

presence of rabbit β -globin genes by Southern blot hybridization. Nine of the mice contained rabbit β -globin genes in copy numbers varying in different individuals from one or two to up to twenty per cell although further experiments are now needed to establish whether the animals are mosaics, with some cells containing more copies and others none.

Four of the positive males were mated with normal females and DNA from the progeny screened for the presence of rabbit globin genes. Out of a total of eighteen progeny screened, six were found to contain rabbit globin sequences. This pattern of inheritance is consistent with a chromosomal location of the foreign DNA and, in a footnote to their paper, Constantini and Lacey describe the results of an *in situ* hybridization experiment showing that most, if not all, copies of the rabbit globin genes in one of their mice are located in the middle of one of the homologues of chromosome 1. The organization of the rabbit β -globin gene copies has been determined in a number of the mice by restriction mapping with various enzymes. Predominantly linear molecules of λ DNA were injected, but the integrated DNA contains the fusion fragment resulting from annealing of the λ cohesive ends. Consequently, the authors suggest that the input λ DNA is ligated to form high molecular weight concatemers and it is these tandem arrays which are then integrated into the chromosome. There is direct evidence that such a mechanism occurs for linear DNA injected into fertilized eggs of *Xenopus laevis*⁸. Also Constantini and Lacey detect minor fragments which are transmitted to progeny mice, and which probably contain the junction between the terminal copies of the foreign DNA oligomers and host chromosomal DNA sequences.

What then of the questions posed at the outset? Are foreign genes which have become stably integrated into the mouse genome expressed, and do they display the correct temporal and tissue specific pattern of gene expression? A newly published study by Wagner and his colleagues at Ohio University, describing work done in collaboration with Hoppe at the Jackson Laboratory suggests that at least the first of these two important goals has been achieved⁹. A proportion of mice, derived from eggs which have been injected with a rabbit β -globin gene were found to contain a rabbit globin polypeptide in their erythrocytes, and this was also true of their progeny. Furthermore, a recent report in *Science*¹⁰, quotes preliminary evidence

obtained by Wagner which indicates that the rabbit globin polypeptide was produced only in red blood cell precursors and not in other tissues of the mouse. If this latter observation is confirmed, the way would seem to be open to determining those features of DNA structure important in controlling gene expression during development. Also, of course, if it has indeed been possible to insert a cloned gene

sequence into the mammalian genome so that it functions correctly, the wider implications are enormous. Leaving aside the controversial question of gene therapy in humans, it seems certain that the genetic manipulation of agriculturally important animals will quickly follow, since, in cattle at least, the techniques of superovulation and reimplantation in foster mothers are now routine procedures. □

Extraterrestrials — where are they?

from Ben Zuckerman

IN THE MIDST of a sometimes depressing reality, many people take conscious or subconscious comfort in the assumption that we are but one of a myriad of advanced technical civilizations co-existing in our Milky Way galaxy. This view — championed by articulate scientific and lay spokesmen — is bolstered by lavish science fiction movies, by reports of UFO encounters of the first, second, and third kinds, and by best selling books about artefacts left behind by so-called ancient astronauts.

Included among the articulate scientific spokesmen is Carl Sagan of Cornell University, whose television programme and book *Cosmos* have brought astronomy into the homes of millions of Americans. Sagan, and some other well known scientists such as Philip Morrison (MIT) and Frank Drake (Cornell University), are considered to be members of the 'optimistic' school of thought on the question of extraterrestrial intelligence. They have argued that 100,000 or more technical civilizations, all of which have arisen independently, may currently exist in our Milky Way galaxy. If there are this many civilizations, then a typical one must exist for a million years or more.

How do the optimists arrive at this value for N , the number of technical civilizations in the Milky Way? Usually they rely on the 'Drake equation' which expresses N as a product of the various probabilities of the origin and evolution of life, intelligence, and technology. Sagan went through this exercise in *Cosmos*. He supplied his estimates for a long string of uncertain factors including, for example, the probability, $P(\text{life})$, that life will originate on an Earth-like planet and the probability that, having originated, it will then evolve to intelligence and technology. Since we really know very little about these probabilities, the optimists rely on the Copernican world view that we are not special. After all, most Europeans once believed that the Earth was located at the centre of the Solar System. After that was shown to be false, it was still commonly believed that the Sun was located at or near

the centre of the Universe. As this now also seems most unlikely, the optimists argue, so should be the view that intelligent life is unique to the Earth given that there are hundreds of billions of stars in the Milky Way and most of them have been shining for at least five billion years.

