of such a heterozygote is nearly normal, at times even indistinguishable from normal ones except by a stringent genetic test. In nuclear transplantation experiments we found that when exposing the amoeba to a lethal agent under certain conditions, damaged cytoplasm harbouring an undamaged nucleus can support viability, whereas an undamaged cytoplasm carrying a damaged nucleus cannot do so (5). It seems in such cases that the nucleus calls the tune and the cytoplasm depends on it for the survival of the cell. A cell is neither nucleus nor cytoplasm alone, but a dynamically interacting whole. It makes as much sense to claim that 'cytoplasm is the gene's way of making more genes' a statement that has given rise to the notion of 'selfish genes' to explain the concept of redundant, so-called 'junk' DNA which survives by tagging on to genes coding for tools for their own replication in its host (6). Current developments in the sciences of genetics, biochemistry, and molecular biology have allowed us to mimic a few important functions of the cytoplasm, with well-defined components, without requiring the whole cytoplasm. These are transcription, translation and replication of the genes 'in vitro'. Such experiments demonstrate that gene expression is dependent on cytoplasmic factors which in turn are coded by the genes. It seems, therefore, that the science of genetics is gradually taking us in a direction which will hopefully give a more accurate understanding of the mechanism of growth and development of cells and organisms. Can any other science or method of inquiry honestly claim a lower level of 'built-in impotency'? I do not think so.

The question of predictability

In the fourth point the authors argue that 'science can never predict exactly what it would be,' because the mathematical description of systems as derived from a new branch of physics called 'Chaos' shows the intrinsic 'unpredictability' of its future states. . This view ignores the fact that Chaos studies attempt to understand the dynamic behaviour of non-linear systems. The current effort

SK Bhattacharya, *18-A,Dhawalgiri, Anushaktinagar, Mumbai, 400 094*

of this new science is to understand behaviour by discovering invariants as well as factors leading to unpredictability.

The motive of this mathematical enterprise is not to predict the behaviour of every constituent atom, which the doctors seem to deliberately overlook when they point to this uncertainty at the atomic level. The excitement of a deeper understanding of the dynamic behaviour of real systems, and the eventual utility of this knowledge, is lost to the authors because nothing less than atom-to-atom prediction will satisfy them. It is worth quoting Ford on Chaos cited by Gleick (8): "God plays dice with the universe," is Ford's answer to Einstein's famous question, "but they are loaded dice. And the main objective of physics now is to find out by what rules were they loaded and how we can use them for our own end." '.

From Mendel to today's geneticists

The absurdity of this puritan demand for the 'ultimate accuracy' in scientific prediction is demonstrated if we reflect on how the branch of mathematics which also deals with complex systems - statistics - has advanced our knowledge. Statistics assumes that we cannot always identify natural processes by observing a single or a few events, because unidentified as well as uncontrollable factors introduce variations creating noise that effectively masks the underlying causes or events. To take the most relevant example, the laws of inheritance deduced by Mendel were based entirely on statistical analysis of the results of controlled crosses (9). Subsequently, on deeper probing of the physical mechanisms involved, the science of genetics has given us knowledge of the basis of several human diseases, besides many other benefits. There is no reason to think that more information about how genes and their product interact would not open up ways to cure genetic disorders in the future. And if Mendel and the later geneticists had not drawn their conclusions until atom-to-atom predictability was achieved, would we have gained any knowledge of the mechanism of inheritance at all? Surely we would have argued endlessly to support and refute any number of theories - some of which would have acquired a mystic aura - to explain away the existence and perpetuation of life without advancing knowledge by an inch.

Not much genetics *per se* is involved in cloning. The genetics element in cloning Dolly for instance was to choose the genotype of the nucleus used. It is, therefore, wrong except in a very loose sense, to club the science of genetics with that of cloning as a technology. More precisely, it is recombinant DNA technology, an offshoot of the science of genetics, that is associated with cloning technology. The new technology promises to be more economical than classical breeding programmes based directly on the science of genetics - without an intervening, well-marked technology - to produce high yielding crop varieties, or sheep and cows with more and better wool and milk respectively. Checking the unethical use of this knowledge is a better option than shutting our eyes to the promises that almost certainly will pay off.

