A stupid cell with all the answers - baker's yeast

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Here's a quiz that you won't be given in any biology course:

1. Which of these creatures has been domesticated longest? a) the horse b) the camel c) the roach d) yeast

2. Who or what is prominently depicted in a wooden model from an ancient Egyptian tomb at Thebes, c. 2000 B.C.? a) King Mentuhotep in a battle b) Queen Hatshepsut in a bathtub c) a dice game in Alexandria d) yeast

3. What's the fastest-growing research subject in biology? a) cancer b) AIDS c) Caenorhabditis elegans (a slimy, translucent worm) d) yeast

The correct answer to all these questions is yeast. Not Candida albicans, the bane of the eleven million American women who suffer from recurring yeast infections, or Epidermophyton flocco- sum, which is responsible for athlete's foot, but Saccharomyces cerevisiae, better known as common baker's yeast. Of the rough- ly 60 genera and 600 species of yeast, microscopic, single-celled fungi that live in colonies, Saccharomyces cerevisiae is the one that swells bread, brews beer, and bubbles champagne. It's also the yest that biologists are probing to get at the intimate de- tails of genes, proteins, and the lacy architecture of living tissue, hoping it will lead them to, among other things, innovative treatments for cancer and AIDS.

Once dismissed by scientists as a "stupid" organism hardly worth its weight in bicarbonate of soda, yeast is now hailed as the most important model for answering the big seductive questions of cellular biology. How do you make a chromosome? How do the thousands of different proteins and en- zymes in a cell know precisely where they're supposed to go, or what they should do once they get there? What signals tell a cell it's time to divide or stop dividing? How does one cell communicate with another, or detect subtle changes in its surroundings? Says Ira Herskowitz, a geneticist at the University of California at San Francisco, "If you want to understand a process at the mo- lecular level, the best -- and in some cases the only -- place to start is with yeast."

Before you protest that yeast is yeast and people are people, and that what's learned from Saccharomyces cerevisiae couldn't apply to us, be warned that the more scientists peer into the yeast cell, the more human it appears. "If you were to break open a human cell and a yeast cell and compare them under a microscope, you'd have a terrible time telling the two apart," says Ron Davis, a Stanford molecular geneticist. Like us, yeast has two genders and reproduces with cells similar to eggs and sperm. It is a true eukaryote: each cell has a nucleus that separates its DNA from the viscous body of the cytoplasm (bacteria and other lowly organisms are prokaryotes, lack- ing a nucleus). Its 17 pairs of chromosomes behave remarkably like our 23 pairs, and can make the same mistakes during reproduction that in humans lead to such chromosomal disorders as Down syndrome. It manufactures enzymes similar to ours, and ferries them around inside itself and re- leases them in much the same way -- and for much the same reasons -- that our pancreatic, liver, or brain cells do. Most surprising, it harbors the oncogenes that are thought to trigger cancer, as well as versions of the viruses responsible for leukemia and AIDS.

"When I started studying yeast, back in the Sixties, people told me I was wasting my time, that yeast was garbage," says Gerald Fink, a molecular biologist at the Whitehead Institute for Biomedical Research in Cambridge, Mass. "They said crazy things, like 'Yeast doesn't have DNA.' Now, every time we go looking in yeast for some supposedly higher biological process, we find it."

Davis wags a thumb and forefinger in the air, as though shaking the familiar red and yellow package of Fleischmann's yeast. "It may be hard to accept," he says, "but these are our relatives."

From a scientific standpoint, however, yeast cells have numerous advantages over Uncle Jake's or Grandma's. Unlike normal human tissue, yeast thrives in a petri dish. It divides once every two hours or so -- whereas some human and mouse cells take twelve hours or more. This means that experiments can be completed more quickly.

