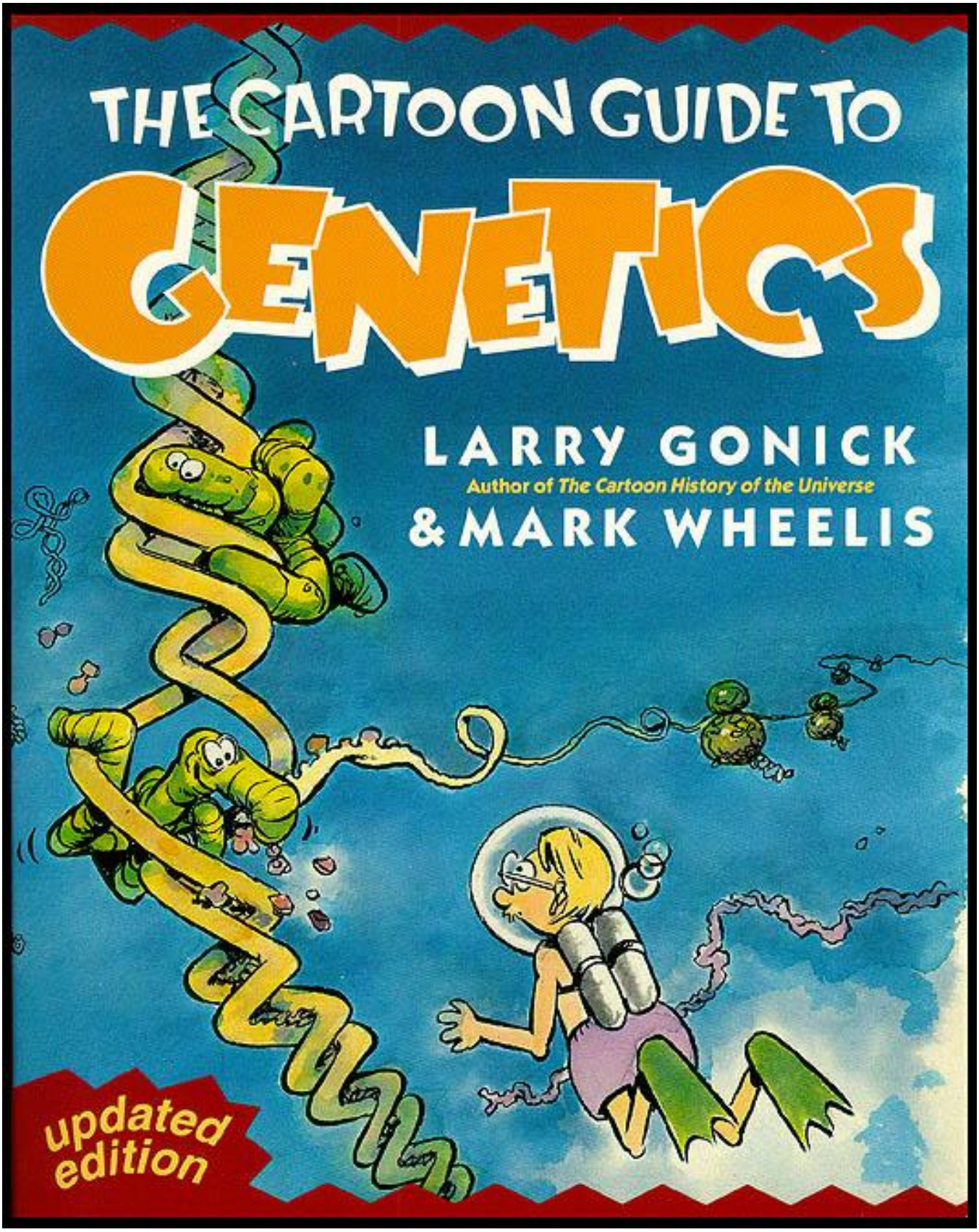
THE CARTOON GUIDE TO GENETICS

LARRY GONICK
Author of *The Cartoon History of the Universe*
& MARK WHEELIS



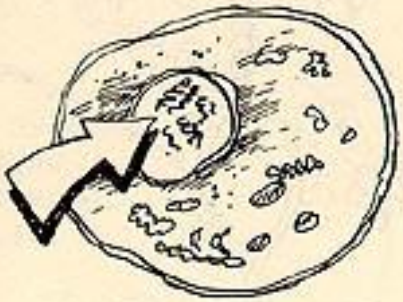
updated edition

PRO AND EU

WE BEGAN BY ASKING ABOUT GORILLAS AND BANANAS, AND ENDED UP INSIDE SOME INSIGNIFICANT LITTLE BUG, *E. COLI*... NOW WHAT CAN WE SAY ABOUT OTHER LIFE FORMS?

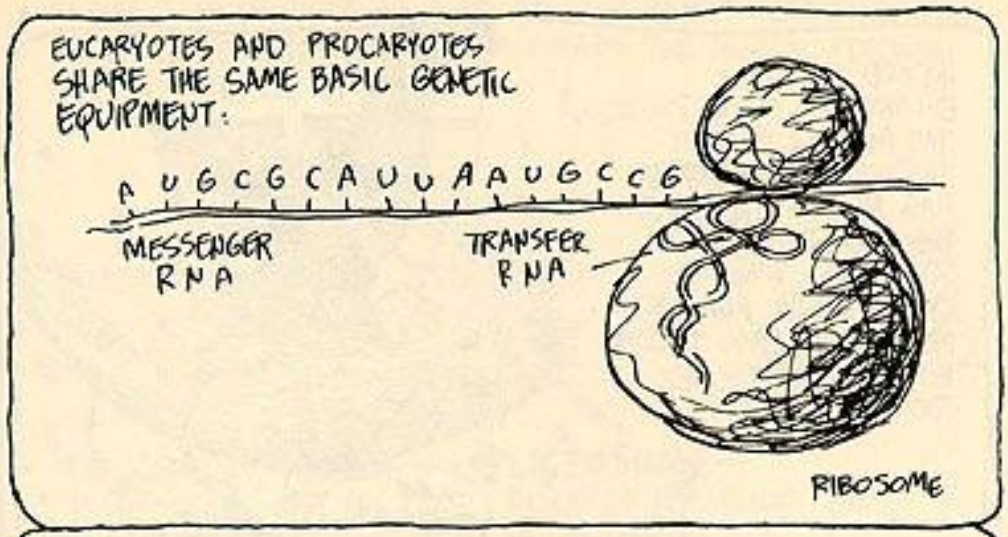
FIRST, SOME MORE *JARGON*: THE CELLS OF PLANTS, ANIMALS, AND OTHER ADVANCED CREATURES — IN FACT, ANY CELL WITH A *NUCLEUS* — IS CALLED A *EUCARYOTE* ("YOU-CARRY-OAT"), MEANING "GOOD NUCLEUS" IN GREEK.

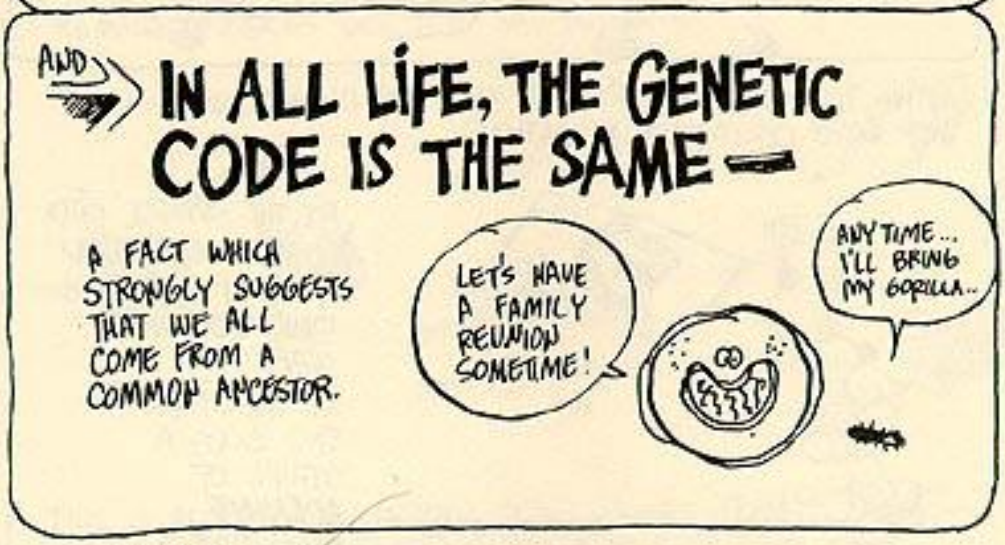
EUCARYOTES CONTAIN ALL SORTS OF BODIES, BUT THE KEY IS THE NUCLEUS, WHICH CONTAINS THE CHROMOSOMES.

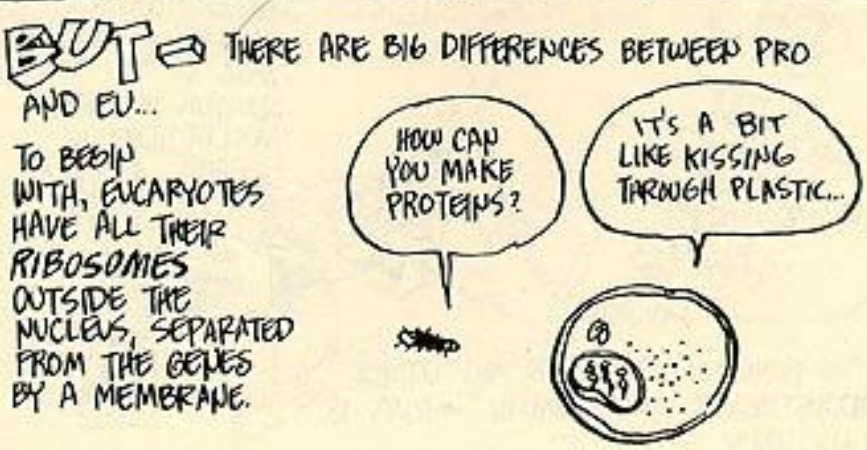


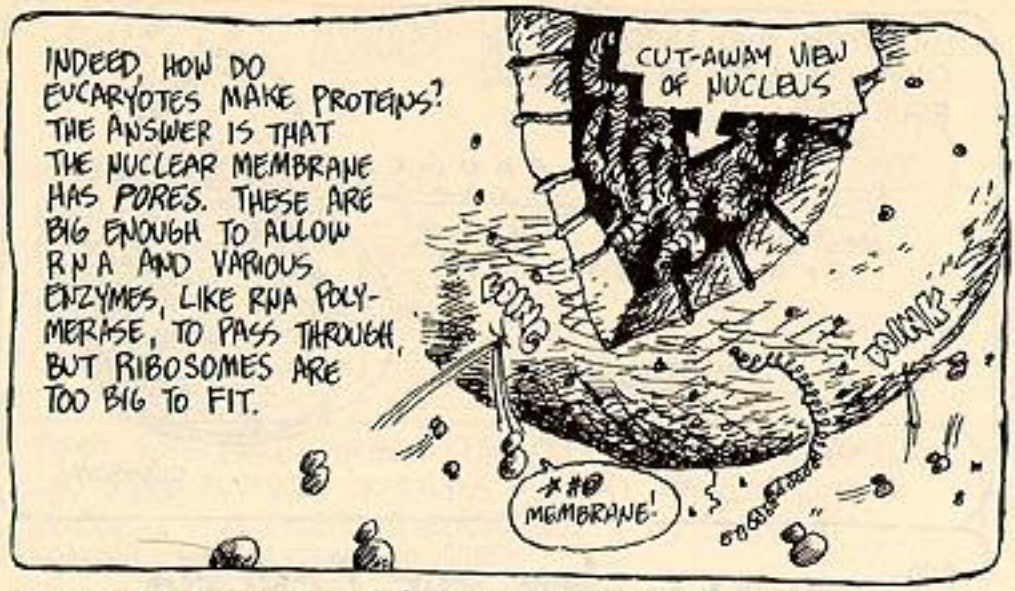
THE TINY BACTERIA, WITH THEIR SIMPLER STRUCTURE, ARE CALLED *PROCARYOTES* ("PRO-CARRY-OATS"), MEANING "BEFORE NUCLEUS" IN GREEK.

THE IDEA IS THAT PROCARYOTES MUST HAVE EVOLVED ***BEFORE*** THE MORE COMPLICATED EUCARYOTES.

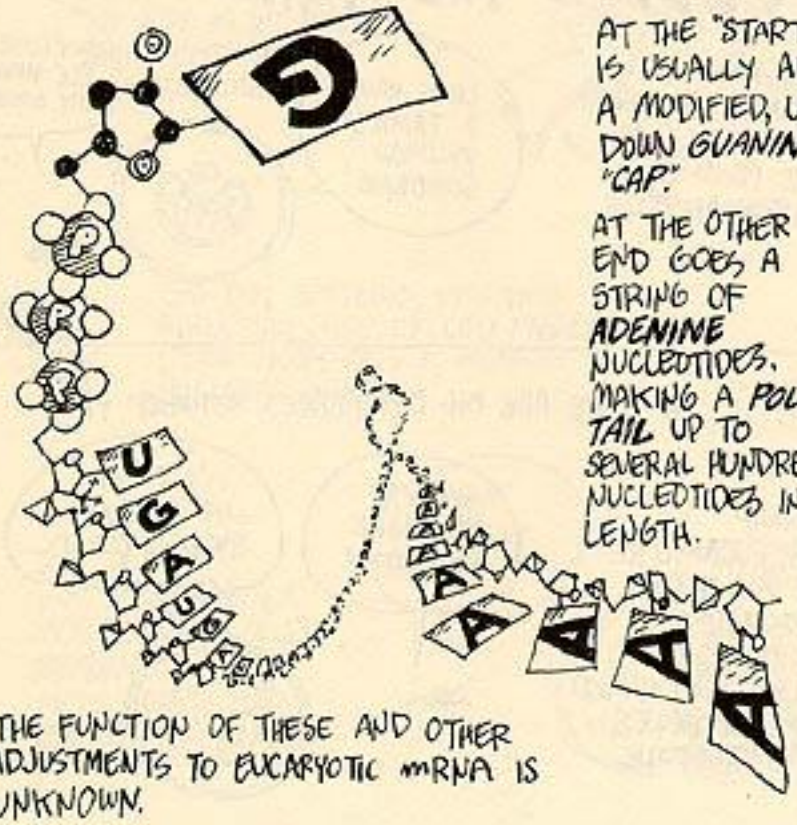

EUCARYOTES AND PROCARYOTES SHARE THE SAME BASIC GENETIC EQUIPMENT:
A U G C G C A U U A A U G C C G
MESSENGER RNA
TRANSFER RNA
RIBOSOME


AND
IN ALL LIFE, THE GENETIC CODE IS THE SAME
A FACT WHICH STRONGLY SUGGESTS THAT WE ALL COME FROM A COMMON ANCESTOR.
LET'S HAVE A FAMILY REUNION SOMETIME!
ANYTIME... I'LL BRING MY GORILLA..