This world view compels them to choose very large values for the probabilities mentioned above. For example, many (most?) scientists would regard $P(\text{life})$ as uncertain by a factor of at least a million. Yet Sagan, in *Cosmos*, purports to know $P(\text{life})$ to two significant figures. His choice of $P(\text{life}) \sim 0.5$ is, ostensibly, the result of taking the *arithmetical* mean of unity, which he prefers, and zero which is preferred by some of the pessimists in this field. Of course, he would have obtained a very different value for N if he had instead set $P(\text{life})$ equal to zero, the *geometrical* mean of 1 and 0. This illustrates the kind of tricks that one can play with the Drake equation.

Until the past few years, there were very few scientists who would argue strongly against this Copernican philosophy. Ten years ago, when I first became seriously interested in this problem, I was sufficiently uncertain of the value of N that I attempted to search, with Patrick Palmer (University of Chicago), for radio signals from another civilization. We pointed the 300- and 140-foot telescopes of the US National Radio Astronomy Observatory towards approximately 670 nearby stars. Since then half a dozen similar attempts have been made by radio astronomers in the United States and Canada. None of these has been successful, unless someone is hiding something in their bottom drawer.

Radio beacons are, of course, but one of many ways that advanced technological societies could make their presence known to scientists here on Earth. The most obvious way would be for the extraterrestrials to send a manned or unmanned probe to our Solar System and, especially, to land one on Earth. That there is no real evidence that this has ever occurred has suggested to Michael Hart (Trinity University) and others that

1. Jaenisch *Proc. natn. Acad. Sci. U.S.A.* 73, 1260 (1976).
2. Jähner & Jaenisch *Nature* 287, 456 (1980).
3. Jaenisch *et al. Cell* 24, 519 (1981).
4. Jenkins, Copeland, Taylor & Lee *Nature* 293, 370 (1981).
5. Harbers, Jähner & Jaenisch *Nature* 293, 540 (1981).
6. Gordon *et al. Proc. natn. Acad. Sci. U.S.A.* 77, 7380 (1980).
7. Wagner *et al. Proc. natn. Acad. Sci. U.S.A.* 78, 5016 (1981).
8. Bendig *Nature* 292, 65 (1981).
9. Wagner *et al. Proc. natn. Acad. Sci. U.S.A.* 78, 6376 (1981).
10. Reported in Research News, *Science* 213, 1488 (1981).

advanced civilizations do not exist anywhere in our galaxy. We may well have the most advanced brains in the entire Milky Way.

At first glance it would seem to be a preposterous extrapolation to jump from the fact that we have not yet uncovered any evidence, either in deep space or in our Solar System, for superior extraterrestrial beings to the conclusion that they don't exist anywhere in the Milky Way. After all, our radio searches have been quite primitive and one can think of lots of reasons why another civilization might not want to go to the trouble and expense of sending complex probes between star systems.

This argument is reasonable if we are trying to understand why only a few civilizations might not want to send out interstellar spaceships. But what if there have been 100,000 or more civilizations, each of which must have existed, on the average, for a million years or more? Just as life and now, especially, intelligent life has transformed the face of the Earth so it might reasonably be expected that most of these 100,000 superior civilizations will have carried out deeds that, at present, we would regard as technological 'miracles'. Suggestions have included colonization and reengineering of the moons and planets of the home solar system to colonization and reengineering of the entire galaxy — all on time scales much less than 10 billion years.

Discussion of the many implications of these arguments filled an entire symposium whose proceedings, *Extraterrestrials — Where Are They?* are scheduled for publication by Pergamon Press in the autumn of 1981. Papers were presented by venerable pundits including, for example, Freeman Dyson (Institute for Advanced Study), Sebastian von Hoerner (National Radio Astronomy Observatory), and Ronald Bracewell (Stanford University) as well as by various comparative newcomers to this field.

