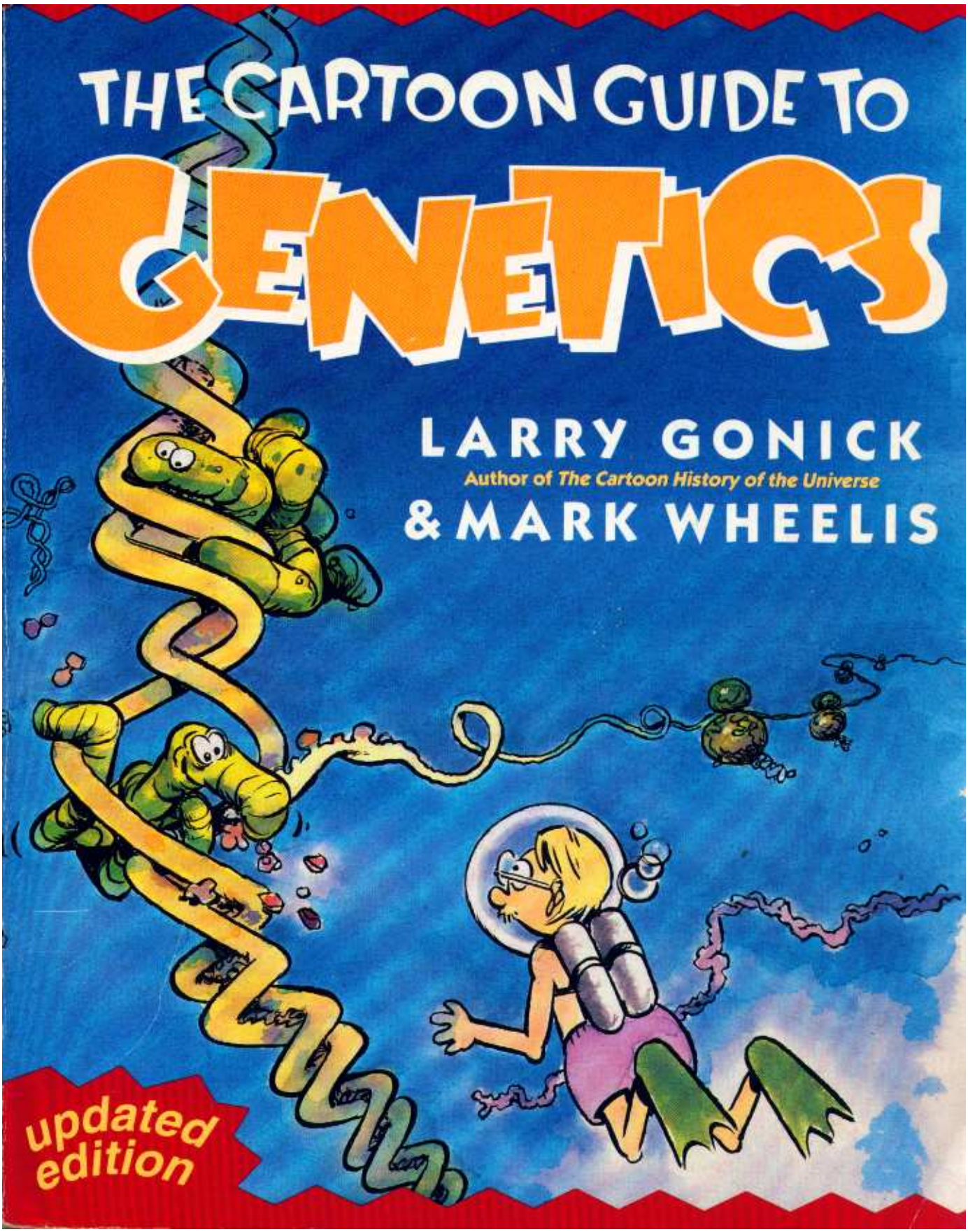
THE CARTOON GUIDE TO GENETICS

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



updated edition

FIRST HARPERPERENNIAL edition published 1991

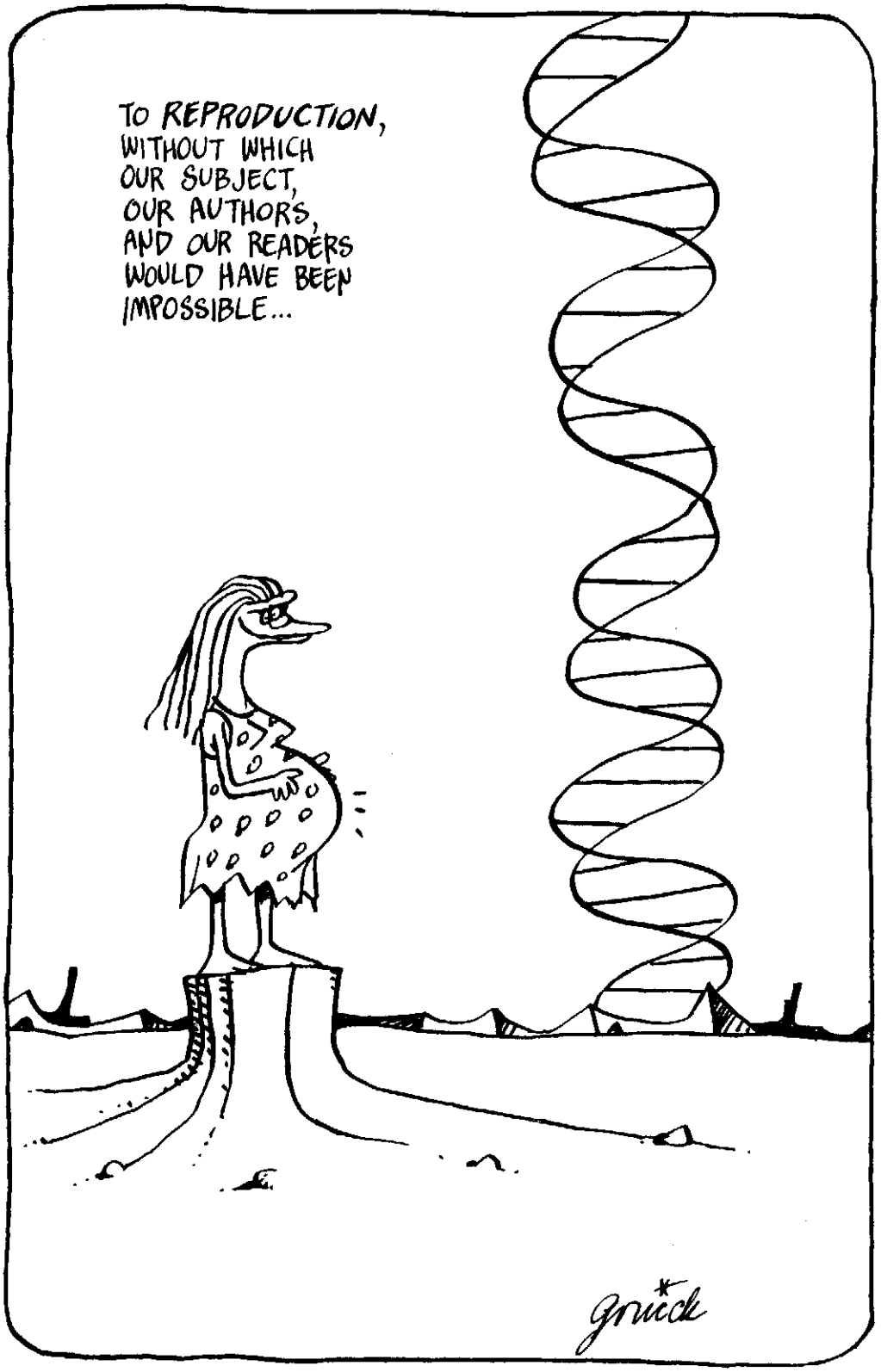
The Library of Congress has cataloged the previous edition of this book as follows:

Gonick, Larry.
The cartoon guide to genetics.

"CO/416."
Includes index.
1. Genetics—Caricatures and cartoons. I. Wheelis, Mark. II.Title.
QH436.G66 1983 575.1'0207 82-48252
ISBN 0-06-460416-0 (pbk.)

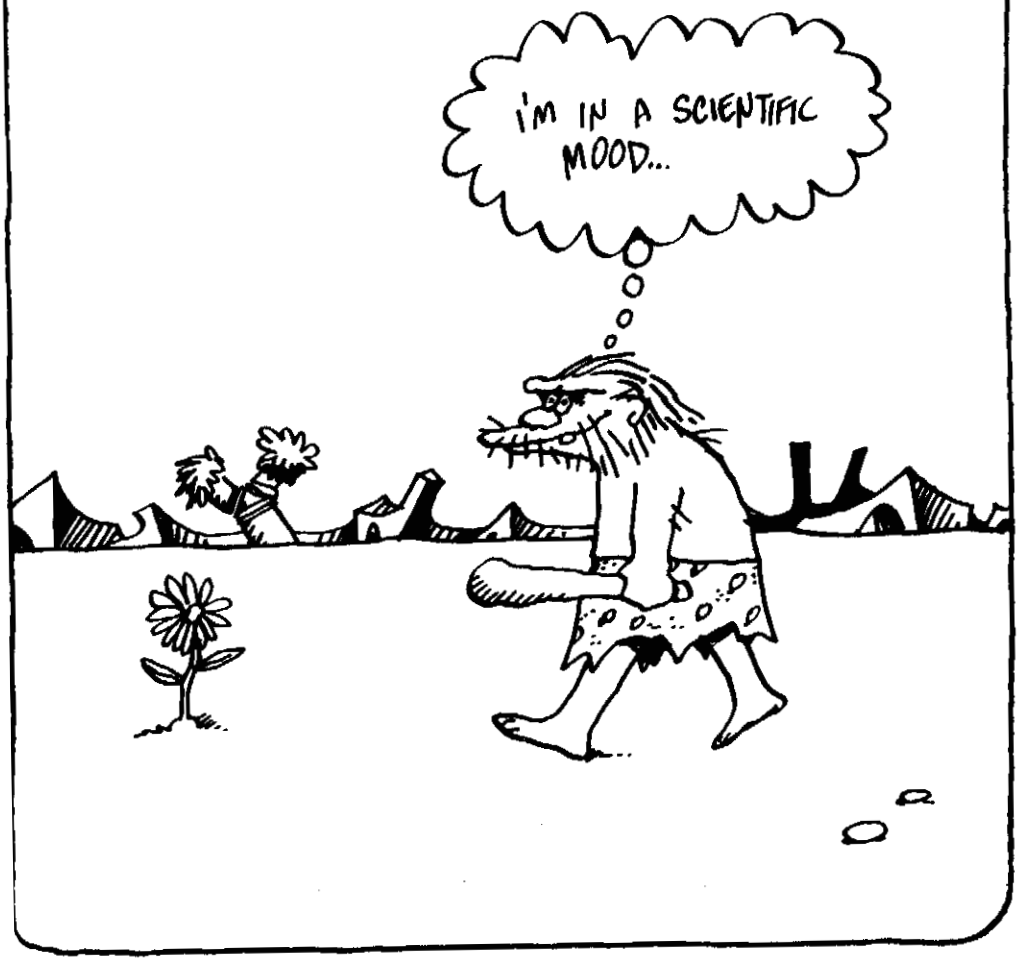
ISBN 0-06-273099-1 (pbk.)

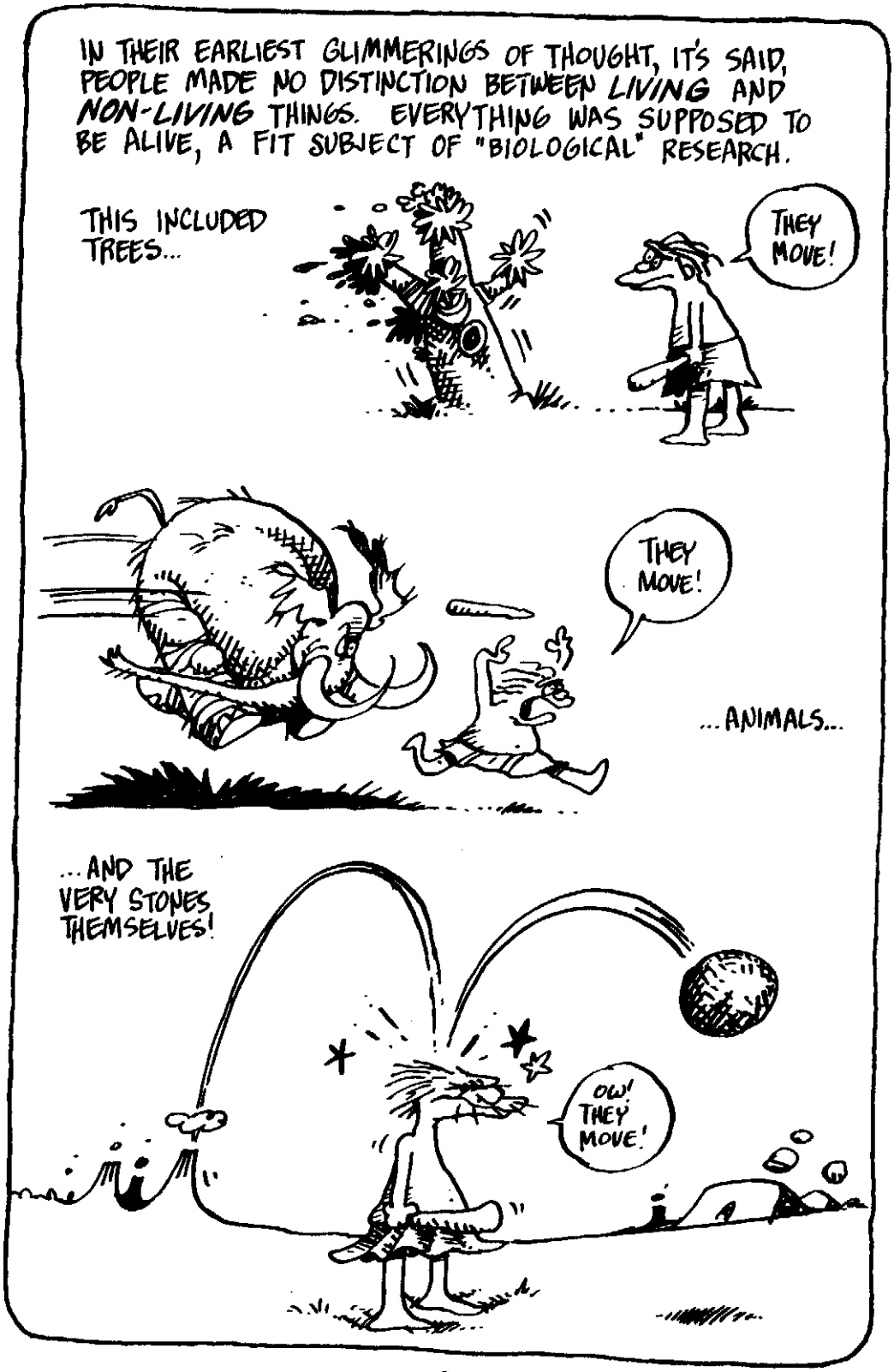
99 00 01 02 RRD-H 30 29 28 27 26 25 24 23 22


TO REPRODUCTION,
WITHOUT WHICH
OUR SUBJECT,
OUR AUTHORS,
AND OUR READERS
WOULD HAVE BEEN
IMPOSSIBLE...
Gruick

IN ANCIENT TIMES...

OUR ANCESTORS HAD A FIRST-HAND KNOWLEDGE OF NATURE. IN THOSE DAYS, EVERYONE WAS A BIOLOGIST, AND THE WORLD WAS A CLASSROOM !!



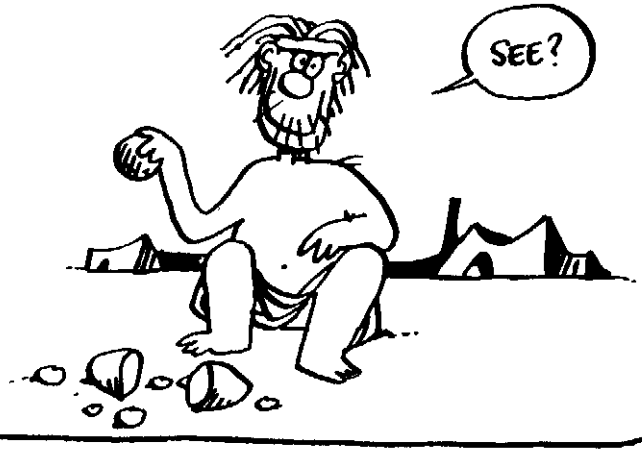

IN THEIR EARLIEST GLIMMERINGS OF THOUGHT, IT'S SAID, PEOPLE MADE NO DISTINCTION BETWEEN LIVING AND NON-LIVING THINGS. EVERYTHING WAS SUPPOSED TO BE ALIVE, A FIT SUBJECT OF "BIOLOGICAL" RESEARCH.
THIS INCLUDED TREES...
THEY MOVE!
THEY MOVE!
...ANIMALS...
...AND THE VERY STONES THEMSELVES!
OW! THEY MOVE!

IN THE COURSE OF THEIR STUDIES, OUR ANCESTORS MUST HAVE NOTICED AN OBVIOUS FACT: SOME THINGS TENDED TO *REPRODUCE* THEMSELVES.

PEOPLE DID IT...

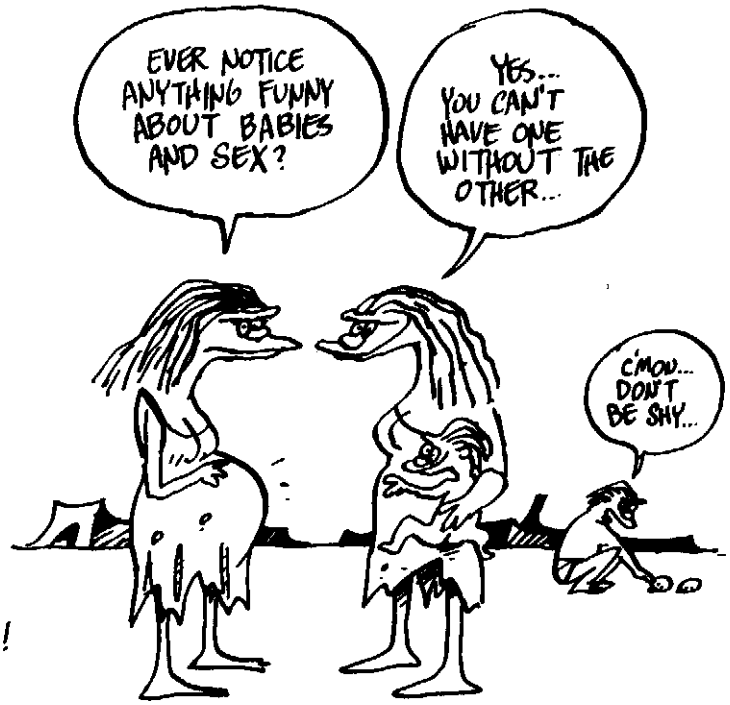
...MAMMOTHS DID IT...

...AND, TO THE PRIMITIVE MIND, IT MAY WELL HAVE SEEMED THAT EVEN *ROCKS* COULD "GIVE BIRTH" TO LITTLE PEBBLES!

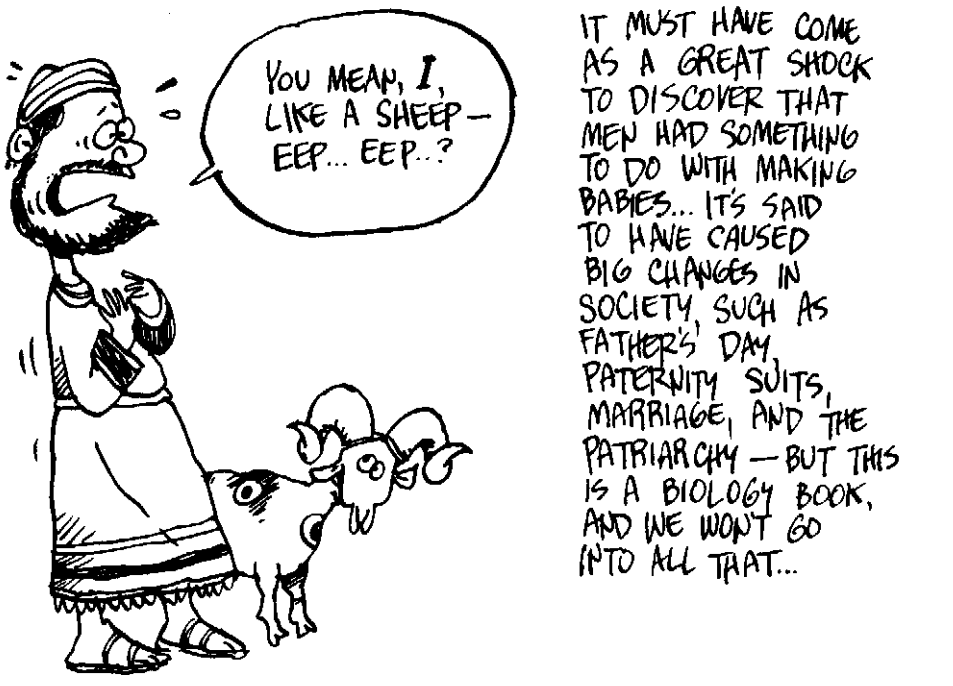


MANY SCHOLARS BELIEVE THAT PRIMITIVE PEOPLE SAW NO CONNECTION BETWEEN REPRODUCTION AND SEX. THE NINE MONTHS BETWEEN CONCEPTION AND BIRTH WAS SUPPOSEDLY ENOUGH TO STYMIE THE SMARTEST STONE-AGER... AND WHAT DOES SEX HAVE TO DO WITH THE REPRODUCTION OF ROCKS??!!

WE MUST ADMIT, THIS THEORY LEAVES US SLIGHTLY SKEPTICAL. IT SEEMS POSSIBLE THAT **MEN** MIGHT HAVE MISSED THE CONNECTION, BUT COULD **WOMEN** HAVE OVERLOOKED WHAT WAS HAPPENING TO THEIR OWN BODIES??!



ENLIGHTENMENT CAME, ACCORDING TO THIS THEORY, WHEN PEOPLE FIRST ***DOMESTICATED ANIMALS*** — AND SAW THEIR REPRODUCTIVE CYCLE CLOSE-UP AND OFTEN: MATING IN ONE SEASON, BIRTH IN ANOTHER.



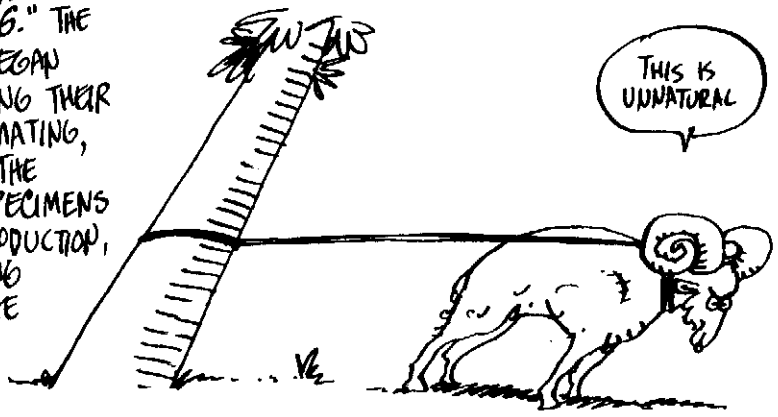
IT MUST HAVE COME AS A GREAT SHOCK TO DISCOVER THAT MEN HAD SOMETHING TO DO WITH MAKING BABIES... IT'S SAID TO HAVE CAUSED BIG CHANGES IN SOCIETY, SUCH AS FATHER'S DAY, PATERNITY SUITS, MARRIAGE, AND THE PATRIARCHY — BUT THIS IS A BIOLOGY BOOK, AND WE WON'T GO INTO ALL THAT...

ALONG WITH THIS CAME THE NOTION THAT *LIKE BEGETS LIKE*— THE FIRST REALLY GENETIC IDEA..

AND SO BEGAN

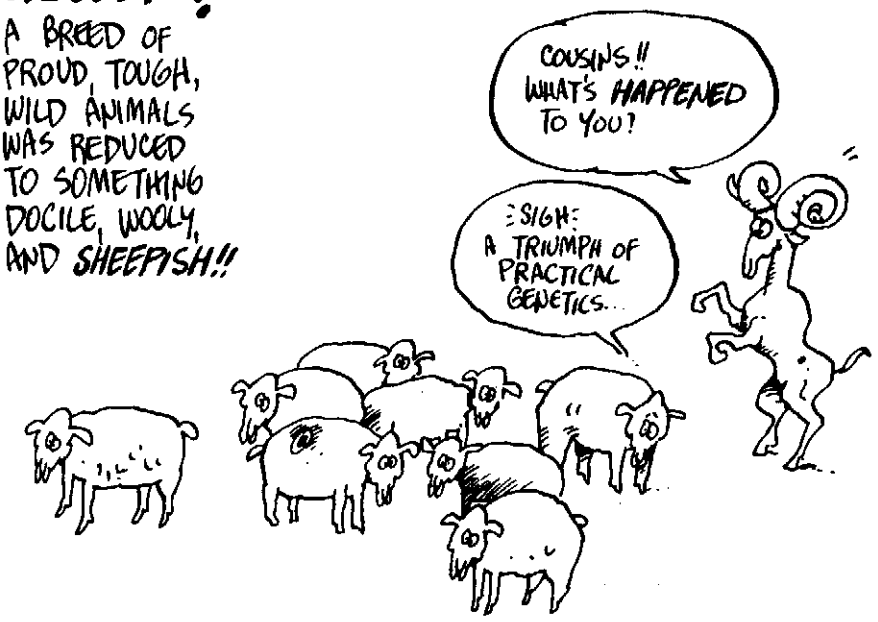
PRACTICAL GENETICS,

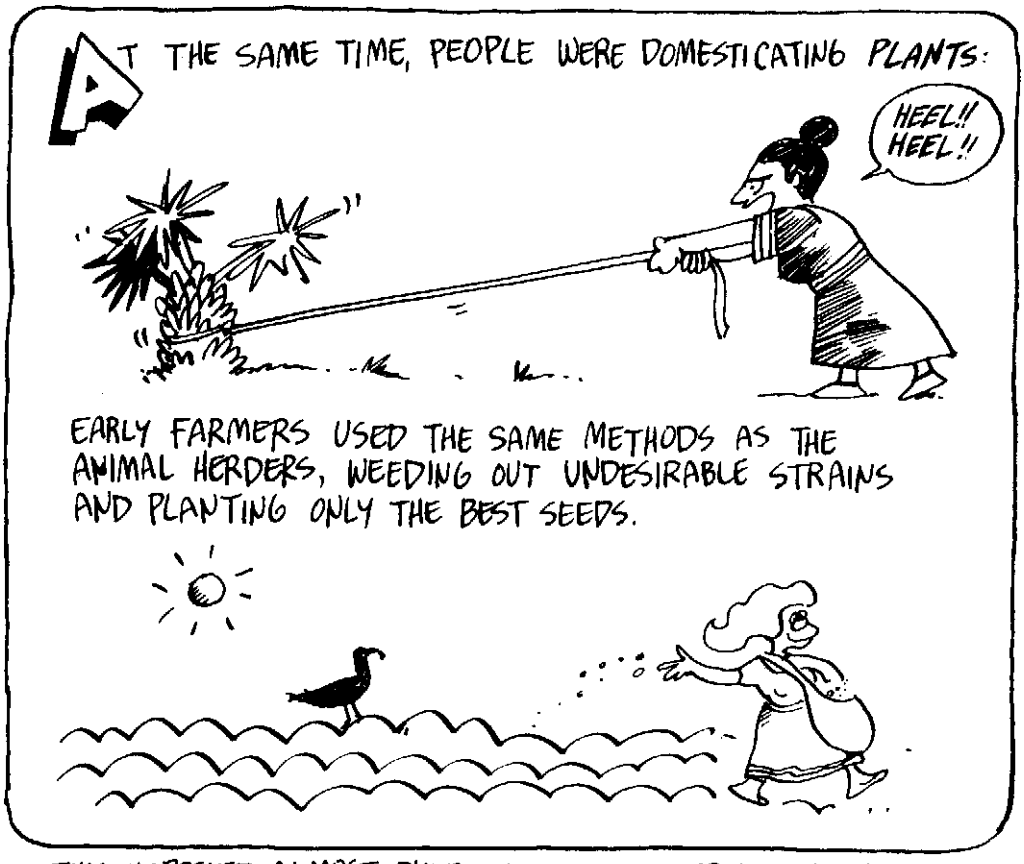
OR "*SELECTIVE BREEDING.*" THE HERDERS BEGAN CONTROLLING THEIR ANIMALS' MATING, CHOOSING THE "BEST" SPECIMENS FOR REPRODUCTION, AND GETTING RID OF THE "WORST."