BUT
THERE ARE BIG DIFFERENCES BETWEEN PRO AND EU...
TO BEGIN WITH, EUCARYOTES HAVE ALL THEIR RIBOSOMES OUTSIDE THE NUCLEUS, SEPARATED FROM THE GENES BY A MEMBRANE.
HOW CAN YOU MAKE PROTEINS?
IT'S A BIT LIKE KISSING THROUGH PLASTIC...



WITHIN THE NUCLEUS, mRNA IS MADE AS IN BACTERIA — BUT THEN COME CERTAIN MODIFICATIONS...

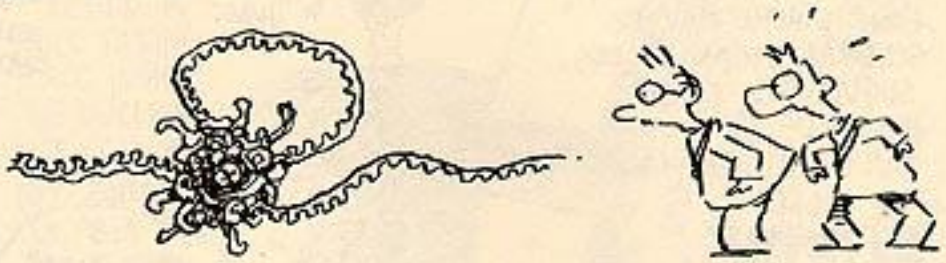


AT THE "START" END IS USUALLY ADDED A MODIFIED, UPSIDE-DOWN *GUANINE* "CAP."

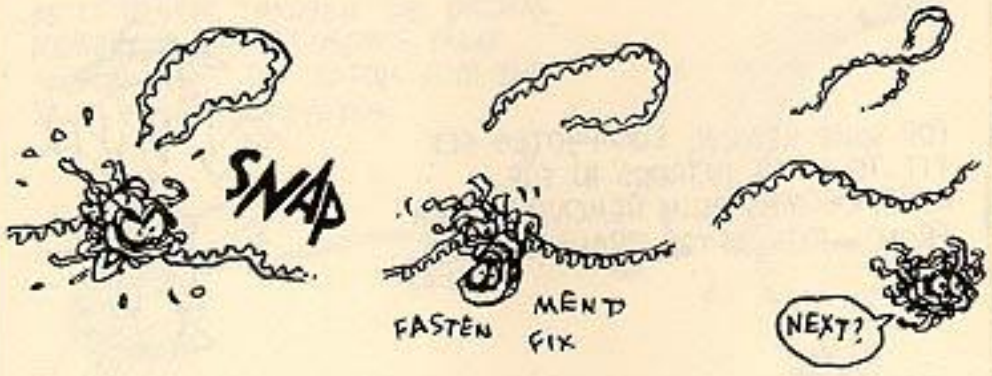
AT THE OTHER END GOES A STRING OF ***ADENINE*** NUCLEOTIDES, MAKING A ***POLY-A TAIL*** UP TO SEVERAL HUNDRED NUCLEOTIDES IN LENGTH.

THE FUNCTION OF THESE AND OTHER ADJUSTMENTS TO EUCARYOTIC mRNA IS UNKNOWN.

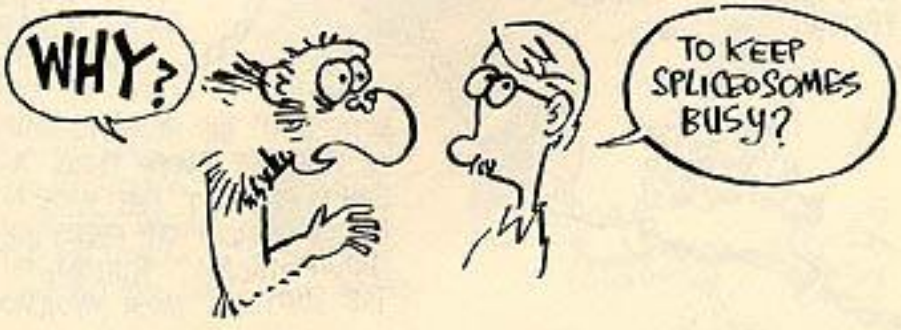
THE NEXT MOVE CAME AS A GREAT SURPRISE TO GENETICISTS: A COMPLEX OF PROTEIN AND RNA GRABS THE mRNA, FORMING LOOPS, LIKE THIS →

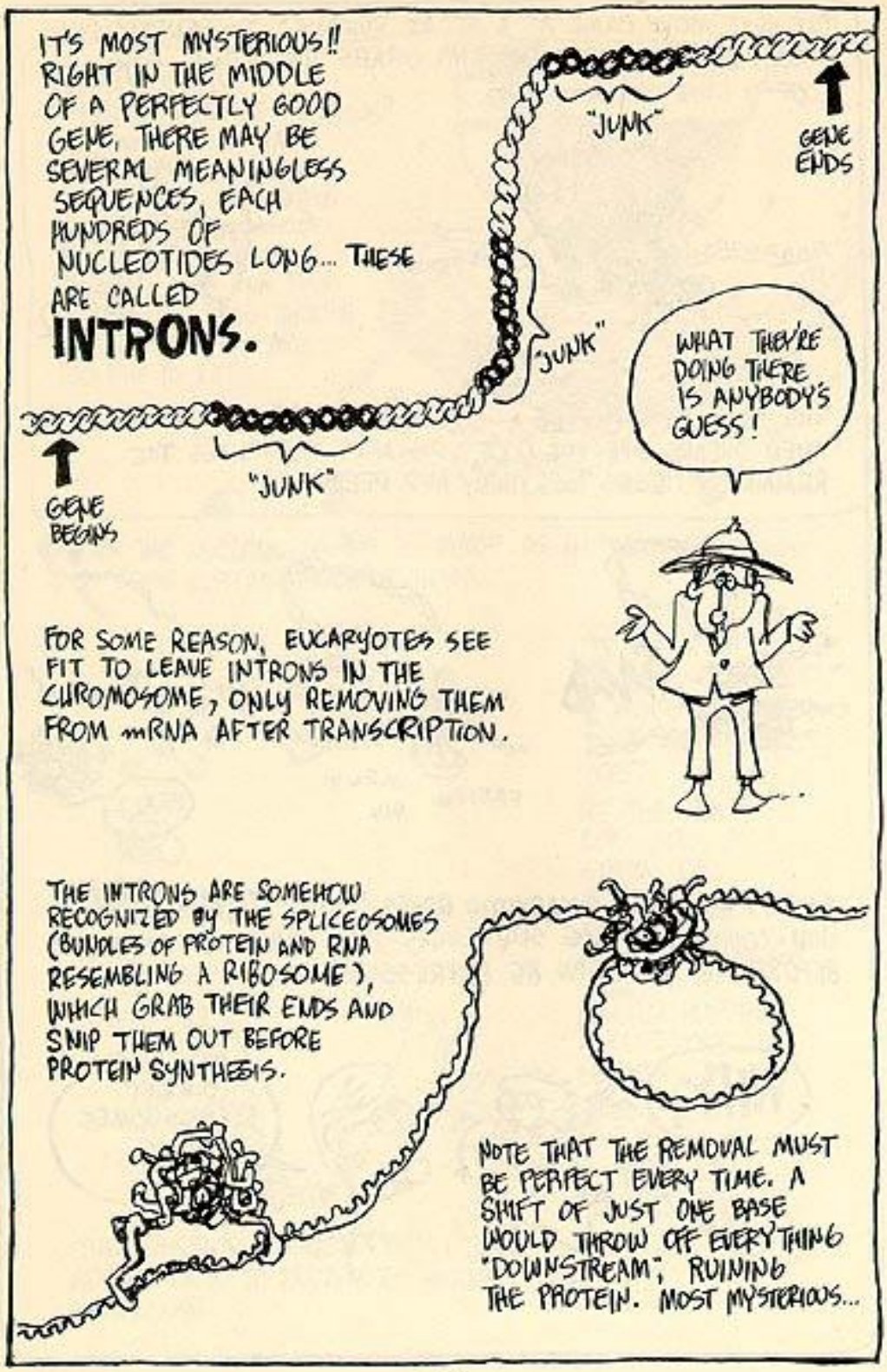


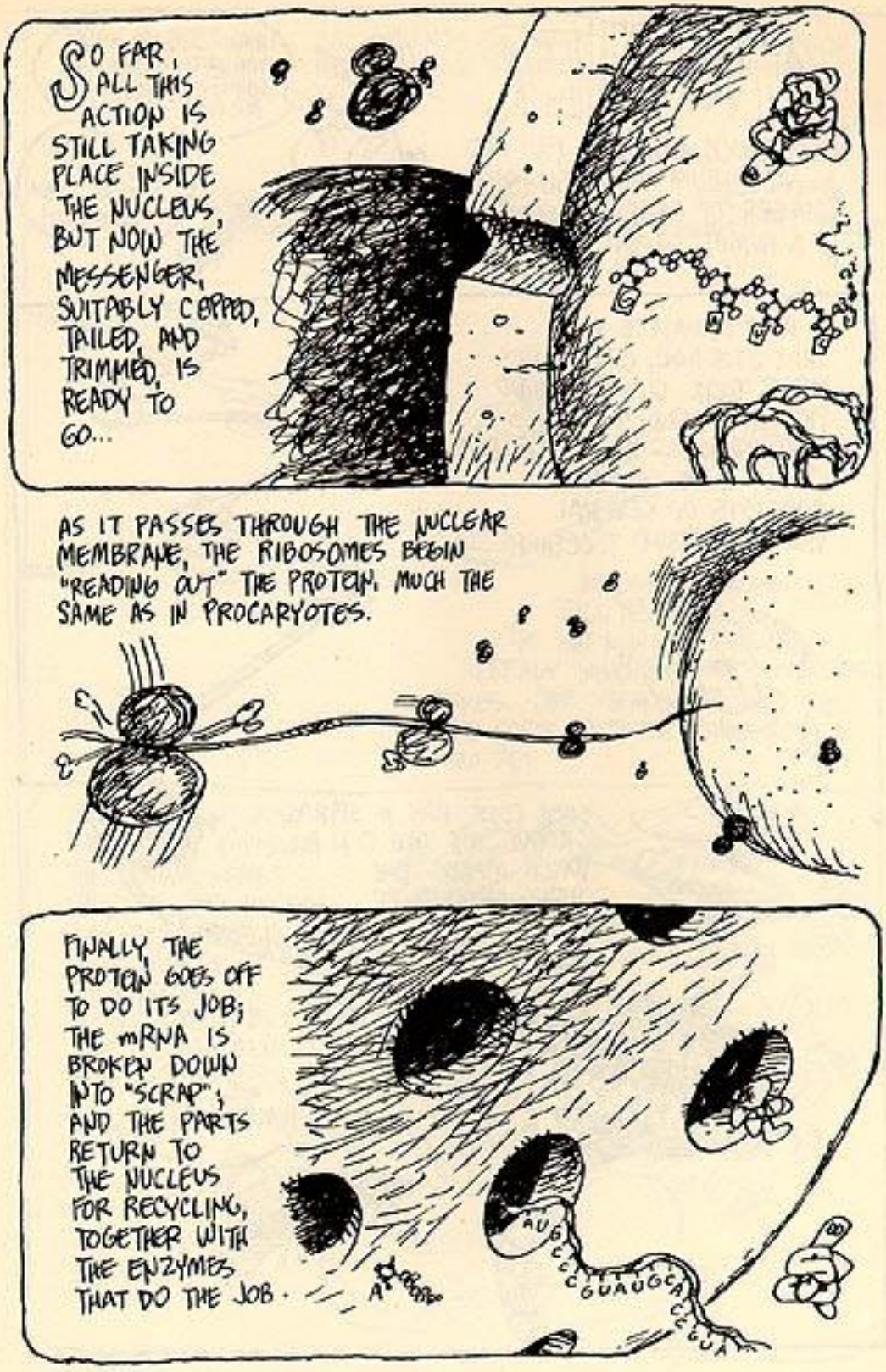
THE COMPLEX — CALLED A **SPLICEOSOME** — THEN SHEARS OFF THE LOOP, DISCARDS IT, SPLICES THE REMAINING PIECES TOGETHER, AND DEPARTS.