The fifth point is wholly a case of mysticism. The authors claim that 'every manifest phenomenon' as it were, 'gets guided by the cosmic noumenon'. This argument entails a vague interpretation of natural phenomena. For instance, there is no hint as to precisely where the evidence of being 'guided' is to be found. The use of the word 'cosmic' to qualify 'noumenon' requires our faith in some intangible, but intuitively knowable object that guides the universe. The little that we do understand of the various natural phenomena by scientific pursuit does not require the assumption of any agency which cannot be quantitatively related to physical phenomena. Science does predict many more phenomena in specific detail than do any of the mystic theories which assume cosmic principles. If our intention is to have confidence in our knowledge, then it must be subject to such tests. We remain uncertain of their worth. This is not to claim that science explains everything, or even to undermine the efforts of the ancient sages who reflected on the nature of the sensuous outer world as well as the intangible worlds of mind and consciousness without the help of sophisticated controlled experiments. However, with the explosion of information in innumerable fields of inquiry, we cannot possibly base our world view on theories which have little to tell us in specific detail that can be easily tested, but draw their nourishment essentially from our ignorance. Insistence on this fundamental position may have led to their stagnation in the past. These philosophies seem to have survived by acquiring a mystic character, demanding unshakeable faith as immunity from exposure of their impotency in practice. In contrast, the faiths, or fundamental postulates, of scientific theories are constantly under question and discarded when sufficient evidence accumulates to give way to newer sets of postulates with more explanatory power (10). Thus does the evolution of scientific theory increase its explanatory power and reduce the inaccuracy of prediction.

One may lament the inaccuracies of current theory, as the authors have, but their explanatory power is higher than those of the mystic theories.

With due respect to Vedas

The authors claim that science and the Vedas allow the 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 others." But the attempt of science is exactly the reverse, as discussed above on Chaos. Science tries to discover the underlying invariant relations in spite of differences. The knowledge as obtained can then be used to predict specific events under controlled conditions

within a predetermined limit of accuracy. With due respect to the Vedic philosophers, we must state that they cannot be used to predict any specific physical interaction. If they were to do so, the consequences are likely to be as varied as those in astrology because they depend entirely on subjective interpretations. If a scientific theory fails when stringent criteria are applied by peers, the failure will be admitted and fresh attempts made after taking care of the exposed weaknesses. Since Vedantic philosophy cannot possibly produce a theory which will subject itself to such constraints, sweeping generalisations cannot be made freely without questions about their practical validity. They may add to the philosophy's profundity but certainly cannot inspire confidence in their powers of prediction. Such minds have more confidence in Newton's laws of motion which predict that a stone thrown up at an angle to the horizontal follows a parabolic trajectory and reaches a target with reasonable accuracy. This knowledge is useful to our day-to-day requirements.

Experimental science more reliable

Philosophy collated from experimental science, therefore, gives more confidence than the mystic ones. Is it not a wonder that even mediocre scientists - according to the authors - have collectively given a more reliable world-view than vedanta has, simply because they opted to test their predictions in carefully designed experiments?

The sixth point argues that going down to the minutest level, no two phenomena can be identical. Hence cloning will not result in identical individuals. The authors then 'breathe a sigh of relief that Genghis Khans will not be duplicated, much less cloned.' Their argument is no argument at all.More undesirable individuals than we could imagine till now can still be born whether or not cloning technology succeeds. But that accuracy is far from the goal of cloning experiments. Cloning will ensure that the members of a clone will have sufficient resemblance (visual and otherwise) to clearly distinguish themselves from others , without caring for atom-to-atom identity.

