any other mutagenic agent hits the strand, breaking it or altering the nature of one of these bases, then the genetic code is altered; a mutation occurs. Genetic repair mechanisms, then, are in the business of correcting such alterations and, as Nasim and other scientists in the field are aware, these mechanisms are cellular enzyme systems.

The role of these repair systems in the production of mutants has been the focus of the work by Dr. Nasim and his group. "We became very interested after a set of experiments involving the irradiation of natural varieties of *S. pombe*, or wild-types as they're called, showed that a small percentage had become radiation-sensitive mutants. The UV light was later shown to have damaged the DNA by linking together two of the thymine bases to form a dimer. Normally, repair enzymes correct such a mistake by excising the thymine dimer and inserting monomeric (single) thymine structures into the appropriate locations so as to preserve the genetic code."

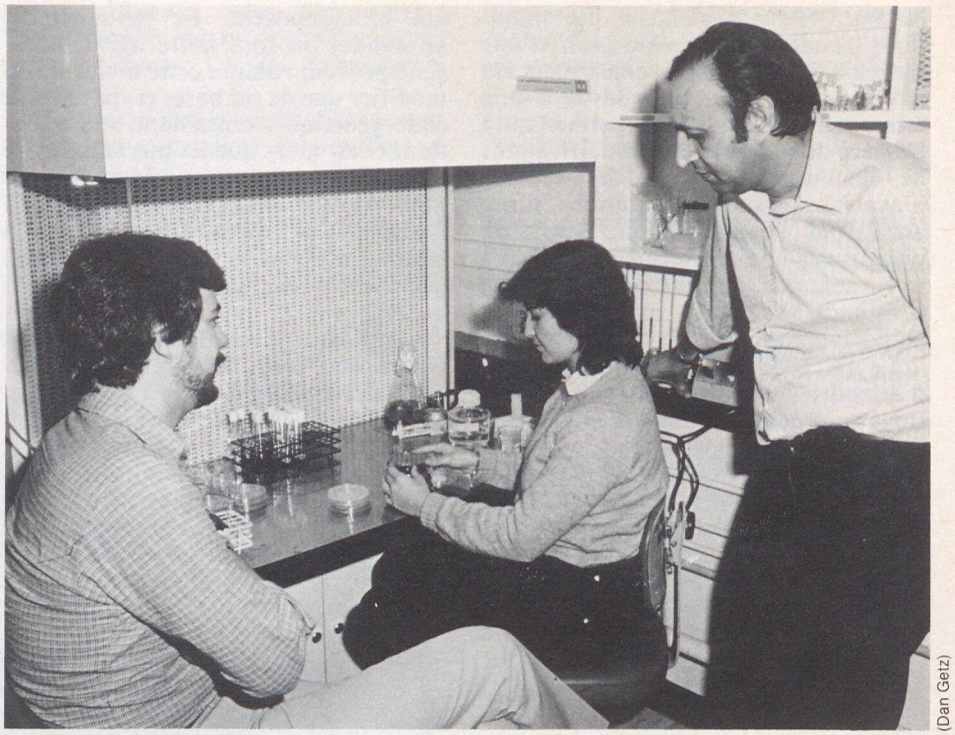
Searching for the genes responsible for the failure of these repair enzymes to correct the error, Nasim characterized 22 different kinds of radiation-sensitive mutants, that is, yeasts with mutations in 22 different locations on their DNA. When exposed once again to UV light, the response in these 22 mutants varied greatly. Some had become "supersensitive" and their survival rate was very low, while others thrived and became much more resistant. "This amazing difference in survival rate of the mutants became the focus of our efforts," explains Nasim. "Several enzyme systems, playing multiple roles in repairing damaged DNA, convey resistance to radiation in a rather complex manner. Which gene controls a particular enzyme repair system and why some are more prone to damage than others are questions which many labs throughout the world are trying to answer."

The implications of this kind of work involve much more than mere answers to questions on the nature of genetic repair systems. When repair of DNA is faulty, a cell can die. In mammalian cells, the as yet unclear chain of events that leads to cancer may indeed originate, in certain cases at least, in such DNA damage. It is already established that some diseases result from faulty DNA repair systems; one of these is a rare hereditary disease called Ataxia telangiectasia (AT). The cells of AT sufferers are unusually sensitive to radiation commonly used in radiotherapy for the treatment of tumors because they possess a faulty repair system responsible for correcting defects in DNA. In these AT patients (the disease occurs in only 24 out of every million live births), the incidence of cancer is 1 in 10, or 1200 times greater than normal risk.

Similarly, people afflicted with another rare hereditary disease called Xeroderma pigmentosum carry a mutation in which the DNA of cells which produce skin fibroblasts does not receive proper maintenance. Such people develop skin cancers when exposed to sunlight; the failure to repair DNA, at least in this disease, seems strongly implicated in the development of cancer.

Concludes Nasim: "Radiation sensitivity, as a starting point, seems to be a good indicator of a cell's ability to repair DNA damage. Radiation-sensitive yeast mutants which remain viable are remarkably useful genetic tools in the elucidation of cellular repair pathways."□

Patricia Montreuil



(Dan Getz)

Anwar Nasim and his colleagues Eric Stephen and Rita Vidoli.

Anwar Nasim et ses collègues Eric Stephen et Rita Vidoli.

Modifying microorganisms

The use of microorganisms with characterized, single gene mutations is by no means confined to the study of repair systems. The industrial applications of yeast strains improved by mutation are very well documented. For example, early laboratory strains of *Penicillium chrysogenum* (the penicillin-producing mold) yielded only a few milligrams of penicillin per litre of culture. Through 21 rounds of mutation by agents like UV light, nitrogen mustard (a powerful chemical mutagen), and X-rays, researchers obtained a strain capable of producing 55 times the initial amount of penicillin.

With an expertise accumulated over the years, Dr. Nasim and his associates are looking forward to applying these techniques and principles to biotechnological ventures. According to Nasim, knowledge of the potential capabilities of the large number of existing, unexplored yeasts is really very limited. By modifying these microorganisms with mutagens and then manipulating them with genetic engineering techniques, new avenues of exciting research will be opened up. The ability to ferment a vast number of organic substrates to the liquid fuels ethanol and methane is only one of the many examples that illustrate the point.

The induction of new mutations into the gene banks of living systems has always been nature's way of carrying out evolution and is now the geneticist's way of introducing valuable new traits into microorganisms.□