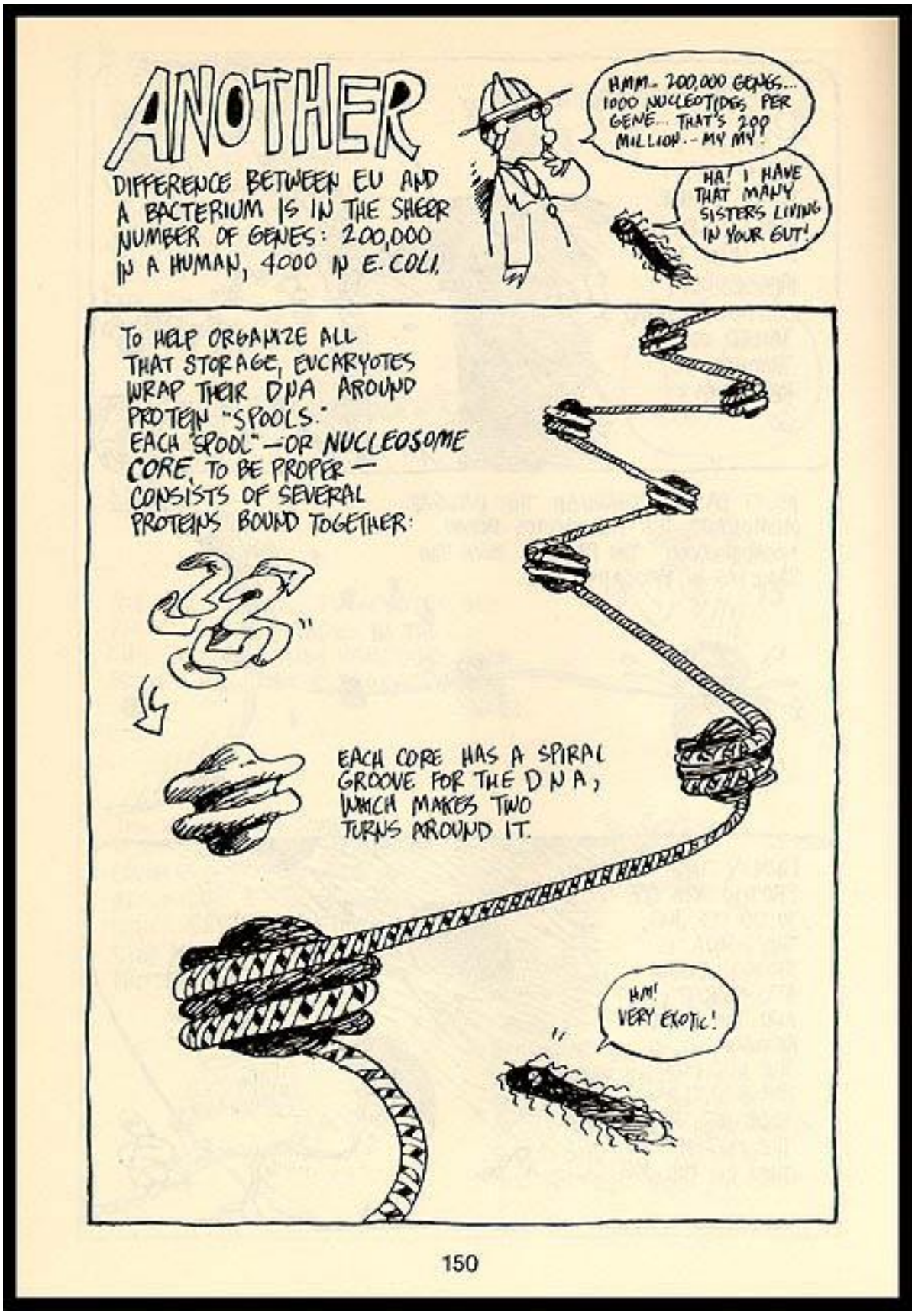


THIS IS BIZARRE! EUCARYOTIC GENES CONTAIN "**JUNK DNA**" — NON-CODING MESSAGE SEQUENCES THAT HAVE TO BE CUT OUT BEFORE THE GENE CAN BE EXPRESSED!!



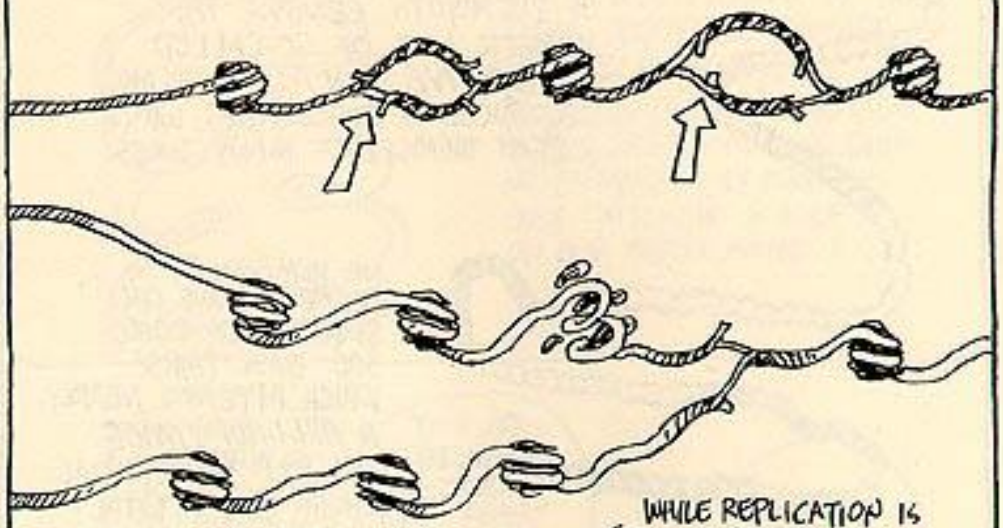

IT'S MOST MYSTERIOUS!! RIGHT IN THE MIDDLE OF A PERFECTLY GOOD GENE, THERE MAY BE SEVERAL MEANINGLESS SEQUENCES, EACH HUNDREDS OF NUCLEOTIDES LONG... THESE ARE CALLED INTRONS.
"JUNK"
GENE ENDS
"JUNK"
"JUNK"
GENE BEGINS
WHAT THEY'RE DOING THERE IS ANYBODY'S GUESS!
FOR SOME REASON, EUCARYOTES SEE FIT TO LEAVE INTRONS IN THE CHROMOSOME, ONLY REMOVING THEM FROM mRNA AFTER TRANSCRIPTION.
THE INTRONS ARE SOMEHOW RECOGNIZED BY THE SPLICEOSOMES (BUNDLES OF PROTEIN AND RNA RESEMBLING A RIBOSOME), WHICH GRAB THEIR ENDS AND SNIP THEM OUT BEFORE PROTEIN SYNTHESIS.
NOTE THAT THE REMOVAL MUST BE PERFECT EVERY TIME. A SHIFT OF JUST ONE BASE WOULD THROW OFF EVERYTHING "DOWNSTREAM", RUINING THE PROTEIN. MOST MYSTERIOUS...


SO FAR, ALL THIS ACTION IS STILL TAKING PLACE INSIDE THE NUCLEUS, BUT NOW THE MESSENGER, SUITABLY CAPPED, TAILED, AND TRIMMED, IS READY TO GO...
AS IT PASSES THROUGH THE NUCLEAR MEMBRANE, THE RIBOSOMES BEGIN "READING OUT" THE PROTEIN, MUCH THE SAME AS IN PROCARYOTES.
FINALLY, THE PROTEIN GOES OFF TO DO ITS JOB; THE mRNA IS BROKEN DOWN INTO "SCRAP"; AND THE PARTS RETURN TO THE NUCLEUS FOR RECYCLING, TOGETHER WITH THE ENZYMES THAT DO THE JOB.
AUG
CCCGUAUGCA
CCGUA



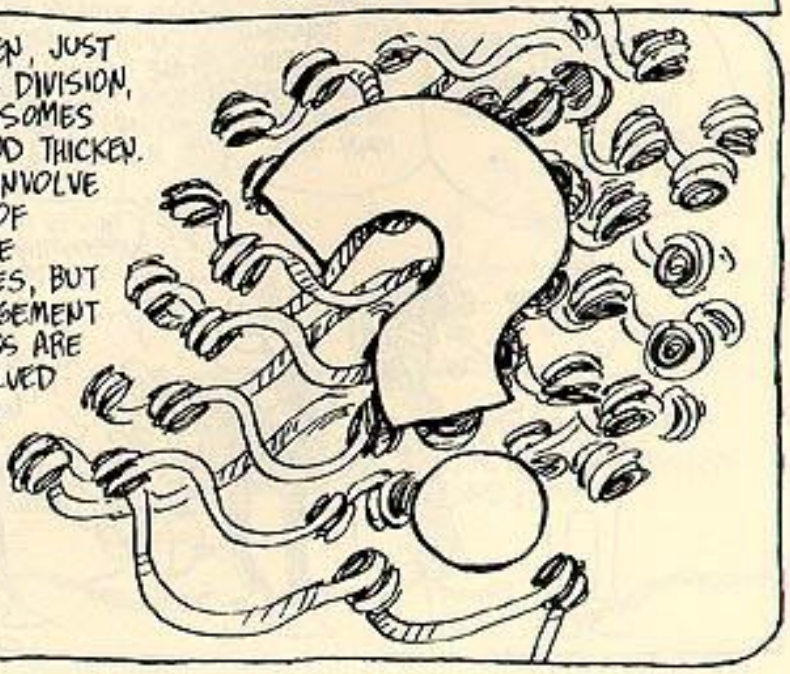
NOTE: There is a mistake on this page: humans have ~21,000 protein-coding genes! Not 200,000!!!!

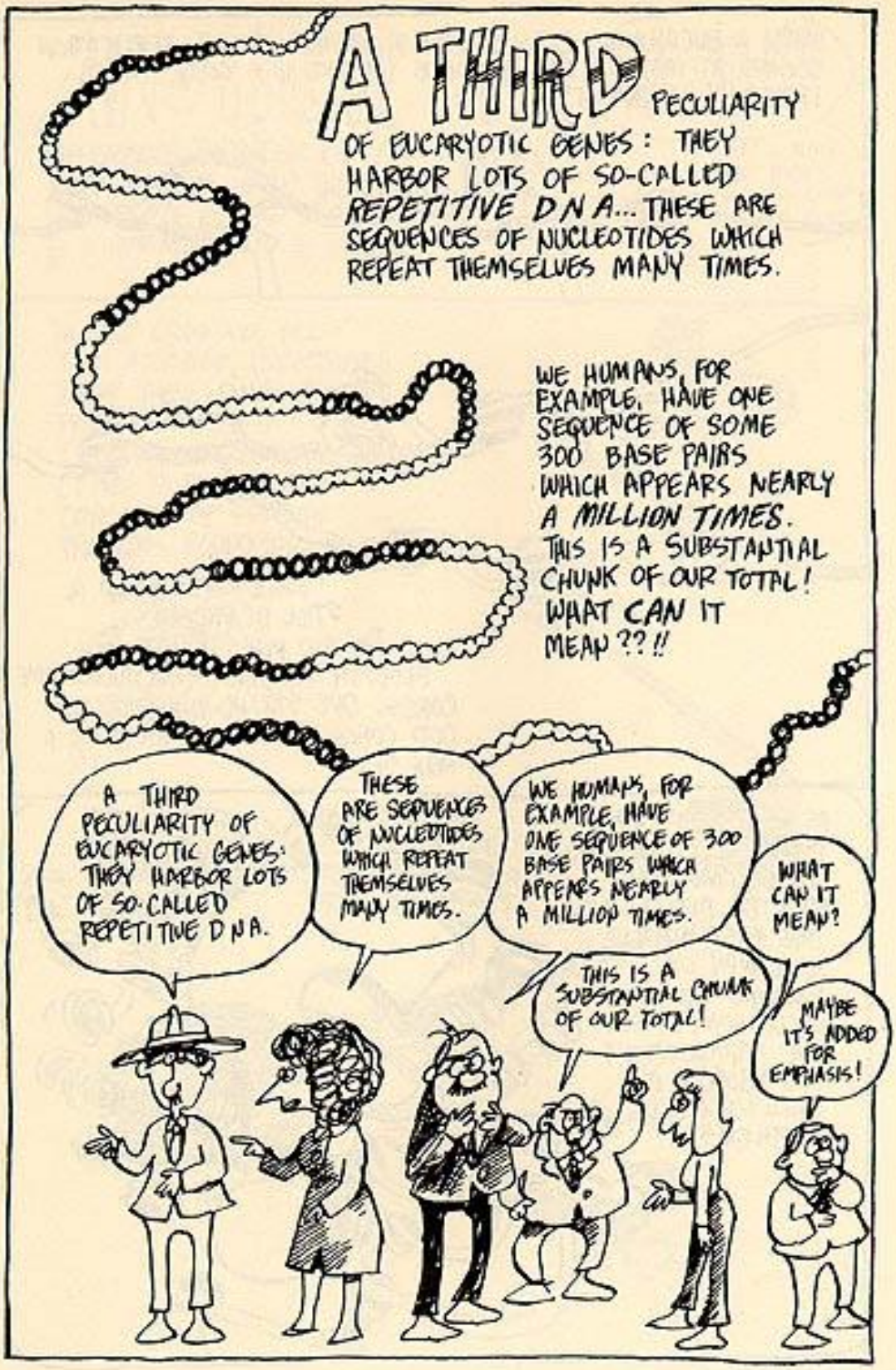
WHEN A EUCARYOTIC CELL WANTS TO DIVIDE, DNA REPLICATION BEGINS AT MANY SITES AT ONCE (UNLIKE IN *E. COLI*, WHERE IT BEGINS AT ONE SITE).

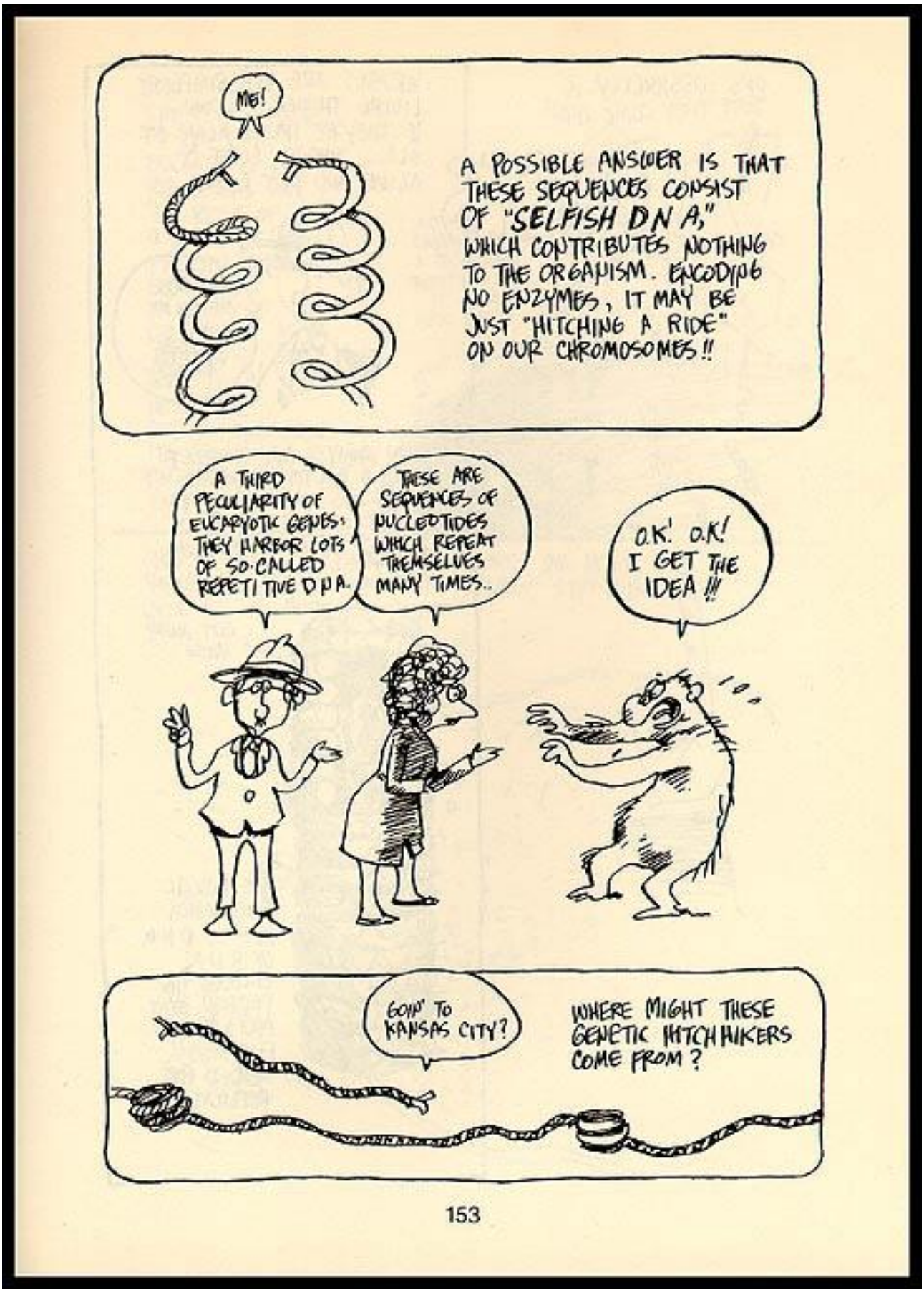


WHILE REPLICATION IS STILL IN PROGRESS, THE TWO NEW STRANDS ARE ALREADY WINDING ONTO NUCLEOSOME CORES. ONE STRAND INHERITS THE OLD CORES, AND THE OTHER GETS A NEW SET.