RESULT?

A BREED OF PROUD, TOUGH, WILD ANIMALS WAS REDUCED TO SOMETHING DOCILE, WOOLY, AND *SHEEPISH!!*





THIS HAPPENED ALMOST EVERYWHERE IN THE WORLD: SCRAWNY WEEDS AND GRASSES WERE GRADUALLY TURNED INTO RICH, PRODUCTIVE CROPS. RICE, WHEAT, BARLEY, AND DATES IN ASIA; CORN, SQUASH, TOMATOES, POTATOES, AND PEPPERS IN AMERICA; YAMS, PEANUTS, AND GOURDS IN AFRICA — ALL SPECIALLY IMPROVED BY HUMANS!!

PLANTS HAVE SEX, TOO... THEY'RE JUST LESS NOISY ABOUT IT THAN ANIMALS.

EARLY ON, PEOPLE NOTICED THE IMPORTANCE OF ***POLLINATION***: POLLEN DUST MUST LAND ON A FLOWER BEFORE IT CAN PRODUCE FERTILE SEEDS.

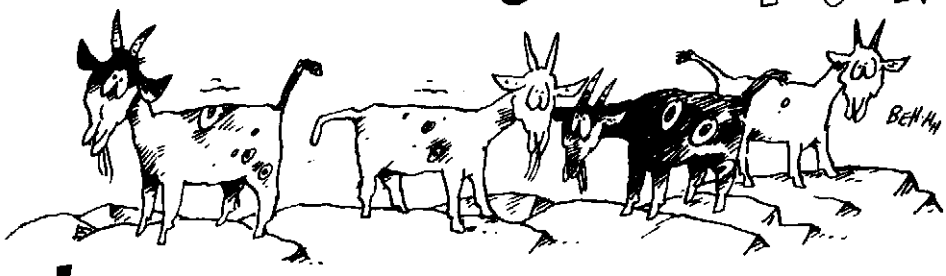
HOWEVER—

THE EARLY FARMERS REALLY DIDN'T KNOW ***WHY*** POLLINATION WORKED—SO THEY ADDED SOME ***MAGIC***, JUST TO BE ON THE SAFE SIDE...

THESE ARE ASSYRIAN PRIESTS, POLLINATING A DATE PALM, AROUND 800 B.C.

THIS COMBINATION OF SCIENCE AND MAGIC IS NICELY ILLUSTRATED BY A BIBLE STORY... *GENESIS*, CHAPTER 30, OR...

THE CASE OF JACOB'S FLOCK



IN THIS STORY, THE PATRIARCH *JACOB* AGREES TO TEND THE FLOCK OF HIS FATHER-IN-LAW *LABAN*. AS PAYMENT, JACOB MAY TAKE ALL THE "SPECKLED AND SPOTTED" ANIMALS FOR HIMSELF, WHILE LABAN KEEPS THE PURE BLACK ONES. THE TWO GROUPS ARE NOT TO INTERBREED.

THE BIBLE DESCRIBES JACOB'S *FERTILITY MAGIC* CAREFULLY: HE STRIPPED THE BARK FROM WILLOW RODS, AND "MADE THE WHITE APPEAR WHICH WAS IN THE RODS", THEN SET THEM NEAR THE WATERING HOLE.

THE IDEA BEHIND JACOB'S ACTION IS THAT ***LIKE BEGETS LIKE***: BY SHOWING THE WHITE IN THE WILLOW RODS, HE WAS TRYING TO BRING OUT THE WHITE IN LABAN'S BLACK ANIMALS !! THIS IS CALLED ***SYMPATHETIC MAGIC***...

THE POINT, GENETICALLY SPEAKING, IS THIS: IN FACT, THE PURE BLACK ANIMALS ***BORE SPECKLED OFFSPRING*** —AND SO JACOB'S FLOCK INCREASED! WHY??

WE'LL COME BACK TO THIS LATER!

HERE WE SEE ACCURATE GENETIC OBSERVATION SIDE-BY-SIDE WITH A NEAR TOTAL LACK OF UNDERSTANDING.

LABAN CERTAINLY DIDN'T GET IT!!

SOME OTHER GENETIC ITEMS FROM ANCIENT HISTORY:

THE CHINESE DISCOVERED "WALTZING" MICE, A MUTATION WHICH CAUSES THE ANIMAL TO STAGGER AROUND IN CIRCLES.

THE HINDUS OBSERVED THAT CERTAIN DISEASES MAY "RUN IN THE FAMILY." MOREOVER, THEY CAME TO BELIEVE THAT CHILDREN INHERIT ALL THEIR PARENTS' CHARACTERISTICS. "A MAN OF BASE DESCENTS CAN NEVER ESCAPE HIS ORIGINS," SAY THE LAWS OF MANU...

XENOPHON, A GREEK, HAD THIS TO SAY ABOUT BREEDING HOUNDS:

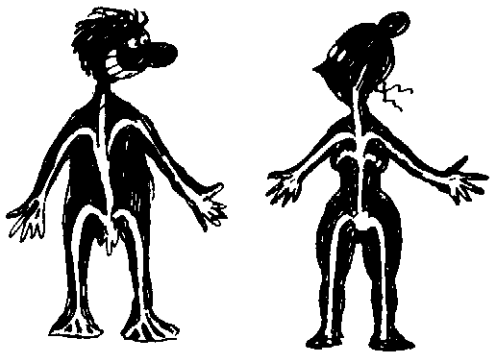
SEVERAL OTHER GREEKS, THINKING MORE DEEPLY THAN XENOPHON, DEVELOPED THE FIRST REAL *THEORIES* OF *HEREDITY*— IN OTHER WORDS, THEY ADDRESSED THE QUESTION: "WHY DO CHILDREN RESEMBLE THEIR PARENTS?"

ACTUALLY, ONE PHILOSOPHER, *SOCRATES*, WONDERED WHY THEY SOMETIMES *DON'T*... HE USED TO SAY THAT THE SONS OF GREAT STATESMEN WERE USUALLY LAZY AND GOOD FOR NOTHING... WE SHOULD ALWAYS BEAR THIS IN MIND, THAT NOT EVERY QUALITY IS INHERITED...

UNFORTUNATELY, BY SUCH UNFLINCHING HONESTY, SOCRATES PROVOKED THE ATHENIANS TO PUT HIM TO DEATH...

THE MOST COHERENT GREEK THEORY OF HEREDITY WAS THAT OF THE FAMOUS DOCTOR *HIPPOCRATES*.

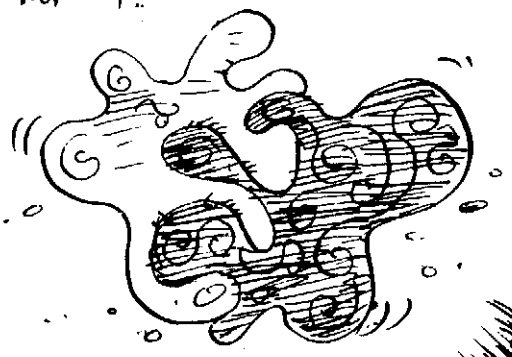
HIPPOCRATES RECOGNIZED THAT THE MALE CONTRIBUTION TO A CHILD'S HEREDITY IS CARRIED IN THE ***SEMEN***. BY ANALOGY, HE ASSUMED THERE WAS A SIMILAR FLUID IN WOMEN.



THESE FLUIDS, HE REASONED, WERE MADE THROUGHOUT THE BODY, AND THEN COLLECTED IN THE REPRODUCTIVE ORGANS.

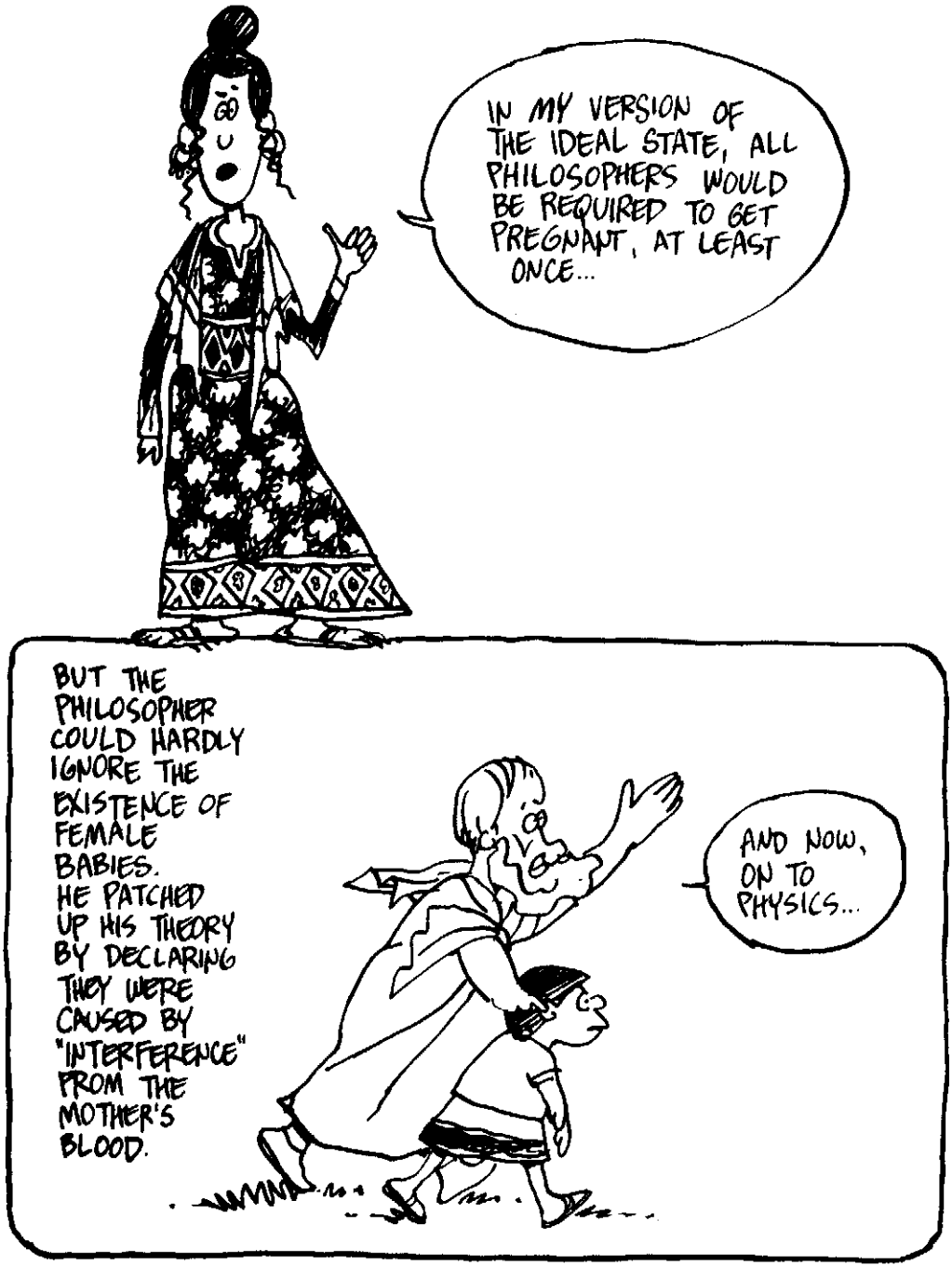
THE SEMEN FROM THE FINGERS HAD THE MATERIAL TO MAKE MORE FINGERS; THAT FROM THE HAIR MADE HAIR, ETC ETC ETC...

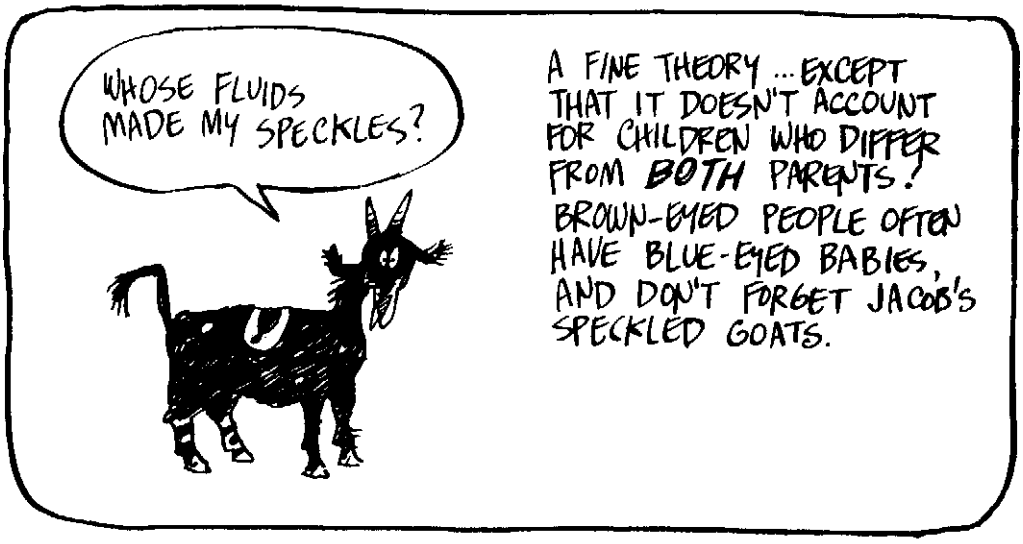
AT CONCEPTION, A SORT OF BATTLE OF THE FLUIDS TOOK PLACE, AND WHETHER THE CHILD'S HANDS WERE MORE LIKE MOM'S OR DAD'S DEPENDED ON WHOSE FINGER-SEMEN WON OUT!!



UNFORTUNATELY, THE GREEK WHOSE IDEAS MOST INFLUENCED LATER GENERATIONS WAS NOT HIPPOCRATES, BUT ***ARISTOTLE.*** WHEN IT CAME TO SCIENCE, ARISTOTLE NEVER LET HIS IGNORANCE STAND IN THE WAY OF HIS THEORIES!!

YES, THERE WAS NO GETTING AROUND IT... THIS SEEMED TO IMPLY THAT ALL CHILDREN OUGHT TO BE *BOYS*... WHO KNOWS? MAYBE THIS REVEALED SOME SUBCONSCIOUS WISH OF ARISTOTLE'S... THE ANCIENT GREEKS DID VALUE BOYS MORE HIGHLY THAN GIRLS.

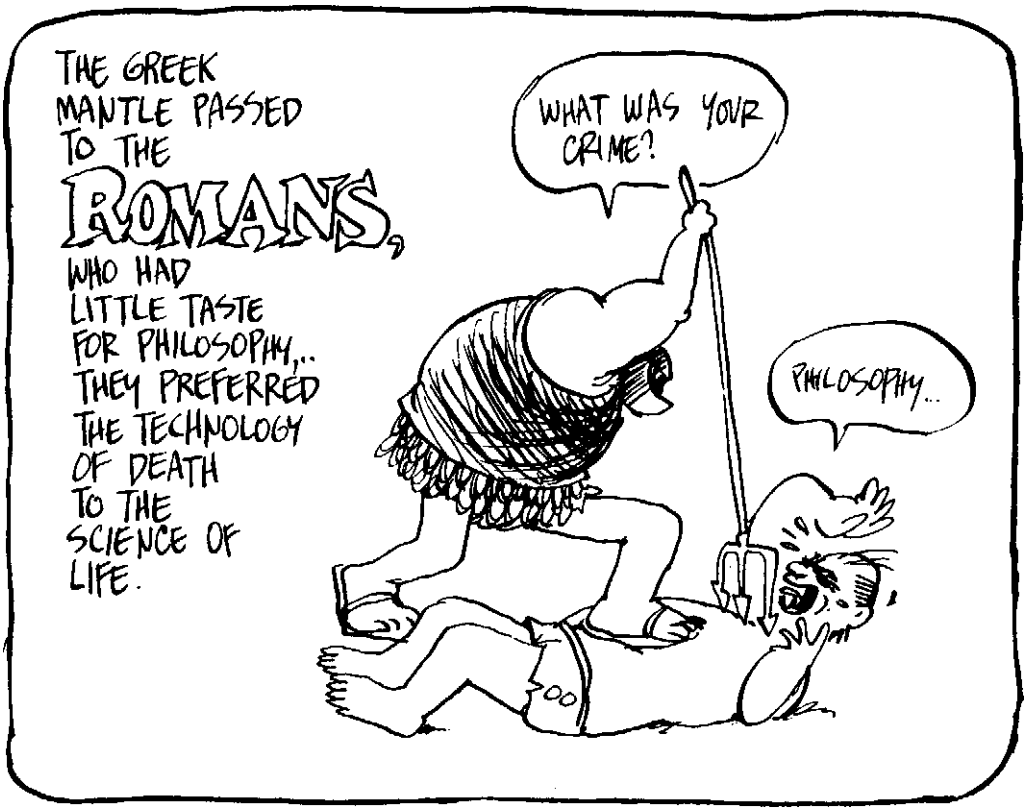




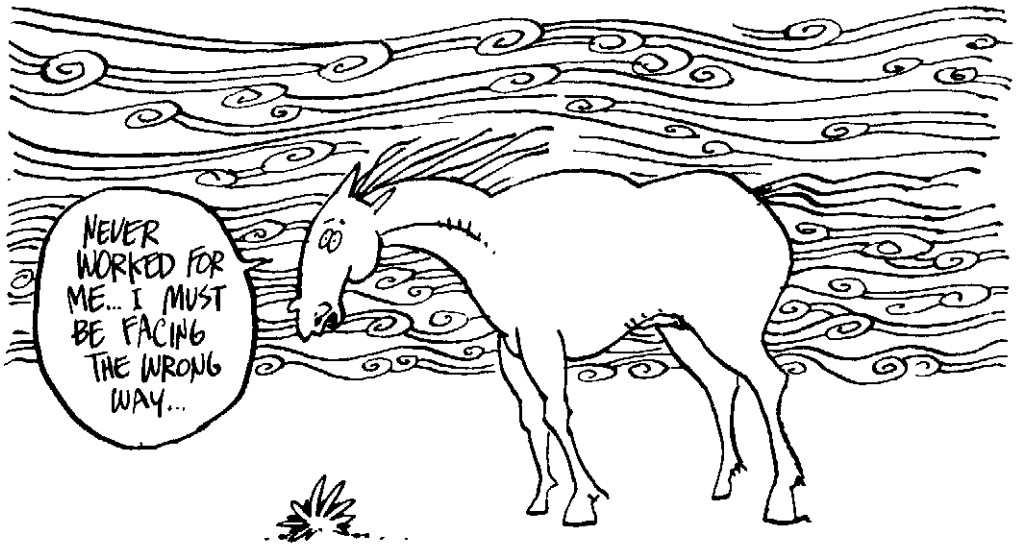
ONE PHILOSOPHER, *EMPEDOCLES*, THOUGHT THIS MIGHT RESULT FROM THE MOTHER'S GAZING LONGINGLY AT STATUES DURING PREGNANCY.

GREEK CIVILIZATION MAY HAVE PERISHED, BUT...

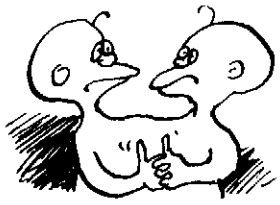
SCIENCE MARCHES ON!



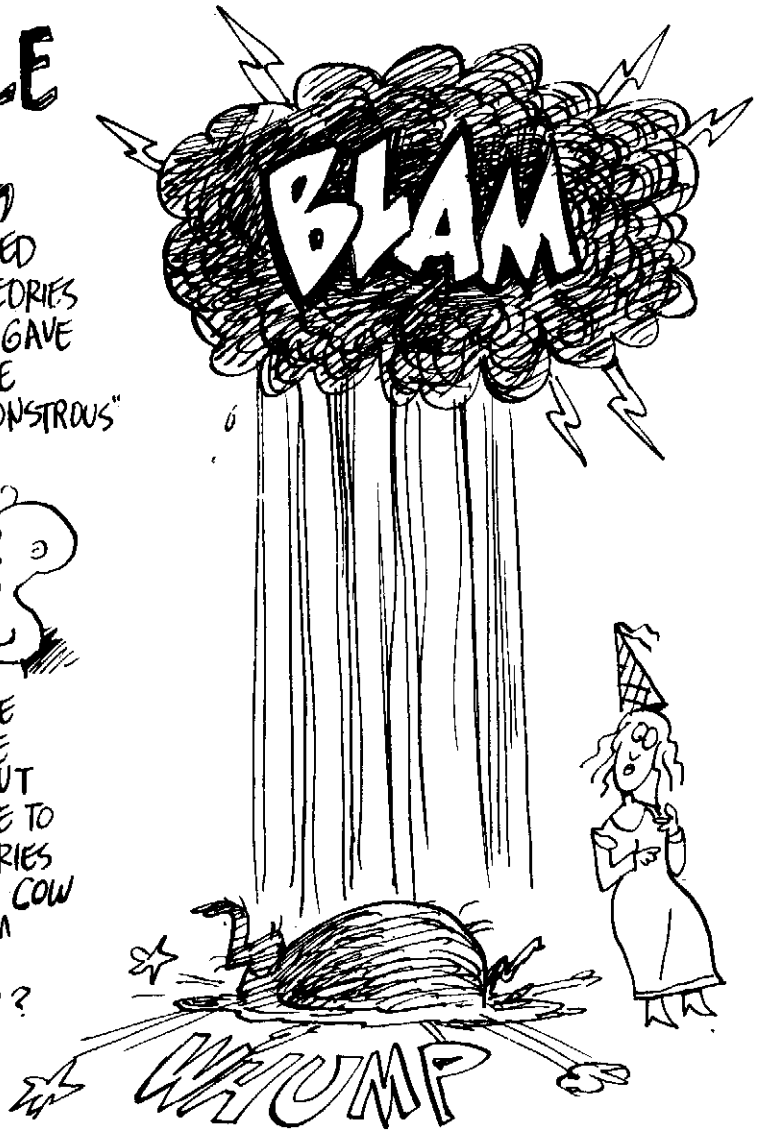
THE ONLY GENETIC IDEA THEY ADDED WAS THAT MARES COULD BE FERTILIZED BY THE WIND...



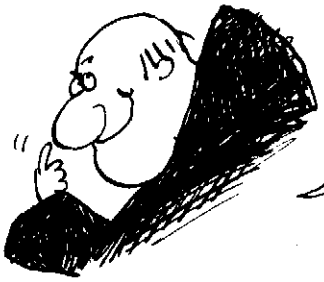
ON THE MIDDLE AGES, SCIENCE FADED FURTHER... THEORIES OF HEREDITY GAVE WAY TO MERE LISTS OF "MONSTROUS" BIRTHS...



SOME OF THESE MAY WELL BE GENUINE — BUT WHAT ARE WE TO MAKE OF STORIES LIKE *HALF A COW* FALLING FROM HEAVEN IN A THUNDERCLAP?



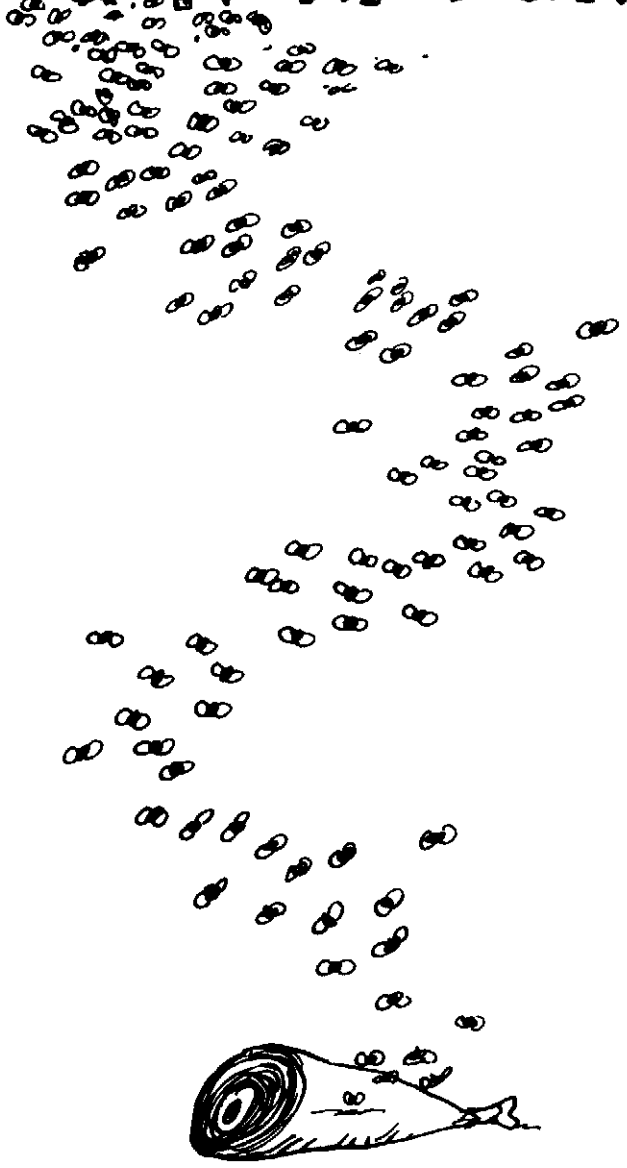
THERE'S ALWAYS THE CHANCE IT WAS JUST A TALL TALE... OR SOMEONE'S IDEA OF A JOKE...



YES... REMINDS ME OF THE ONE ABOUT THE PRIORESS, THE ARCHDEACON, AND THE TWO-HEADED SWINE...

ONE MEDIEVAL IDEA ESPECIALLY IMPEDED UNDERSTANDING. IT WAS CALLED:

SPONTANEOUS GENERATION



ORIGINATING WITH THE GREEKS, THIS WAS THE BELIEF THAT ***LIVING ORGANISMS*** COULD ARISE ("SPONTANEOUSLY") FROM NON-LIVING MATTER.

MAGGOTS WERE SUPPOSED TO COME FROM DECAYING MEAT... HORSEHAIR TURNED INTO WORMS... AND FROGS, MICE, AND BUGS WERE NOTHING BUT SLIME COME TO LIFE!!

IT'S NOT HARD TO IMAGINE WHY SPONTANEOUS GENERATION SEEMED PLAUSIBLE: IN A WORLD WHERE SLIME WAS COMMON, ONE SAW IT HAPPEN EVERY DAY!

YOU SEE HOW BELIEF IN SPONTANEOUS GENERATION CONFLICTS WITH "GENETIC" THINKING? IF A FROG COMES FROM SLIME, IT DOESN'T MAKE MUCH SENSE TO TALK ABOUT INHERITED QUALITIES, DOES IT??

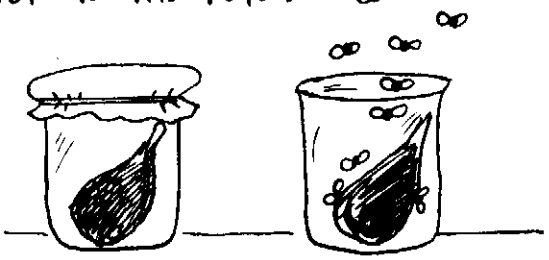
NOT MUCH FAMILY RESEMBLANCE, IS THERE?