Yeast has only about 10,000 genes, less than three per cent of the 400,000 found in human cells, and so can be more easily mapped and analyzed in fine detail. And yeast genes are as supple as Play-Doh. By exposing dishes of yeast cells to radiation or mutagenic chemicals, scientists can generate a vast sideshow of mutant strains. The behavior of those mutants can be studied for clues to the roles of their genes in genetic defects. Through genetic engineering, biologists can knock out or reorganize genes scattered along yeast chromosomes, a difficult undertaking with human DNA owing to its greater complexity. "One way to put it," says James Hicks, a geneticist at the Research

Institute of Scripp's Clinic in

La Jolla, Calif., "is that yeast just opened its arms and said,

'Take me!' "

And biologists have obliged. Scientists who once struggled with inbred mice or ungainly slices of human tissue are skipping down the evolutionary scale to take on yeast. "I had a guy come see me the other day -- one of the best cell biologists in the world," says

Herskowitz. "He's working with this enzyme that's just been discovered, called kinesin, and his greatest hope is that the enzyme exists in yeast." There isn't a university of major, or even middling, stature that isn't trying to hire yeast geneticists; more than twenty per cent of the biology department at MIT is now engaged in yeast research, and the figures aren't much lower at Harvard, Princeton, and other institutions with outstanding departments.

"You want a good illus- tration of how things have changed?" says Fink. He bounds over to his office bookshelf and pulls down several volumes. "These are the proceedings from the first yeast meeting held at Cold Spring Harbor, in 1975," he says, referring to the famous biology symposium held on Long Island every other summer. The volume is perhaps a quarter of an inch thick and contains a scant 80 reports. "This is 1977," he says, holding up a book triple the size of its 1975 forebear. "And 1981" -- almost an inch thick -- "and the most recent, from 1985." This one is even thicker and contains 390 reports. The proceedings for 1987, he says proudly, will have to be split into two volumes. "The biggest problem in the yeast field now is finding a facility large enough to hold a meeting," says Davis. "Today we have to look for an amphitheater, or a football stadium, or maybe a small city." At a recent international gathering of geneticists, someone drew a plot showing that if the current exponential trend continues, by 1995 everybody alive will be studying yeast.

Like poverty, yeast has always been with us. The Egyptians are believed to have discovered its extraordinary properties 6,000 years ago, when a few stray spores drifted into an open vat of freshly crushed grapes, converting the juice into wine. Early oenologists had no idea how the fun- gus worked -- or even that it was alive -- but they carefully culled the white yeast sediment that fell to the bottom of every batch of wine and added it to the next generation of juice. It didn't take long, legend has it, before some inspired baker of flatbread, looking to add flavor to his wares, put a little wine in his dough -- and, to his surprise, soon found it was rising. The twin arts of brewing and bread baking were awarded equal stature in the ancient world; in the tomb of a rich estate owner at Thebes, mentioned in the above quiz, a brewery is depicted right beside a bakery.

In many languages the word for yeast derives from a description of what it does, rather than what it is: the French levure comes from the verb to raise; the German hefe, from to lift; and the English word is derived from the Greek zestos, boiled. The Israelites considered yeast to be so important that the hardship of having to do without it during the Exodus is still recalled at Passover by the practice of eating only unleavened bread. "Why is this night different from all other nights?" asks Hersko witz, reciting a line from the Passover Seder. "Because the ancient Hebrews didn't have any Jewish yeast geneticists with them."

In the 1850s, long before any geeticists, Jewish or otherwise, became fascinated with yeast, Louis Pasteur discovered that fermentation is the metabolic by-product of feasting yeast. Until then, people believed that fermentation occurred either spontaneously -- the way maggots were thought to arise spontane- ously from putrefied meat -- or through some inorganic reaction similar to the oxidation of iron into rust. Pasteur analyzed droplets of grape juice at various stages of fermentation and demonstrated that live cells were responsible for converting the rich sugar of the juice into primarily two compounds: carbon dioxide and ethyl alcohol. He then boiled the wine, killing the yeast, halting fermentation, and making his name a household word; to pasteurize means

to kill microorganisms with heat. "Pasteur's work marks the beginning of modern biology," says David Botstein, a yeast geneticist at MIT.