AS WE'VE SEEN, JUST BEFORE CELL DIVISION, THE CHROMOSOMES SHORTEN AND THICKEN. THIS MUST INVOLVE SOME WAY OF PACKING THE NUCLEOSOMES, BUT THE ARRANGEMENT AND PROCESS ARE STILL UNSOLVED PROBLEMS.




A THIRD PECULIARITY OF EUCARYOTIC GENES: THEY HARBOR LOTS OF SO-CALLED REPETITIVE DNA... THESE ARE SEQUENCES OF NUCLEOTIDES WHICH REPEAT THEMSELVES MANY TIMES.
WE HUMANS, FOR EXAMPLE, HAVE ONE SEQUENCE OF SOME 300 BASE PAIRS WHICH APPEARS NEARLY A MILLION TIMES. THIS IS A SUBSTANTIAL CHUNK OF OUR TOTAL! WHAT CAN IT MEAN ??!!
A THIRD PECULIARITY OF EUCARYOTIC GENES: THEY HARBOR LOTS OF SO-CALLED REPETITIVE DNA.
THESE ARE SEQUENCES OF NUCLEOTIDES WHICH REPEAT THEMSELVES MANY TIMES.
WE HUMANS, FOR EXAMPLE, HAVE ONE SEQUENCE OF 300 BASE PAIRS WHICH APPEARS NEARLY A MILLION TIMES.
WHAT CAN IT MEAN?
THIS IS A SUBSTANTIAL CHUNK OF OUR TOTAL!
MAYBE IT'S ADDED FOR EMPHASIS!


ME!
A POSSIBLE ANSWER IS THAT THESE SEQUENCES CONSIST OF "SELFISH DNA," WHICH CONTRIBUTES NOTHING TO THE ORGANISM. ENCODING NO ENZYMES, IT MAY BE JUST "HITCHING A RIDE" ON OUR CHROMOSOMES!!
A THIRD PECULIARITY OF EUCARYOTIC GENES: THEY HARBOR LOTS OF SO-CALLED REPETITIVE DNA.
THESE ARE SEQUENCES OF NUCLEOTIDES WHICH REPEAT THEMSELVES MANY TIMES..
O.K! O.K! I GET THE IDEA !!!
GOIN' TO KANSAS CITY?
WHERE MIGHT THESE GENETIC HITCHHIKERS COME FROM?

ONE POSSIBILITY IS THAT THEY COME FROM

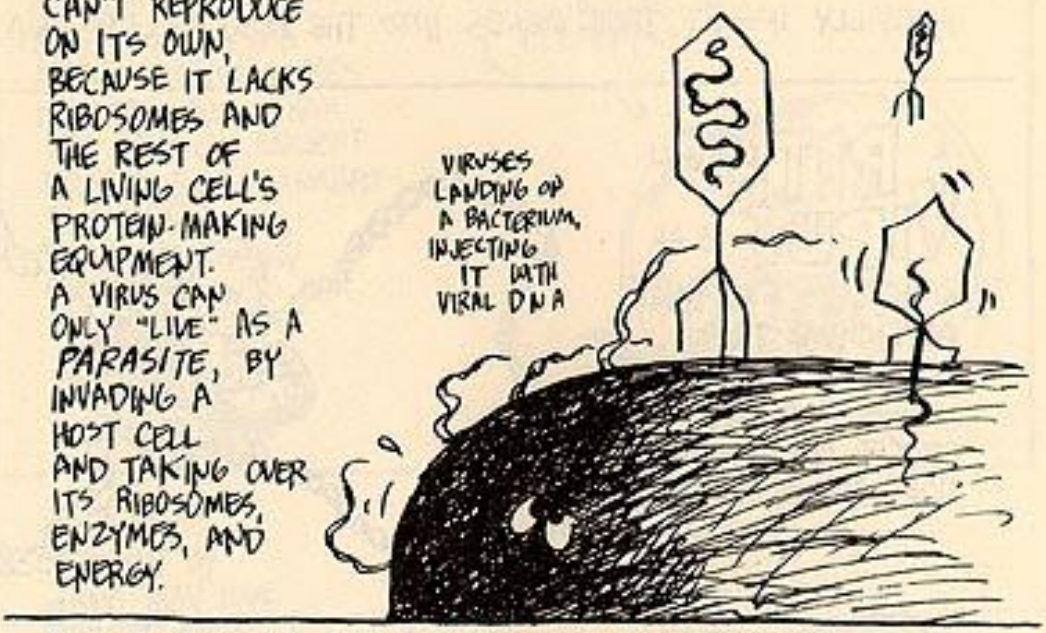
VIRUSES

VIRUSES ARE THE SIMPLEST LIVING THINGS KNOWN— IF THEY'RE TRULY ALIVE AT ALL... THEY'RE SORT OF ALIVE AND NOT ALIVE...

EVEN SIMPLER AND SMALLER THAN A BACTERIUM, A VIRUS HAS ONLY TWO PARTS: A BIT OF *NUCLEIC ACID* WRAPPED UP IN A *PROTEIN COAT*:

THE NUCLEIC ACID, WHICH MAY BE DNA OR RNA, ENCODES THE PROTEIN COAT AND A FEW ENZYMES NEEDED FOR REPLICATION.

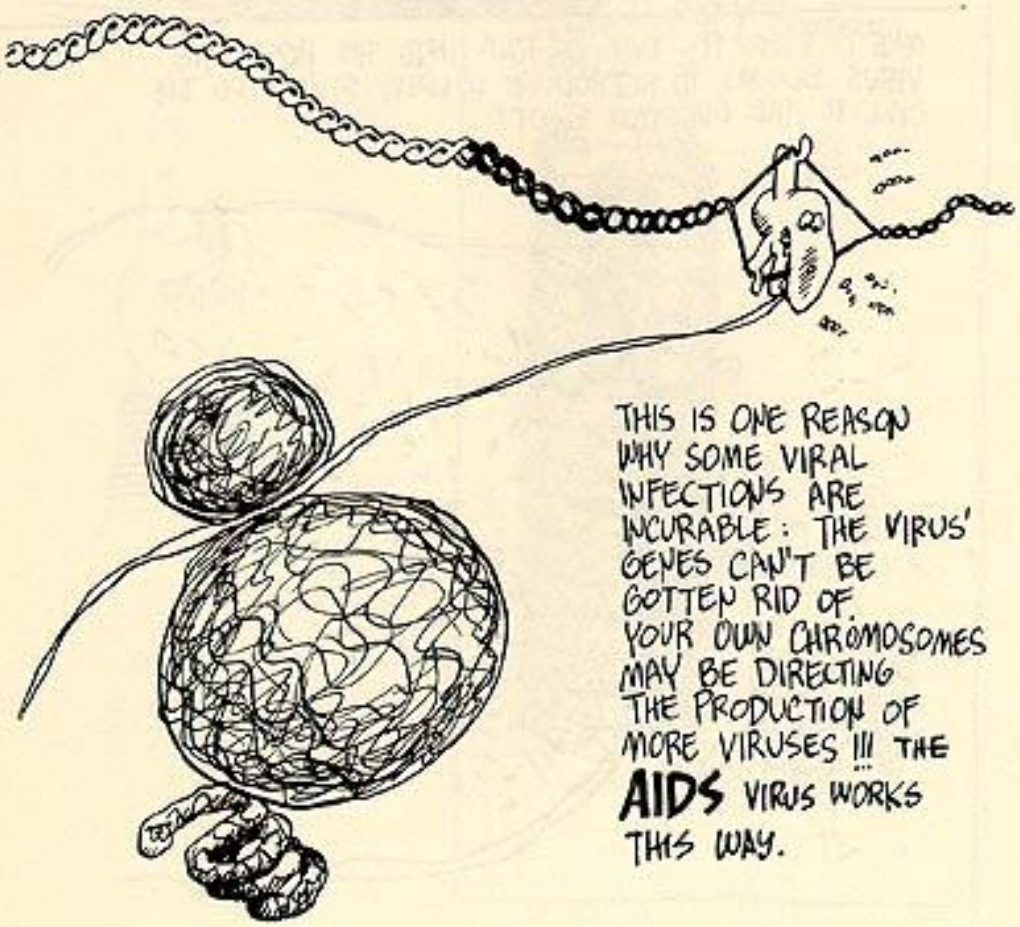
BUT A VIRUS CAN'T REPRODUCE ON ITS OWN, BECAUSE IT LACKS RIBOSOMES AND THE REST OF A LIVING CELL'S PROTEIN-MAKING EQUIPMENT. A VIRUS CAN ONLY "LIVE" AS A *PARASITE*, BY INVADING A HOST CELL AND TAKING OVER ITS RIBOSOMES, ENZYMES, AND ENERGY.



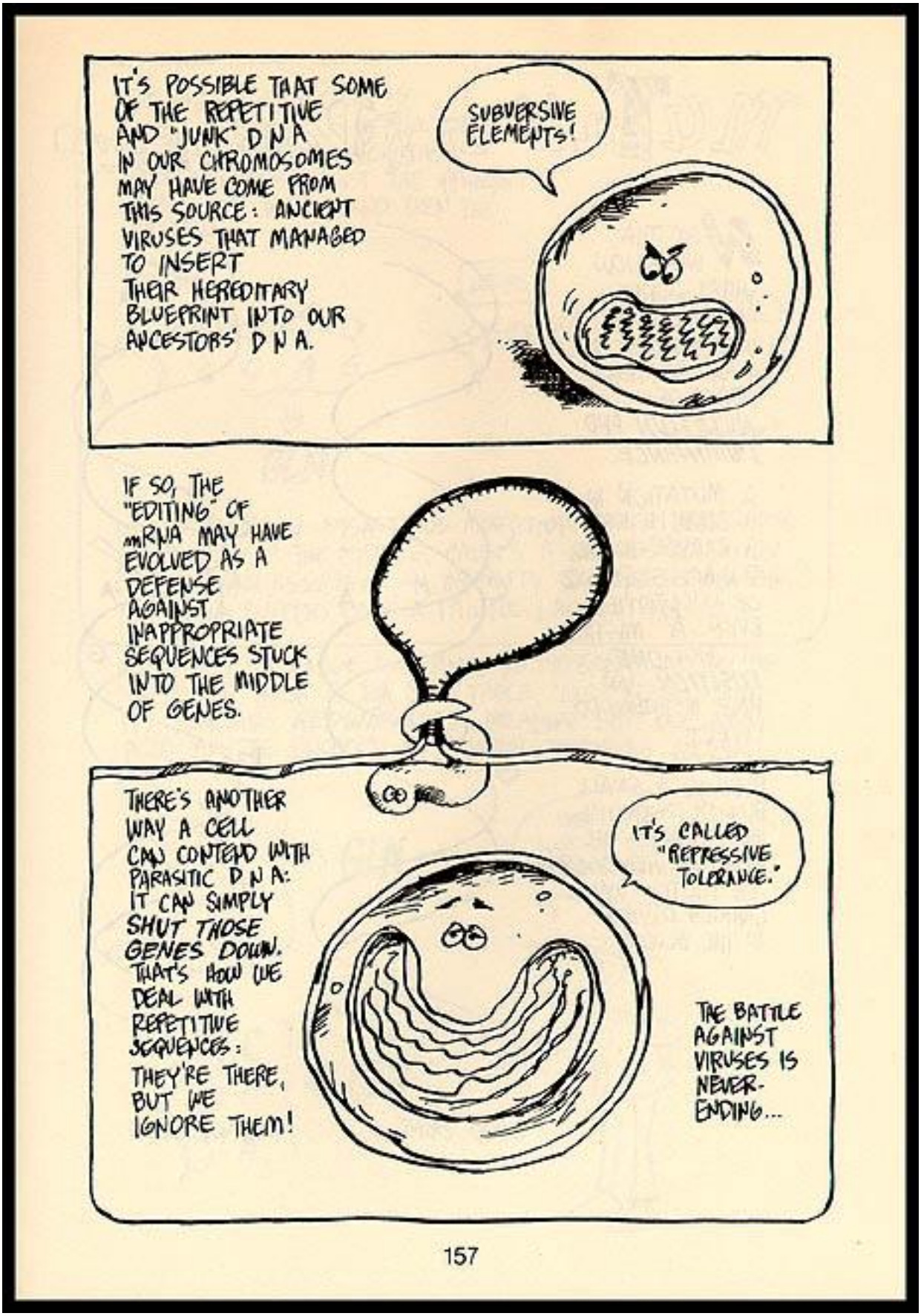
ONCE IT GETS ITS DNA OR RNA INTO THE HOST, THE VIRUS BEGINS TO REPRODUCE WILDLY, STRAINING THE CELL TO THE BURSTING POINT!