BUT – AS WE MENTIONED, SCIENCE MARCHES ON...

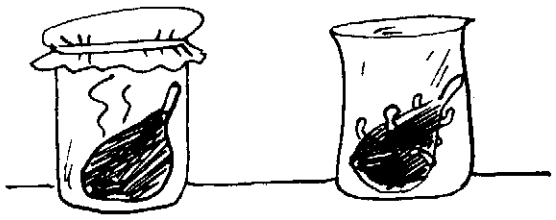
AND IN THE 17TH CENTURY, A SIMPLE EXPERIMENT SUCCESSFULLY CHALLENGED SPONTANEOUS GENERATION..

THE ELEGANT DEMONSTRATION WAS PERFORMED BY THE ITALIAN *FRANCESCO REDI*...

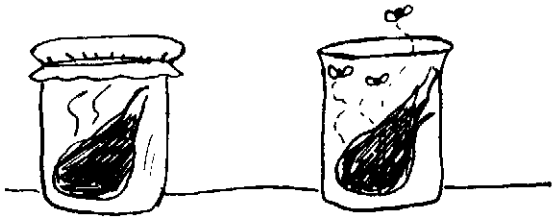
REDI PLACED PIECES OF FRESH MEAT IN JARS... SOME OF THE JARS HE CAPPED TIGHTLY WITH CHEESE-CLOTH, WHILE LEAVING THE REST OPEN TO THE FLIES...



AFTER SOME TIME HAD PASSED, REDI FOUND MAGGOTS *ONLY* IN THE OPEN JARS.



THE MAGGOTS GREW, STIFFENED INTO COCOONS, AND FINALLY EMERGED AS FULLY FORMED FLIES!

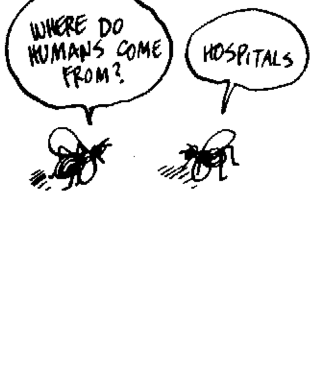


THUS, REDI HAD SHOWN THAT MAGGOTS COME FROM FLIES, AND FLIES COME FROM MAGGOTS. NOTHING VISIBLE HAD BEEN "SPONTANEOUSLY GENERATED" FROM THE ROTTING MEAT!!

BUT THE "SPONTANEOUS GENERATORS" WEREN'T DOWN YET...

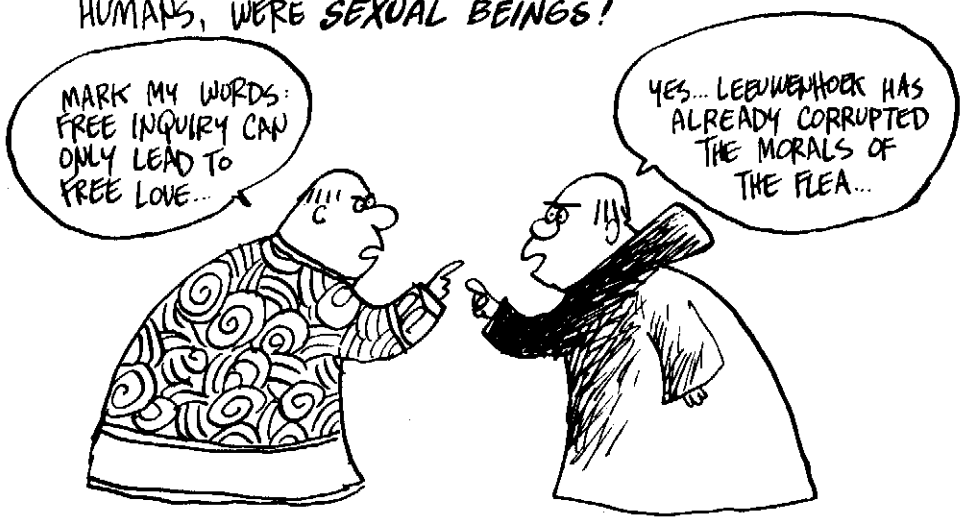
PEOPLE STILL BELIEVED THAT FLEAS CAME FROM SAND, WEEVILS FROM GRAIN, EELS FROM THE DEW, ETC, ETC, ETC...

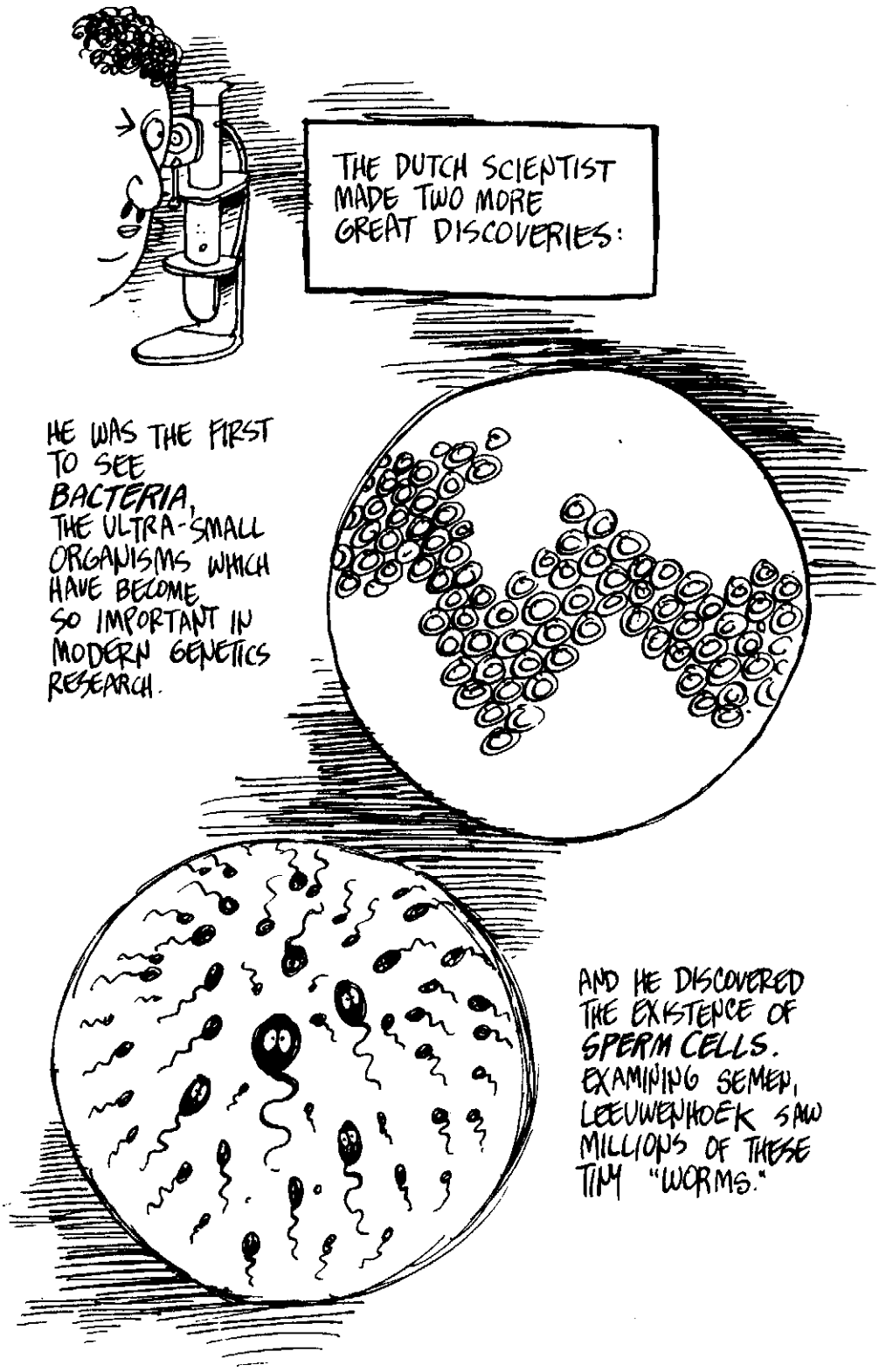
FLEAS, EELS, AND WEEVILS, IN TURN, WERE DISPOSED OF BY **ANTON** VAN **LEEUWENHOEK** ("LAY-VEN-HOOK"), AN AMATEUR DUTCH SCIENTIST AND THE FIRST TO MAKE SYSTEMATIC USE OF THE ***MICROSCOPE***.

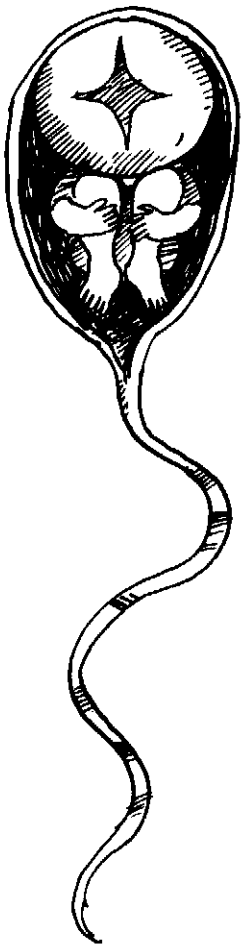


USING HIS SIMPLE INSTRUMENT — JUST AN EXCELLENT EYEPIECE REALLY — LEEUWENHOEK FOLLOWED THE LIFE HISTORIES OF VARIOUS SMALL CREATURES. HIS TREATISE ON THE FLEA IS A CLASSIC!!

HE DISCOVERED THAT FLEAS, LIKE FISH, DOGS, AND HUMANS, WERE ***SEXUAL BEINGS!***

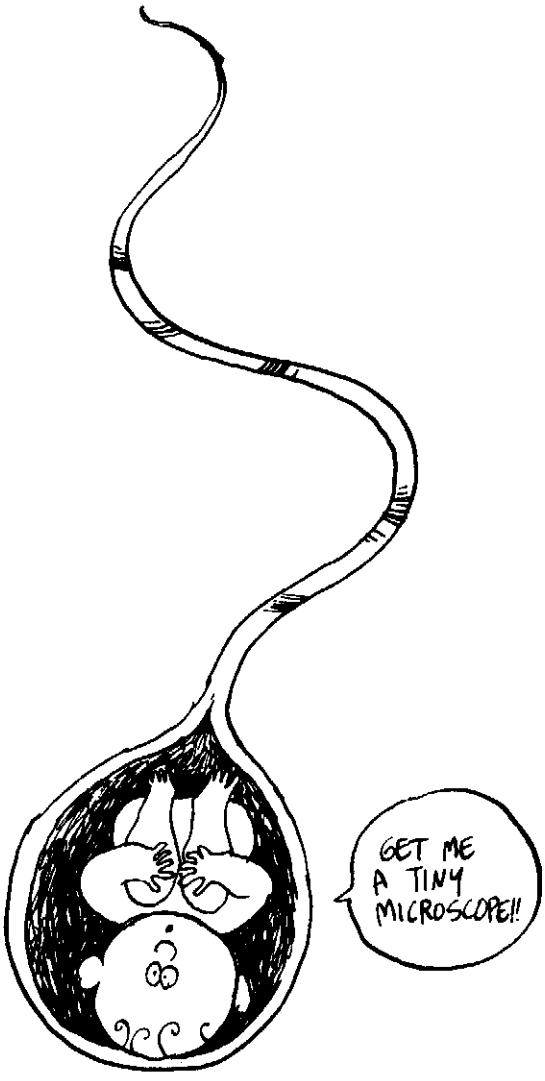



THE DUTCH SCIENTIST MADE TWO MORE GREAT DISCOVERIES:
HE WAS THE FIRST TO SEE BACTERIA, THE ULTRA-SMALL ORGANISMS WHICH HAVE BECOME SO IMPORTANT IN MODERN GENETICS RESEARCH.
AND HE DISCOVERED THE EXISTENCE OF SPERM CELLS. EXAMINING SEMEN, LEEUWENHOEK SAW MILLIONS OF THESE TINY "WORMS."



ONE MIGHT SAY THAT THIS DISCOVERY OPENED A WHOLE CAN OF WORMS... OR THAT IT SPAWNED WRONG IDEAS... FOR INSTANCE, LEEUWENHOEK HIMSELF BELIEVED EACH SPERM CELL CONTAINED A COMPLETE NEW ORGANISM IN MINIATURE.

THE OBVIOUS PROBLEM WAS: IF THIS "PRE-FORMED" ORGANISM WAS A BOY, IT MUST ALREADY HAVE TINY TESTICLES, WHICH WOULD CONTAIN MINIATURE SPERM, WHICH WOULD EACH HAVE EVEN TINIER PREFORMED ORGANISMS... AD INFINITUM ET ABSURDUM !!!



EX OVO OMNIA

(AS LONG AS WE'RE TALKING LATIN!)

WHILE LEEUWENHOEK SPECULATED ABOUT SPERM, OTHER SCIENTISTS WERE LOOKING INTO THE FEMALE ROLE IN REPRODUCTION...

WILLIAM *HARVEY* (1578-1657) STUDIED THE DEVELOPMENT OF THE CHICK EMBRYO AND CONVINCED HIMSELF THAT *ALL* ANIMALS MUST COME FROM *EGGS*. "EX OVO OMNIA," HE SAID: "OUT OF EGG, ALL."

HARVEY BEGAN THE HUNT FOR THE *MAMMALIAN EGG*.

HE PERSUADED THE KING TO LET HIM LOOK FOR MAMMAL EGGS IN THE ROYAL DEER PARK... DOZENS OF DISSECTED DEER LATER, HARVEY HAD TO ADMIT FAILURE.

FOR 200 YEARS THE HUNT WENT ON... AND STILL NO ONE COULD LOCATE THE ELUSIVE EGG.

IT'S NOT HARD TO SEE WHY NOT... NOT ONLY IS THE MAMMALIAN EGG MICROSCOPIC, IT'S ALSO FAIRLY RARE...

MAMMALS "LAY" VERY FEW EGGS: A HUMAN FEMALE PRODUCES ONLY ONE A MONTH, IN CONTRAST TO THE MALE AND HIS TENS OF MILLIONS OF SPERM CELLS.

BUT THE SEARCH WENT ON... THERE WERE SOLID REASONS FOR BELIEVING MAMMALS HAD EGGS: WE HAVE OVARIES AND OVIDUCTS... IT WOULD BE PRETTY SILLY NOT TO HAVE EGGS, TOO...

YES, PEOPLE ARE JUST HIGHLY EVOLVED CHICKENS!

IN FACT, SCIENTISTS GREW SO SURE EGGS WERE THERE, THAT WHEN ONE WAS FINALLY SEEN—A DOG'S EGG, IN 1827—IT CAME AS MORE OF A RELIEF THAN A SURPRISE!!

HEY! DOGS GOT EGGS!

YOO-HOO!

OVER HERE!

I SAW IT!

HEY!

:SIGH: IT'S ABOUT TIME...

THE ONLY REMAINING RIDDLE WAS ANSWERED WHEN *OSCAR HERTWIG* OBSERVED THAT *FERTILIZATION* WAS THE UNION OF A SINGLE SPERM WITH A SINGLE EGG.

YOU'RE NOT SINGLE ANY MORE!

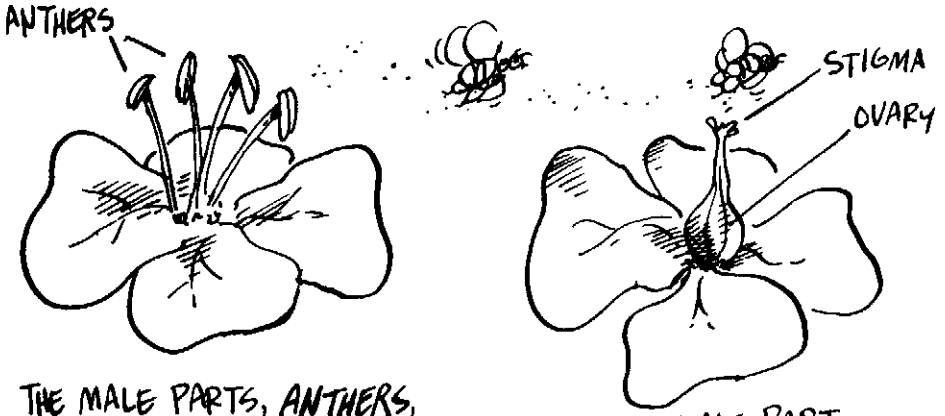
MEANWHILE...

SOME PROGRESS HAD BEEN MADE IN THE QUESTION OF *PLANT SEX.*

BY 1700, THE SEXUAL NATURE OF PLANTS HAD BEEN LARGELY RESOLVED BY *CAMERARIUS* (1665-1721), WHOSE NAME EVEN SOUNDS LIKE A PLANT...

CAMERARIUS SHOWED THAT *FLOWERS* BORE SEX ORGANS QUITE LIKE THOSE OF ANIMALS.

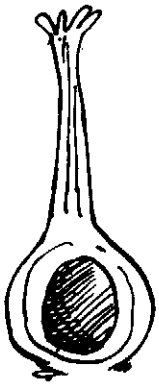
AND THEY STICK THEM RIGHT IN THE AIR... SHAMEFUL!



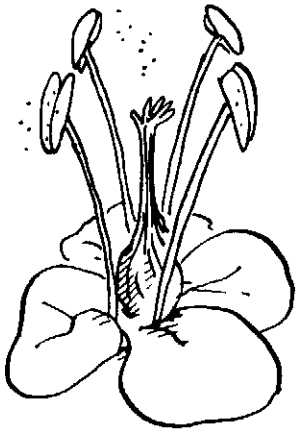
THE MALE PARTS, *ANTHERS*, CONTAIN POLLEN, WHICH IS LIKE SPERM IN ANIMALS.

THE FEMALE PART IS THE *STIGMA*, TO WHICH THE POLLEN ATTACHES.

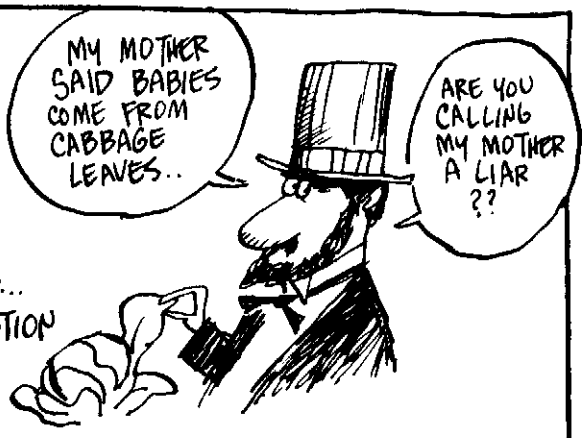
THE POLLEN (OR PART OF IT) THEN PENETRATES TO THE OVARY, CAUSING SEEDS TO DEVELOP



JUST TO COMPLICATE MATTERS, MANY FLOWERS HAVE BOTH MALE AND FEMALE ORGANS— AND SO THEY CAN FERTILIZE THEMSELVES.



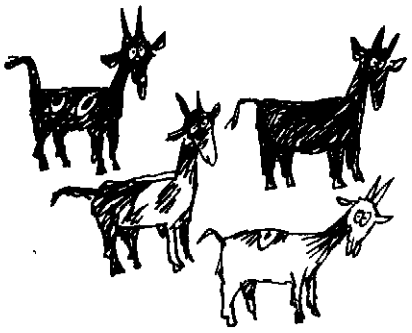
SO BY THE EARLY 1800's, BOTH PLANTS AND ANIMALS WERE KNOWN TO BE SEXUAL... THE MALE CONTRIBUTED POLLEN OR SPERM; THE FEMALE EGGS... AND SPONTANEOUS GENERATION WAS ON ITS LAST LEGS — ALMOST...



TO BREED OR NOT TO BREED ?

LET'S SEE WHAT THEY ALREADY KNEW FROM EXPERIENCE:

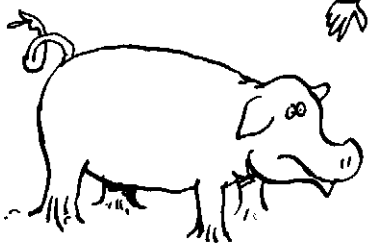
1. SOME ***STABLE VARIETIES*** NEARLY ALWAYS BREED TRUE, THEIR OFFSPRING HAVING THE SAME CHARACTERISTICS AS THEIR PARENTS. SOME COMMON EXAMPLES ARE MACKINTOSH APPLES, ARABIAN HORSES, LABRADOR RETRIEVERS, PEOPLE WITH BLUE EYES, ETC ETC ETC...



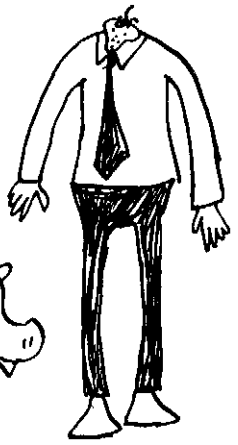
ON THE OTHER HAND, SOME BREEDING GROUPS SHOW GREAT VARIATION. JACOB'S FLOCK IS AN EXAMPLE OF VARIABLE COLOR. PEOPLE WITH BROWN EYES CAN HAVE BLUE-EYED CHILDREN.

2. IT IS SOMETIMES POSSIBLE TO MATE PARENTS FROM TWO DIFFERENT VARIETIES TO FORM **HYBRIDS.** FOR EXAMPLE, A MULE IS HALF HORSE AND HALF DONKEY. OF COURSE, NOT ALL HYBRIDS ARE POSSIBLE !!!

IMPOSSIBLE HYBRIDS:



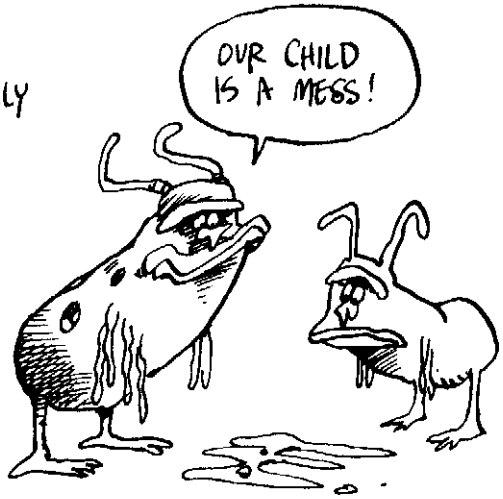
PIG/TREE

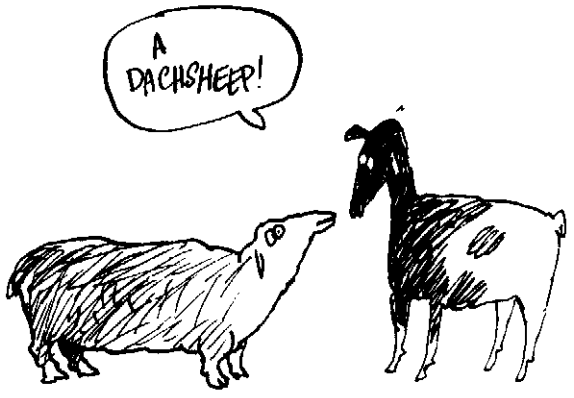


HUMAN/STRAWBERRY

HYBRIDS ARE DIFFICULT TO PREDICT... THEY MAY SEEM VIRTUALLY IDENTICAL TO ONE PARENT, OR THEY MAY COMBINE FEATURES OF BOTH— AND WHEN HYBRIDS BREED WITH HYBRIDS, THE RESULT IS VARIATION IN THE EXTREME!!

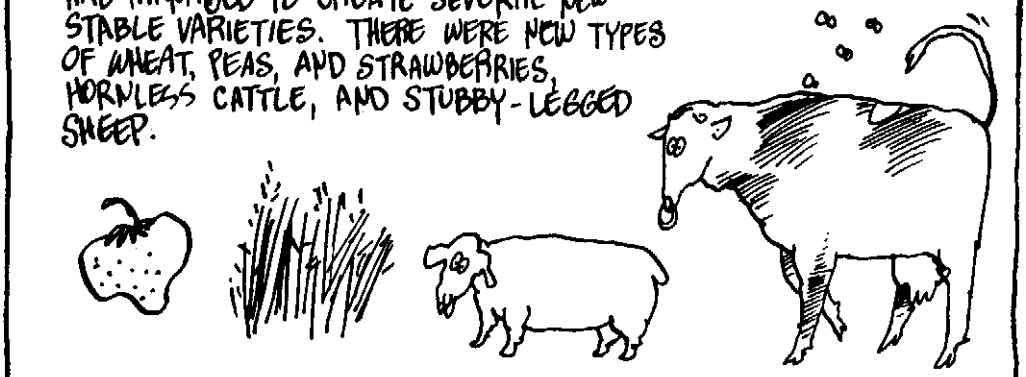
3. ALL VARIETIES, EVEN STABLE ONES, OCCASIONALLY PRODUCE "***SPORTS***"— OFFSPRING DIFFERENT FROM EITHER PARENT. THESE ARE OFTEN GROSSLY DEFECTIVE "MONSTROSITIES"...





BUT SOMETIMES THE SPORT DIFFERS ONLY SLIGHTLY, LIKE THE STUBBY-LEGGED SHEEP WHICH APPEARED AROUND 1800.

BY CROSSING THESE SPORTS BACK WITH NORMAL TYPES, 19TH-CENTURY FARMERS HAD MANAGED TO CREATE SEVERAL NEW STABLE VARIETIES. THERE WERE NEW TYPES OF WHEAT, PEAS, AND STRAWBERRIES, HORNLESS CATTLE, AND STUBBY-LEGGED SHEEP.



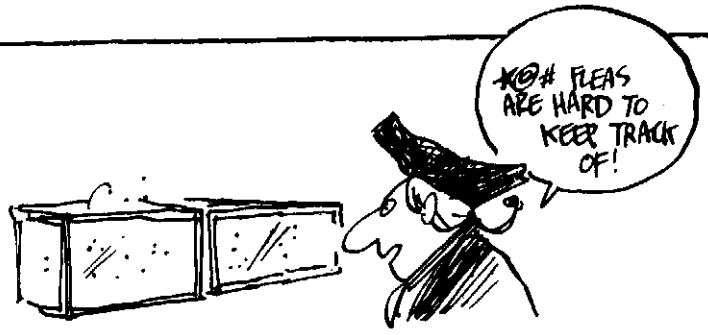
BUT IT WAS STILL A MATTER OF TRIAL AND ERROR... IT DIDN'T ALWAYS WORK... AND SO PEOPLE BEGAN TO WONDER IF THERE MIGHTN'T BE A SCIENTIFIC WAY OF SELECTING ADVANTAGEOUS TRAITS TO CREATE NEW VARIETIES.

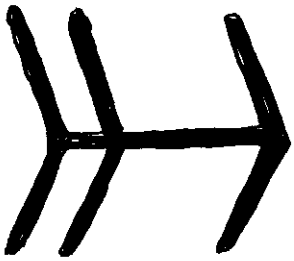
HOWEVER,

DESPITE A GOOD DEAL OF WORK, NO TRULY GENERAL LAWS OF INHERITANCE WERE DISCOVERED.

SOME INVESTIGATORS CONFUSED THEMSELVES BY CROSSING BREEDS THAT DIFFERED IN TOO MANY CHARACTERISTICS...

OTHERS FAILED TO KEEP A CAREFUL COUNT OF THE NUMBER OF VARIETIES PRODUCED FROM EACH CROSS.





INDEED, THE PROBLEM SEEMED HOPELESS... GRADUALLY, SCIENTISTS GAVE UP TRYING AND TURNED TO EASIER PROBLEMS... AND THAT IS WHY, WHEN THE LAWS OF INHERITANCE WERE FINALLY FIGURED OUT, THE DISCOVERY WAS IGNORED FOR THIRTY YEARS...