In the seventh point, the authors' zeal to shake the foundation of the science of genetics fails to note that in these rapidly developing sciences, the shortcomings of the older definitions are noticed much earlier than they would be in other, more slowly progressing areas - and none at all in fossilised subjects. For instance, in less than 150 years, the term 'factor', introduced by Mendel, was more precisely defined as 'gene' with the growth of formal genetics. Now 'gene' is being found inadequate because of advances in molecular genetics, so that informed textbook writers warn readers not to go by the older definition. These ambiguities and uncertainties, misinterpreted as the weaknesses of genetics, have apparently prevented the authors from getting the magnificent view that this science provides. These 'weaknesses' are a sure sign of the heightened pace of development of genetics.

Unfortunately, one cannot say the same about Vedanta philosophy today. The students of this philosophy have hardly felt pressure to change technical terms (like *advityam* or *nityam* referred to by the authors) in spite of their cumulative experience of several centuries. Is it fair to belittle ancient sages who did not have the advantage of modern knowledge by dragging their theories centrestage today to compete with some of the more successful modern theories and concepts? We should have the humility to admit that our post-Vedic scholars missed the head start given to them in the intellectual race by Uddalaka Aruni more than two thousand years ago, even before Thales of Miletus, as the first natural scientist (11). The lesson is: just as the West is learning from us what not to do, we should learn from our past what not to do if we wish to build a robust intellectual tradition.

That a single ge[illegible]r[illegible] multitude of functions can easily be demonstrated by a simple model system for genetic studies, such as e. coli.

In the eighth point, the authors go through an abstract exercise to come 'straight to the conclusion that any single gene must control a myriad of cells and processes.' A cursory glance at even the older textbooks of genetics would have concluded that more accurately for several organisms and helped them get a more reliable understanding. The calculations, as explained below, actually convey the wrong impression. It is well known that in most organisms functional genes can broadly be divided into two classes - regulatory and structural genes. The regulatory genes control several functions whereas structural genes may determine one or at most a few functions. For example, in e.coli, a gene codes for the enzyme beta-galactosidase which specifically cleave lactose into galactose and glucose. A defect in this gene will block the growth if lactose is the only carbon source available, but permit growth in several other sugars such as galactose, arabinose, etc. A regulatory gene, crp, which controls expressions of many genes which permit growth on several sugars besides lactose, codes for a regulatory protein, CRP or CAP. A defect in this gene and therefore the defective protein coded by it, will block the growth in all the sugars under its regulation including lactose, even if the structural gene coding galactosidase is intact (4). The point is that not any but certainly some genes control a myriad of processes in most organisms and it is unlikely to be different in human beings. This knowledge is older than the estimates of the number of genes and nucleotides in the human genome, which even now is only tentative. Yet the authors chose the latter to arrive at their conclusion which gives to all the estimated genes equal weightage for functional complexity. In the process they also missed the lead given by Damasio, who they quote partially for their calculations.

The generality of the conclusion given

above on more solid grounds even for the human genome would have immediately followed and restrained them from making the statement that the 'HUGO project is not going to provide geneticists a tinkerer's paradise'. Genes which control the development for higher organisms belong to the regulatory class just described. Continuing the text from which the authors have taken numbers for the estimates and left (12): "Moreover, genetically induced formation of tissues is assisted by interaction among cells in which cell adhesion molecules and substrate addition molecules play an important role. What happens among cells, as development unfolds, actually controls, in part, the expression of genes that regulate developments n the first place..." and more directly suggested in the next paragraph:

"The genome helps set the precise or nearly precise structure of a number of important systems and circuits in the evolutionary old sectors of the human brain. ..The principal role of the structures in these sectors is to regulate basic life processes without recourse to mind and reason..."

Without going into the molecular details of the mechanisms of developmental processes, at least some but certainly not every single gene will control a myriad of processes even in human beings. The authors' apprehension that tampering with genes that control /decontrol cancer could affect several other functions in the body in unknown ways is an oft-repeated warning and must be taken seriously to stop both the romantics and the unscrupulous elements from transgressing ethical limits. The apprehension will also grow unless resources marked for these investigations are diverted to basic research to understand the functions of the target genes in sufficient molecular detail.