THAT'S A TYPICAL LIFE-STYLE (OR NON-LIFE-STYLE) FOR A VIRUS, BUT SOME VIRUSES ARE EVEN SNEAKIER: THEY ACTUALLY INSERT THEIR GENES INTO THE HOST CELL'S DNA.

A **RETRO-VIRUS** IS AN RNA VIRUS ENCODING AN ENZYME THAT MAKES A DNA COPY OF ITS RNA AND SPLICES IT INTO THE HOST CHROMOSOME.



THIS IS ONE REASON WHY SOME VIRAL INFECTIONS ARE INCURABLE: THE VIRUS' GENES CAN'T BE GOTTEN RID OF. YOUR OWN CHROMOSOMES MAY BE DIRECTING THE PRODUCTION OF MORE VIRUSES !!! THE **AIDS** VIRUS WORKS THIS WAY.

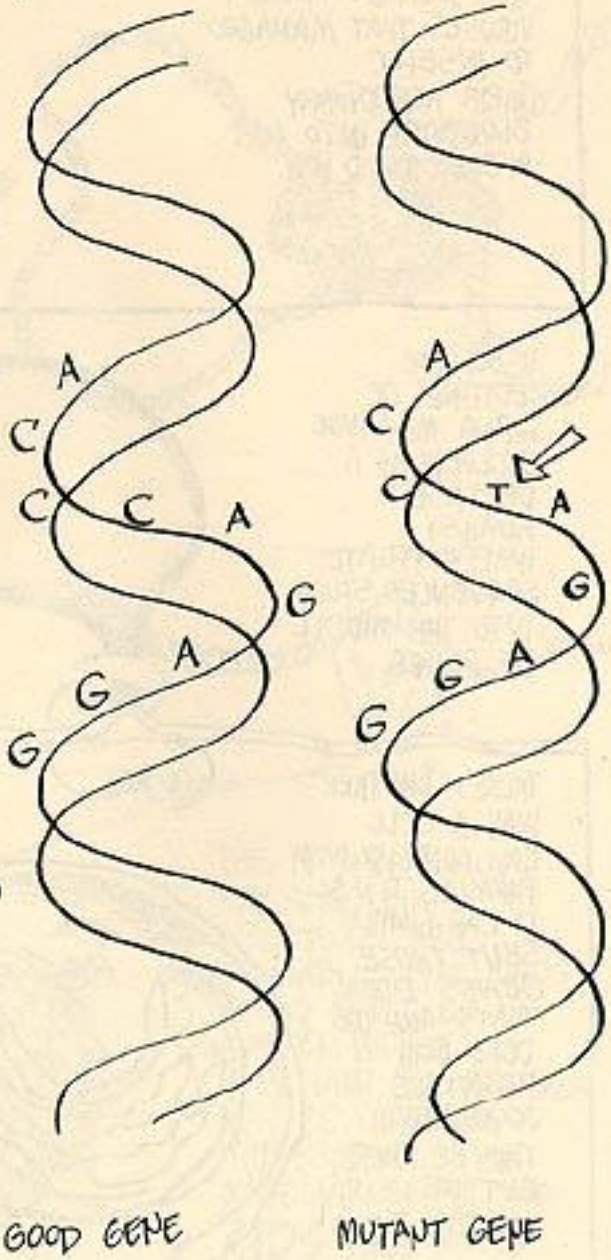

IT'S POSSIBLE THAT SOME OF THE REPETITIVE AND "JUNK" DNA IN OUR CHROMOSOMES MAY HAVE COME FROM THIS SOURCE: ANCIENT VIRUSES THAT MANAGED TO INSERT THEIR HEREDITARY BLUEPRINT INTO OUR ANCESTORS' DNA.
SUBVERSIVE ELEMENTS!
IF SO, THE "EDITING" OF mRNA MAY HAVE EVOLVED AS A DEFENSE AGAINST INAPPROPRIATE SEQUENCES STUCK INTO THE MIDDLE OF GENES.
THERE'S ANOTHER WAY A CELL CAN CONTEND WITH PARASITIC DNA: IT CAN SIMPLY SHUT THOSE GENES DOWN. THAT'S HOW WE DEAL WITH REPETITIVE SEQUENCES: THEY'RE THERE, BUT WE IGNORE THEM!
IT'S CALLED "REPRESSIVE TOLERANCE."
THE BATTLE AGAINST VIRUSES IS NEVER-ENDING...

Mutation & Dominance (again!)

Now that we know what genes really are, we can get a much better grasp of *MUTATION* and *DOMINANCE*.

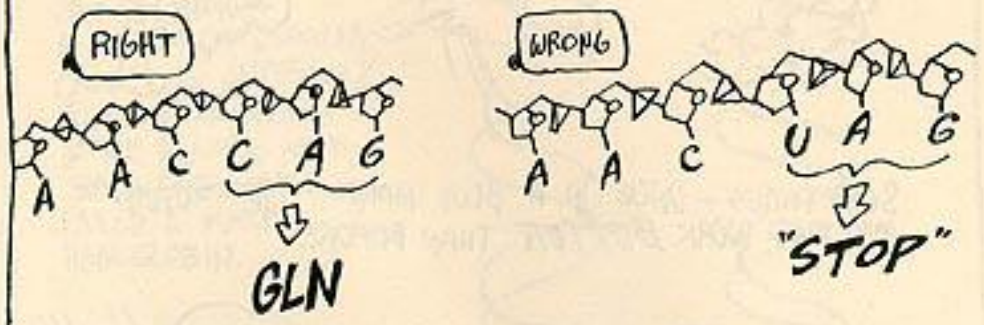
A mutation in a gene is just a change in the DNA's sequence of nucleotides. Even a mistake at just *ONE POSITION* can have a profound effect.

Here is a small but devastating mutation in the gene for *HEMOGLOBIN*, the protein which carries oxygen in the blood.



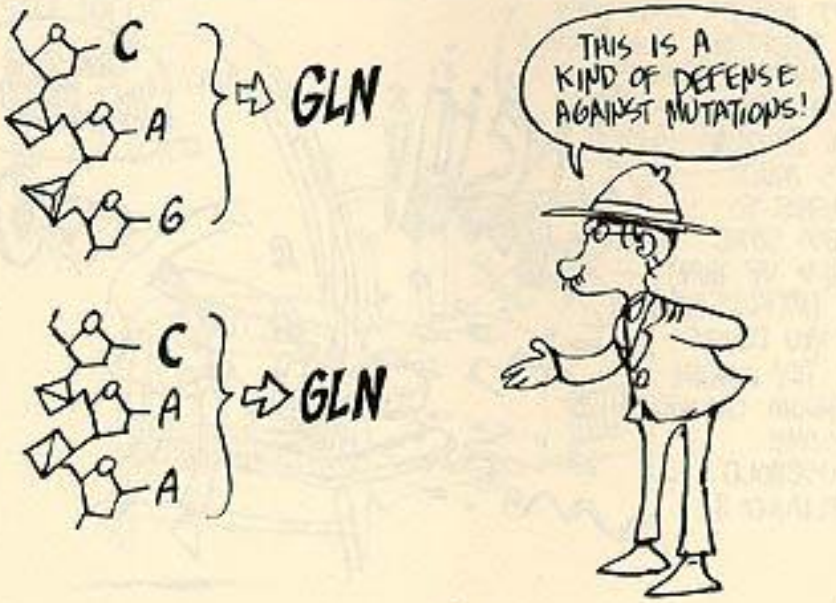
GOOD GENE MUTANT GENE

THE REASON, OF COURSE, IS THAT THE CHANGE IS REFLECTED IN THE *PROTEIN* WHICH THE GENE ENCODES... FIRST THE mRNA COMES OUT WRONG, AND THEN THE PROTEIN...



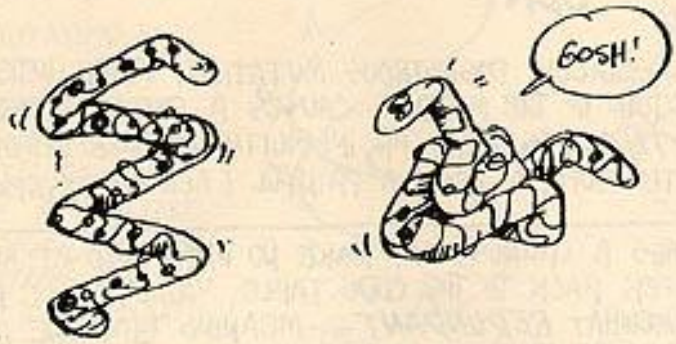
THIS ESPECIALLY DISASTROUS MUTATION, WHICH INTERRUPTS THE PROTEIN IN THE MIDDLE, CAUSES A SERIOUS CONDITION CALLED *THALASSEMIA*, AN INABILITY TO MAKE HEMOGLOBIN. THE VICTIM SUFFERS FROM A PAINFUL LACK OF OXYGEN.

SOMETIMES A CHANGE MAY MAKE NO DIFFERENCE AT ALL. IF YOU REFER BACK TO THE CODE TABLE, YOU'LL RECALL THAT IT'S SOMEWHAT *REDUNDANT* — MEANING THAT ONE AMINO ACID MAY BE ENCODED BY SEVERAL DIFFERENT CODONS.



OCCASIONALLY, THE "MISTAKEN" AMINO ACID MAY FIT IN FAIRLY WELL (THOUGH USUALLY LESS THAN PERFECTLY).

SOMETIMES — ONCE IN A BLUE MOON — THE PROTEIN MAY EVEN WORK *BETTER* THAN BEFORE.

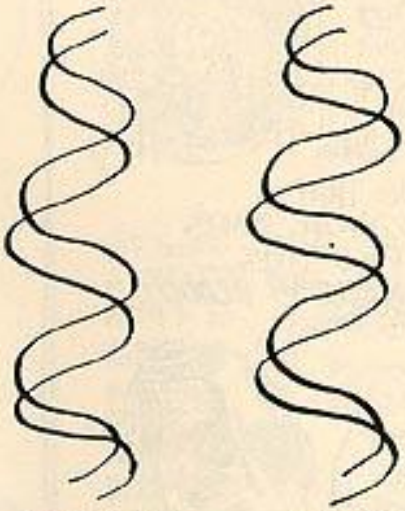


BUT MOST OF THE TIME, A MUTATION JUST RUINS THE PROTEIN. IT'S MUCH EASIER TO MESS SOMETHING UP THAN TO IMPROVE IT! IF YOU DOUBT IT, TRY MAKING RANDOM CHANGES IN SOME HOUSEHOLD APPLIANCE!!

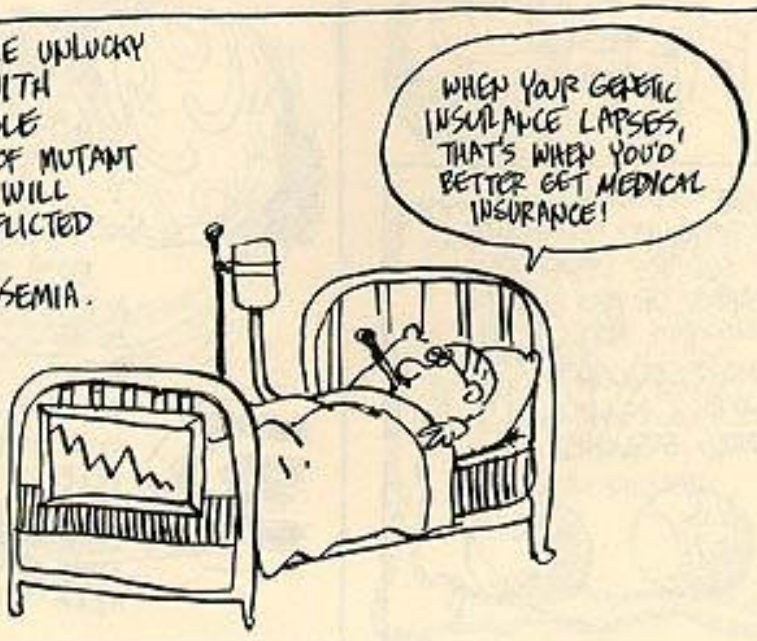
EARLIER (p. 81)

WE NOTED THAT MOST MUTATIONS ARE *RECESSIVE*. NOW WE CAN SEE WHY: A MUTATION USUALLY CAUSES AN *INABILITY* TO MAKE AN ENZYME. IN THE EXAMPLE ABOVE, THE MUTANT GENE FAILED TO MAKE HEMOGLOBIN.

HOWEVER, WE HAVE *TWO SETS* OF CHROMOSOMES. EVEN IF A MUTATION AFFECTS ONE OF THEM, THE "INSURANCE" GENE WILL STILL PRODUCE ITS ENZYME.



ONLY THE UNLUCKY SOUL WITH A DOUBLE DOSE OF MUTANT GENES WILL BE AFFLICTED WITH THALASSEMIA.

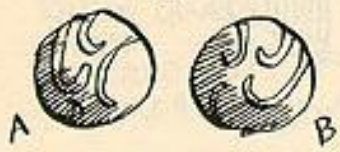


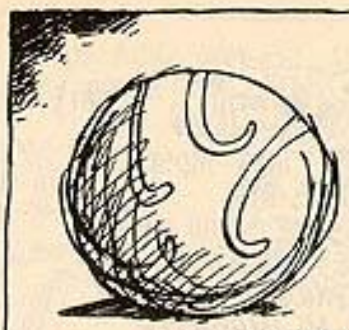
WE DIDN'T MENTION IT EARLIER, BUT SOME ALLELES CAN BE

CO-DOMINANT,

MEANING THAT A HETEROZYGOTE MAKES BOTH PHENOTYPES. AN EXAMPLE IS *BLOOD GROUPS.*

THERE IS A GENETICALLY DETERMINED SEQUENCE OF SUGARS LYING ON THE SURFACE OF RED BLOOD CELLS. ONE ALLELE, I^A, MAKES SEQUENCE A. ANOTHER ALLELE, I^B, MAKES SEQUENCE B.