MONK FINDS GENE; WORLD YAWNS!

FIFTY YEARS OF RESEARCH HAD FAILED TO FIND ANY PRECISE LAW OF INHERITANCE. OBVIOUSLY, DISCOVERING THE RIGHT FORMULA, IF POSSIBLE, WAS A JOB REQUIRING SUPERHUMAN PATIENCE, UNLIMITED TIME, AND, AS IT HAPPENED, A MIRACLE OF LUCK.

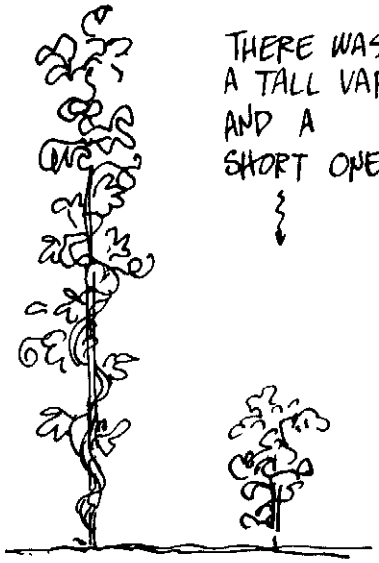
NO WONDER IT HAPPENED IN A MONASTERY...

GREGOR MENDEL

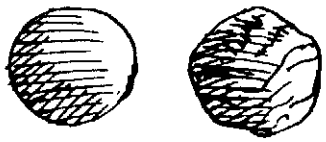
(1822 - 1884) WAS AN AUGUSTINIAN MONK FROM BRÜNN, AUSTRIA. IN HIS SPARE TIME, MENDEL BRED PEA PLANTS IN THE MONASTERY GARDENS.

BUT MENDEL WAS NOT JUST AN AMATEUR GARDENER, BUT A ***SCIENTIST*** WHO STUDIED HIS PEA PLANTS MOST CAREFULLY — HE CALLED THEM HIS "CHILDREN."

CHOOSING PEAS WAS THE MIRACLE OF LUCK: THEY ARE PERFECTLY SUITED TO GENETIC RESEARCH, WITH A NUMBER OF STABLE VARIETIES WHICH MAY FORM HYBRIDS:



THERE WAS A TALL VARIETY AND A SHORT ONE...



ONE TYPE MADE SMOOTH, ROUND PEAS, WHILE ANOTHER'S WERE LUMPY AND WRINKLED...

SOME PODS WERE PLUMP, WHILE OTHERS WERE PINCHED...

THERE WERE GREEN PEAS AND YELLOW; GREY SEED-COATS AND WHITE; WHITE FLOWERS AND PURPLE. THERE WERE DIFFERENCES IN THE COLOR OF THE UNRIPE PODS, THE COLOR OF SEED ALBUMIN, AND THE POSITION OF THE FLOWERS.

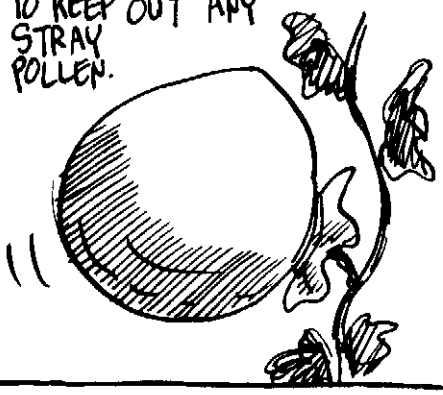
EVERY PEA FLOWER HAS BOTH MALE AND FEMALE ORGANS, SO THEY ORDINARILY FERTILIZE THEMSELVES.

HOW MENDEL MADE HYBRIDS:

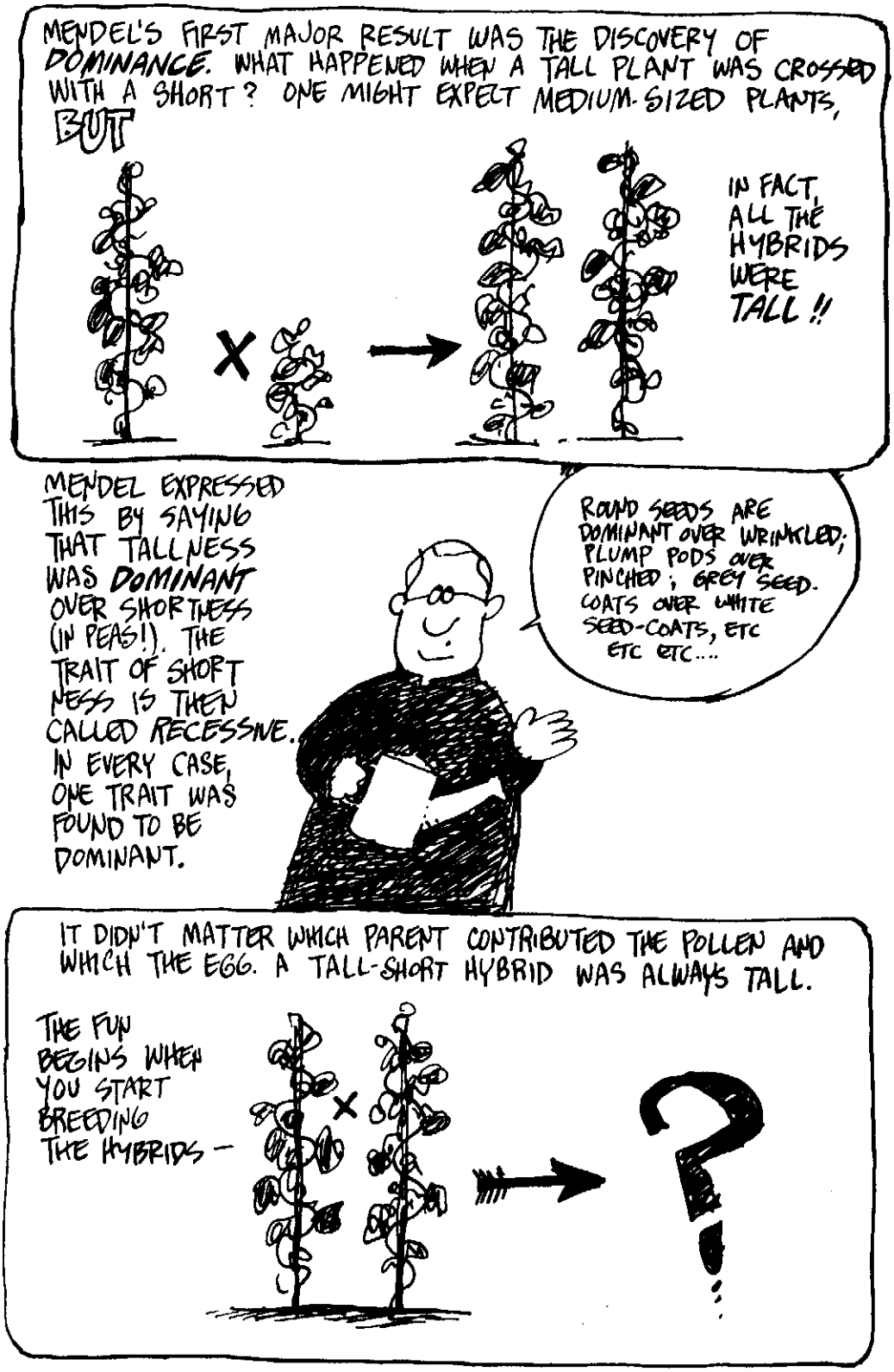
FIRST HE SNIPPED OFF THE ANTHERS WHILE STILL IMMATURE TO PREVENT "SELFING."

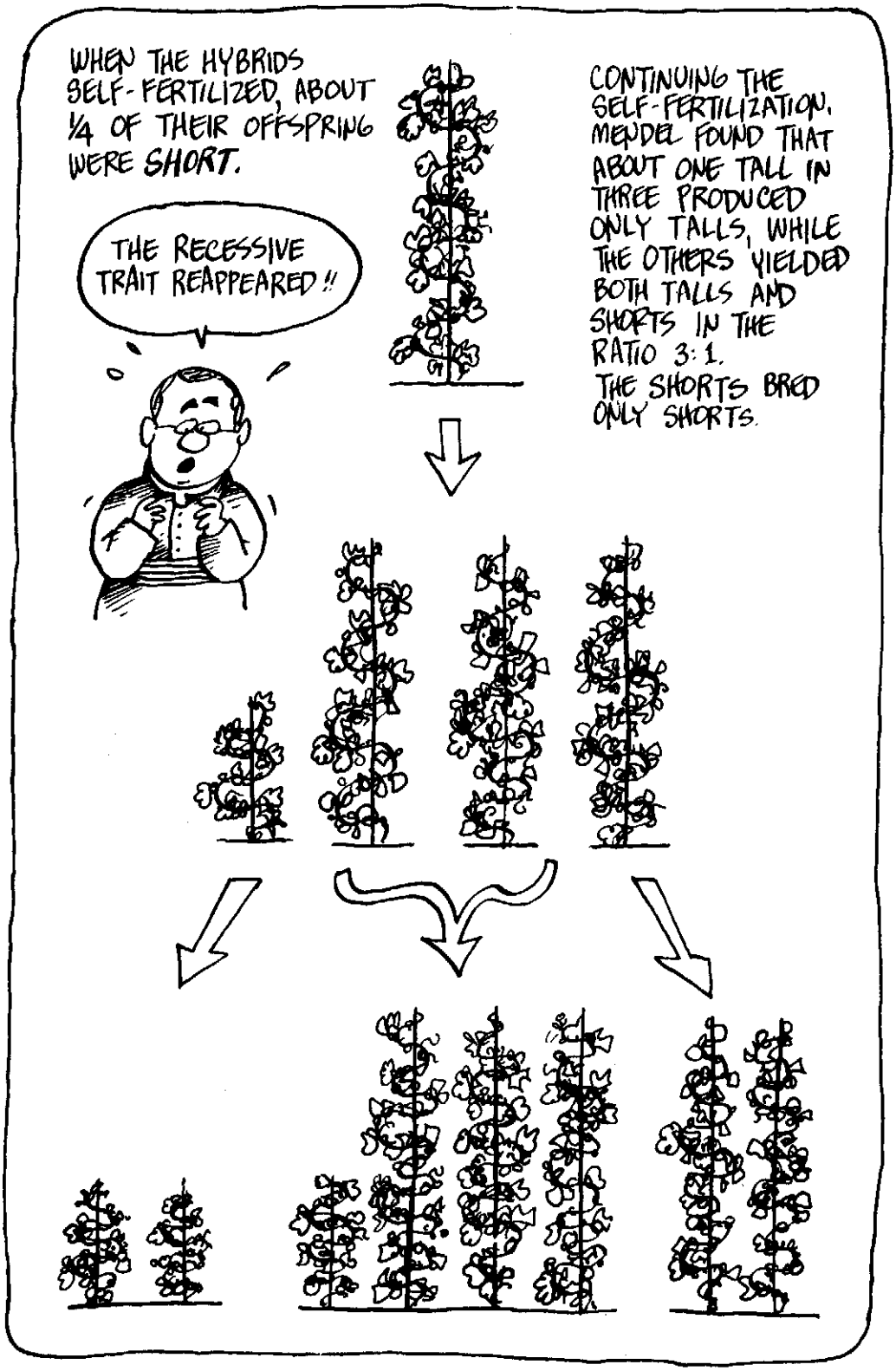
THEN HE DUSTED THE STIGMA WITH POLLEN TAKEN FROM THE DESIRED "FATHER."

FINALLY, HE TIED BAGS OVER THE FLOWERS TO KEEP OUT ANY STRAY POLLEN.



IN THIS WAY MENDEL WAS ABLE TO CONTROL THE PARENTAGE OF EACH GENERATION.


MENDEL'S FIRST MAJOR RESULT WAS THE DISCOVERY OF DOMINANCE. WHAT HAPPENED WHEN A TALL PLANT WAS CROSSED WITH A SHORT? ONE MIGHT EXPECT MEDIUM-SIZED PLANTS, BUT
IN FACT, ALL THE HYBRIDS WERE TALL!!
MENDEL EXPRESSED THIS BY SAYING THAT TALLNESS WAS DOMINANT OVER SHORTNESS (IN PEAS!). THE TRAIT OF SHORTNESS IS THEN CALLED RECESSIVE. IN EVERY CASE, ONE TRAIT WAS FOUND TO BE DOMINANT.
ROUND SEEDS ARE DOMINANT OVER WRINKLED; PLUMP PODS OVER PINCHED; GREY SEED-COATS OVER WHITE SEED-COATS, ETC ETC ETC....
IT DIDN'T MATTER WHICH PARENT CONTRIBUTED THE POLLEN AND WHICH THE EGG. A TALL-SHORT HYBRID WAS ALWAYS TALL.
THE FUN BEGINS WHEN YOU START BREEDING THE HYBRIDS —
?

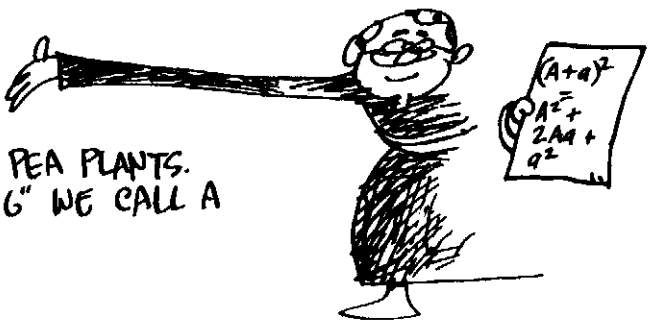

WHEN THE HYBRIDS SELF-FERTILIZED, ABOUT ¼ OF THEIR OFFSPRING WERE SHORT.
THE RECESSIVE TRAIT REAPPEARED!!
CONTINUING THE SELF-FERTILIZATION, MENDEL FOUND THAT ABOUT ONE TALL IN THREE PRODUCED ONLY TALLS, WHILE THE OTHERS YIELDED BOTH TALLS AND SHORTS IN THE RATIO 3:1. THE SHORTS BRED ONLY SHORTS.

MENDEL'S INTERPRETATION:

IT'S MATHEMATICAL!

THERE IS SOMETHING IN POLLEN AND EGG WHICH DETERMINES THE HEIGHT OF PEA PLANTS. THIS "SOMETHING" WE CALL A

GENE.

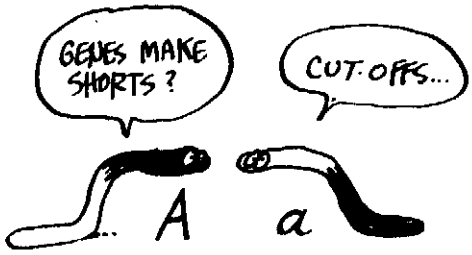


EACH POLLEN GRAIN AND EGG HAS ONE HEIGHT GENE, SO THE PLANT FORMED BY THEIR UNION HAS ***TWO.***

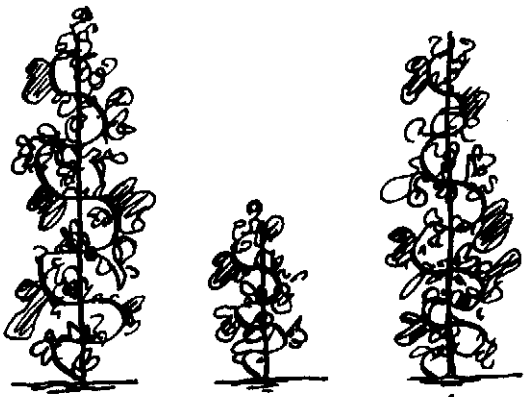
THE GENE MAY BE ONE OF TWO DISTINCT TYPES, OR

ALLELES.

ONE ALLELE, *A*, IS FOR *TALLNESS*; THE OTHER ONE, *a*, IS FOR *SHORTNESS.*

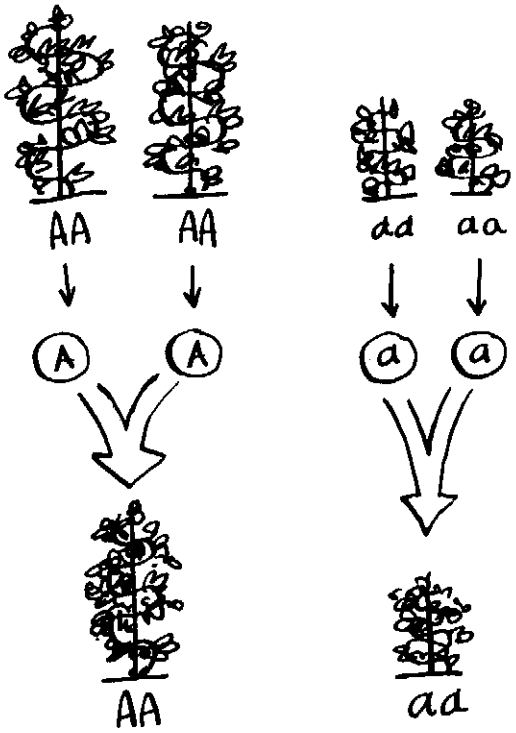


A PLANT MAY HAVE THE SAME OR DIFFERENT ALLELES.



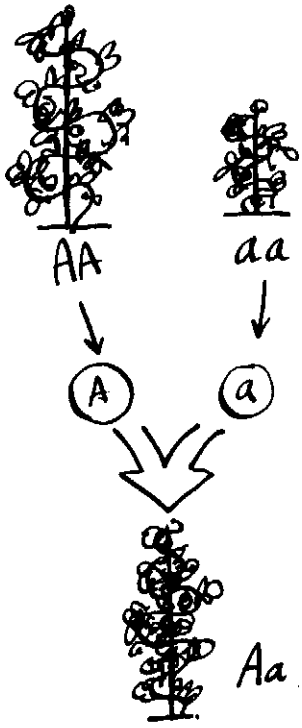
THE ALLELE *A* IS *DOMINANT* OVER *a*. THAT IS, THE PLANT WITH THE COMBINATION *Aa* IS TALL. THE ALLELES DO NOT "BLEND."

WHAT HAPPENS WHEN AA BREEDS WITH AA? POLLEN AND EGG EACH GET ONE COPY OF THE GENE... IN THIS CASE, THE ALLELES ARE THE SAME - A - SO THE OFFSPRING WILL AGAIN BE AA, OR TALL. LIKEWISE, aa CAN YIELD ONLY aa. THESE ARE THE STABLE SHORT & TALL VARIETIES.

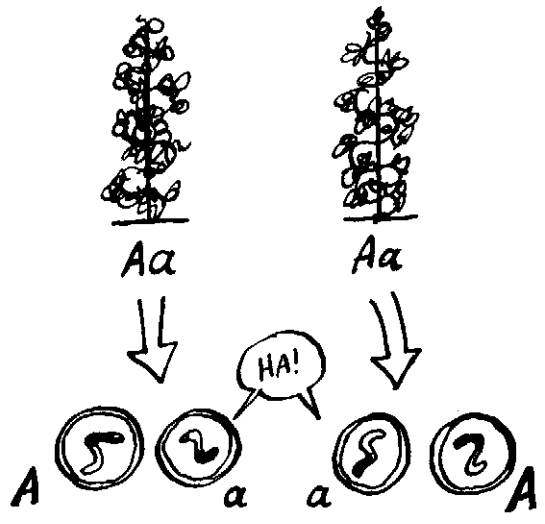


MENDEL'S FIRST HYBRID WAS A CROSS BETWEEN AA AND aa: THE POLLEN (OR EGG) FROM AA CONTAINS ONLY A, WHILE THE EGG (OR POLLEN) FROM aa CONTAINS ONLY a.

RESULT: Aa, WHICH IS TALL.



WHEN THE HYBRID SELF-FERTILIZES, ITS ALLELES A AND a ARE SORTED OUT RANDOMLY AMONG THE POLLEN GRAINS AND EGGS. BOTH A AND a APPEAR, AND IN ROUGHLY EQUAL PROPORTIONS.



WHEN EGGS AND POLLEN UNITE, THERE ARE FOUR POSSIBILITIES:

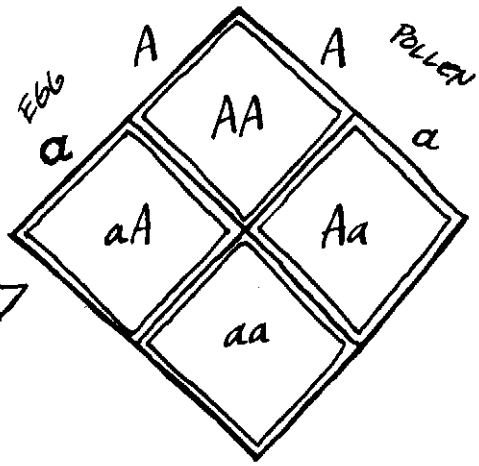
SHORT POLLEN, SHORT EGG

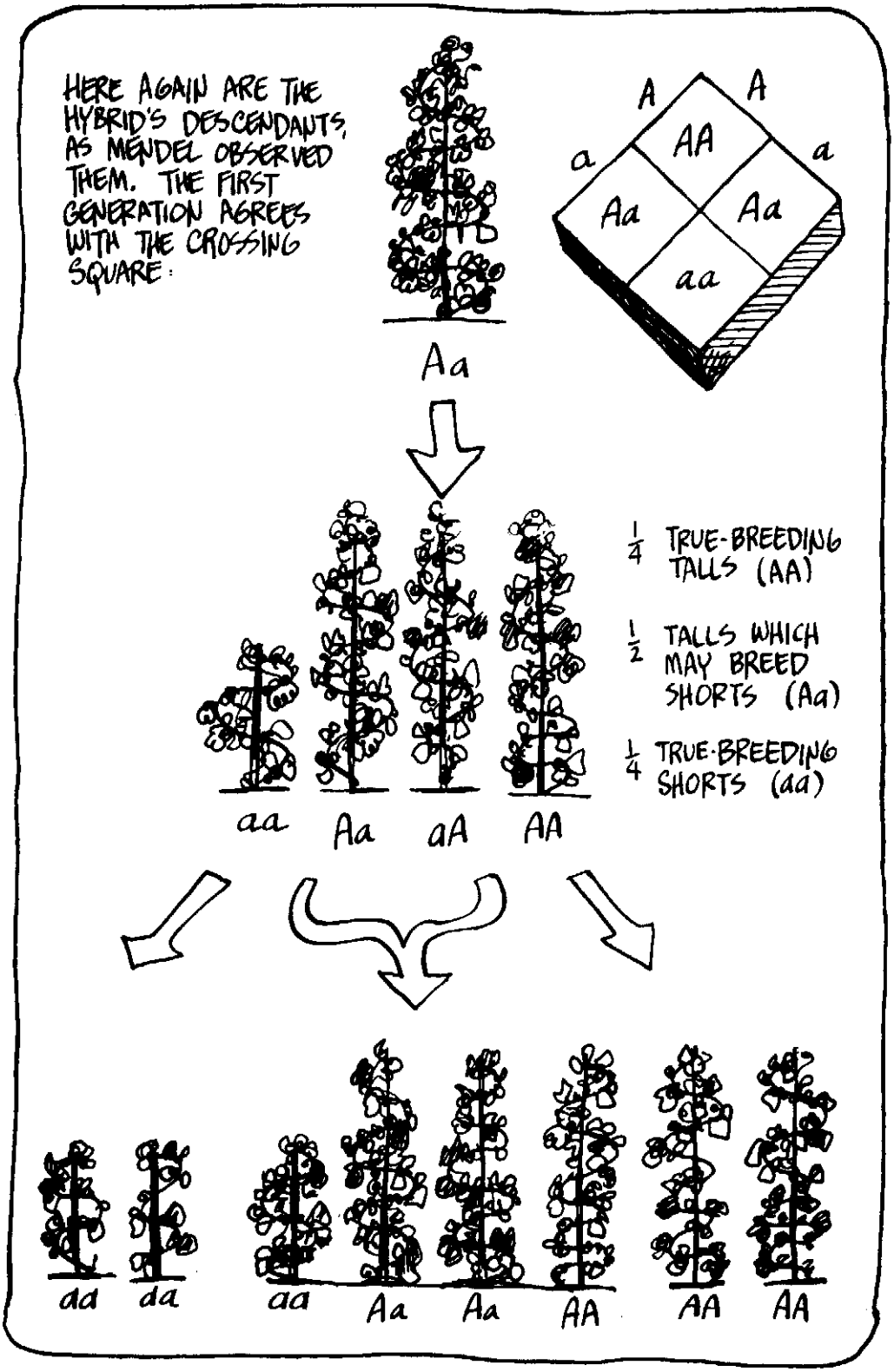
TALL POLLEN, SHORT EGG

SHORT POLLEN, TALL EGG

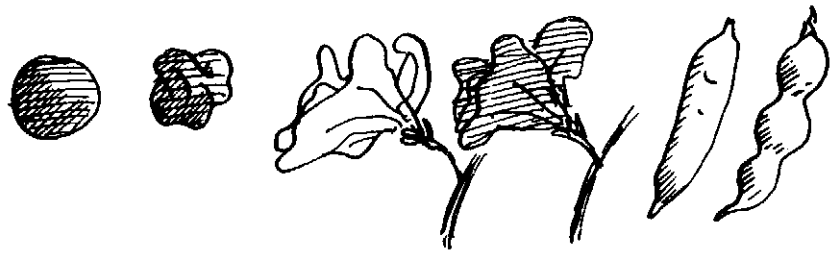
TALL POLLEN, TALL EGG

WHICH ARE SUMMARIZED IN THIS SQUARE: EACH POSSIBLE OFFSPRING APPEARS IN ONE OF THE SMALL BOXES.




HERE AGAIN ARE THE HYBRID'S DESCENDANTS, AS MENDEL OBSERVED THEM. THE FIRST GENERATION AGREES WITH THE CROSSING SQUARE:
A
A
a
a
AA
Aa
Aa
aa
Aa
1/4 TRUE-BREEDING TALLS (AA)
1/2 TALLS WHICH MAY BREED SHORTS (Aa)
1/4 TRUE-BREEDING SHORTS (aa)
aa
Aa
aA
AA
aa
aa
aa
Aa
Aa
AA
AA
AA

MENDEL ALSO CROSSED SMOOTH-PEA PLANTS WITH WRINKLED, PURPLE FLOWERS WITH WHITE, ETC ETC ETC. IN EVERY CASE, HE FOUND THE CHARACTERISTIC TO BE CONTROLLED BY A SINGLE GENE WITH TWO DIFFERENT ALLELES, ONE OF WHICH WAS DOMINANT OVER THE OTHER.

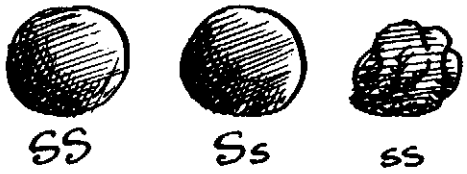


SO IT SEEMED THAT POLLEN AND EGG WERE BOTH FULL OF THESE LITTLE "SOMETHINGS," ONE FOR EVERY HEREDITARY TRAIT OF THE ORGANISM. PRETTY CROWDED!

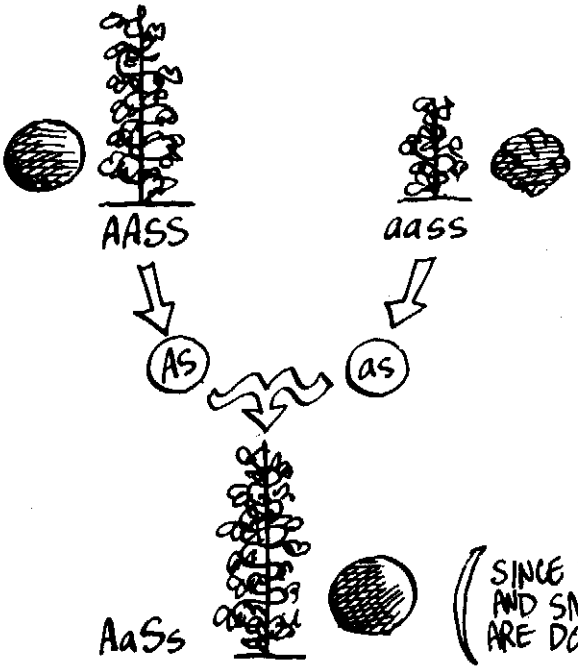
WITHOUT EVER SEEING A GENE, MENDEL CONCLUDED THAT HEREDITY IS CONTROLLED BY THESE "ATOMS OF INHERITANCE," WHICH NEVER BREAK OR BLEND, MAINTAINING THEIR CHARACTER FROM GENERATION TO GENERATION.