If we assume that it is possible to acquire such knowledge in model systems such as animal and tissue cultures, there is no reason to be pessimistic about the possibility of judicious 'tinkering' of a limited number of well-studied genes and the interactions associated with these genes and their products. Obviously, premature or unethical adventurism will need to be checked even then by a vigilant scientific community and informed public criticism. But the scientific community cannot shy away from its responsibility of understanding the basic processes involved, provided, of course, that its commitment to science and its utility for human welfare is genuine. Clearly, this will require immense efforts by the global scientific community (unfortunately, we Indians lag far behind) considering the complexity of the human body and for ethical grounds, its inaccessibility as a guinea pig. We must certainly exercise ethical restraint but follow the reasonable path as Damasio (13) has chosen: "I am skeptical of science's presumption to objectivity. I have a difficult time seeing scientific results, especially in neurobiology, as anything but provisional approximations, to be enjoyed for a while and discarded as soon as a better account becomes available. But the skepticism about the current reach of science, especially as it concerns the mind, does not imply diminished enthusiasm for the attempt to improve provisional approximations"

Ethical issues being considered

Improving approximations is considered by Damasio more fruitful than throwing up one's hands in despair for want of stringent accuracy in knowledge. The Human Genome Project (nicknamed HUGO) shares the same limitations and the enthusiasm of Damasio. With remarkable foresight by its promoters, in the first major international meeting in October 1988 to form different advisory groups, Nancy Wexler was designated to chair the ELSI (ethical, law and social implications) working group. About three percent of the Genome fund was also earmarked for the purpose (14). This should put to rest any doubts ab

the sensitivity and concern for ethics of those who are working for HUGO. When such knowledge accumulates in molecular detail, along with the results from the HUGO project, it may even appear natural and not too risky to tinker with human genes in attempts to cure diseases by gene therapy, though not perhaps in the immediate future. It is time we thought differently about the missing 'black hat' which the blind man is searching for in the dark room. Advances in scientific knowledge may cure a blind man, and he may even see the black hat by using special gadgets-- the hat that others missed because they did not develop an appropriate gadget -- and therefore believed did not exist in the dark room. As far as the HUGO project is concerned, many of us who listened to James Watson at TIFR on December 1, 1997, felt that the black hat does exist there. We got a fleeting glimpse only because Watson succeeded in opening the door of the dark room a little to let some light in.

Critical opinion with responsibilities

To conclude, the science of genetics will not be affected by hysterical criticism though if the slander is carried too far, we in India may lose the benefits of its findings. While critical opinion is always welcome, there is a concomitant responsibility to concede the beneficial aspects of the object of criticism. Moreover, no alternative to the existing methodology of scientific pursuit has been offered or even hinted at by the authors. In my view, intellectual honesty is compromised when atom-to-atom prediction is insisted upon without suggesting an alternative means. I have shown how this is not only unnecessary but regressive as well, for its potential to confuse rather than clarify the real issues and dilemmas, ethical or otherwise, for young students and researchers. Those monitoring the scientific community's own internal debate will find such criticism disorganised and incoherent. The inevitable consequence is an erosion of

support and goodwill. We will neither regain the intellectual vigour needed to pursue scientific and technological activities in the proper spirit in the modern context nor meet society's material expectations, something badly needed to come out of the poverty and intellectual stupor that are threatening to become our identifying marks.

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Some intenet humour...

Do all diagnostic procedures require pre-certification?
No. Only those you need.
What are pre-existing conditions?
This is a phrase used by the grammatically challenged when they want to talk about existing conditions. Unfortunately, we appear to be pre-stuck with it.
What should I do if I get sick while traveling?
Try sitting in a different part of the bus.
No, I mean what if I'm away from home and I get sick?
You really shouldn't do that. You'll have a hard time seeing your primary care physician. It's best to wait until you return, and then get sick.
I think I need to see a specialist, but my doctor insists he can handle my problem. Can a general practitioner really perform heart transplant right in his office?
Hard to say, but there's no harm giving him a shot at it.
What accounts for the largest portion of health care costs?
Doctors trying to recoup their investment losses.
Will health care be any different in the next century?
No, but if you call right now, you might get an appointment by then.

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