In this issue

Fish research

First there was the green revolution, then the white and now a Piscine one is upon us. From fish, we are told, comes good food, good science and the understanding of what makes sense in the human genome (Yes!). Invest in fish research and soon the discerning Bengali will be eating a boneless variety of transgenic *Hilsa* grown in her backyard tank on a diet of garbage and bio-degradable plastic. Sounds like the preaching of a vacuum-cleaner salesman who has joined the Department of Fisheries, doesn't it?

Well, let's look at what lies behind all this recent excitement. Developmental biologists have in the recent past deciphered many important rules that underlie how organisms are made. Their understanding stems mainly from experiments on worms, flies and frogs, from baker's yeast and from looking at the way flowers develop in an otherwise useless weed called *Arabidopsis*. From these seemingly random meandering in witches' brew have emerged some important generalizations. For example, the identity of units of the bodies of flies, mouse and human may be specified by very similar mechanisms. However, to understand *vertebrate* development even better we need organisms other than the mouse and the frog. Much of mouse development takes place *in utero* and when the pup is delivered it is already almost completely formed. Thus a close examination of early development is difficult, although the powerful genetics and molecular methods available make the mouse a very useful model system. The frog egg has proved invaluable for the study of vertebrate development and molecular methods have allowed classical questions to be addressed in sharper ways. But what developmental biologists needed was a vertebrate whose egg they could watch develop and with which they could do genetics in the manner they were accustomed to doing with the fruit fly *Drosophila melanogaster*. Inspired by the work of the late George Streisinger who developed the genetics of the zebrafish, many developmental biologists have adopted this animal as a model for the study of vertebrate developmental genetics. Streisinger and Shankar Chakravarty demonstrated how features of zebrafish development could allow the rapid screening for recessive mutations. Zebrafish development from the fertilized egg can be watched under the dissecting microscope easily and studies on this animal have received a recent big boost with the movement of major *Drosophila* workers into this area. They have begun to address questions, in zebrafish, to which they provided such elegant answers in their study of early development in the fruit fly. Christiane Nusslein-Volhard and her colleagues study how the co-ordinates of the egg are specified and have recently shown how many aspects of patterning are conserved between fish and flies. Chuck Kimmel and his colleagues at Oregon use zebrafish to study nervous system and muscle development and a strong school has developed in the University of Oregon at Eugene. Sudipto Roy (**page 629**) examines some recent studies, largely from the Oregon school, on the development of the zebrafish nervous system.

The pufferfish *Fugu rubripes* has been much in the news recently. If you are served something that looks like a pufferfish, an expensive delicacy, in a Japanese restaurant, ask your spouse or boss or whoever your dinner companion is, to take a bite while you go for a short walk. If, on your return, you find you have a body on your hands, it is likely that you have been served pufferfish. Apart from its grisly use in eliminating your loved ones, *Fugu rubripes* has another important feature: a genome size that is the most compact known for a vertebrate. In contrast, humans have loads of DNA whose function biologists are unable to decipher. Many have concluded, therefore, that much of this DNA is junk. *Fugu* philes say that looking carefully at the genome of this deadly fish may tell us what the minimum information requirements are for constructing a vertebrate. *Fugu* research has been pioneered by Sydney Brenner who some years earlier chose the worm *Ceanorhabditis elegans* as a model for the study of animal genetics. Brenner's success with the worm, his other major contributions to molecular biology and his exceedingly sharp mind suggest that the pufferfish should not be sneezed at. An analysis of *Fugu* research is presented on **page 627**. Pandian *et al.* summarize a recent report (**page 633**) on the study of the *Fugu* genome and wave the flag for fish research. Pandian and his colleagues also argue that investment in fish molecular biology is essential to usher a revolution that will make India a major producer of edible fish. Padhi and Mandal caution us (**page 624**) on how to do this and how not to. Pandian and his colleagues also review methods for the transfer of foreign genes into fish (**page 635**).

Research on fish had been neglected, but not anymore as the reports in this issue show. It is certain that we will learn a lot about how animals are made and genomes organized from the study of fish. It is also true that to get good inexpensive cultured fish we must invest in their study. But, just as the other revolutions have had their fierce admirers and critics you will get to hear a lot more on the subject from many sides before you get to eat an inexpensive, all-season, transgenic *Hilsa*.

K.VR

DNA gyrase as drug target

When antibiotics like penicillin began to be used, they were hailed as a miracle drugs. By killing bacteria that cause many of the worst infectious diseases, they saved countless lives. But this did not last for ever. For example tuberculosis (TB), the infectious disease described in the ancient Indian texts, has been the focus of attention in recent times. It is the leading cause of deaths worldwide from a single infectious agent and accounts for nearly 7 per cent of all deaths in developing countries. This has prompted WHO to declare a global emergency warning that the disease would claim 30 million lives in the next decade. An alarming fact is the link between TB and AIDS. In US, tuberculosis has emerged as an increasing cause of mortality among persons infected with HIV. The spread of AIDS in India (with an estimated million AIDS carriers) has given a boost to TB here as well. The weakened immune system in AIDS patients, leads not only to tubercular infections but also to other mycobacterial diseases.

In the early nineteen hundreds, the BCG vaccine was developed based on a bovine tubercule bacilli and this vaccine was subsequently used widely. TB was then thought to have been brought under control. Effective treatments for the disease came with the introduction of front line drugs like streptomycin, rifampicin, isoniazid and pyrazinamide. The effectiveness of BCG was questioned (first in the Chengalpet experiments in South India) and with appearance of tubercle bacteria resistant to the front line drugs, the disease has now assumed alarming proportions. Some of the recent clinical isolates are resistant to several drugs. Emergence of such multiple drug-resistant strains has resulted in an urgent need to develop new drugs. Recombinant DNA techniques have been invoked to develop vaccines against *M. tuberculosis*, but this process is a time consuming one and may not meet the immediate needs. So chemotherapy would be the only alternative to meet the pressing needs.

Researchers from the Indian Institute of Science, were amongst the earliest to work on the biology of *M. tuberculosis*; to try to find a molecular basis for the slow growing nature of mycobacteria; and to define possible targets of drug action. The molecular basis of isoniazid resistance was also reported by these workers. Recently extensive work has been carried out on this aspect elsewhere also.

We publish a very interesting paper by Madhusudan *et al.* (page 664) on the cloning of DNA gyrase genes from *M. tuberculosis*. DNA gyrase is an essential enzyme responsible for the formation of topological forms of DNA. The maintenance of DNA topology is vital for several cellular events such as replication and gene expression. Inhibition of DNA gyrase results in arrest of these major cellular events leading to cell death. Interestingly these enzymes are found only in bacteria and do not share all the properties with the cellular enzymes controlling DNA topology. Because of the absence of a real counterpart in the hosts, this key molecule could serve as an ideal target for conventional or rational drug design. The cloning of gyrase genes and additional genetic manipulations should help to characterize the protein and this should form a basis for drug screening experiments. Though resistance to drugs is a common occurrence, DNA gyrase offers scope to a variety of inhibitors and should prove to be an effective target. Research efforts of this kind could be a first step towards countering the resurging tubercle bacteria.