FINALLY, MENDEL MADE CROSSES BETWEEN PLANTS DIFFERING IN *TWO* CHARACTERISTICS — FOR EXAMPLE, A TALL PLANT WITH SMOOTH SEEDS AND A SHORT PLANT WITH WRINKLED SEEDS. THE QUESTION HERE IS: ARE HEIGHT AND SMOOTHNESS CORRELATED SOMEHOW, OR DO THEY ACT INDEPENDENTLY WHEN THE PLANT REPRODUCES??

CALL THE ALLELE FOR SMOOTH SEEDS **S**, AND THAT FOR WRINKLED SEEDS *s*. **S** IS DOMINANT, SO



THE CROSS IS BETWEEN AASS AND aass.



(SINCE TALLNESS AND SMOOTHNESS ARE DOMINANT)

NOW FOR THE SELF-POLLINATION OF THE HYBRID:

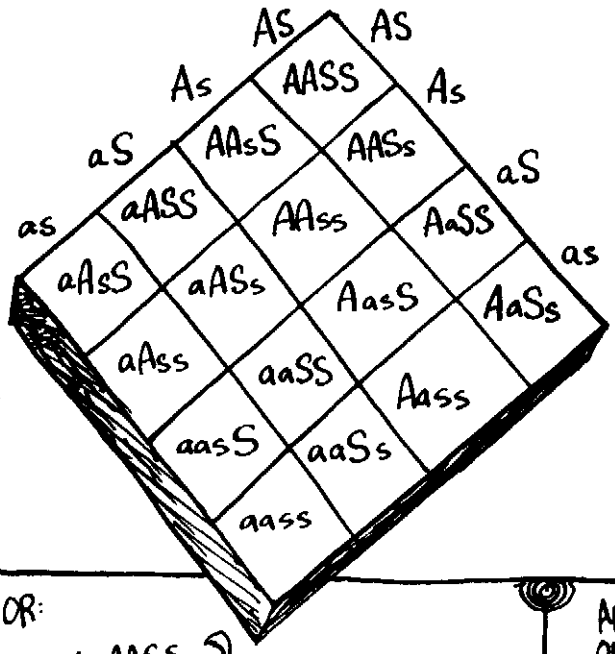
IF THE GENES FOR HEIGHT AND SMOOTHNESS SORT OUT INDEPENDENTLY OF EACH OTHER, THEN ALL THESE POSSIBLE POLLENS AND EGGS WOULD BE EQUALLY LIKELY:

AS

As

aS

as



IN WHICH CASE, THE CROSSING SQUARE LOOKS LIKE THIS.

OR:

1 AASS 2 AASs 2 AaSS 4 AaSs	}	9 TALL, SMOOTH
1 AAss 2 Aass	}	3 TALL, WRINKLED
1 aaSS 2 aaSs	}	3 SHORT, SMOOTH
1 aass		1 SHORT, WRINKLED

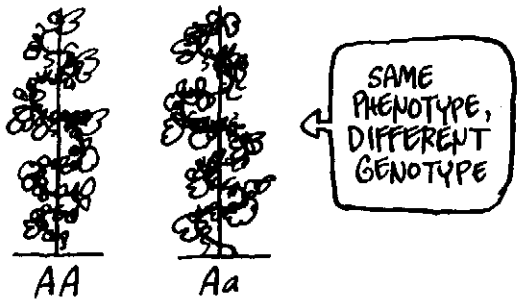
AND THIS IS WHAT MENDEL OBSERVED — A RATIO OF 9:3:3:1. THIS EXPERIMENT, AND OTHERS WITH DIFFERENT COMBINATIONS, PROVED THE ***PRINCIPLE OF INDEPENDENT ASSORTMENT***: THE ALLELES OF ONE GENE SORT OUT INDEPENDENTLY OF THE ALLELES OF ANOTHER. (WE'LL SOON SEE THAT THIS 'PRINCIPLE' ISN'T QUITE TRUE!)

NOW THAT WE'VE SEEN HOW GENES WORK, HERE'S A BIT OF GENETICS JARGON, IN CASE YOU SHOULD EVER WANT TO EAVESDROP ON A MODERN GENETICIST...

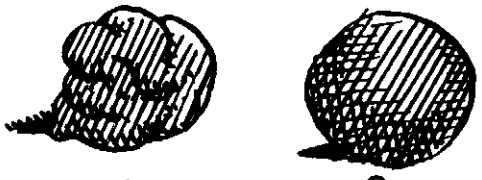
THIS GEN-TEK DEAL MEANS *ELEPHANT BUCKS*, BABY... WE'RE TALKING RECOMBIWANT BANK ACCOUNTS, PROFESSOR...

WELL... NOT *THAT* KIND OF JARGON...

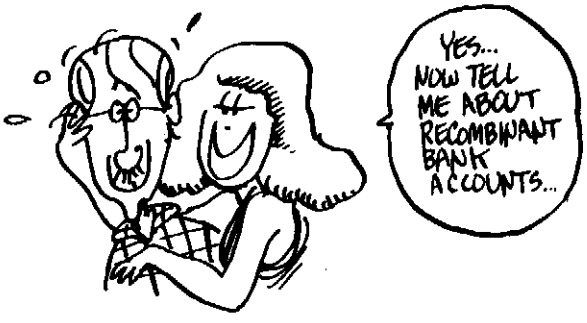
GENETICISTS DISTINGUISH BETWEEN AN ORGANISM'S ***PHENOTYPE*** – WHAT IT LOOKS LIKE – AND ITS ***GENOTYPE*** – WHAT ALLELES IT HAS.



AN ORGANISM IS ***HOMOZYGOUS*** WITH RESPECT TO A GIVEN GENE IF ITS TWO ALLELES ARE THE ***SAME***, AND ***HETEROZYGOUS*** IF THEY'RE DIFFERENT.

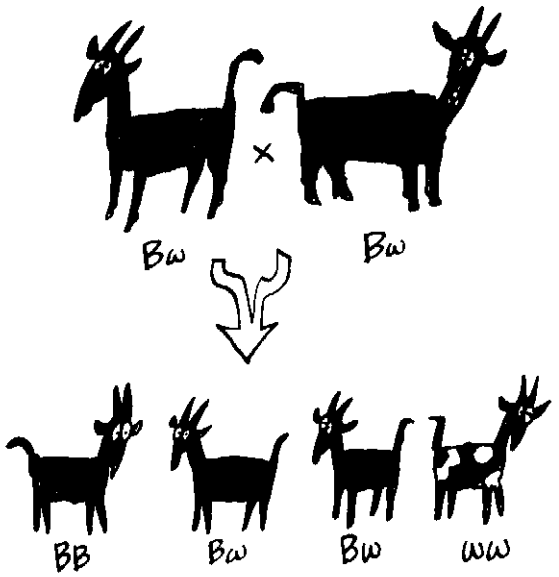


SO NOW YOU KNOW WHAT A GENETICIST MEANS BY "PHENOTYPICALLY SMOOTH, GENOTYPICALLY HETEROZYGOUS."



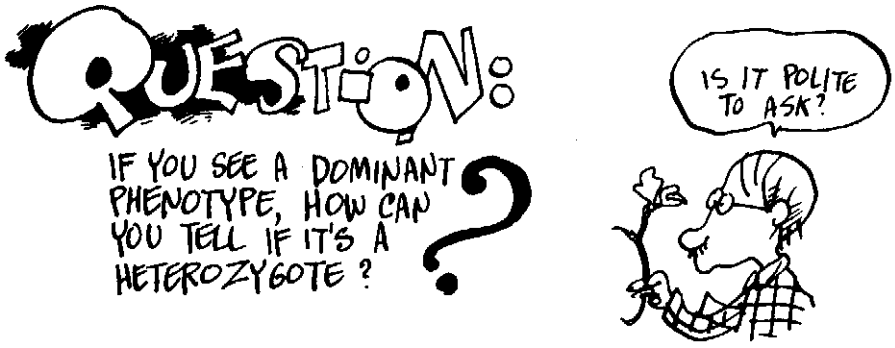
INCIDENTALLY — WE'RE NOW IN A POSITION TO UNDERSTAND JACOB'S SPECKLED FLOCK:

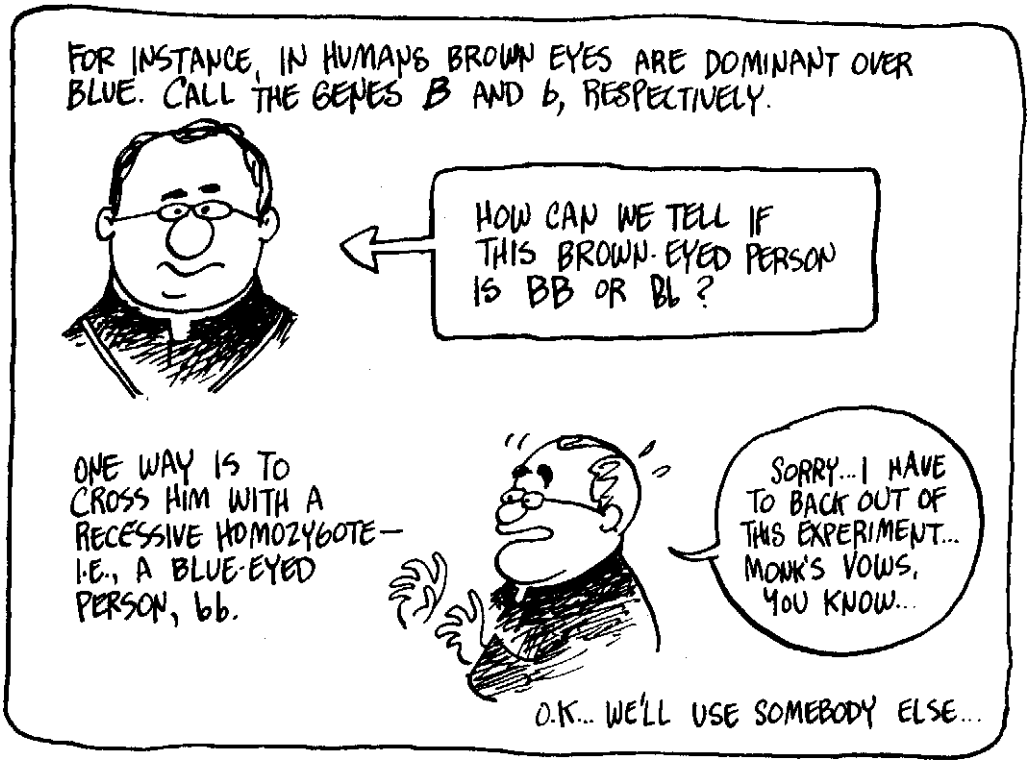
THE ALLELE FOR A BLACK COAT, CALL IT *B*, WAS DOMINANT. THERE WAS ALSO A *RECESSIVE* ALLELE, *w*, FOR WHITE SPECKLES. MANY OF LABAN'S PHENOTYPICALLY BLACK ANIMALS SECRETLY HARBORED THIS *w*, SO THEIR KIDS WERE SOMETIMES SPECKLED.*

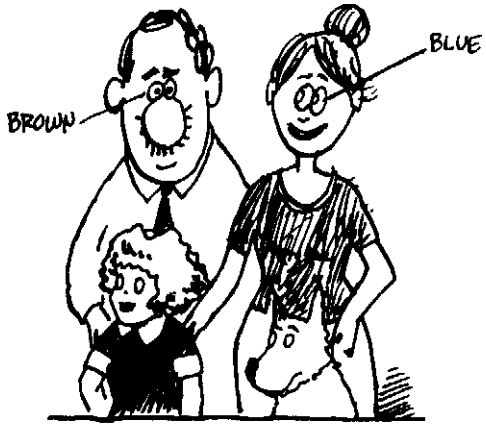


IN OTHER WORDS —

* ACTUALLY, THE GENETICS OF COAT COLOR ARE MORE COMPLEX, BUT THE PRINCIPLE IS THE SAME: RECESSIVE ALLELES.



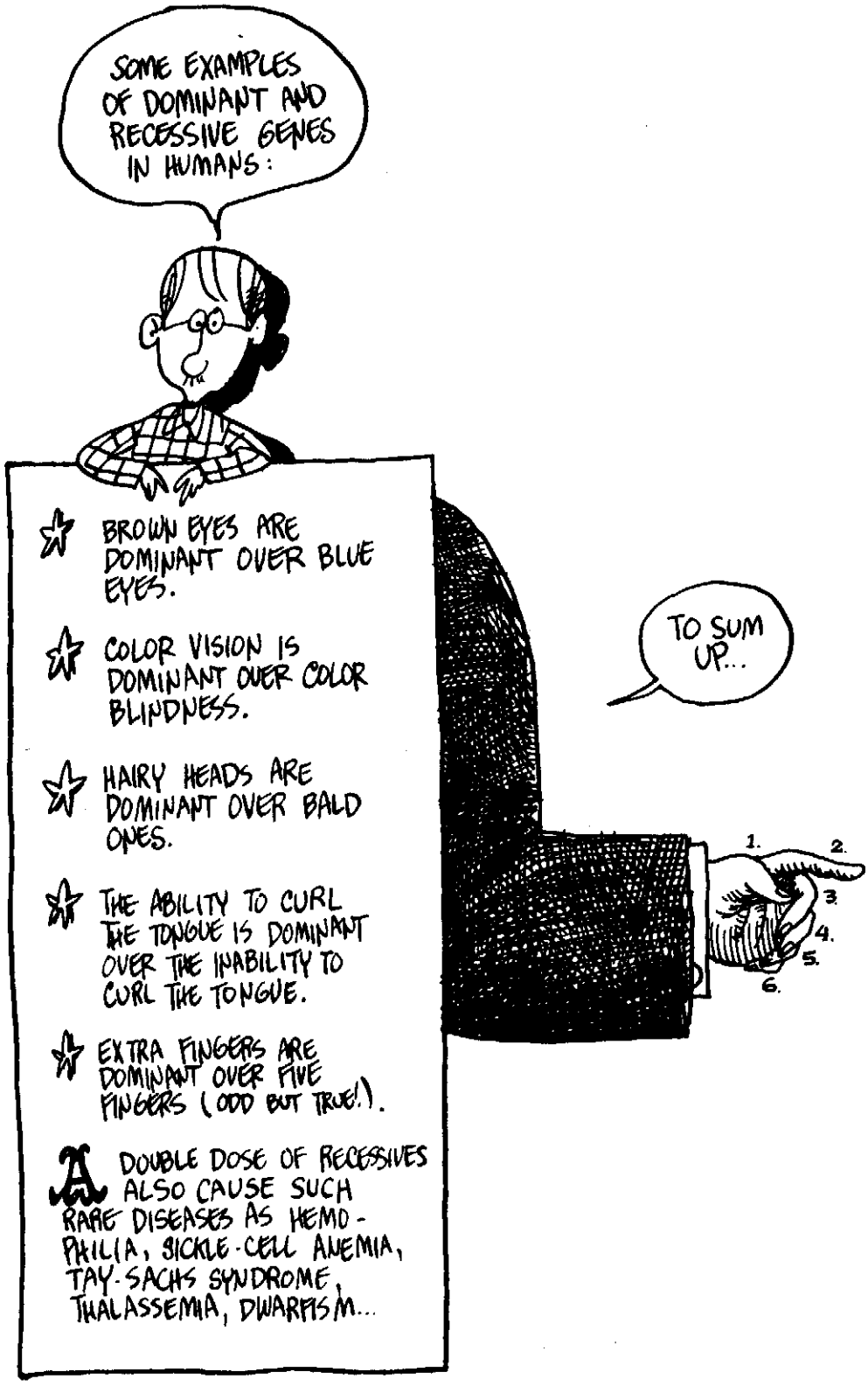




IF ANY OF THE LITTLE HYBRIDS HAS BLUE EYES, THE BROWN-EYED PARENT MUST HAVE BEEN A ***HETEROZYGOTE***, Bb. IF HE HAD BEEN BB, ALL THE CHILDREN WOULD HAVE BEEN Bb, WITH BROWN EYES.

FOR EXAMPLE, MY FIRST WIFE HAS BROWN EYES, AND I HAVE BLUE EYES. ONE OF OUR SONS HAS BLUE EYES; ONE HAS BROWN EYES. THEREFORE, MY FIRST WIFE MUST BE *HETEROZYGOUS*. (THE BLUE-EYED BOY MUST HAVE ONE ALLELE FROM HER.) TRY DOING THE SQUARE!

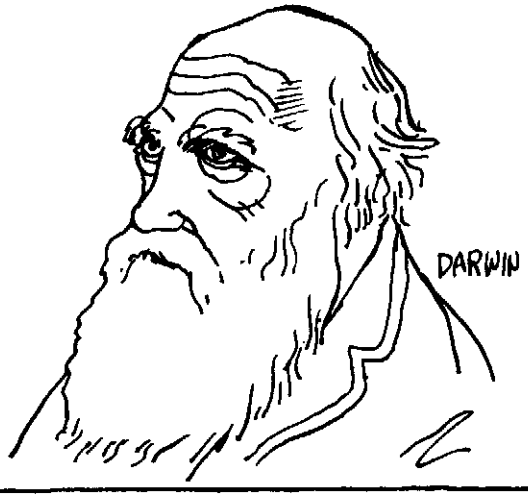
MY SECOND WIFE HAS BLUE EYES LIKE ME. IF OUR CHILD HAD *BROWN* EYES, WHAT WOULD WE MAKE OF THAT? BETTER ASK THE MILKMAN!!


SOME EXAMPLES OF DOMINANT AND RECESSIVE GENES IN HUMANS:
BROWN EYES ARE DOMINANT OVER BLUE EYES.
COLOR VISION IS DOMINANT OVER COLOR BLINDNESS.
HAIRY HEADS ARE DOMINANT OVER BALD ONES.
THE ABILITY TO CURL THE TONGUE IS DOMINANT OVER THE INABILITY TO CURL THE TONGUE.
EXTRA FINGERS ARE DOMINANT OVER FIVE FINGERS (ODD BUT TRUE!).
A DOUBLE DOSE OF RECESSIVES ALSO CAUSE SUCH RARE DISEASES AS HEMOPHILIA, SICKLE-CELL ANEMIA, TAY-SACHS SYNDROME, THALASSEMIA, DWARFISM...
TO SUM UP...
1.
2.
3.
4.
5.
6.

WE'LL SEE SHORTLY THAT NOT ALL THESE POINTS ARE EXACTLY CORRECT... DOMINANCE IS SOMETIMES ONLY PARTIAL... THERE ARE ORGANISMS WITH ONLY A SINGLE SET OF GENES... AND SOME WITH FOUR SETS... AND DEVIATIONS FROM INDEPENDENT ASSORTMENT TURN OUT TO BE VERY IMPORTANT...

MENDEL PRESENTED HIS THEORY IN 1865 TO THE BRÜNN NATURAL SCIENCE SOCIETY... IT PUT THEM TO SLEEP.

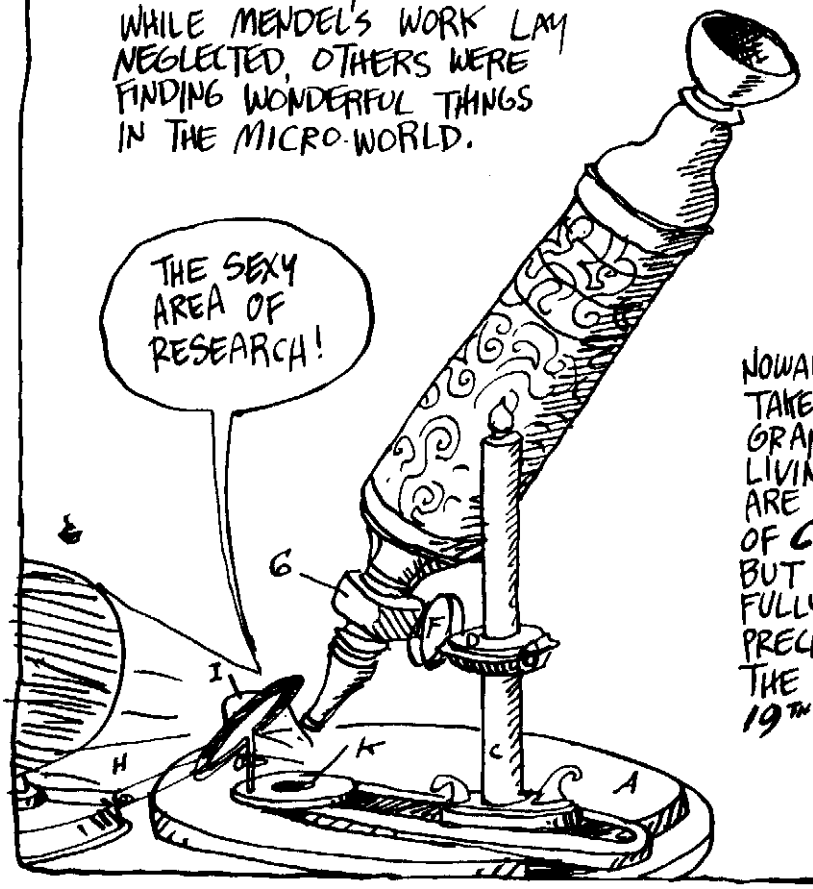
UNFORTUNATELY, NOBODY CARED ABOUT THE PROBLEM ANY MORE... IT HAD GONE OUT OF FASHION... AND, BESIDES, SINCE 1859, BIOLOGISTS HAD BEEN DISTRACTED BY THE NEW THEORY OF *EVOLUTION*, AND COULDN'T BE BOTHERED WITH MENDEL'S EQUATIONS.



BY THE TIME MENDEL DIED, THE SCIENTIFIC COMMUNITY HAD TOTALLY FORGOTTEN HIS WORK. "MY TIME WILL COME," HE SAID, NOT LONG BEFORE HIS DEATH IN 1884...

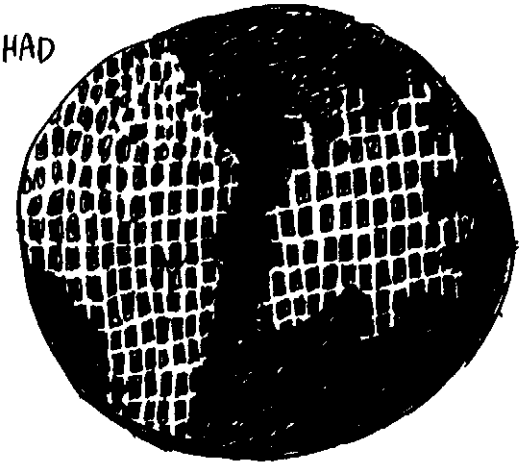
NOW YOU SEE THEM...

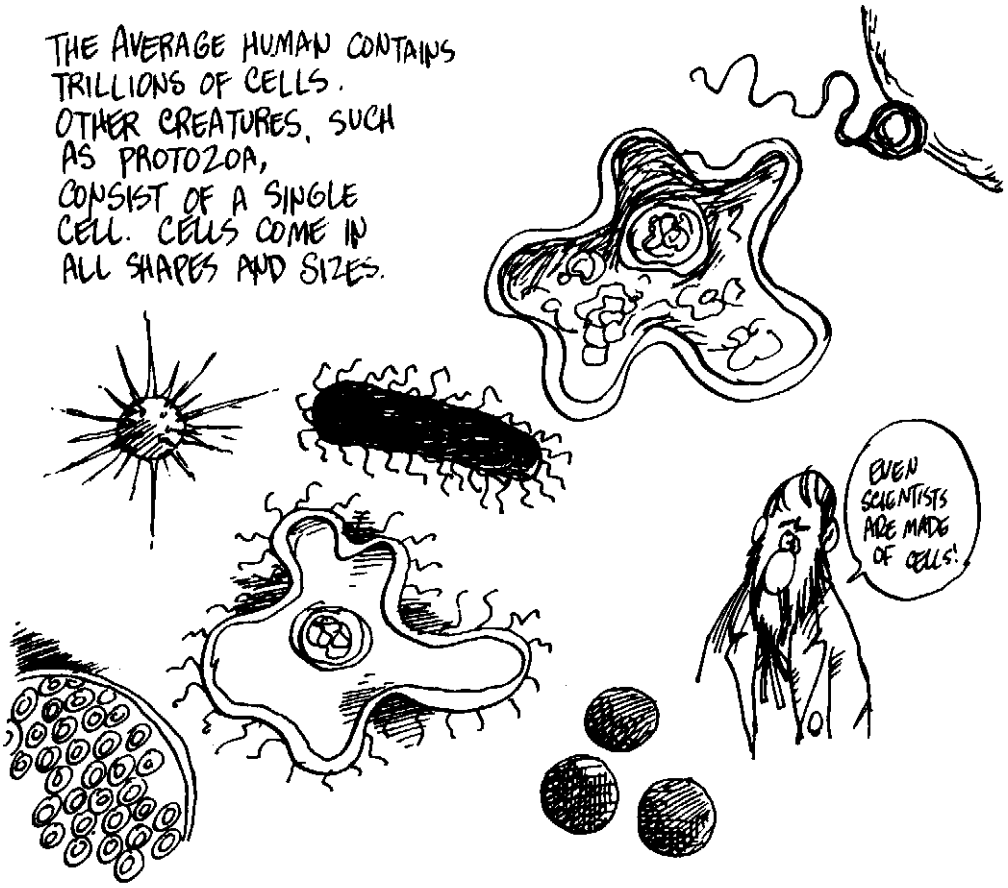
WHILE MENDEL'S WORK LAY NEGLECTED, OTHERS WERE FINDING WONDERFUL THINGS IN THE MICRO-WORLD.



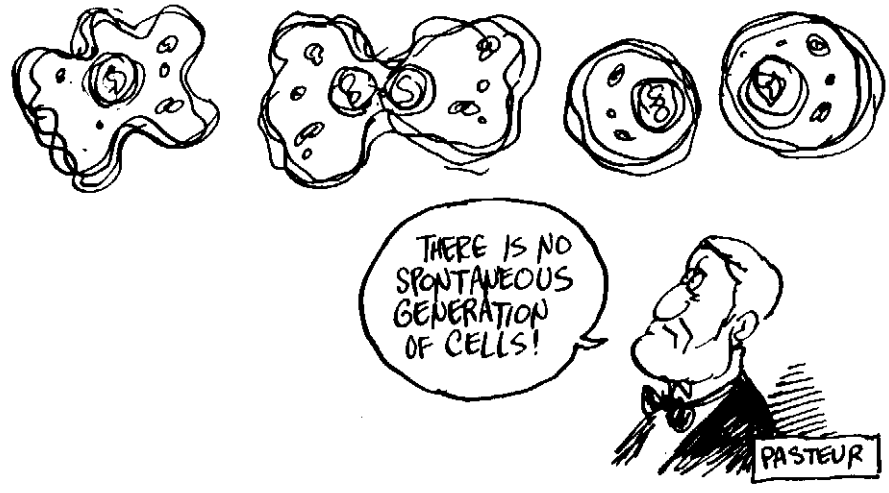
NOWADAYS, WE TAKE IT FOR GRANTED THAT ALL LIVING THINGS ARE MADE UP OF ***CELLS*** — BUT THIS WASN'T FULLY APPRECIATED UNTIL THE LATE 19TH CENTURY.