Modern biochemistry, the study of enzymes, among other things, was also born of yeast. In fact, the word enzyme came from the Greek "in yeast," and with good reason: the first enzymes were isolated from Saccharomyces. In 1896, German chemist Eduard Buchner ground yeast with sand and then pressed the broken cells until a viscous yellow fluid seeped out. He had intended to use the fluid for pharmaceutical studies and added cane sugar to preserve it. But, surprisingly, without the yeast cells the fluid still fermented the sugar. This seemed to contradict Pasteur's theory that living cells were required to convert sugars into alcohol. Buchner extracted the fermentation enzymes from yeast, and determined that they remained active as long as they weren't destroyed by boiling. The particulars of the biochemical process were soon mapped for both fermentation and the raising of dough. It turned out that which of these occurs depends on the amount of oxygen avail- able. Saccharomyces eats sugar wherever it can find it (hence the name, which means sugar fungus). When confined to the oxygen-poor atmosphere of the brewer's vat, yeast breaks down the sugar anaerobically: each carbohydrate molecule is transformed into equal amounts of carbon dioxide and ethyl alcohol. Yeast in bread dough works aerobically, turning carbohydrates primarily into carbon dioxide, which makes the dough rise. That's why you must repeatedly knead dough before baking it: to deliver a renewed supply of oxygen to the yeast.

In the half century after Buchner's discoveries, biochemists used yeast to perform enzymatic experiments, not because of its elegance as an organism but because huge supplies of it could be bought for pennies from the neighborhood bakery. "Any time we wanted to do something, we'd wander down to the bake shop," says Graham Stewart, technical director of the Labatt Brewing Co. of London, Ont., who began his yeast career in 1962 at the University of Wales in Cardiff. "And we'd come back laden with enormous blocks of the stuff. Yeast was so bleeding cheap." In the search for arcane enzymes involved in energy metabolism, the synthesis of amino acids, and other processes, yeast cells were pulverized en masse, with little regard for their specialized re- productive cycle.

But beginning around 1950 a few geneticists realized that yeast was much better alive than dead. Not only does it have a nucleus, but it also has the capacity to survive with either a duplicate set of chromosomes, in what's known as the diploid state, or with a single set, as a haploid (see diagrams, pages 80-81). In other words, a yeast cell may have either two copies of every gene or one copy.

When food is plentiful, yeast cells exist as diploid cells and multiply rapidly through a process called mitosis. To reproduce, a diploid duplicates all its chromosome pairs and then divides into a mother cell and a daughter bud, each containing dual copies of every chromosome.

In lean times, yeast doesn't have many options for surviving -- it can't just trot off to find fresh reservoirs of sweets. What it can do is sporulate, which is rather like going into hibernation. It stops dividing and undergoes meiosis, the production of its equivalent of sperm and egg cells. It duplicates its chromosome pairs, and each of the four resulting chromosome sets is incorporated into a tiny cell. Each cell has a gender, called (for reasons known only to Carl Linde- gren, who first used the terms in 1943, when he was at Washington University in St. Louis) either a or alpha. The four cells develop within the mother cell as a unit, encased in thick sugar coats that allow them to weather deprivation. Upon encountering a food supply, the cells burst from the shell and begin to grow as haploids. They can reproduce mitotically, like their parent diploids, but produce only haploid offspring. These haploid cells may have sex, in the Platonic sense of two halves becoming a whole. When an alpha cell comes close enough to touch an a cell, the two fuse to form a diploid and the cycle begins anew.

Yeast's oscillation between haploidy and diploidy offers geneticists a chance to study a broad array of mu tations. And biologists love a good mutant -- not out of

ghoulish curiosity but because the behavior of a mutant gene provides the best insights into the functions of a healthy one. "Often the only way to understand what's right with something is to see what happens when it goes wrong," says David Baltimore, the director of the Whitehead Institute.