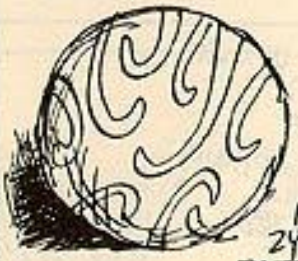


I^AI^A

IF HOMOZYGOUS FOR I^A YOUR BLOOD HAS ONLY SEQUENCE A. THIS IS *TYPE A BLOOD.*

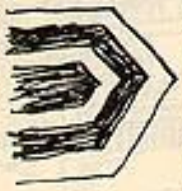
I^BI^B

IF HOMOZYGOUS FOR I^B, YOU HAVE *TYPE B BLOOD.*



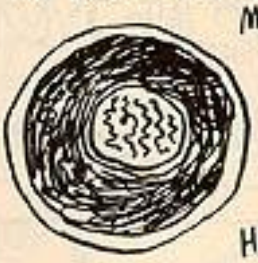
I^AI^B

A HETERO-ZYGOTE MAKES BOTH SEQUENCES, AND HAS *TYPE AB BLOOD.*



AND FINALLY, THERE IS A THIRD ALLELE, I^O, MAKING NO SUGAR SEQUENCE. *TYPE O* BLOOD IS *RECESSIVE.*

A RED BLOOD CELL BEGINS ITS EXISTENCE AS A BONE MARROW CELL, A PERFECTLY GOOD EUCARYOTE, BUT LACKING IN HEMOGLOBIN.

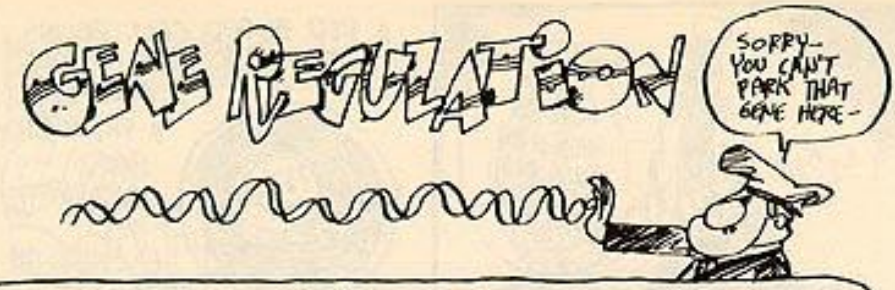


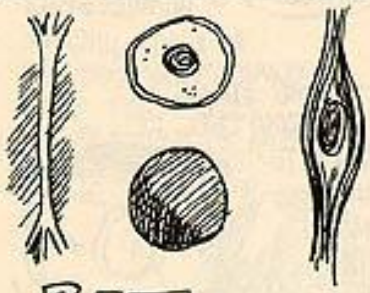
AT SOME POINT, A MARROW CELL BEGINS TO CHANGE... AMONG OTHER THINGS, IT BEGINS TO MAKE HEMOGLOBIN.

EVENTUALLY, IT EMERGES AS A FULLY DEVELOPED RED BLOOD CELL.

GENETICALLY, THE POINT IS THIS: THE HEMOGLOBIN GENE WAS THERE ALL THE TIME, BUT IT WASN'T ALWAYS EXPRESSED— WHICH BRINGS US TO OUR NEXT SUBJECT...

GENE REGULATION

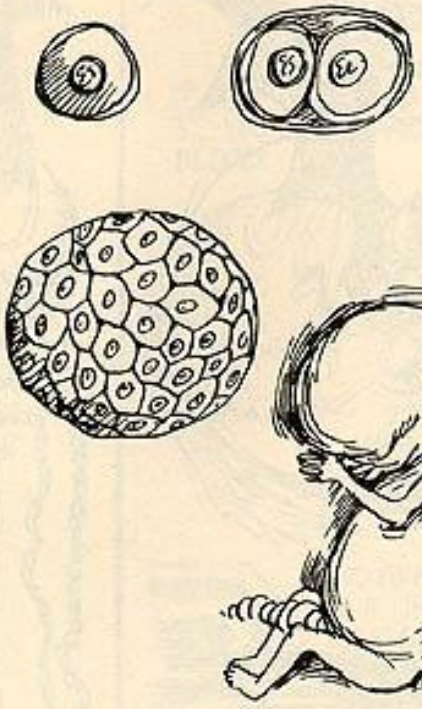




ALL THE HIGHER LIFE FORMS EXHIBIT AN IMPRESSIVE COLLECTION OF CELL TYPES: NERVE, BLOOD, MUSCLE, SKIN, EYE, LYMPH, ETC ETC ETC...

BUT

DESPITE THEIR DIFFERENCES, ALL THESE CELLS HAVE PRECISELY THE SAME SET OF GENES*, BECAUSE THEY ARISE FROM ONE FERTILIZED EGG BY THE PROCESS OF MITOSIS, WHICH DUPLICATES THE CHROMOSOMES.



*AS USUAL, THERE ARE EXCEPTIONS!!

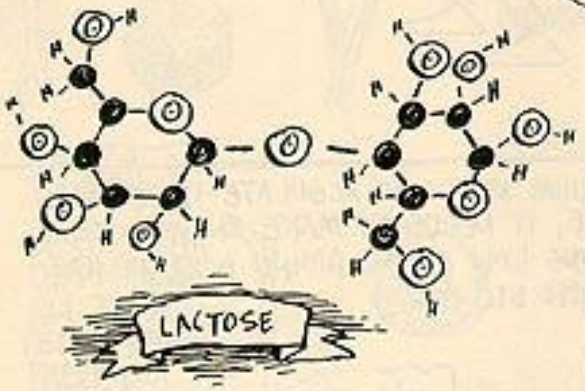
CLEARLY, DIFFERENT GENES COME INTO PLAY IN DIFFERENT CELLS... SO EACH CELL MUST HAVE WAYS OF "DECIDING" WHICH GENES TO "TURN ON" AND WHEN TO DO IT...

OTHERWISE, ONE DREADS THE RESULTS!

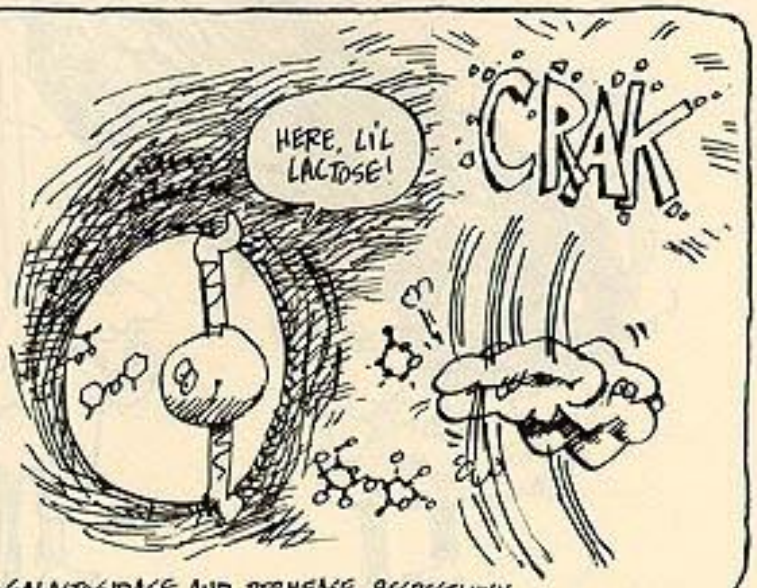
EVEN THE LOWLY BACTERIUM NEEDS TO REGULATE ITS GENES. WHEN FOOD IS AVAILABLE, IT NEEDS TO MAKE ENZYMES TO DIGEST IT; WHEN IT RUNS LOW ON AN AMINO ACID, IT HAS TO SYNTHESIZE MORE; ETC ETC ETC...

AS USUAL, THE QUESTION HAS BEEN MOST THOROUGHLY STUDIED IN *E. COLI*.

THE FIRST TO FIND A FORM OF GENE REGULATION WERE THE FRENCH SCIENTISTS **JACQUES MONOD** AND **FRANÇOIS JACOB**, IN THE LATE 1950's. THEY EXAMINED *E. COLI*'s ABILITY TO DIGEST THE SUGAR **LACTOSE**.



IN THE PRESENCE OF LACTOSE, *E. COLI* PRODUCES TWO ENZYMES, CALL THEM **Y** AND **Z***. **Z** OPENS THE CELL WALL TO LACTOSE, AND **Y** BREAKS THE SUGAR IN HALF.



*REAL NAMES: BETA-GALACTOSIDASE AND PERMEASE, RESPECTIVELY

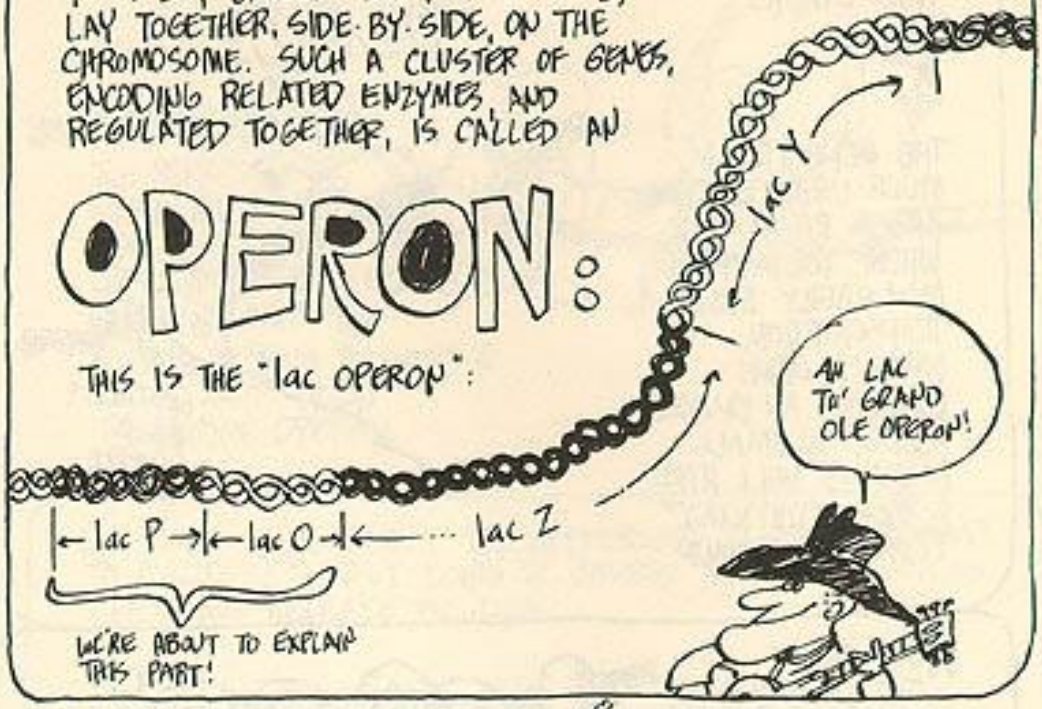
WITHOUT GOING INTO THE DETAILS OF THEIR EXPERIMENTS, WHICH WERE QUITE INVOLVED, HERE ARE SOME OF MONOD AND JACOB'S MAIN RESULTS:

THIS EXPERIMENT WAS MORE DIFFICULT THAN A CHEESE SOUFFLÉ!

FIRST, THEY FOUND THAT THE GENES FOR Y AND Z, CALLED "lac Y" AND "lac Z," LAY TOGETHER, SIDE-BY-SIDE, ON THE CHROMOSOME. SUCH A CLUSTER OF GENES, ENCODING RELATED ENZYMES, AND REGULATED TOGETHER, IS CALLED AN

OPERON.

THIS IS THE "lac OPERON":

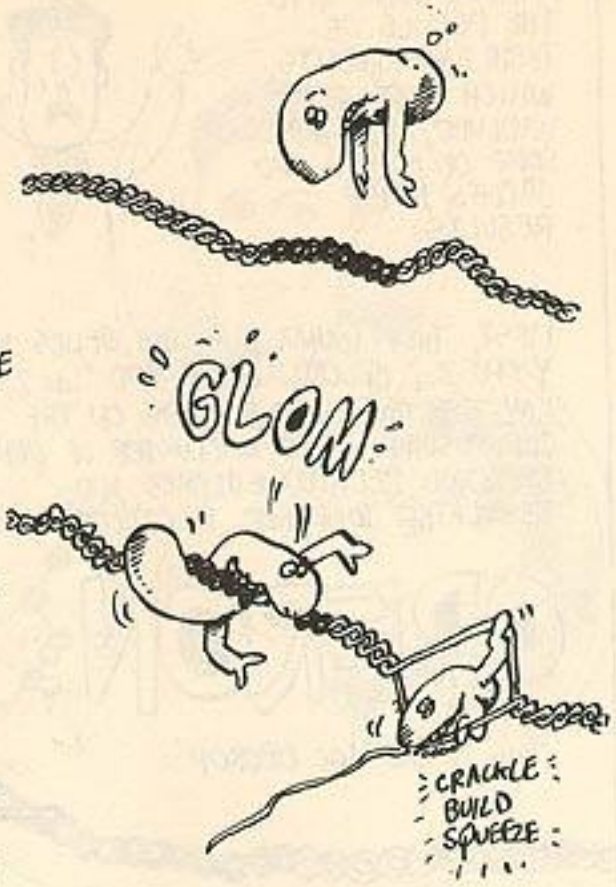


AT THE START OF THIS (AND EVERY) OPERON IS A *PROMOTER* REGION, HERE CALLED lac P. THIS IS THE SITE WHERE THE ENZYME *RNA POLYMERASE* BINDS ONTO THE DNA TO BEGIN TRANSCRIBING THE MESSAGE INTO mRNA. (SEE p. 133.)

The first

TYPE OF REGULATION IS SIMPLE: SOME PROMOTER REGIONS ARE MORE ATTRACTIVE TO RNA POLYMERASE THAN OTHERS.

THE GENE FOR A MUCH-USED ENZYME HAS A PROMOTER WHERE POLYMERASE MAY EASILY BEGIN TRANSCRIPTION, WHILE A GENE ENCODING AN ENZYME NEEDED IN SMALL AMOUNTS WILL HAVE A MORE "DIFFICULT" PROMOTER REGION.