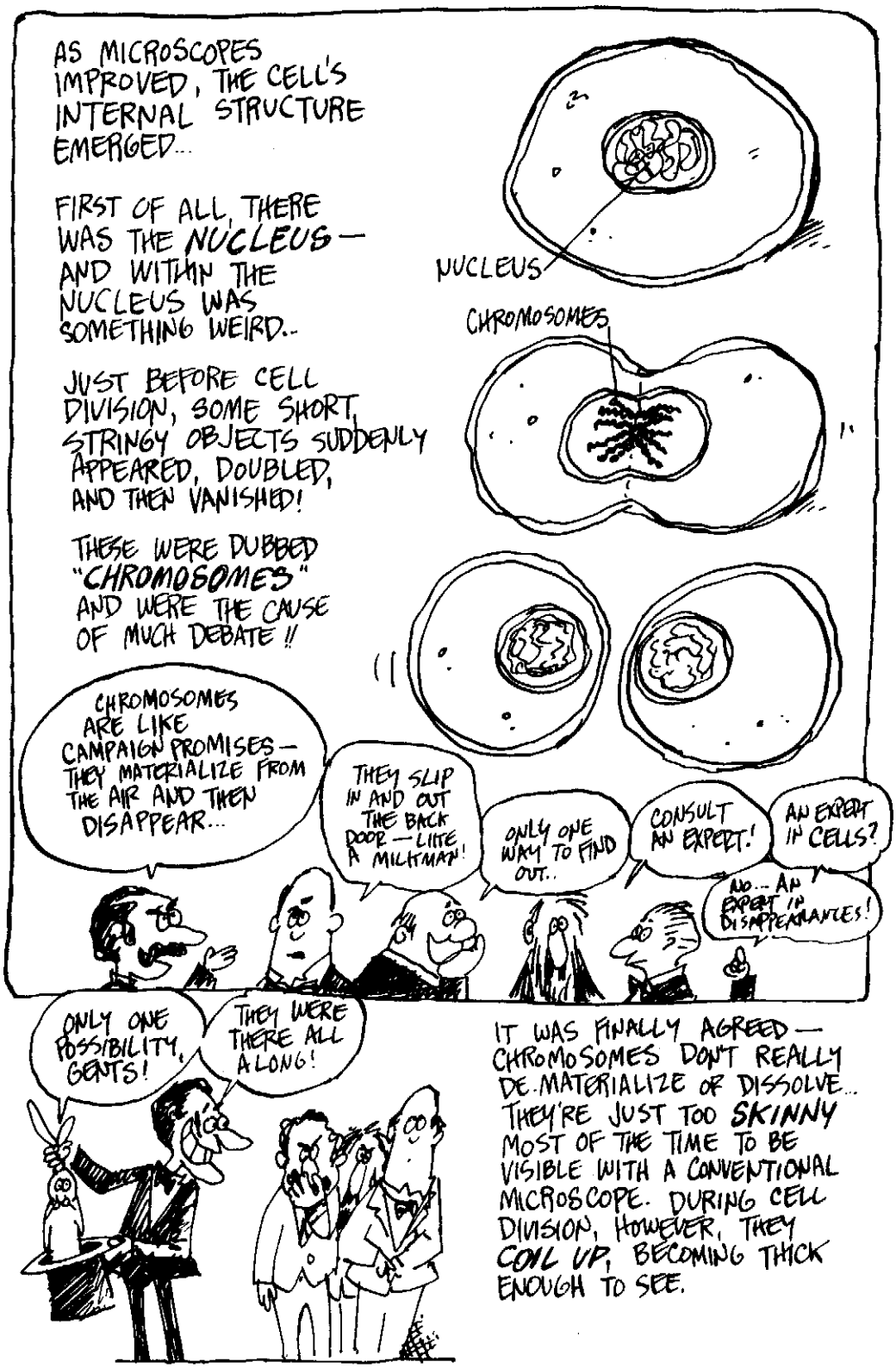
AS FAR BACK AS THE 1600's, ROBERT HOOKE (1635-1703) HAD NOTICED THE CELLULAR STRUCTURE OF CORK. BUT IT WASN'T UNTIL THE 1800's THAT SCIENTISTS, ARMED WITH BETTER MICROSCOPES, REALIZED THAT ALL OF US ARE DIVIDED INTO LITTLE COMPARTMENTS.





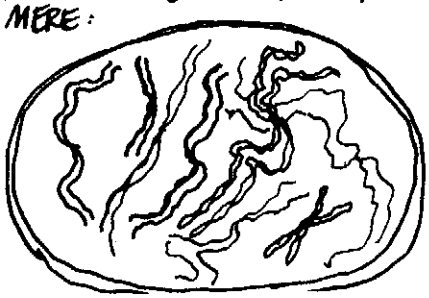
MOREOVER, SCIENTISTS SAW THAT ALL CELLS COME FROM THE ***DIVISION*** OF A PRE-EXISTING CELL. BEFORE DIVISION, EVERYTHING IN THE CELL IS DOUBLED.



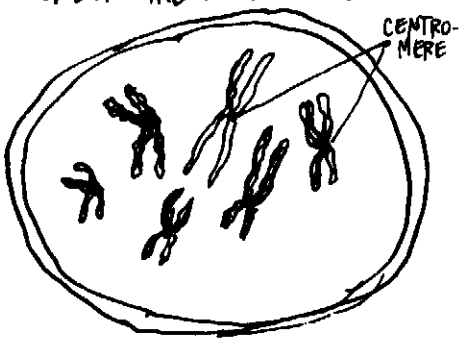

AS MICROSCOPES IMPROVED, THE CELL'S INTERNAL STRUCTURE EMERGED...
FIRST OF ALL, THERE WAS THE NUCLEUS — AND WITHIN THE NUCLEUS WAS SOMETHING WEIRD..
JUST BEFORE CELL DIVISION, SOME SHORT, STRINGY OBJECTS SUDDENLY APPEARED, DOUBLED, AND THEN VANISHED!
THESE WERE DUBBED "CHROMOSOMES" AND WERE THE CAUSE OF MUCH DEBATE!!
NUCLEUS
CHROMOSOMES
CHROMOSOMES ARE LIKE CAMPAIGN PROMISES — THEY MATERIALIZE FROM THE AIR AND THEN DISAPPEAR...
THEY SLIP IN AND OUT THE BACK DOOR — LIKE A MILKMAN!
ONLY ONE WAY TO FIND OUT..
CONSULT AN EXPERT!
AN EXPERT IN CELLS?
NO... AN EXPERT IN DISAPPEARANCES!
ONLY ONE POSSIBILITY, GENTS!
THEY WERE THERE ALL ALONG!
IT WAS FINALLY AGREED — CHROMOSOMES DON'T REALLY DE-MATERIALIZE OR DISSOLVE... THEY'RE JUST TOO SKINNY MOST OF THE TIME TO BE VISIBLE WITH A CONVENTIONAL MICROSCOPE. DURING CELL DIVISION, HOWEVER, THEY COIL UP, BECOMING THICK ENOUGH TO SEE.

CAREFUL STUDY REVEALED WHAT HAPPENS TO CHROMOSOMES DURING CELL DIVISION.

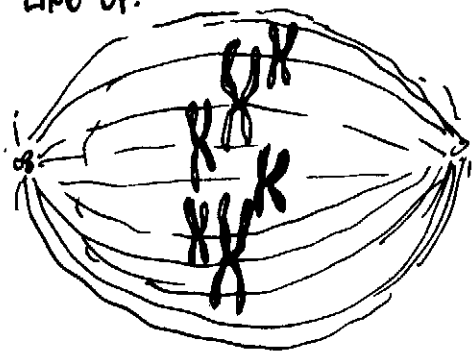
FIRST—WHILE STILL INVISIBLE—THE CHROMOSOMES DUPLICATE THEMSELVES, REMAINING ATTACHED AT A SPOT CALLED THE CENTROMERE:



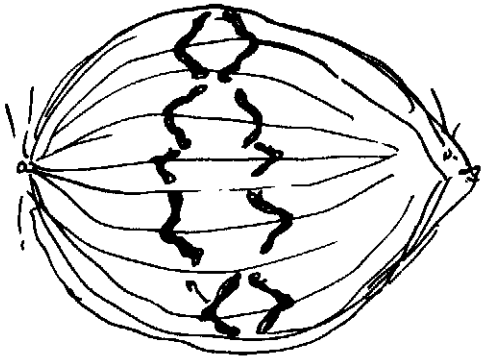
NEXT THEY THICKEN AND SHORTEN, BECOMING VISIBLE UNDER THE MICROSCOPE.



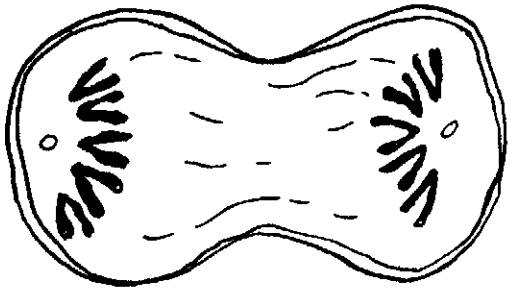
THE MEMBRANE AROUND THE NUCLEUS DISSOLVES, AND A FIBROUS *SPINDLE* FORMS, ON WHICH THE CHROMOSOMES LINE UP.



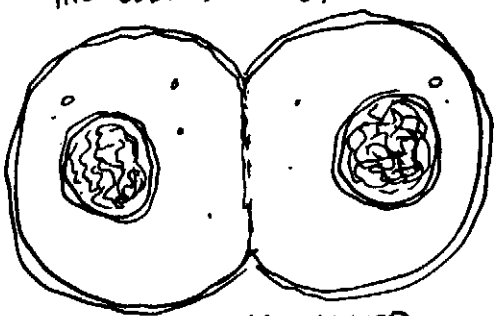
THE CENTROMERES DIVIDE AS THE SPINDLE FIBERS TUG THE CHROMOSOME PAIRS APART.



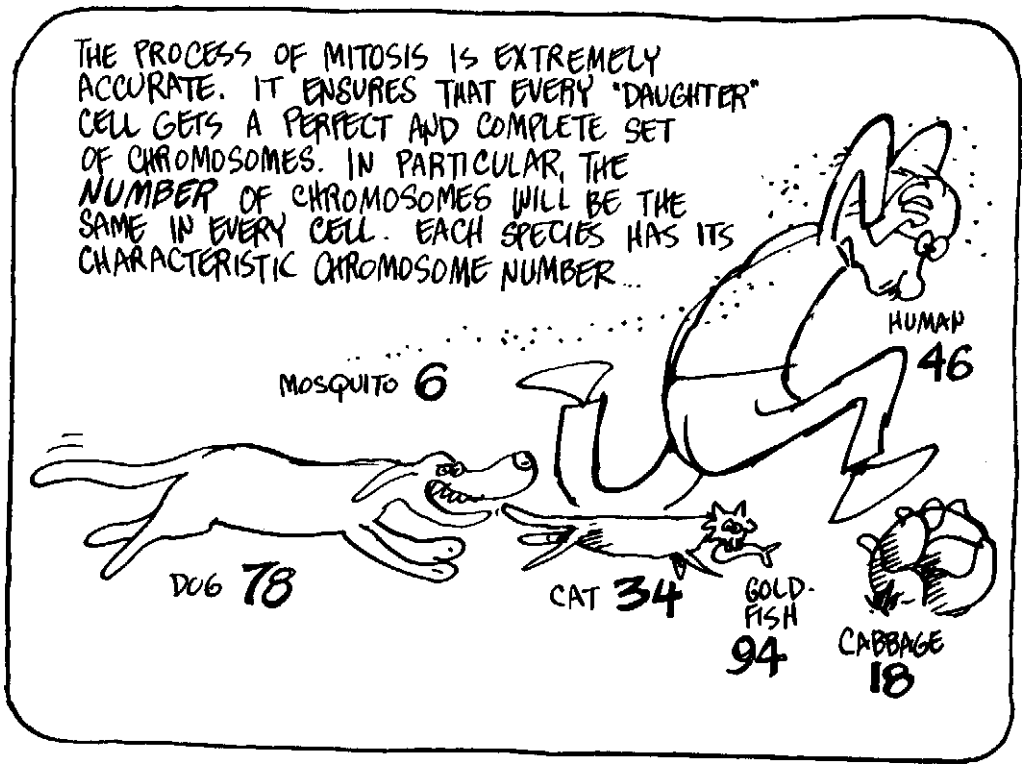
THE CHROMOSOMES ARRIVE AT THE OPPOSITE POLES, AND THE SPINDLE DISPERSES.



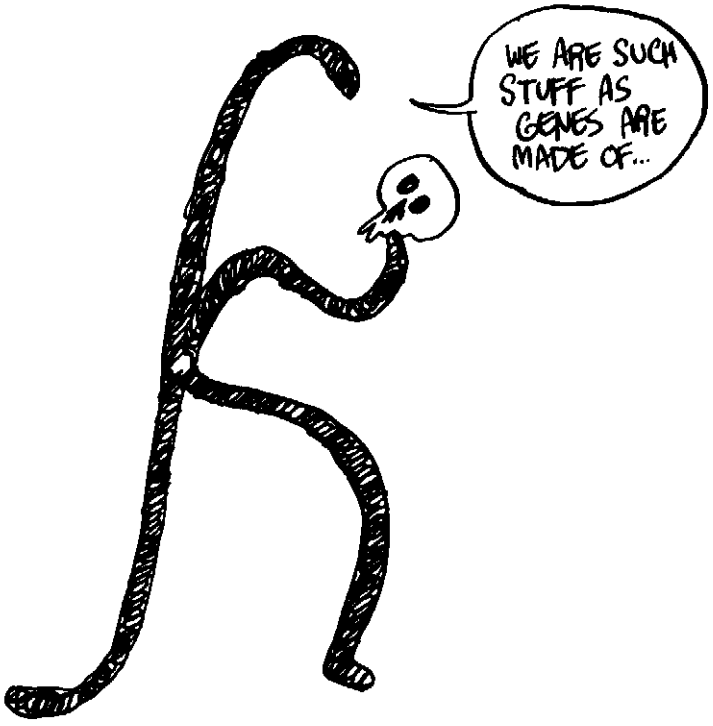
THE NUCLEAR MEMBRANE REFORMS; THE CHROMOSOMES UNWIND INTO INVISIBILITY; AND THE CELL DIVIDES.

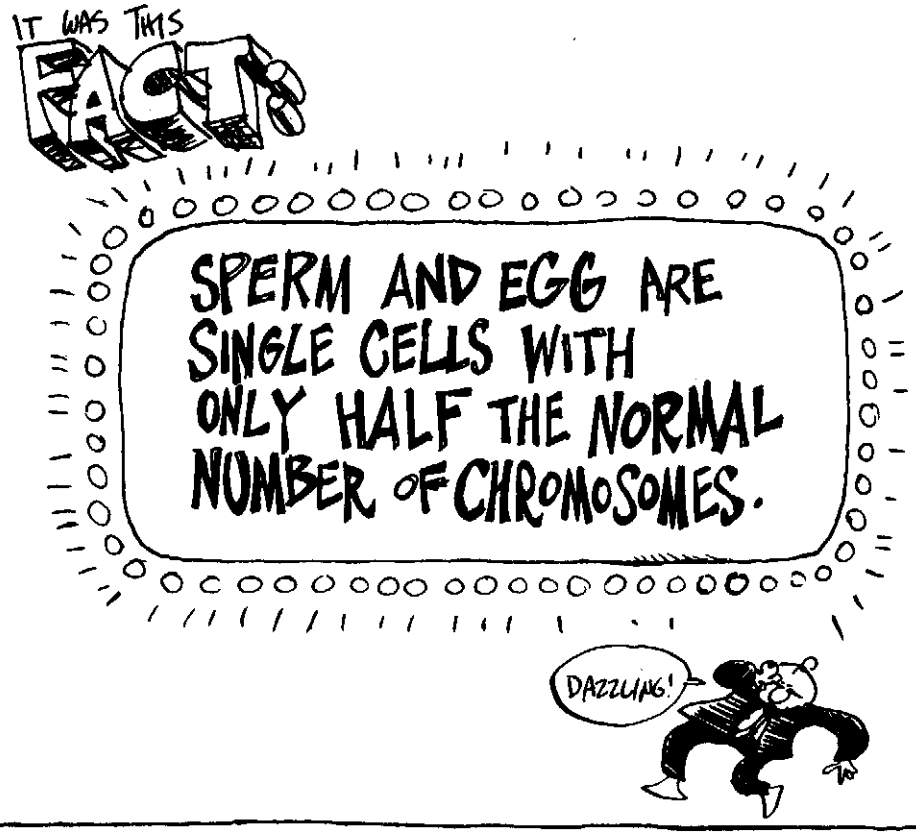


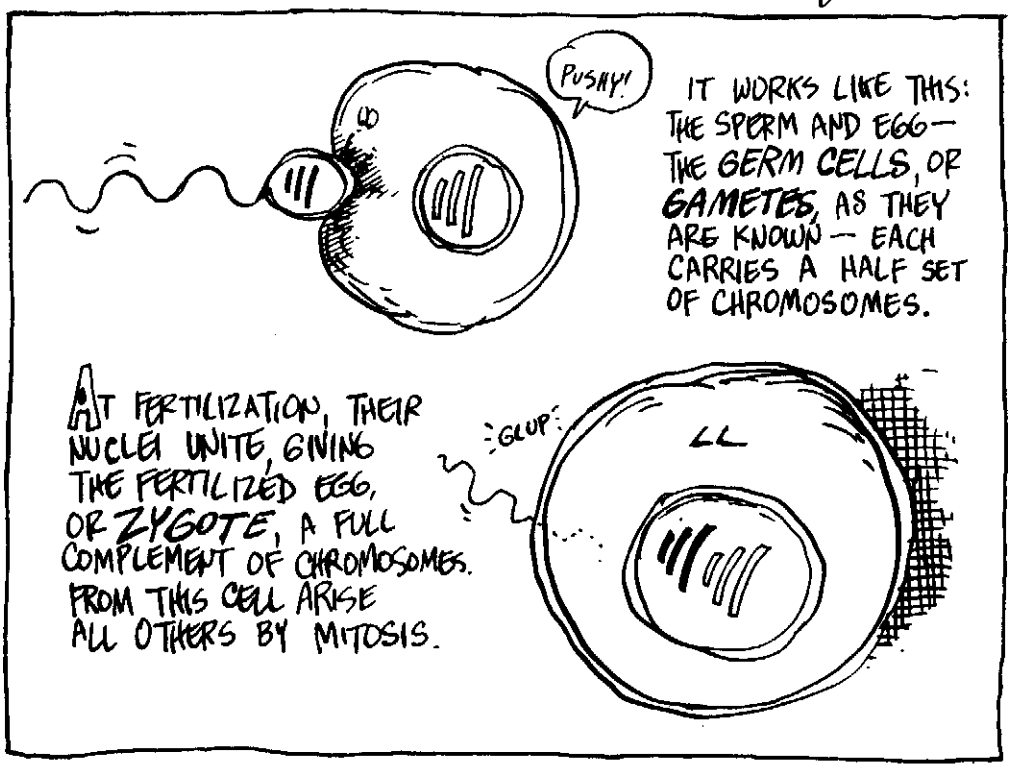
THIS PROCESS IS CALLED ***MITOSIS.***

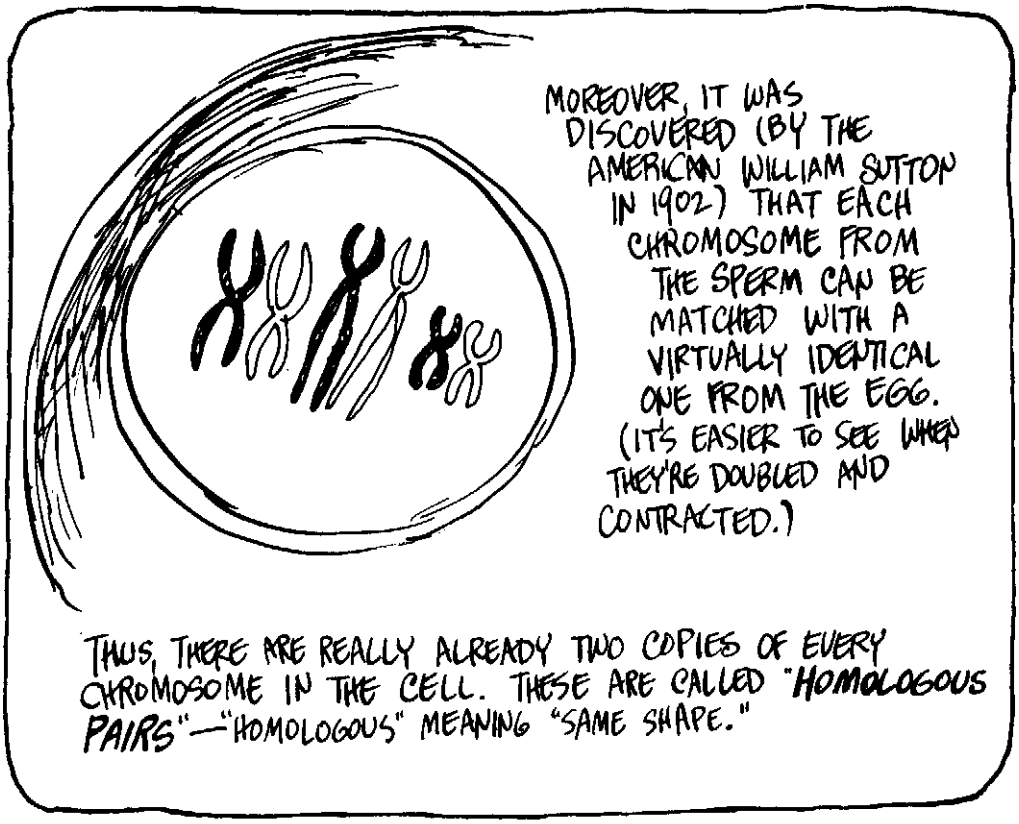


YOU MAY HAVE NOTICED THAT ALL THESE NUMBERS ARE *EVEN*. THERE IS A GOOD REASON FOR THIS — A REASON THAT POINTS TO THE CHROMOSOMES AS THE VERY MATERIAL OF HEREDITY ITSELF!

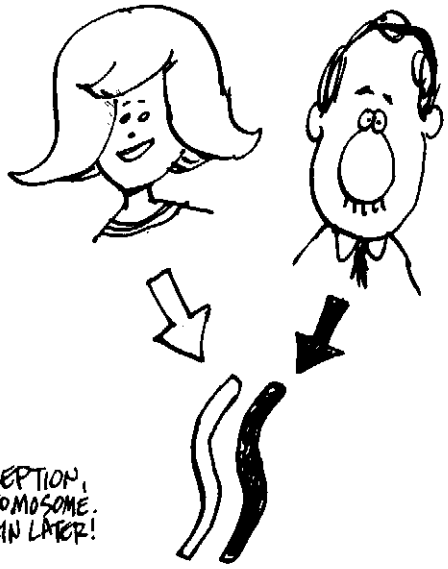



IT WAS THIS
FACT!
SPERM AND EGG ARE SINGLE CELLS WITH ONLY HALF THE NORMAL NUMBER OF CHROMOSOMES.
DAZZLING!


PUSHY!
n
IT WORKS LIKE THIS: THE SPERM AND EGG— THE GERM CELLS, OR GAMETES, AS THEY ARE KNOWN — EACH CARRIES A HALF SET OF CHROMOSOMES.
AT FERTILIZATION, THEIR NUCLEI UNITE, GIVING THE FERTILIZED EGG, OR ZYGOTE, A FULL COMPLEMENT OF CHROMOSOMES. FROM THIS CELL ARISE ALL OTHERS BY MITOSIS.
GLUP
2n



HUMANS, FOR EXAMPLE, WITH 46 CHROMOSOMES, REALLY HAVE 23* HOMOLOGOUS PAIRS: ONE FROM EACH PAIR COMES FROM MOM AND ONE FROM DAD.

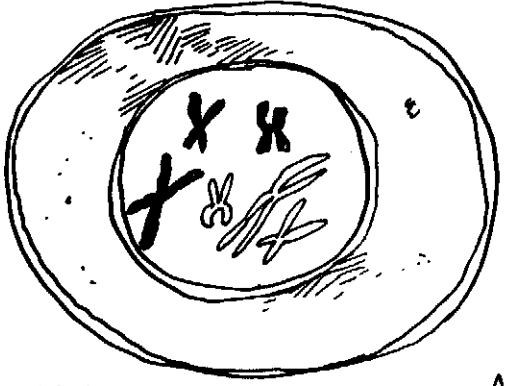


THIS SUGGESTS THAT THERE MUST BE A SPECIAL KIND OF CELL DIVISION JUST FOR MAKING GAMETES...

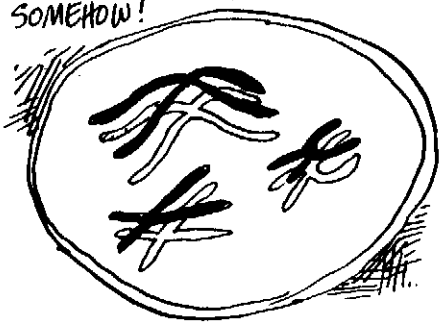
*WITH ONE EXCEPTION, THE SEX CHROMOSOME. WE'LL EXPLAIN LATER!

THIS PROCESS, CALLED ***MEIOSIS***, IS ACTUALLY A ***DOUBLE*** DIVISION:

AS IN MITOSIS, THE CHROMOSOMES DOUBLE AND THICKEN:

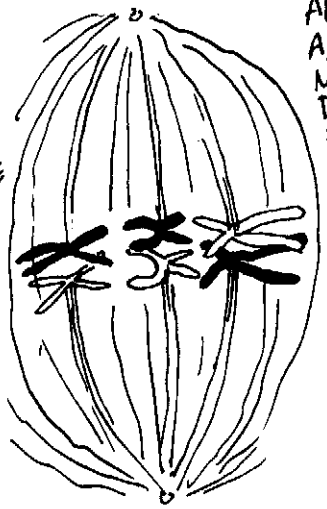


BUT THEN THE ***HOMOLOGOUS*** CHROMOSOMES PAIR OFF -- SOMEHOW!

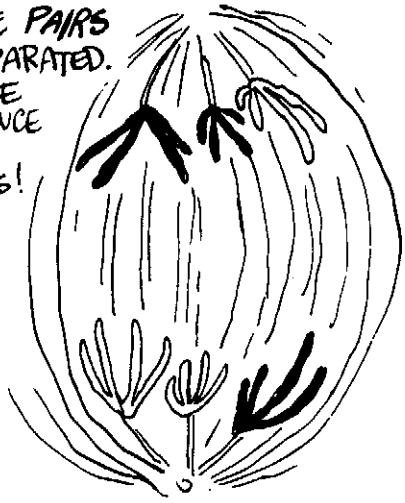


AGAIN THE SPINDLE FIBERS FORM AND THE CHROMOSOME QUARTETS ("TETRADS") LINE UP...

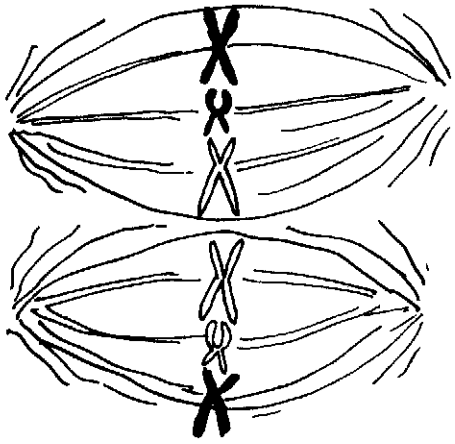
(MORE ON THIS LATER!)