The shift from diploid to haploid makes yeast an ideal laboratory for studying both dominant and recessive mutations. A dominant mutation is one that shows up even if only one copy of a diploid cell's genes is affected; many cancers result from dominant mutations in genes controlling cell growth.

A recessive mutation only reveals itself if both copies of a gene are identically altered, or if the normal copy is somehow rendered inactive. A classic example of a recessive disorder in man is sickle cell anemia. A person with one copy of the normal hemoglobin gene and one copy of the mutant sickle cell gene suffers no apparent ill effects. But if both parents carry the mutant gene, each of their offspring has a one-in- four chance of receiving a double hit, and thus of contracting the disease.

It's exceedingly difficult to study recessive mutations with most laboratory animals, because you can't know whether an animal carries the defective gene until it produces offspring. In yeast, though, what's recessive to a diploid cell is dominant in half its haploid offspring. A yeast biologist can take a diploid cell that possesses a recessive trait, force it into meiosis, and study the effects of the mutant gene -- which, on average, will turn up in two of every four haploids -- freed of the masking effects of a healthy counterpart.

Depending on the role of the affected gene, the mutated haploid may grow slower or faster than a normal one, require exotic nutrients, refuse to divide, be unable to mate, or otherwise behave pathologically. The nature of the handicap reveals how the healthy gene ordinarily works. "We're like auto mechanics," says Leland Hartwell, a geneticist at the University of Washington. "You come in to get your car repaired, and the mechanic asks, 'Does it start?' Yes, it starts. 'Well, then, does it go anywherewhen it's started?' You say, no, it doesn't move. So then the mechanic knows there must be a problem in the gear box. That's what we do -- tinker with parts."

Other yeast biologists refer to Hartwell as the grandfather of cell-cycle mutations. He earned this honorific in the late 1960s, when he created hundreds of mutant strains of yeast that are now the foundation of much of genetic analysis. He and his students exposed plate after plate of yeast colonies to mutagenizing chemicals. They gathered yeast with mutations that affected different stages of the cell's life cycle. Many of the treated cells perished

under the toxic onslaught, but enough survived to exhibit an array of dominant and recessive mutations.

Some of the mutant cells were also temperature sensitive: at room temperature, they looked and acted like healthy yeast, but if the heat in the incubator was jacked up to 100 degrees F. the mutations were activated, and the cells ceased growing at whatever stage of the cycle was governed by the mutated gene. (Normal yeast cells aren't affected by such heat.) Hartwell was able to flick different genes on and off just by twiddling the thermostat -- like stop-action photography, he says.

After Hartwell had exposed his mutants to the so-called non-permissive temperature, or that temperature at which the mutation expressed itself, he examined the sizes and shapes of the different cells, now stopped dead in their tracks. That analysis allowed him to gauge which genetic wires had been crossed. Some cells couldn't divide: a crucial gene controlling DNA synthesis could have been perturbed. Some of the cells' buds remained stuck to the mother cell's side: a gene controlling chromosome separation may have been shut down.

Over several years Hartwell identified fifty or so genes involved in various stages of the cell cycle and grouped them according to their general contribution -- those that regulate DNA synthesis, those that orchestrate chromosome separation, and so on. His work was far more than a technical tour de force. Many of the genes he identified are factors in cell division. In yeast, these genes direct mitosis and meiosis, and Hartwell thinks similar genes control cell division in human DNA. "Cell growth is cell growth," he says, "and the means of regulating that growth are likely to have been at least partly conserved through the ages."

As Hartwell was finishing his identifications, another age was beginning: the era of genetic engineering. With the advent of recombinant DNA technology, biologists began using the genetic probes and enzymes first found in E. coli to manipulate yeast genes -- in the same way that other researchers were cloning genes from fruit flies, rats, and man. But those studying yeast weren't satisfied with imitating everybody else. Yeast was too exceptional and too versatile to be treated like a mere rodent or insect. Through a collaborative effort involving half a dozen labs -- a rarity in the Darwinian world of basic research -- yeast biologists figured out how best to rework cloning protocols to suit their beloved organism. "It was really great, getting together as a team, instead of trying to snipe at your competitors," says Hicks. "That's why we've been able to push the technology so far, and still have fun doing it."