Although many scientists find the arguments that *N* must be a very small number (\sim unity) quite compelling, few, if any, believe them to be so compelling that we should abandon searches for radio or infrared radiation from extraterrestrial beings. It is, therefore, ironic that Senator William Proxmire (Wisconsin) has entered these arguments into the Congressional Record of 30 July 1981 as part of his justification for prohibiting the use of federal funds during fiscal year 1982 for a modest radio search programme under consideration by NASA's Ames Research Center and the Jet Propulsion Laboratory. (He also felt that NASA wanted to search in the wrong place: "I have always thought that if [our best scientists] were going to look for intelligence, they ought to start right here in Washington. It is hard enough to find intelligent life right here. It may even be harder, I might say, than finding it outside

our Solar System.")

A few years ago Proxmire succeeded in deleting federal funds earmarked for a similar NASA search programme and gave NASA one of his Golden Fleece awards. Frank Drake, in return, gave Proxmire honorary membership of the Flat Earth Society but all to no avail. NASA has attempted to keep the programme alive, albeit at a minimal level, by using discretionary funds but the recent congressional action has stopped even that, at least for 1982.

This decision seems unfortunate for two reasons. First, there is considerable public interest in the search for intelligent life, judging, for example, from the response to

Cosmos and the growing popularity of courses on "Life in the Universe" on college campuses. Second, and more generally, is it really in the best interests of American science for individual Congress-people to fiddle with relatively minor items (about a million dollars a year) in the much larger budgets of major institutions such as NASA? Or, in the absence of a congressional vote of 'no confidence' in the NASA leadership, shouldn't the latter group, in conjunction with their scientists and engineers, be the ones who determine expenditures at the megadollar level? □

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Histone gene organization: paradigm lost

from Larry Kedes and Rob Maxson

THE organizations of sea urchin and *Drosophila melanogaster* histone genes were shown, even before the era of gene splicing, to be remarkably similar: both are repeated in the hundreds and arranged in tandem units, each unit containing the intimately linked genes for five major histone proteins. While the differences between the sea urchin and the fruitfly histone gene topology hinted that the order and polarity of the genes within a species can be gently shuffled, the similarity between species so widely separated in evolutionary terms seemed to establish a paradigm for histone gene arrangement and lead to the confident expectation that similar arrangements would be found in intervening phyla.

However, a rash of recent reports of different patterns of histone gene organization in a number of different vertebrate species, including examples of scattered and often solitary genes, has dispatched classical notions about their fixed organization. The authors responsible for the new observations have been quick to point out the difference between the more familiar sea urchin-fruitfly tandem organization and the vertebrate dispersed topology and to speculate on its significance. Human¹⁻³, mouse⁴, chicken^{5,6} (see this issue of *Nature*, p.49) and toad⁷⁻⁹ genes have now been cloned. Not only are the genes differently arranged in comparison with the classical paradigm, but they seem scattered and separated by long stretches of non-histone DNA (for an extensive review see ref 10). While a few coding regions remain clustered, they are not at all arranged in clean-cut tandem repeats. Some coding regions are solitary and separated, by at least 10 to 20 kilobases, from their fellows. None seem to be an

identical copy of any other suggesting that dispersion allows, or at least associates with, evolutionary drift in gene sequence. Each coding region seems to be present only in tens per haploid genome. How close the histone gene members of this newly discovered diaspora are to one another in the genomic landscape has yet to be determined. An earlier report¹¹, using *in situ* hybridization, suggests that the human genes may be landmen: the locus seemed confined to the telomere of chromosome 7 but the genes are scattered over the entire distal third of the long arm.

Recent findings in our own laboratory suggest that the distinction between clustered and dispersed histone gene organization is not a strict interspecies difference. As pointed out by a number of workers, a gradual shift in expression occurs during early sea urchin development: the activity of the several hundred-fold tandem clustered 'early' gene set is reduced in favour of the expression of a set of 'late' histone genes of much lower copy number. Some features of late sea urchin histone gene organization have now come to light with the cloning of several examples¹². The late genes are scattered and shuffled not unlike those described for the vertebrate examples mentioned above. Genes coding for isoforms of the same histone exhibit extensive nucleotide sequence divergence. And to complicate matters, not all of the vertebrate genes follow the same model: histone genes in the newt¹², *Notophthalmus viridescens*, share all the topological features of the sea urchin and fruitfly clustered arrangement except that each repeat unit is separated by a long

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