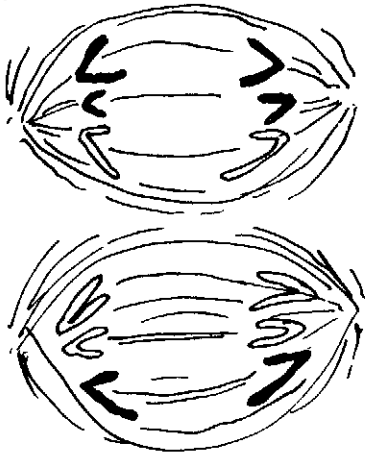
AND THE ***PAIRS*** ARE SEPARATED. NOTE THE DIFFERENCE FROM MITOSIS!



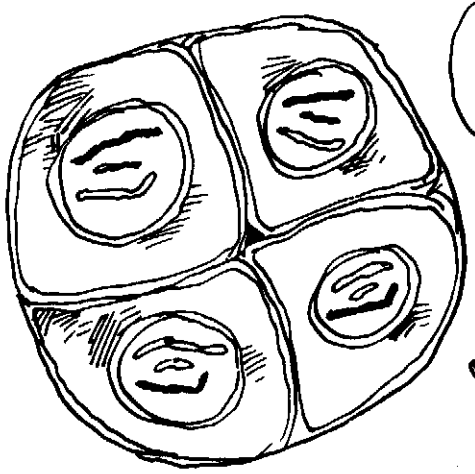
WHEN THEY REACH THE POLES, THE SPINDLE VANISHES AND ***NEW*** SPINDLES FORM "THE OTHER WAY."



THE CHROMOSOMES THEN SEPARATE, AS IN MITOSIS.

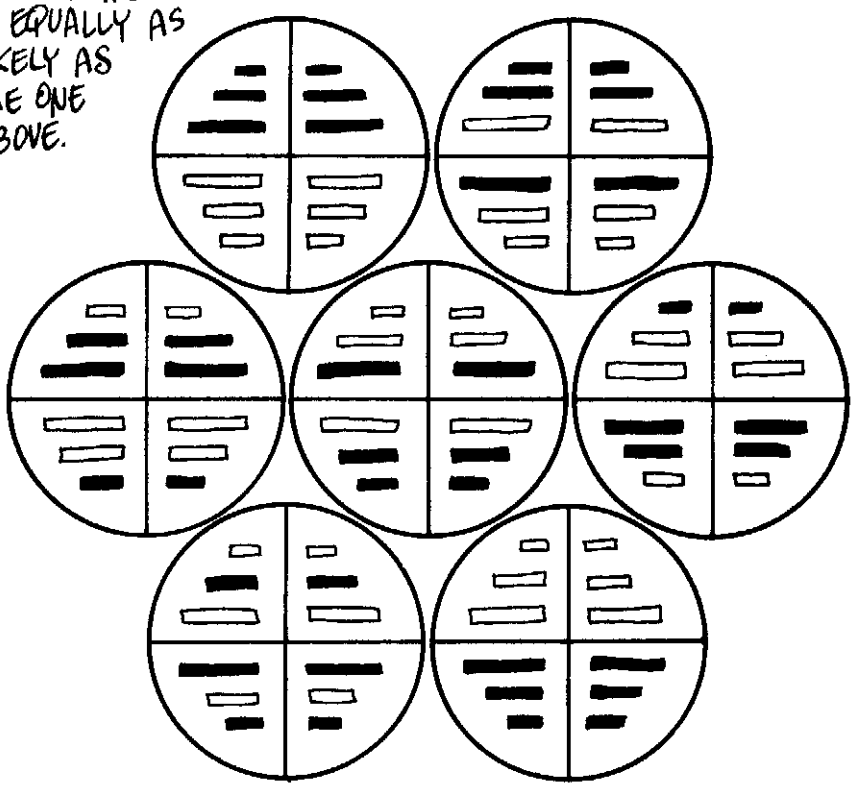


MEIOSIS RESULTS IN **FOUR** CELLS, EACH WITH **HALF** THE CHROMOSOMES OF THE ORIGINAL. COUNT 'EM — 3 VS. 6 IN THIS CASE.



BUT ALWAYS ONE FROM EACH HOMOLOGOUS PAIR!

NOTE THAT **WHICH** COPY ("HOMOLOG") OF EACH CHROMOSOME GOES TO WHICH CELL IS COMPLETELY RANDOM. EACH OF THESE COMBINATIONS IS EQUALLY AS LIKELY AS THE ONE ABOVE.



THAT IS, THE CHROMOSOMES OBEY THE LAW OF INDEPENDENT ASSORTMENT.

TOWARD THE END OF THE 19TH CENTURY, THREE SCIENTISTS, WORKING INDEPENDENTLY, MORE OR LESS DUPLICATED THE AUSTRIAN MONK'S EXPERIMENTS AND RESULTS. THEY WERE:


IN THE YEAR 1900, ALL THREE SEARCHED THE SCIENTIFIC LIBRARIES FOR PRECURSORS OF THEIR OWN WORK, AND ALL FOUND GREGOR MENDEL!
OOPS!
OOPS!
OOPS!
DUMMKOPF!
SCHWEIN!
BIF
BIF
NEXT TIME I BRING UP THE REAR, OK?
AFTER THEY HAD FINISHED KICKING THEMSELVES, DEVRIES, CORRENS, AND TSCHERMAK ANNOUNCED MENDEL'S DISCOVERY TO THE WORLD. WITHIN TWO YEARS, WILLIAM SUTTON HAD SEEN HOMOLOGOUS PAIRS OF CHROMOSOMES IN GRASSHOPPER CELLS, AND SCIENCE HAD SEEN THE LIGHT!!
GOOD THING I INVENTED THE LIGHT!

TO SUMMARIZE:

WHAT EXACTLY DID THEY REALIZE?

CHROMOSOMES BEHAVE LIKE GENES. THEY RETAIN THEIR IDENTITY IN HYBRIDS, AND THEY SEGREGATE INDEPENDENTLY WHEN GERM CELLS ARE MADE. THEREFORE, IT'S LOGICAL TO ASSUME THAT GENES LIE ON CHROMOSOMES. (THERE MUST BE MANY GENES ON EACH ONE, BECAUSE THERE MUST BE FAR MORE GENES THAN THE FEW DOZEN CHROMOSOMES TYPICAL OF MOST SPECIES.)

THE DISCOVERY OF HOMOLOGOUS PAIRS REALLY CINCHED THE CONNECTION TO MENDEL'S FINDINGS. REMEMBER, EACH CELL HAS A PAIR OF ALLELES FOR EACH GENE. NOW IT WAS REALIZED THAT:

THE TWO COPIES OF A GIVEN GENE LIE AT THE SAME POINT ON HOMOLOGOUS CHROMOSOMES.

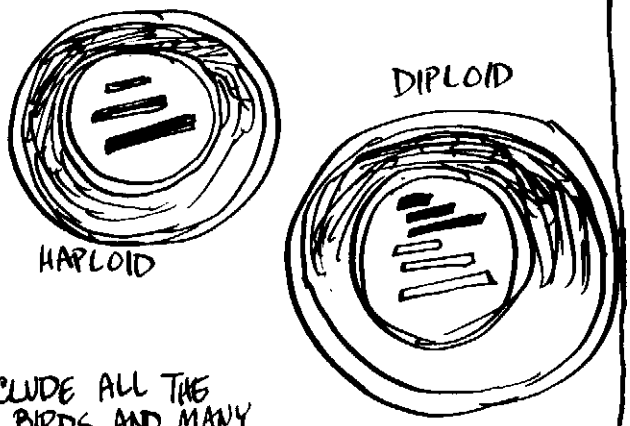
I.E., IF ONE GENE FOR HEIGHT LIES HERE →

← THEN THE OTHER COPY MUST BE HERE

ALL THIS TURNS OUT TO BE TRUE... BUT ONCE PEOPLE LOOKED MORE DEEPLY INTO THE MATTER, THEY DISCOVERED A FEW THINGS MENDEL HADN'T REALIZED...

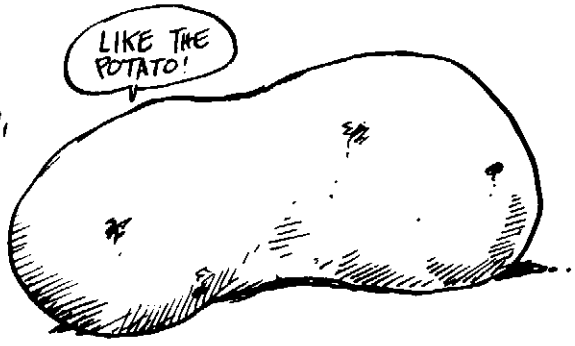
FOR ONE THING, NOT ALL ORGANISMS HAVE A DOUBLE SET OF CHROMOSOMES. MANY LOWER SPECIES, LIKE SOME FUNGI, HAVE JUST A SINGLE SET.

A CELL WITH A SINGLE SET OF CHROMOSOMES IS CALLED **HAPLOID**; ONE WITH TWO SETS IS CALLED **DIPLOID**. OUR BODY CELLS ARE DIPLOID, WHILE OUR GERM (SEX) CELLS ARE HAPLOID.



DIPLOID ORGANISMS INCLUDE ALL THE FAMILIAR MAMMALS AND BIRDS AND MANY PLANTS. HAPLOIDS INCLUDE MALE HONEY BEES, MANY FUNGI, AND ASEXUAL ONE-CELLED CREATURES.

BESIDES ALL THESE, THERE ARE ALSO **POLYPLOID** ORGANISMS, WITH MULTIPLE SETS OF CHROMOSOMES. A SURPRISING NUMBER OF EVERYDAY PLANTS ARE POLYPLOID. (NOT PEAS, THOUGH!!)



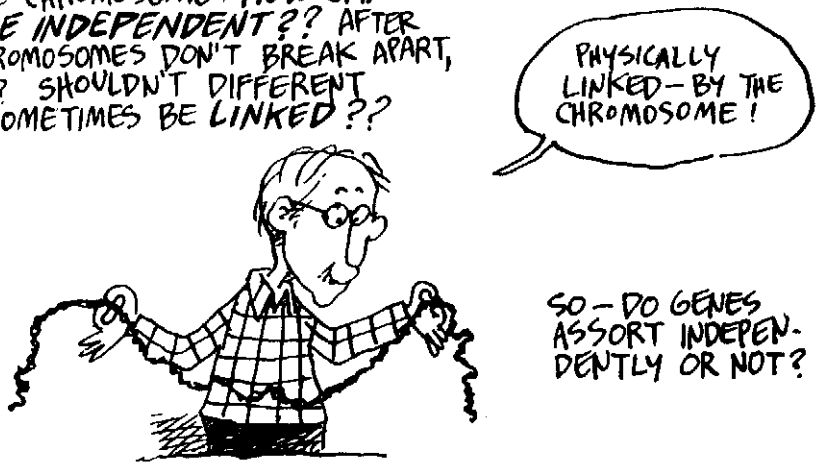
THE OTHER MAIN PROBLEM WITH MENDEL'S THEORY WAS THE PRINCIPLE OF INDEPENDENT ASSORTMENT. A PRECISE MEASURE OF HOW WRONG IT WAS LED TO THE ABILITY TO MAP OUT EXACTLY WHERE ON THE CHROMOSOME EACH OF ITS GENES MIGHT LIE... READ ON...


MAPMAKING
TO MENDEL—AND HIS HEIRS—GENES WERE JUST ABSTRACTIONS, LETTERS YOU COULD JUGGLE TO EXPLAIN AND PREDICT HOW HEREDITARY QUALITIES WOULD BE PASSED ALONG TO FUTURE GENERATIONS.
THEY'RE LIKE GHOSTS — INFLUENTIAL BUT INSUBSTANTIAL!
NOW IT APPEARED THAT GENES WERE ACTUAL, PHYSICAL OBJECTS. THEY LAY IN SOME ORDER ALONG THE CHROMOSOMES OF EVERY CELL, AND THE TWO ALLELES OF EACH GENE WERE ON THE TWO CHROMOSOMES OF A HOMOLOGOUS PAIR.
THEY'RE AS REAL AS BUMPS IN THE ROAD!
ONE MIGHT WONDER IF IT'S POSSIBLE TO MAKE A GENE MAP SHOWING JUST WHERE ON EACH CHROMOSOME ALL THESE HEREDITARY UNITS MIGHT LIE!!

THE ANSWER TO THIS DEPENDED ON A SEEMING ***PARADOX***, FOR IN ONE RESPECT MENDEL'S FINDINGS CONFLICTED WITH THE OBSERVED BEHAVIOR OF CHROMOSOMES...

OBSERVE: THE NUMBER OF GENES MUST BE TREMENDOUS TO GOVERN A COMPLEX ORGANISM, BUT THE NUMBER OF CHROMOSOMES IN A CELL IS FAIRLY SMALL. A PEA PLANT HAS JUST ***7 PAIRS*** OF CHROMOSOMES, A HUMAN ***23***.

THE PROBLEM: IF TWO GENES LIE ON THE SAME CHROMOSOME, ***HOW CAN THEY BE INDEPENDENT??*** AFTER ALL, CHROMOSOMES DON'T BREAK APART, DO THEY? SHOULDN'T DIFFERENT GENES SOMETIMES BE ***LINKED??***



WELL, IT TURNED OUT TO BE SORT OF HALF-AND-HALF...

1 THERE IS LINKAGE BETWEEN CERTAIN GENES.... BUT

2 CHROMOSOMES ALSO ENGAGE IN A GOOD DEAL OF *GENE SWAPPING*, OR (AS IT'S CALLED) *CROSSING OVER*.

TO ILLUSTRATE, LET'S LOOK AT THE EXAMPLE OF THE ORDINARY, GARDEN-VARIETY *TOMATO*.

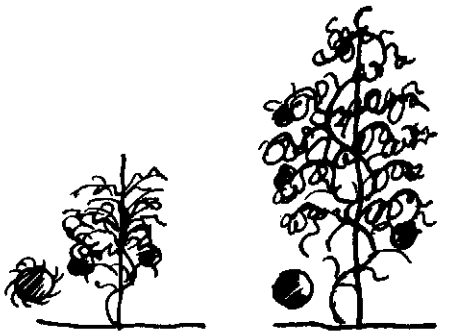
...AND TRY NOT TO EAT THE EXAMPLE UNTIL AFTER CLASS..

TOMATOES HAVE A SKIN-TEXTURE GENE WITH A RECESSIVE ALLELE, *p*, WHICH CAUSES *HAIRY FRUIT*. (OF COURSE, YOU DON'T OFTEN SEE THESE IN THE MARKET!)

LIKEWISE, THE HEIGHT GENE HAS A RECESSIVE ALLELE, *d*, CAUSING DWARF PLANTS.

THE RESPECTIVE DOMINANT ALLELES ARE p^+, WHICH CAUSES SMOOTH FRUIT, AND d^+, WHICH MAKES TALL PLANTS.

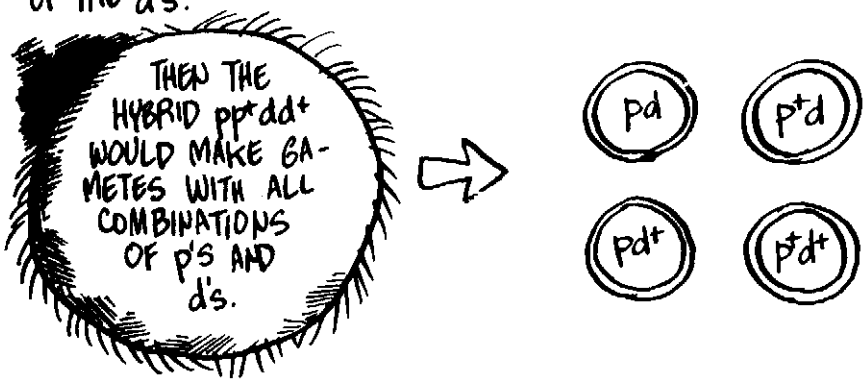
TO TEST THE PRINCIPLE OF INDEPENDENT ASSORTMENT, WE CAN CROSS A DOUBLE RECESSIVE, *ppdd*, WITH A HETEROZYGOTE, pp^+dd^+.



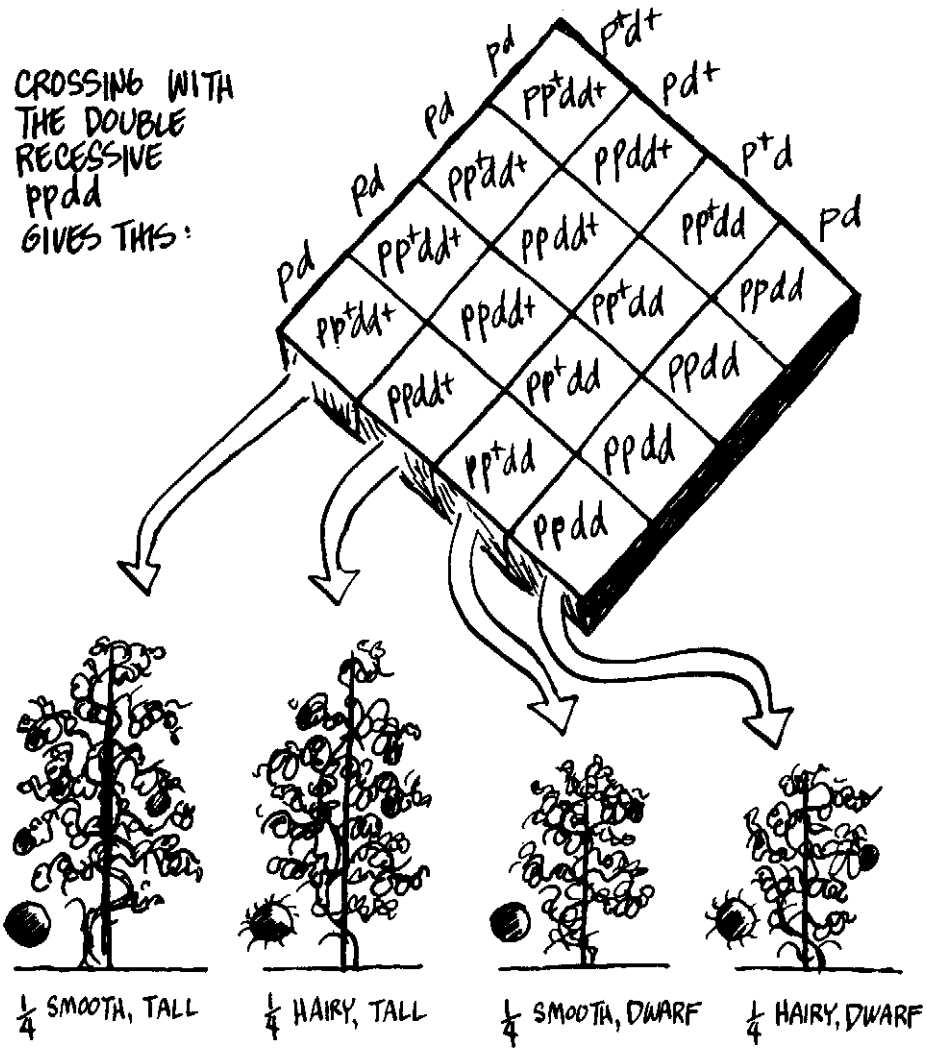
HAIRY, DWARF
ppdd

SMOOTH, TALL
pp^+dd^+

SUPPOSE MENDEL WAS RIGHT, AND THE p's WERE INDEPENDENT OF THE d's.

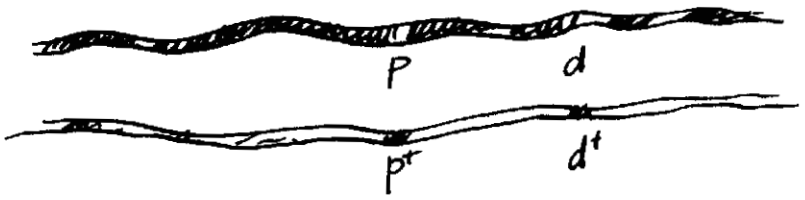


CROSSING WITH THE DOUBLE RECESSIVE ppdd GIVES THIS:

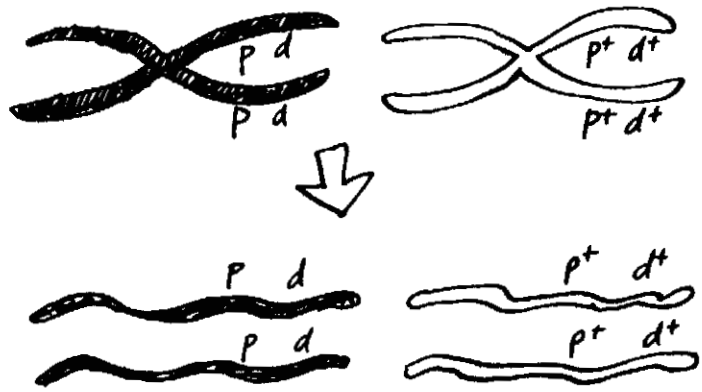


$\frac{1}{4}$ SMOOTH, TALL $\frac{1}{4}$ HAIRY, TALL $\frac{1}{4}$ SMOOTH, DWARF $\frac{1}{4}$ HAIRY, DWARF

NOW SUPPOSE p AND d LIE ON THE SAME CHROMOSOME. THEN THE HYBRID pp^+dd^+ HAS ITS ALLELES ON A HOMOLOGOUS PAIR:

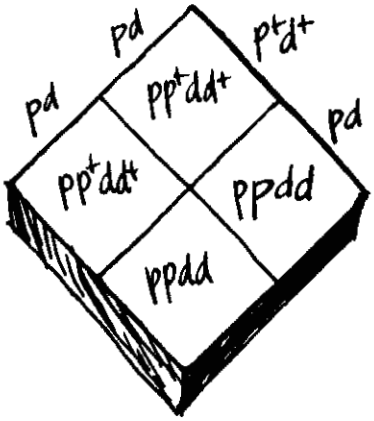


DURING MEIOSIS, THEY ARE SORTED OUT LIKE THIS:



IN THIS CASE, ONLY TWO TYPES OF GAMETES CAN BE MADE: pd AND p^+d^+, RATHER THAN THE FOUR PREDICTED BY MENDEL.

CROSSING WITH THE DOUBLE RECESSIVE ppdd, WE GET

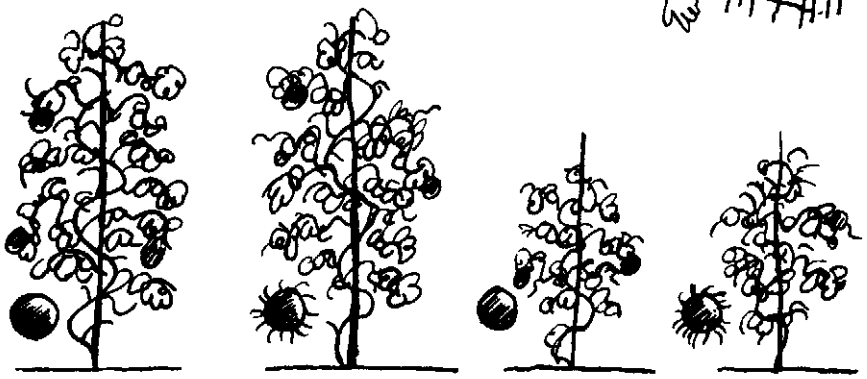


½ SMOOTH, TALL
pp^+dd^+

½ HAIRY, DWARF
ppdd

WHEN THE CROSS IS ACTUALLY MADE, WHAT DOES ONE ACTUALLY GET: A 50:50 SPLIT OR AN EQUAL 4-WAY SPLIT?

IT SEEMS THAT *NEITHER* PREDICTION IS CORRECT. ALL FOUR TYPES DO APPEAR, BUT IN THESE PROPORTIONS:

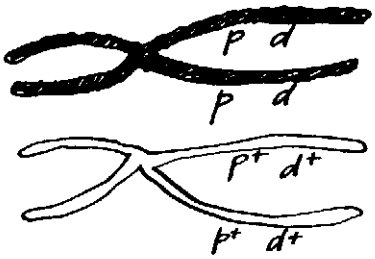


SMOOTH, TALL	HAIRY, TALL	SMOOTH, DWARF	HAIRY, DWARF
$pp^{+}dd^{+}$	$ppdd^{+}$	$pp^{+}dd$	$pp\ dd$
48%	2%	2%	48%

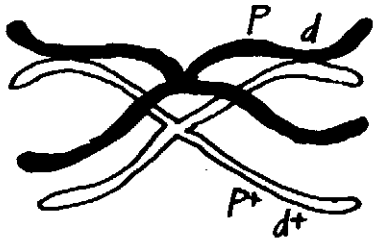
IT'S CERTAINLY CLOSER TO THE PREDICTION BASED ON LINKAGE THAN TO MENDEL'S. BUT IF P AND d ARE LINKED, THEN WHERE DID THOSE 2% COMBINATIONS COME FROM??

NOT TO PROLONG THE MYSTERY — THE GENES p AND d *ARE* ON THE SAME CHROMOSOME, BUT CHROMOSOMES CAN *EXCHANGE GENES*. IT'S CALLED ***CROSSING OVER***:

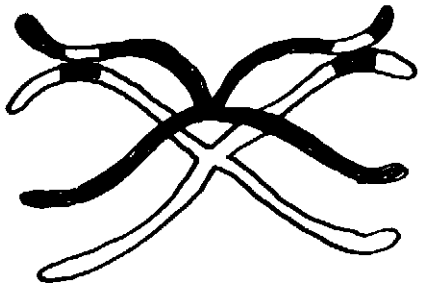
DURING MEIOSIS, HOMOLOGUES LINE UP WITH CORRESPONDING ALLELES OPPOSITE ONE ANOTHER.



