## Human gene cloning: the storm before the lull?

SIR—Hardly a week goes by without an article in *Nature* describing the cloning of a human DNA sequence. Yet it is barely nine years since the first cloning of a human gene sequence, chorionic somatomammotropin, was reported in *Nature*[1]. Since then, some five hundred different human gene sequences plus many anonymous DNA segments, have been reported in a total of nearly 2,500 independent published articles[2] (as evidenced in *Gene Communications*, a quarterly updated newsletter obtainable from the authors on request). Such an exponential increase in knowledge accumulation is by no means unique. Examples of this phenomenon have included the literature explosions associated with cyclic AMP after the introduction of the second messenger hypothesis in 1958[2] and the discovery and analysis of hereditary amino acidopathies after the advent of chromatographic methods[3].

We calculate that were the present growth in the number of reports of cloned genes to be maintained, their number would overtake the total number of biological publications in 1992 and that of all scientific publications by 1994 (Fig. 1), still leaving the majority of the human genome untouched. However, this year the first signs of a plateau are becoming evident. It is interesting to speculate upon the various factors which might affect publication rates over the next few years.

A slow-down factor could be the finite size of the human genome ($3 \times 10^9$ base pairs) — although the number of gene sequences which it contains, perhaps in excess of 100,000, is sufficiently large to ensure that there is a long way to go before any law of diminishing returns begins to operate. But given its limited and already stretched resources, the scientific community will sooner or later have to decide whether it can afford the not inconsiderable redundancy so characteristic of research efforts in this area.

This redundancy of effort is apparent from the number of independent reports of the cloning of certain human DNA sequences. For example, the cloning of adenosine deaminase and of T-cell receptor α and β chain cDNAs have each been achieved eight times. There are 17 separate reports of a cloned c-*myc* genomic sequence and 33 independent reports of the cloning of the β-globin gene, although, in fairness, some of these are mutant alleles. While a certain degree of competition is to be expected and indeed welcomed in science, redundancy on this scale clearly calls for some more effective means of coordinating research efforts at the international level. It is, however, to be expected that no such let-up is likely in the hunt for those gene sequences deemed worthy of commercial exploitation. Presumably, strong competition will still characterize the drive to clone genes coding for proteins of economic and/or medical importance. Furthermore, an ever increasing number of laboratories are involving themselves directly or indirectly with cloning and mapping the human genome. The synthesis of molecular biology and human genetics seems able to attract an increasing number of adherents. How long the cloning fashion will be able to lure young researchers remains an open question, but for most laboratories, cloning is not an end in itself, but a means to an end, for example, functional analysis, spawning further booms in clone analysis.

One further factor which will affect publication rates is the future editorial policy of the eighty or so journals that at present publish these reports. Although to some extent offset by the likely future increase in journal numbers, the number of published cloning reports should tend to decline as a result of a probably tightening-up of standards and criteria for article acceptability. It is anticipated that authors will be expected to report on a larger number of sequences, a more complete sequence or to have undertaken in-depth structural or functional studies. Cloning data may in the forseeable future have to be relegated to an information repository in the form of an electronic data base, a development which will be accelerated by novel, more effective cloning, genome walking and sequencing strategies[4]. It remains to be seen whether the level of acceptance of such novel means of data storage and transfer is sufficient for any appreciable effect to become apparent in the near future.

Perhaps the rate of human gene cloning may even decline because people are simply getting bored with it. But it is also true that man's feeling of self-importance will probably not be satisfied until the last bit of his genome has been sequenced and filed somewhere.

JORG SCHMIDTKE
MICHAEL KRAWCZAK
*Institut für Humangenetik,*
*Gosslerstasse 12d,*
*D-3400 Göttingen, FRG*
DAVID N. COOPER
*Department of Neurochemistry,*
*Institute of Neurology,*
*University of London,*
*Queen Square,*
*London WC1N 2NS, UK*

1. Shine, J. *et al. Nature* **270**, 494 (1977).
2. Jost, U.-P. & Rickenberg, H.V. *A. Rev. Biochem.* **40**, 471 (1971).
3. Scriver, C.R. *Br. med., Bull.* **25**, 35 (1969).
4. Palca, J. *Nature* **321**, 371 (1986).

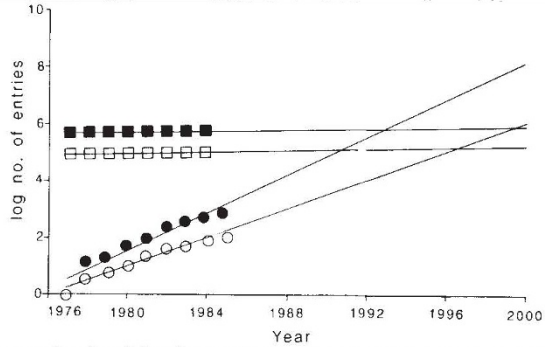


**Fig. 1** Exponential growth of publications per annum on cloned human DNA sequences: all reports (filled circles) and first reports on protein coding sequences (open circles). For comparison the number of publications covered by *Biological Abstracts* (open squares) and *Science Citation Index* (filled squares) are given.

## Immunotoxins to combat AIDS

SIR—Of the three therapeutic approaches to acquired immune deficiency syndrome (AIDS) suggested by Klatzmann and Montagnier[1], Singer and Shearer[2] have highlighted the possibility of attenuation of the $CD4^+$ cells, which are the host for the virus associated with AIDS (HTLV-III/LAV), by infusing monoclonal anti-CD4 or anti-class II HLA reagents.

A more reasonable approach, we suggest, would be to use immunotoxins[3] — conjugates of a specific antibody and a plant or bacterial toxin — directed specifically to the $CD4^+$ cells. The toxic moiety is a ribosome inactivating protein (RIP)[4], either a single A chain or both an A chain and a B chain (which is a monovalent lectin). Immunotoxins containing A-chain RIPs have a definite advantage over the two-chain RIPs as they can be made absolutely target specific[5]. There is now good evidence that only one molecule of the enzymatic, toxic A chain entering the cytoplasm of a cell is sufficient to bring about the cell's destruction by totally inactivating its protein-synthesizing machinery[6]. Immunotoxins offer the advantage of providing both specificity of targeting through the antibody moiety and extremely effective inhibition of messenger RNA translation (which is increased by orders of magnitude by the product of the *tat-III* gene of HTLV-III/LAV in infected cells[7]) by virtue of the toxophore moiety.

By subverting the stratagem used by the virus for its replication, the administration