This cooperation yielded a technique, called transformation (see diagram, page 82), that revolutionized yeast ge- netics, enabling yeast researchers to do something other biologists couldn't: create mutations in any genes they chose to study. In an archetypal

experiment, Fink, Hicks and Albert Hinnen, a molecular biologist now at Ciba-Geigy in Basel, used a diploid cell in which both the genes that control the synthesis of leucine, an amino acid fundamental to fungal growth, were mutated. A healthy copy of the leucine gene was tucked into a bacterial plasmid, a circle of DNA that penetrates nuclear membranes. When rapidly dividing yeast mutants were flooded with those plasmids, one was occasionally fooled: it swapped its own faulty leucine gene for the plasmid-borne interloper, thereby becoming transformed. The transformed cells were able to grow without leucine added to their culture medium -- proof that they possessed at least one copy of the normal leucine-making gene. And the DNA of the transformed yeast contained pieces of the bacterial plasmid -- evidence that the yeast and the plasmid had actually swapped a segment of DNA.

The spectacular success of the Fink-Hicks-Hinnen ex- periment meant that yeast biologists no longer had to rely on randomly generated mutations. A gene could be pinched from the yeast, changed, and then inserted back into just the right spot on the chromosome. With mammalian cells, scientists don't have the freedom to pick and choose, don't have control. A cloned gene in the nucleus of an animal cell integrates itself randomly into the DNA. "Animal cell people have to take what they can get," says Fink. "They'd kill to have something like transformation." When you transform a yeast cell, says Scott Powers, a yeast biologist at Cold Spring Harbor, "you feel as though you're playing God."

The new opportunities provided by yeast transformation have already yielded a remarkable pay-off, a synthetic vaccine against hepatitis B, the disabling and sometimes fatal liver disease. Researchers at Merck and Co. and at Chiron, a California biotechnology company, created the vaccine by inserting a hepatitis B gene into yeast nuclei. The transformed yeast cells began to manufacture large quantities of a protein from the virus's outer shell. This protein was then isolated and purified to produce a vaccine.

Transformation has also allowed yeast researchers to tackle some of the deepest mysteries of cell biology -- among them the nature of the cytoskeleton, the filamentous beams and girders that give a cell its shape and flexibility.

One body of research has focused on a cytoskeletal protein named actin. John Abelson of Caltech, for example, wondered whether yeast might have actin, too. So he combed through yeast DNA with an actin gene probe purified from chicken brains. (If the yeast had a gene even distantly related to animal-cell actin, the chicken DNA would link with it.) Six years ago Abelson struck a mother lode. Yeast did have an actin gene, and it wasn't a third cousin once removed to the chicken gene but almost an identical twin. If the amino acid sub-units encoded by the two genes are compared, they turn out to be 91 per cent alike. It was an astounding example of evolutionary conservation and a strong indication that any knowledge about actin gleaned from yeast would almost certainly apply to man, whose actin is probably closely related to the actin of other vertebrates.

To study actin's function in yeast, Botstein created yeast with an actin gene that was disabled only at raised temperatures. When grown at 100 degrees F., the yeast was incapacitated. Without an actin infrastructure, its internal compartments appeared swollen; it had difficulty secreting enzymes; and, unable to divide without actin, the yeast soon died. Botstein's results indicated that actin is an octopus of a protein, whose arms manipulate a variety of cellular activities, from structural rganization to enzyme shipment.