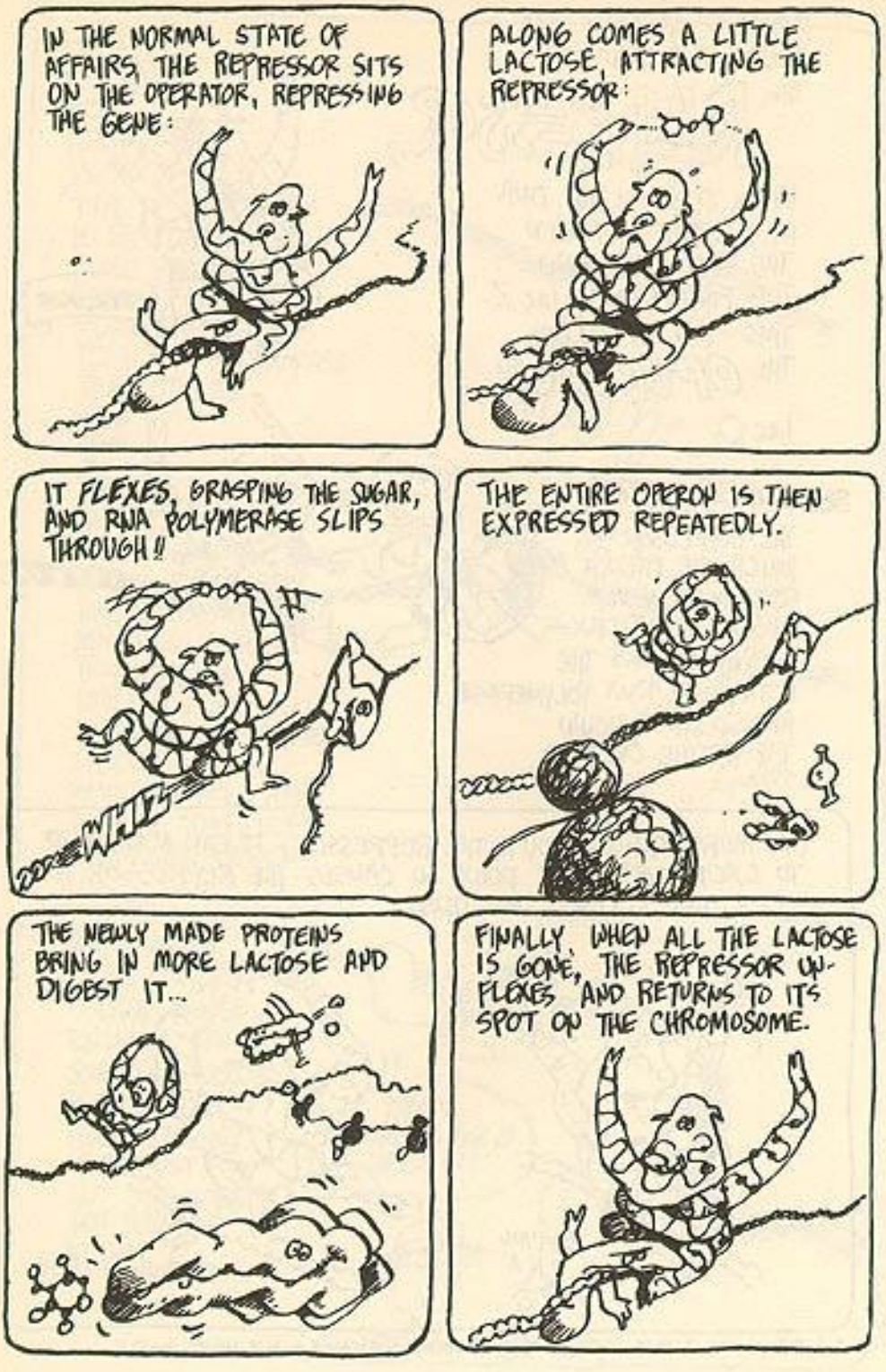
WHAT ABOUT THE LACTOSE OPERON, WHOSE ENZYMES ARE SOMETIMES NEEDED IN QUANTITY (WHEN LACTOSE IS PRESENT), BUT OTHERWISE NOT NEEDED AT ALL ??

MONOD + JACOB'S IDEA:
THERE IS A PROTEIN,
THE REPRESSOR,
WHICH SITS ON THE DNA
AT A SPOT BETWEEN
THE PROMOTER AND
THE FIRST GENE, lac Z.
THIS SPOT IS CALLED
THE OPERATOR,
lac O.

THE REPRESSOR—
WHICH THE FRENCH
SCIENTISTS NEVER
OBSERVED DIRECTLY—
SIMPLY BLOCKS THE
ACTION OF RNA POLYMERASE
AND SO SHUTS DOWN
THE ENTIRE OPERON.

ONE MORE THING ABOUT THE REPRESSOR: IT CAN ALSO BIND TO *LACTOSE**—BUT DOING SO CAUSES THE REPRESSOR TO "FLEX" AND RELEASE THE DNA:

* ACTUALLY NOT LACTOSE ITSELF, BUT A DERIVATIVE SUBSTANCE — BUT NEVER MIND !!


IN THE NORMAL STATE OF AFFAIRS, THE REPRESSOR SITS ON THE OPERATOR, REPRESSING THE GENE:
ALONG COMES A LITTLE LACTOSE, ATTRACTING THE REPRESSOR:
IT FLEXES, GRASPING THE SUGAR, AND RNA POLYMERASE SLIPS THROUGH!!
WHEE!
THE ENTIRE OPERON IS THEN EXPRESSED REPEATEDLY.
THE NEWLY MADE PROTEINS BRING IN MORE LACTOSE AND DIGEST IT...
FINALLY, WHEN ALL THE LACTOSE IS GONE, THE REPRESSOR UNFLEXES AND RETURNS TO ITS SPOT ON THE CHROMOSOME.

REPRESSORS TURN OUT TO BE A COMMON WAY TO REGULATE "INDUCIBLE" ENZYMES— I.E., ENZYMES WHICH ARE MADE IN RESPONSE TO A CHEMICAL-LIKE LACTOSE... BUT DESPITE THIS BRILLIANT IDEA, MONOD AND JACOB COULD NEVER ACTUALLY FIND A REPRESSOR. IT REMAINED A THEORETICAL POSSIBILITY...

...UNTIL 1967, WHEN WALTER GILBERT AND B. MÜLLER-HILL, USING VERY REFINED TECHNIQUES, WERE ABLE TO ISOLATE THE ELUSIVE PROTEINS.

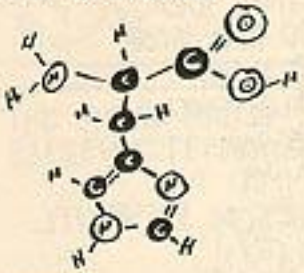
THEIR RESULTS MADE PLAIN WHY IT HAD BEEN SO HARD TO FIND THEM: A SINGLE *E. COLI* BACTERIUM HAS ONLY *FIVE* TO *TEN* MOLECULES OF LAC REPRESSOR. LATER, GILBERT MANAGED TO BREED MUTANT *E. COLI* THAT PRODUCED IT IN MUCH LARGER AMOUNTS....

ANOTHER METHOD OF GENE REGULATION GOES BY THE NAME OF:

ATTENUATION

AND ITS SUCCESSOR, ELEVEN-TUATION!

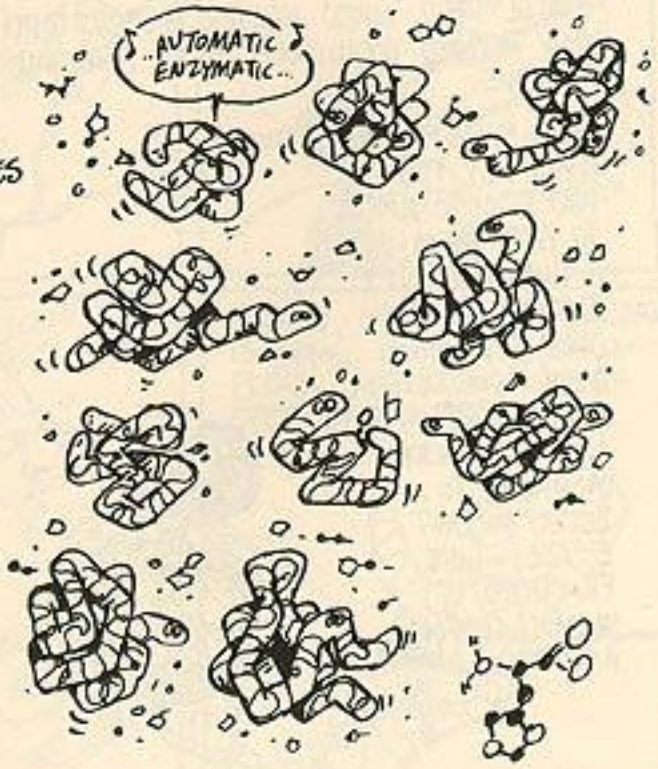
THIS GOVERNS AN E. COLI OPERON RESPONSIBLE FOR CONSTRUCTING THE AMINO ACID *HISTIDINE*.

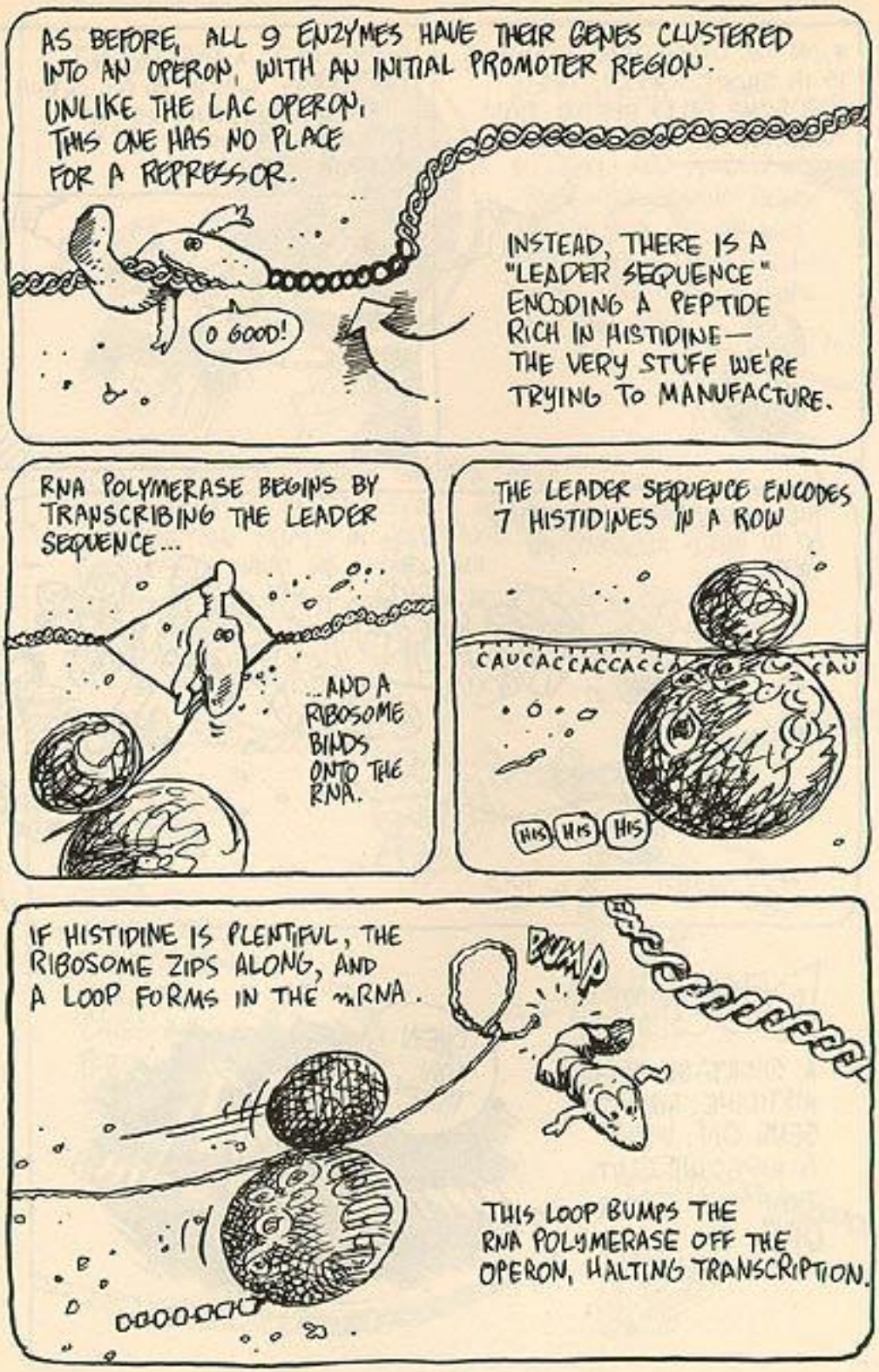


WHEN E. COLI RUNS LOW ON THIS ESSENTIAL STUFF THE BACTERIUM PRODUCES A GROUP OF *NINE* PROTEINS, WHICH CAN BUILD HISTIDINE MOLECULES FROM SCRATCH.

..AUTOMATIC ENZYMATIC..

AN ENZYMATIC ASSEMBLY LINE!




AS BEFORE, ALL 9 ENZYMES HAVE THEIR GENES CLUSTERED INTO AN OPERON, WITH AN INITIAL PROMOTER REGION.
UNLIKE THE LAC OPERON, THIS ONE HAS NO PLACE FOR A REPRESSOR.
O GOOD!
INSTEAD, THERE IS A "LEADER SEQUENCE" ENCODING A PEPTIDE RICH IN HISTIDINE— THE VERY STUFF WE'RE TRYING TO MANUFACTURE.
RNA POLYMERASE BEGINS BY TRANSCRIBING THE LEADER SEQUENCE...
...AND A RIBOSOME BINDS ONTO THE RNA.
THE LEADER SEQUENCE ENCODES 7 HISTIDINES IN A ROW
CAUCACCACCACC
CAU
HIS HIS HIS
IF HISTIDINE IS PLENTIFUL, THE RIBOSOME ZIPS ALONG, AND A LOOP FORMS IN THE mRNA.
BUMP
THIS LOOP BUMPS THE RNA POLYMERASE OFF THE OPERON, HALTING TRANSCRIPTION.

IF, ON THE OTHER HAND, HISTIDINE IS IN SHORT SUPPLY, THE RIBOSOME FALLS BEHIND THE POLYMERASE.

IN THIS CASE, A **DIFFERENT** LOOP FORMS, WHICH, BY PREVENTING THE FIRST LOOP, ENABLES THE POLYMERASE TO GO ON, AND THE OPERON IS EXPRESSED!

THE NEWLY MADE PROTEINS GO TO WORK ASSEMBLING HISTIDINE.