In a similar series of experiments, Botstein has used yeast to explore the gene for another cytoskeletal protein -- tubulin, the main constituent of the microtubules that weave through the cytoplasm of all our cells. The actin and tubulin work is important because, as the principal structural elements in all living tissue, these proteins are among the first to go awry when cells turn cancerous. Biologists believe it's through the loss of architectural stability that malignant cells break away from a primary tumor and begin to spread, or metastasize. By understanding how actin and tubulin work, researchers have a better chance of designing cancer drugs that inhibit the dilapidation of the cytoskeleton.

In addition to helping in the analysis of proteins, yeast is assisting scientists in prying apart the structure of chromosomes. Until yeast came to their aid, biologists had on- ly a vague idea of what chromosomes were; all they knew was that genes were somehow divvied up among them. To probe that structure, Davis and his students at Stanford identified the genetic sequences in yeast that control the movement of chromosomes during division: the centromere, the tiny button in the center of a chromosome, and the telomeres, the caps found at each end. Davis found he could plug any segment of DNA -- even one from a bacterium or a man -- between the centro- mere and telomere sequence of a yeast chromosome and introduce the artificially created chromosome into a yeast nu- cleus. The yeast cell would treat the new chromosome as a member of the family, replicating the ungainly string of DNA during mitosis and meiosis. The artificial chromosome was regarded by the host yeast as the real thing. "That's all there is to a chromosome -- the stuff

between telomere and centromere," says Davis. "The mystery is gone."

Through yeast research, Davis is now trying to pinpoint the proteins that latch on to the centromere during meiosis, when the chromosomes are tugged apart. It's at the centromere, he believes, that disastrous flaws can occur during chromosome separation in human reproduction -- as when two copies of chromosome 21, rather than one, are mistakenly apportioned to a sperm or egg cell, resulting in Down syndrome. "Our goal is to identify the moment when medications are most likely to be effective in encourag- ing chromosome segregation," Davis says. "For older women who wish to bear children, such drugs could help prevent birth defects. All this and more from a simple little fungus."

Yeast may also help researchers unravel the mysteries of AIDS. In 1985, Fink found something vaguely like an AIDS virus in yeast. To be sure, these viral particles don't make yeast immune-deficient, and there are certainly no yeast white blood cells for them to attack. But the fungal virus, like the lethal human microbe, is a retrovirus: meaning that, rather than carrying its own DNA to commandeer the cell's machinery directly, it copies its genetic information into the host cell's DNA. "Retroviruses may be the price yeast pays for being too much like an animal cell," says Fink. "Our understanding of how the human AIDS virus is regulated is especially wimpy. These retroviral particles in yeast give us our best shot at filling in the molecular blanks."

Yeast researchers agree that Herskowitz is Hartwell's heir as the pre-eminent practitioner of their speciality. He has brought yeast to developmental biology, the study of how a single fertilized egg blooms into a complex creature with a nose, brain, toenails, and islets of Langerhans. A central question posed by developmental biology is why, if every cell in our body has the same set of chromosomes, liver genes are flipped on in liver tissue while the genes for, say, skin are shut down. This is called genetic differentiation. "It's true that a yeast cell will never grow up into something that can toss a basketball," says Herskowitz, "but its genes are regulated by the same kind of signals that turn genes on and off during man's development."

Herskowitz has focused on yeast's best approximation of genetic differentiation, something called yeast mating types, or gender. Normally, yeast diploids are conformists. Not only do they all look round and white, but in each cell the same genes are activated and the same proteins produced. However, when haploids are generated during meiosis, sexual specialization begins. Both alpha and a cells are endowed with the same 10,000 genes, but a slightly different selection of those genes is switched on in each type, a difference that becomes evident during mating. When an alpha is ready for yeastian intercourse, it secretes a hormone known as alpha factor, which has a dramatic effect on any nearby a cell. The a cell immediately stops dividing; it changes into a pear shape that yeast biologists have nicknamed "shmoo" after the Al Capp cartoon character; its surface gets sticky; and it secretes a factor, which causes identical changes in the alpha cell. "I call it foreplay," says Hartwell. The two haploids then merge into a diploid, at which point the alpha and a genes on both chromosome sets are shut down. The new diploid loses its sexuality and reverts to the drab state at which it began.