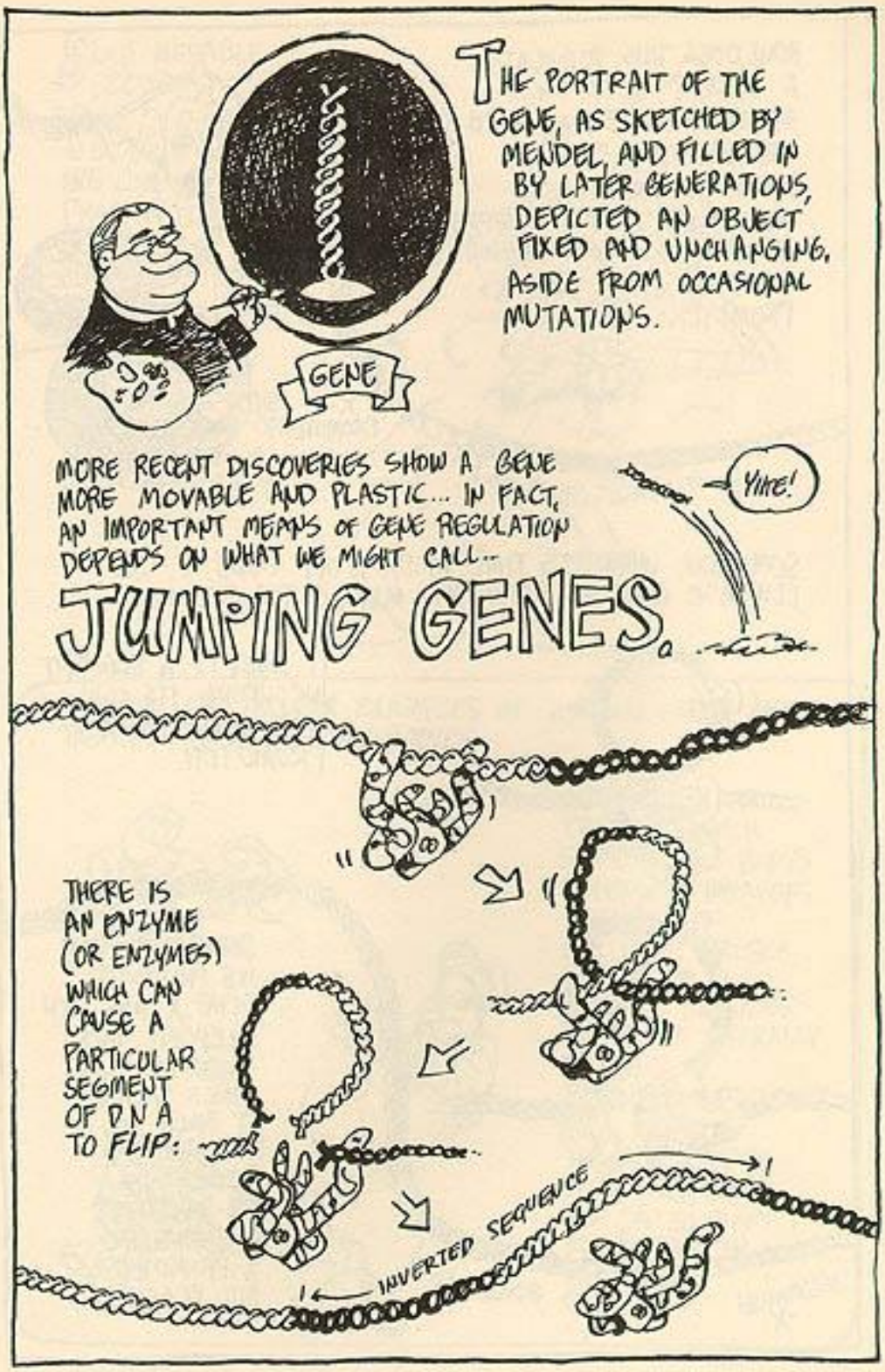
SIGH

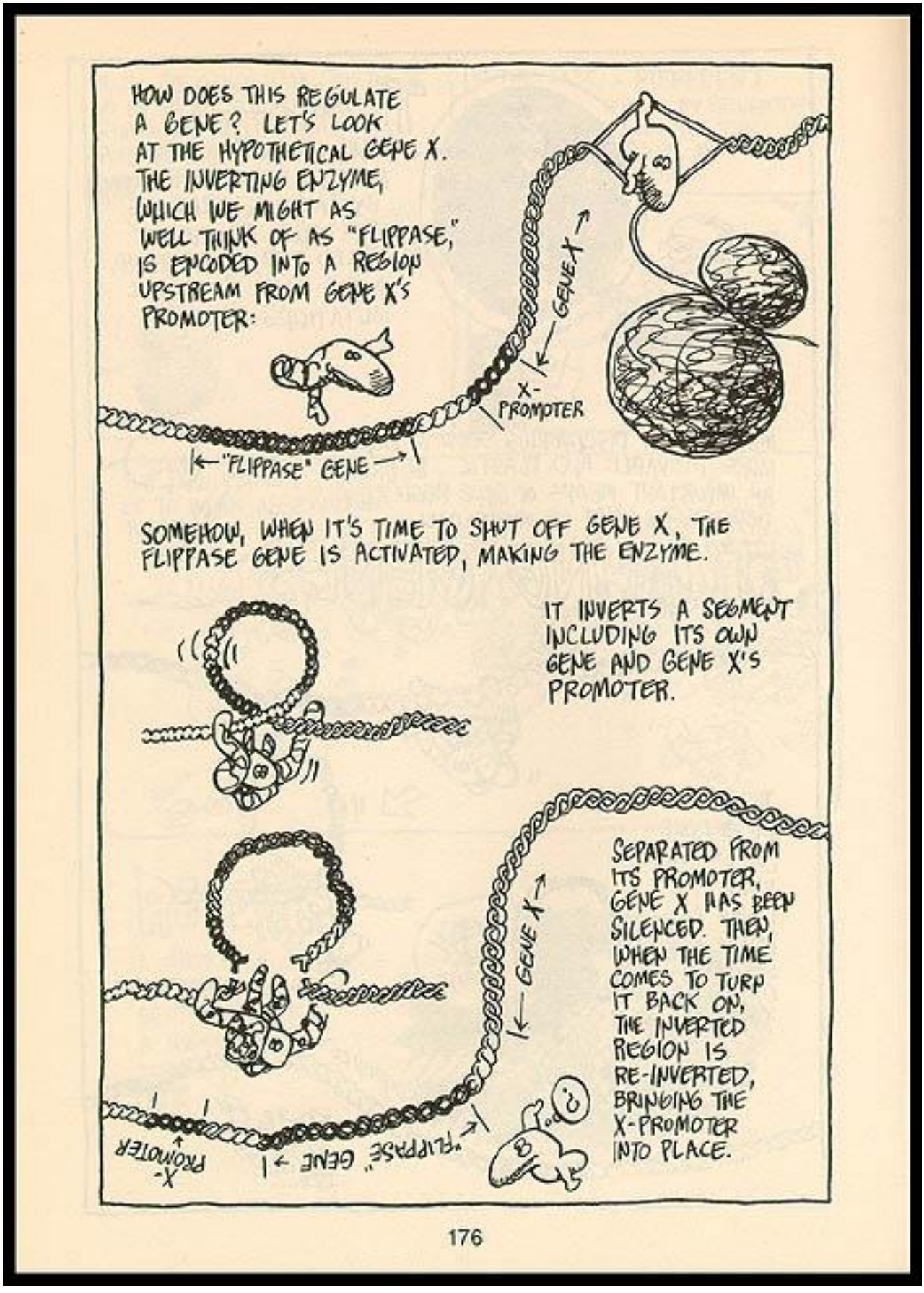
THIS HIS RIS

RESULT?

A SHORTAGE OF HISTIDINE TURNS THE GENE **ON**, WHILE A HISTIDINE GLUT TURNS IT **OFF**.

CHEW ON THAT!


GENE
THE PORTRAIT OF THE GENE, AS SKETCHED BY MENDEL, AND FILLED IN BY LATER GENERATIONS, DEPICTED AN OBJECT FIXED AND UNCHANGING, ASIDE FROM OCCASIONAL MUTATIONS.
MORE RECENT DISCOVERIES SHOW A GENE MORE MOVABLE AND PLASTIC... IN FACT, AN IMPORTANT MEANS OF GENE REGULATION DEPENDS ON WHAT WE MIGHT CALL...
YIKE!
JUMPING GENES.
THERE IS AN ENZYME (OR ENZYMES) WHICH CAN CAUSE A PARTICULAR SEGMENT OF D.N.A TO FLIP:
INVERTED SEQUENCE

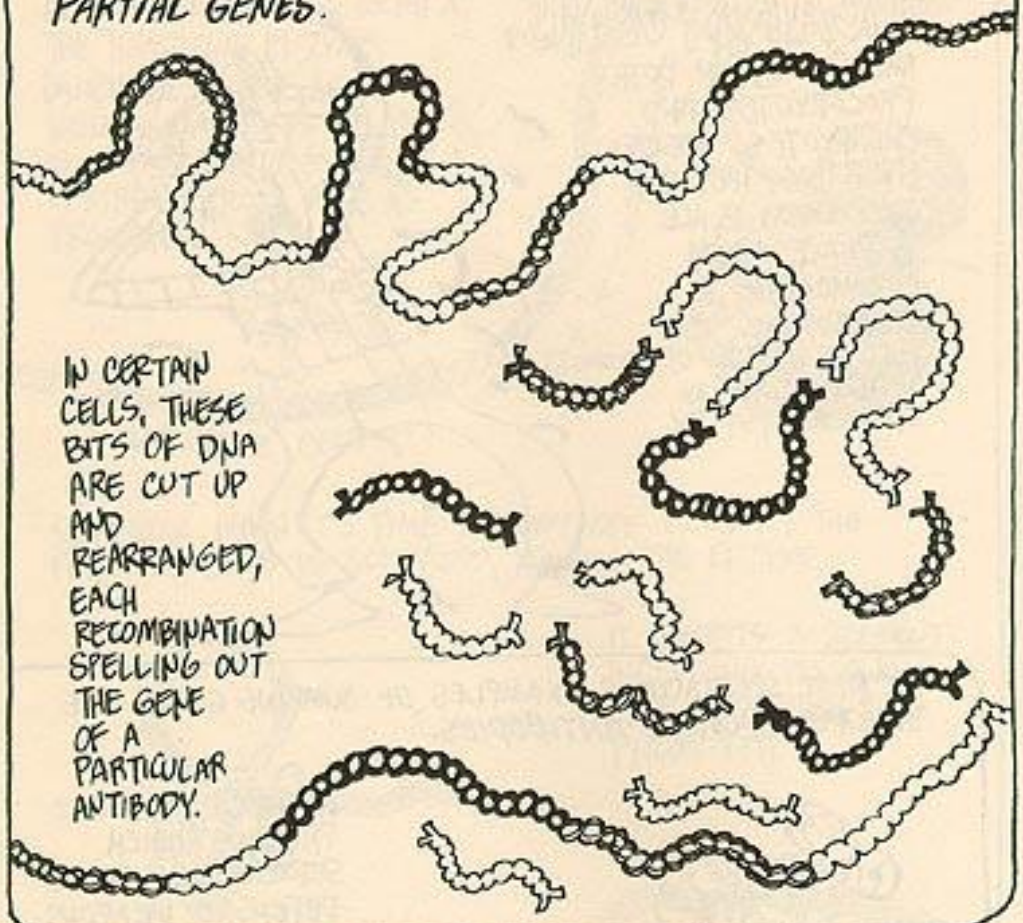

HOW DOES THIS REGULATE A GENE? LET'S LOOK AT THE HYPOTHETICAL GENE X. THE INVERTING ENZYME, WHICH WE MIGHT AS WELL THINK OF AS "FLIPPASE," IS ENCODED INTO A REGION UPSTREAM FROM GENE X'S PROMOTER:
GENE X
X-PROMOTER
"FLIPPASE" GENE
SOMEHOW, WHEN IT'S TIME TO SHUT OFF GENE X, THE FLIPPASE GENE IS ACTIVATED, MAKING THE ENZYME.
IT INVERTS A SEGMENT INCLUDING ITS OWN GENE AND GENE X'S PROMOTER.
SEPARATED FROM ITS PROMOTER, GENE X HAS BEEN SILENCED. THEN, WHEN THE TIME COMES TO TURN IT BACK ON, THE INVERTED REGION IS RE-INVERTED, BRINGING THE X-PROMOTER INTO PLACE.
GENE X
"FLIPPASE" GENE
X-PROMOTER

SUCH MOVABLE SECTIONS, OR **TRANSPOSONS**, ARE COMMON IN BOTH PROCARYOTES AND EUCARYOTES. BESIDES INVERTING, THEY CAN JUMP FROM PLACE TO PLACE, FROM CHROMOSOME TO CHROMOSOME. THE FULL FUNCTION OF TRANSPOSONS IS STILL A MYSTERY.

THE MOST SPECTACULAR EXAMPLES OF JUMPING GENES ARE THE ONES ENCODING *ANTIBODIES*.

ANTIBODIES ARE PROTEINS WHICH SERVE AS THE BODY'S DEFENSIVE WEAPONS. THEY ATTACK BACTERIA, VIRUSES, AND OTHER HARMFUL INVADERS. THERE ARE LITERALLY BILLIONS OF POTENTIAL ANTIBODIES, EACH KEYED TO THE EXACT SHAPE OF ITS "ENEMY." HOW CAN SO MANY BE ENCODED IN GENES?

RATHER THAN HAVING BILLIONS OF GENES FOR ANTIBODIES, THE CHROMOSOMES CARRY A "TOOL KIT" OF A FEW HUNDRED *PARTIAL GENES*.



IN CERTAIN CELLS, THESE BITS OF DNA ARE CUT UP AND REARRANGED, EACH RECOMBINATION SPELLING OUT THE GENE OF A PARTICULAR ANTIBODY.

HOW THE ORGANISM REGULATES THIS PROCESS IS STILL A RIDDLE, AS ARE MOST MATTERS OF EUCARYOTIC GENE REGULATION: THE QUESTION OF HEMOGLOBIN (p. 163), FOR EXAMPLE, REMAINS WITHOUT AN ANSWER.

IT'S CLEAR THAT THE FLEXIBLE GENES OF EUCARYOTES WILL BE AN ACTIVE AREA OF RESEARCH IN YEARS TO COME.