Says Herskowitz, "Our question was, How do the sexual genes know to turn on in the haploid and turn off in the diploid?" In 1975, Herskowitz, assisted by Hicks and Jeffrey Strathern, then graduate students, found his extraordinary answer in something called the mating type, or MAT locus, a master regulatory switch. The MAT locus is a place on the yeast DNA where sequences are changed in mother cells to make one or the other of the two sexes. Herskowitz calls this theory of genetic programming the cassette model (see diagram), because the MAT locus is like a cassette deck, waiting for its genetic tape to be changed. In a diploid cell, the MAT locus is shut down, its genes silent. But when a diploid duplicates its chromosomes to generate haploids, the separate genes for a-ness or alpha-ness, scattered at various sites throughout the chromosomes, are activated in a predetermined sequence, controlled by instructions from the MAT. A powerful switch, or promoter, at the beginning of the locus allows either the a or the alpha tape to begin playing. A haploid can perform the duties of its designated gender, including secreting factors and respond- ing to the attentions of the opposite sex.

The cassette model provided a glimpse of how sets of genes may be controlled from one cell type to the next -- an important concept for developmental biology. The difference between muscle tissue and bone tissue may be not a single gene but large genetic groups. And those groups presumably must be controlled in a strictly coordinated manner -- perhaps through MAT- like loci. "It's not hard to imagine a cassette mechanism regulating the development of different tissue types," says Hicks.

Using these results as a model, scientists can begin examining how flies grow wings, how mice grow whiskers and -- eventually -- how Dr. J grew his pogo-stick legs. However, even these insights don't link yeast as closely to man as does the recent and spectacular discovery of genes associ- ated with ancer in yeast. Michael Wigler of Cold Spring Harbor, the man credited with this finding, is one of those biologists who gladly traded animal cells for yeast. For five frustrating years he had been studying the ras genes, a class of genes isolated from human tumors of the bladder, breast, colon, and lung. He and others had determined that ras genes existed normally in the cells of all men and animals, and that a mutation in a single one somehow sparked cancerous growth.

Although the ras genes had been cloned and analyzed, nobody could figure out how they touched off rabid cell division. Mammalian cells are too labyrinthine to allow biologists to trace the molecular pathway of a lone protein. So when Wigler's postdoc, Scott Powers, located a ras gene in yeast, Wigler was delighted. He was even more so when he learned that, for lengthy stretches,

the yeast ras was 85 per cent identical to mammalian ras.

With assistance from James Broach, a distinguished yeast molecular biologist now at Princeton, Wigler's group put together a yeast ras gene with a mutation that corresponded precisely to a cancerous mutation of the human ras. The transformed yeast cells acted as if they were cancerous. Even when deprived of nu- trients, the mutant haploids maintained their voracious appetites, refusing to enter a resting stage.

Wigler found that the yeast ras gene creates a protein that boosts the level of a molecule called cyclic AMP. Cyclic AMP, in turn, regulates the cell metabolism in such a way as to raise the general level of activity of the cell. "We were jumping up and down at that discovery," says Wigler. "We thought we'd found the secret to cancer."

Unfortunately, the answer may not be so simple. When Wigler's group tested their hypothesis by injecting mutant ras proteins into cells of the African toad Xenopus, there was no measurable increase in cyclic AMP. But Wigler still believes the ras genes of yeast and animals look too much alike for there not to be some biochemical correlation, and he's still looking for one.

If his search succeeds, the discovery will have a dramatic impact on cancer treatment. By some estimates, a mutation in the ras gene may be responsible for as many as 40 per cent of all tumors. And once the biochemistry of a gene is understood, it's a fairly straightforward step to determine where along the biochemical process to intervene. It would be premature to claim that yeast will show the way to a cure for cancer. But, given how useful to science yeast has already proved to be, don't count out that possibility.