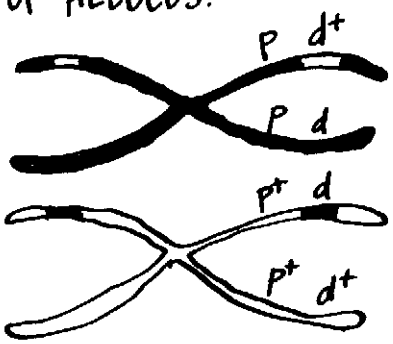
AT CERTAIN POINTS, SEEMINGLY "CHOSEN" AT RANDOM, THE CHROMOSOMES TOUCH:



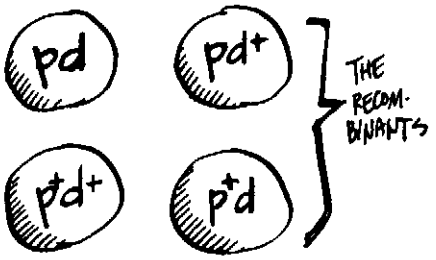
SOME SEGMENTS ***CROSS OVER***:



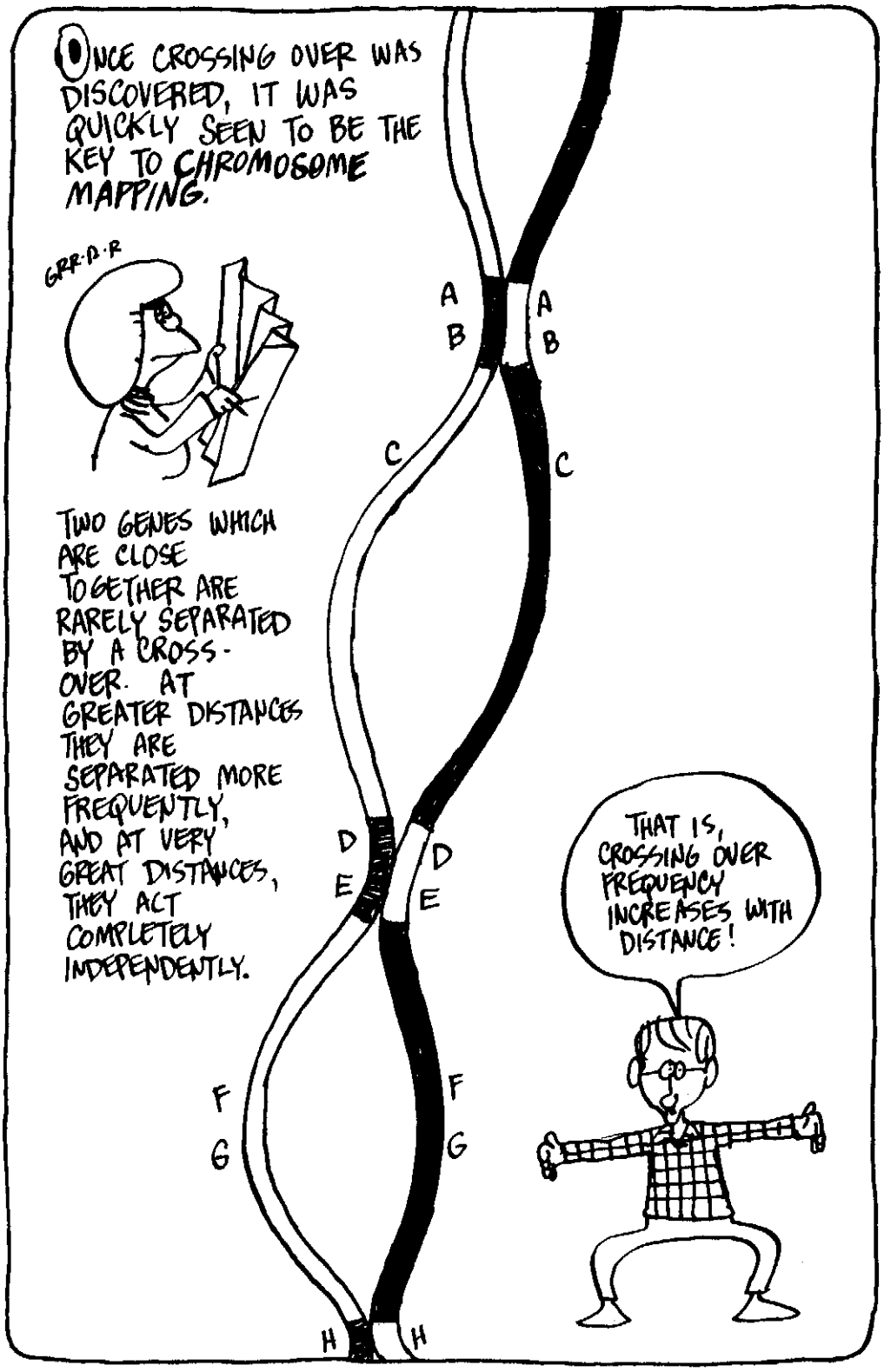
WHEN THEY SEPARATE, THEY HAVE NEW COMBINATIONS OF ALLELES.



WHEN THAT HAPPENS TO OUR HETEROZYGOTE, SOME OF THE RESULTING GAMETES GET THE "RECOMBINANT" CHROMOSOMES. HENCE THE EXCEPTIONAL CROSSES!



NOTE: THANKS TO CROSSING OVER, THE CHROMOSOMES YOU PASS ALONG TO YOUR OFFSPRING ARE NOT EXACTLY YOUR OWN, BUT RATHER A SHUFFLED-TOGETHER COMBINATION!


ONCE CROSSING OVER WAS DISCOVERED, IT WAS QUICKLY SEEN TO BE THE KEY TO CHROMOSOME MAPPING.
GRR·D·R
TWO GENES WHICH ARE CLOSE TOGETHER ARE RARELY SEPARATED BY A CROSS-OVER. AT GREATER DISTANCES THEY ARE SEPARATED MORE FREQUENTLY, AND AT VERY GREAT DISTANCES, THEY ACT COMPLETELY INDEPENDENTLY.
A
B
C
D
E
F
G
H
THAT IS, CROSSING OVER FREQUENCY INCREASES WITH DISTANCE!

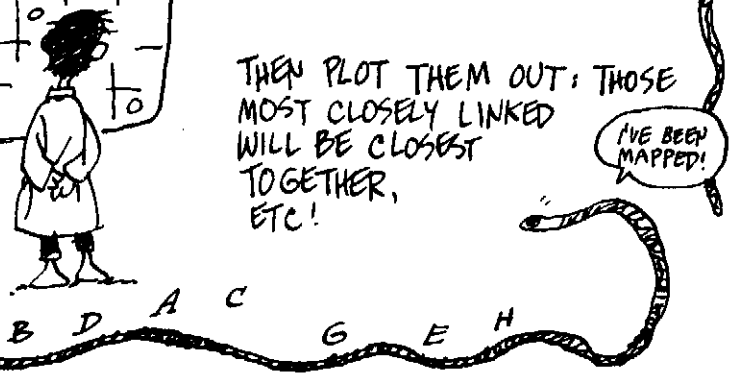
SO HERE'S HOW YOU MAKE A GENE MAP WITHOUT EVER SEEING A SINGLE GENE:

FIRST MAKE A VAST NUMBER OF CROSSES BETWEEN INDIVIDUALS DIFFERING IN VARIOUS PAIRS OF TRAITS...

	A	B	C	D	E	F	G	H
A	0	.27	.03	.04	.33	.48	.19	.41
B	.27	0	.24	.31	.36	.45	.16	.44
C	.03	.24	0	.07	.30			
D	.04	.31	.07	0				
E	.33	.36	.30	.	0			
F	.48	.45				0		
G	.19	.16					0	
H	.41	.44						0

NEXT, SEE HOW OFTEN EACH PAIR IS SEPARATED BY CROSSING OVER (BY LOOKING AT THE OFFSPRING).

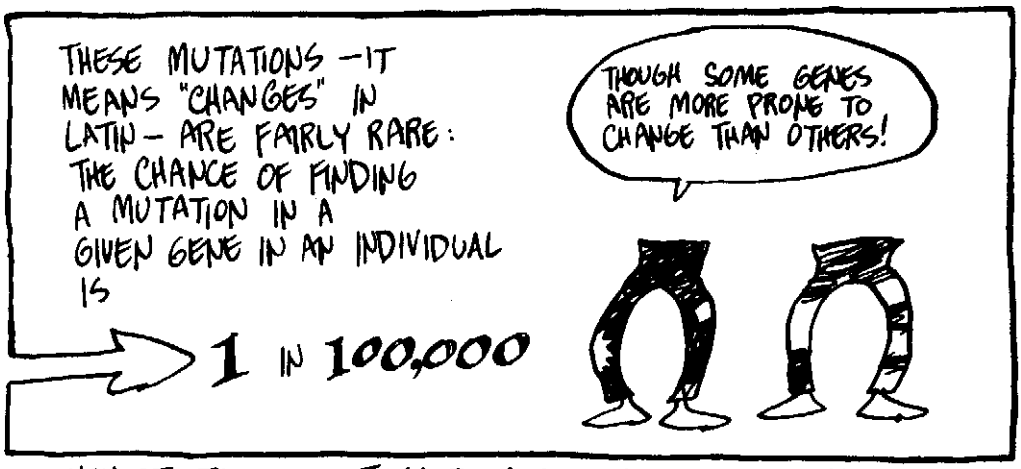
THEN PLOT THEM OUT: THOSE MOST CLOSELY LINKED WILL BE CLOSEST TOGETHER, ETC!



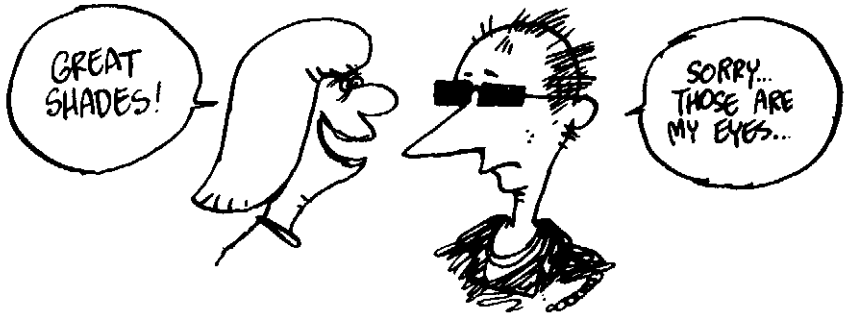
F B D A C G E H

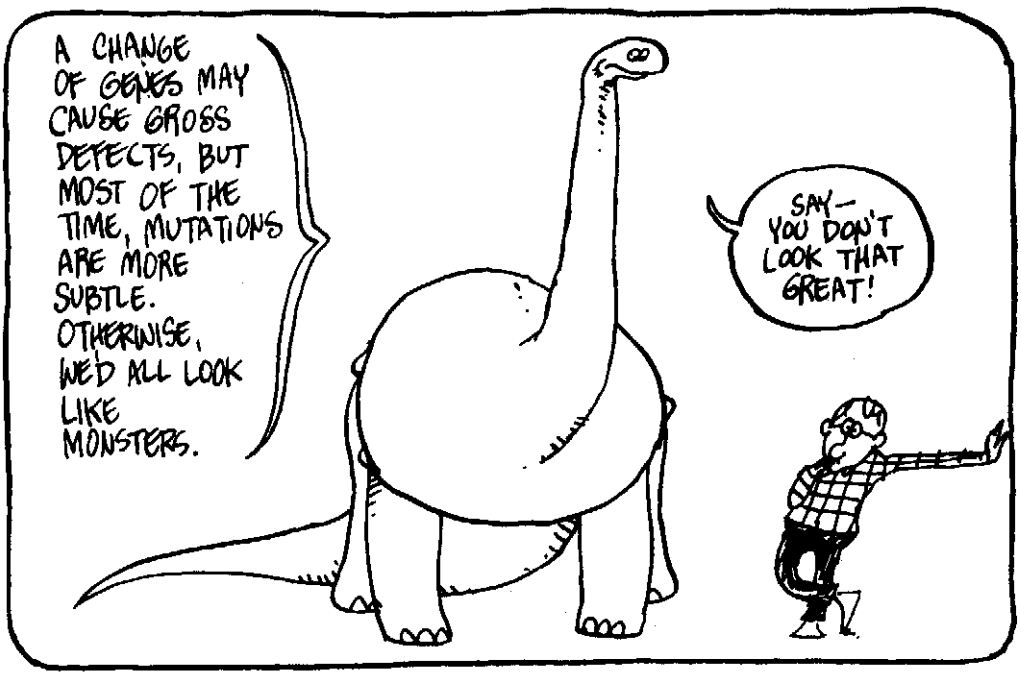
SINCE 1913, MAPPING HAS BEEN APPLIED TO A VARIETY OF ORGANISMS. NEARLY 1000 GENES HAVE BEEN MAPPED IN THE BACTERIUM *E. COLI*; ABOUT 300 IN THE TOMATO; 200 IN THE HOUSE MOUSE...; AND A FEW HUNDRED IN HUMAN BEINGS, ALTHOUGH THIS WAS DONE BY DIFFERENT MEANS...

MUTATION, OR A CHANGE OF GENES



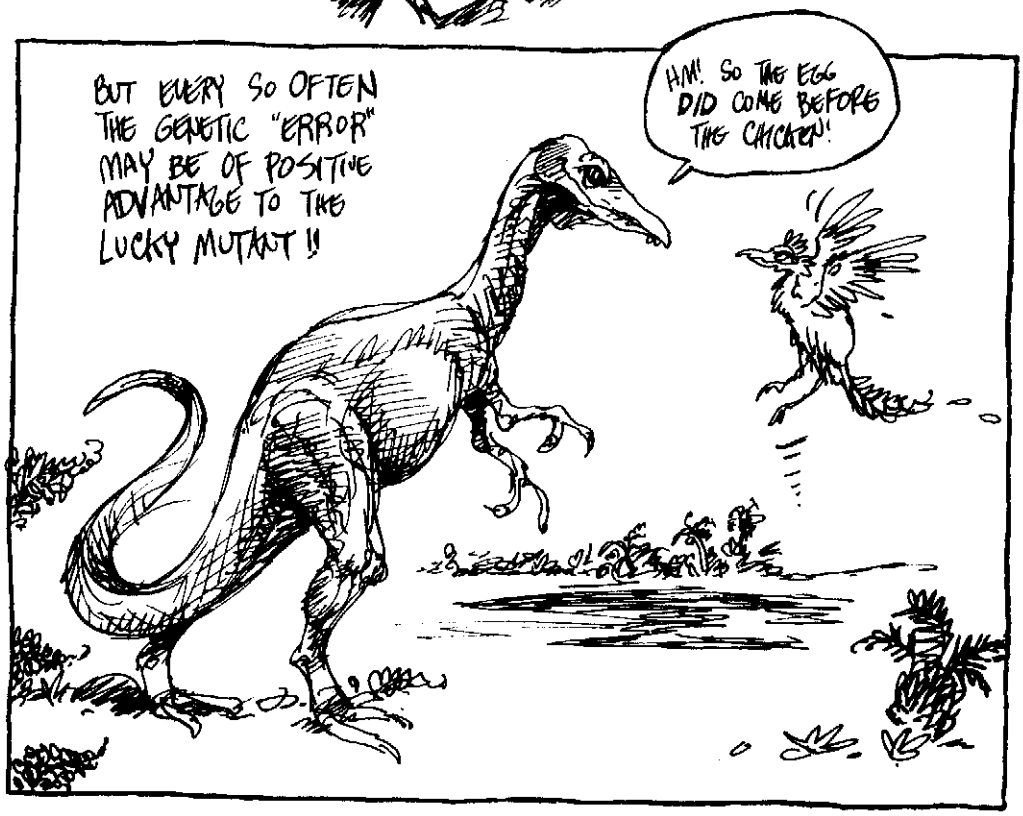
EVEN AT THIS RATE, THEY DO ADD UP! A HUMAN HAS SOME 200,000 GENES, SO WE CARRY AN AVERAGE OF TWO NEW MUTATIONS APIECE.

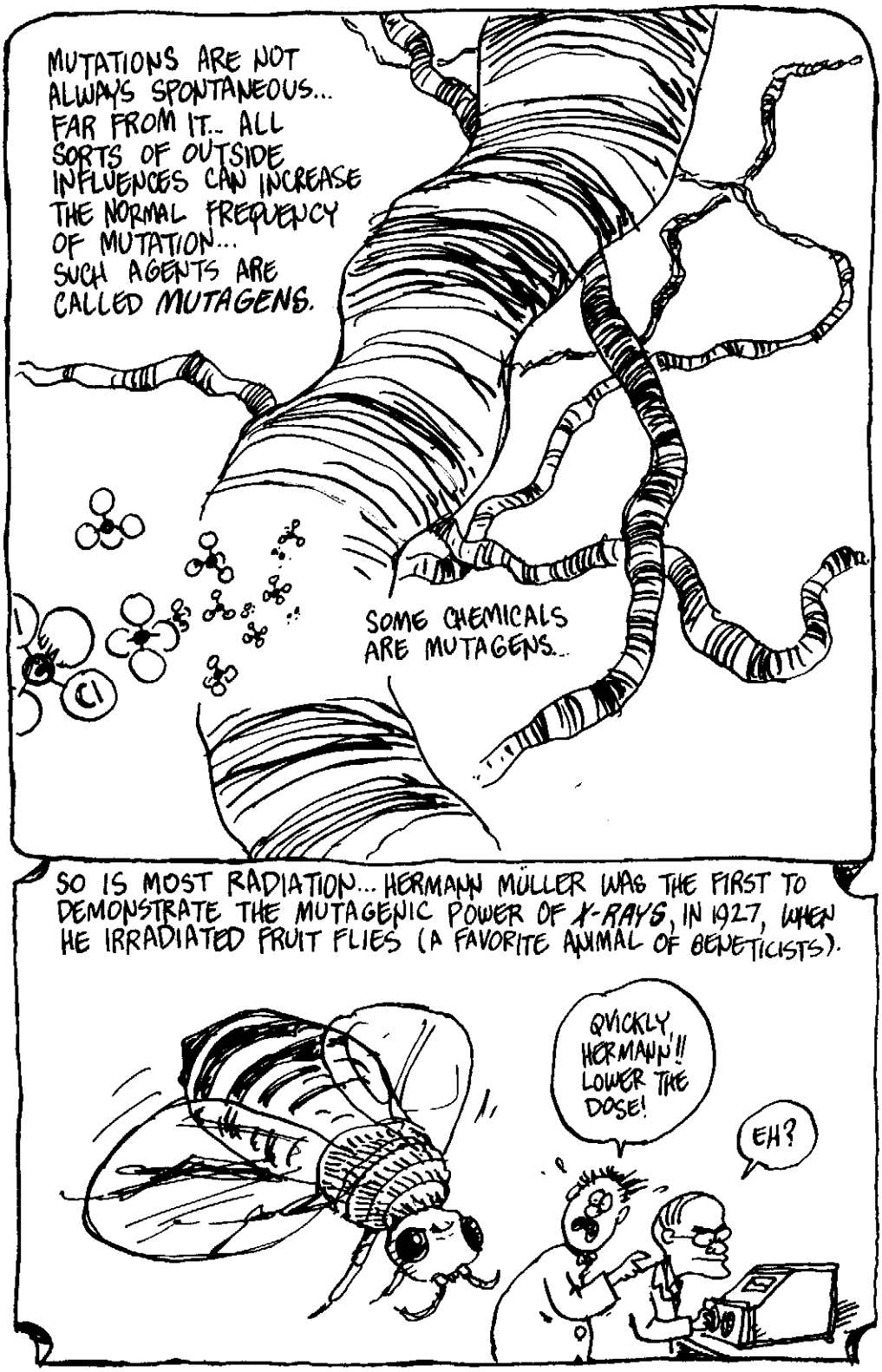


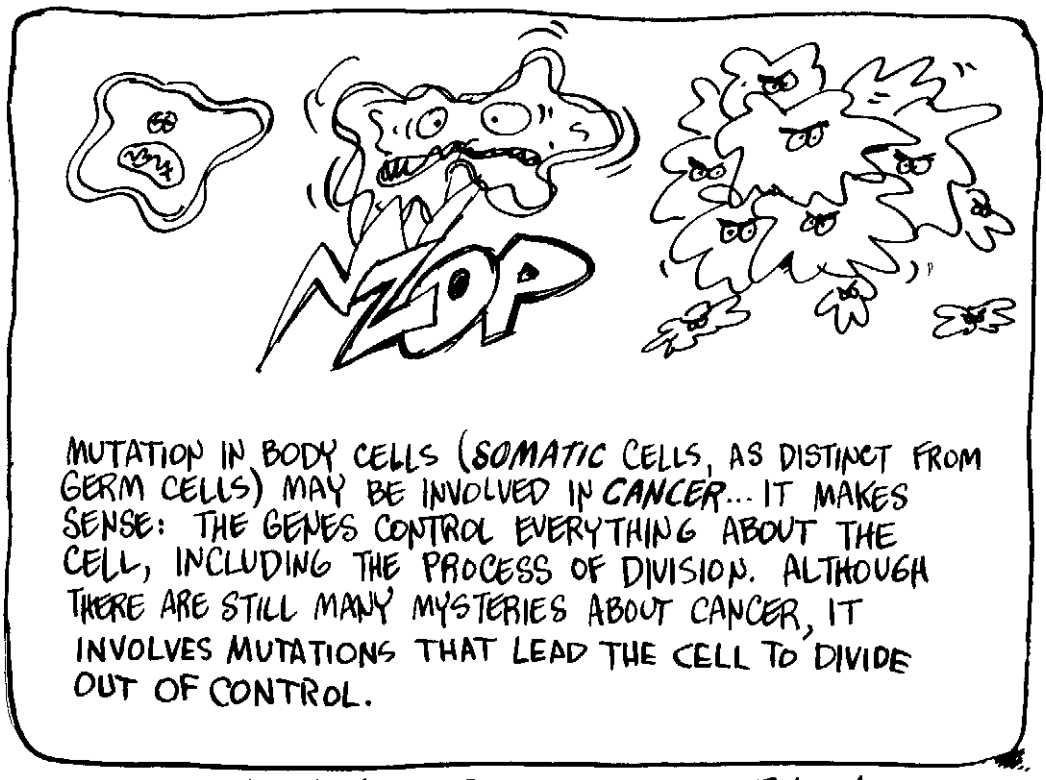


SOMETIMES, MUTATIONS MERELY RESULT IN A NEW ***RECESSIVE ALLELE***, LIKE HAIRINESS IN TOMATOES. YOU DON'T SEE ANYTHING AT ALL UNTIL TWO INDIVIDUALS WITH THE SAME MUTATION MATE TO FORM A HOMOZYGOTE. THEN ——

SOMETIMES MUTATIONS ARE COMPLETELY SILENT — PRODUCING NO CHANGE AT ALL — AND SOMETIMES THEY CAUSE CHANGES SO SLIGHT AS TO BE BARELY PERCEPTIBLE....

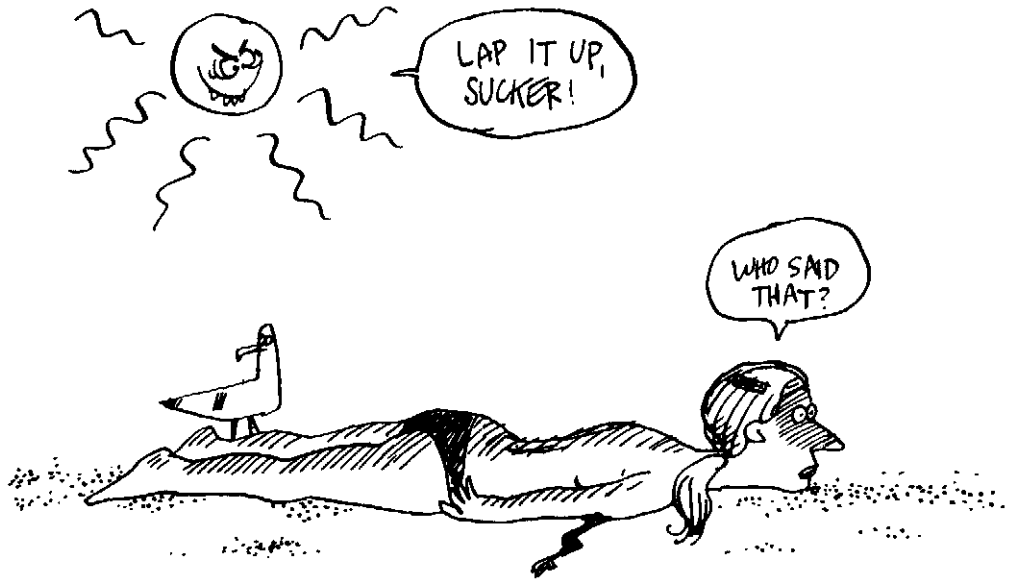



MUTATIONS ARE NOT ALWAYS SPONTANEOUS... FAR FROM IT.. ALL SORTS OF OUTSIDE INFLUENCES CAN INCREASE THE NORMAL FREQUENCY OF MUTATION... SUCH AGENTS ARE CALLED MUTAGENS.
SOME CHEMICALS ARE MUTAGENS..
Cl
SO IS MOST RADIATION... HERMANN MÜLLER WAS THE FIRST TO DEMONSTRATE THE MUTAGENIC POWER OF X-RAYS, IN 1927, WHEN HE IRRADIATED FRUIT FLIES (A FAVORITE ANIMAL OF GENETICISTS).
QUICKLY, HERMANN!! LOWER THE DOSE!
EH?



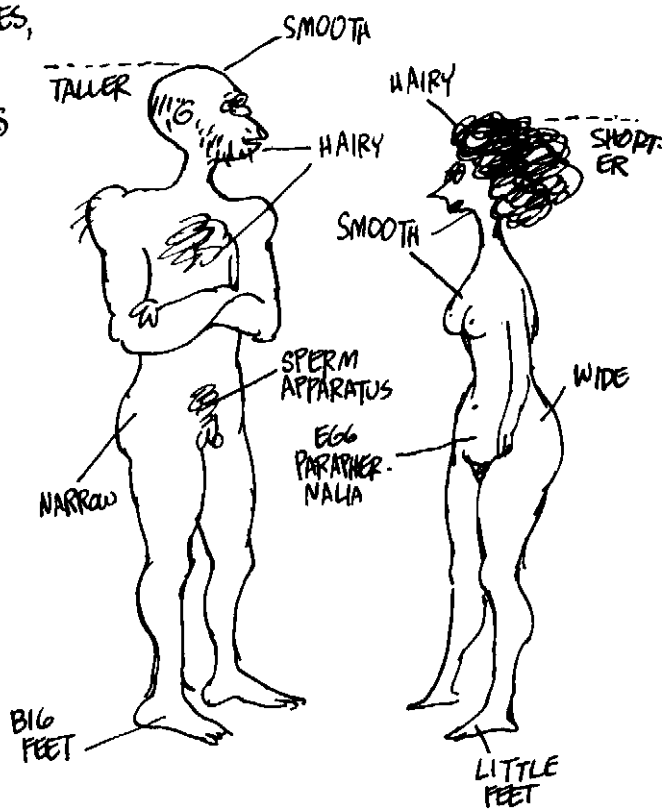
MUTATION IN BODY CELLS (*SOMATIC* CELLS, AS DISTINCT FROM GERM CELLS) MAY BE INVOLVED IN *CANCER*... IT MAKES SENSE: THE GENES CONTROL EVERYTHING ABOUT THE CELL, INCLUDING THE PROCESS OF DIVISION. ALTHOUGH THERE ARE STILL MANY MYSTERIES ABOUT CANCER, IT INVOLVES MUTATIONS THAT LEAD THE CELL TO DIVIDE OUT OF CONTROL.

MANY MUTAGENIC AGENTS ARE ALSO *CARCINOGENIC* (CANCER-CAUSING) — WHICH IS WHY THE FOOD + DRUG PEOPLE LOOK OUT FOR MUTAGENIC FOOD ADDITIVES... AND WHY YOU SHOULD LIMIT YOUR SUNBATHING, ESPECIALLY IF YOU HAVE PALE SKIN. (ULTRAVIOLET LIGHT IS MUTAGENIC.)



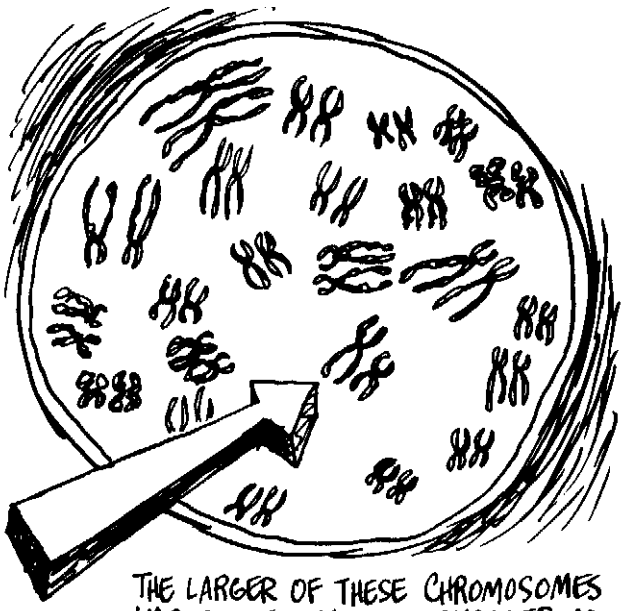
WHAT DETERMINES SEX?

THE COLOR OF PEA FLOWERS, THE TEXTURE OF TOMATOES, THE PINCHING OF PEA PODS—EACH OF THESE QUALITIES IS RULED BY A SINGLE GENE... BUT WHAT GOVERNS THAT MOST *OBVIOUS*, *INTERESTING*, AND (IN HUMANS) *SUBSTANTIAL* DIFFERENCE BETWEEN INDIVIDUALS: THE DIFFERENCE BETWEEN *MALE* AND *FEMALE*?



THROUGHOUT HISTORY, SO MANY THINKERS TACKLED THIS QUESTION THAT ONE 18TH-CENTURY WRITER WAS INSPIRED TO COMPILE "262 GROUNDLESS HYPOTHESES." HIS OWN GROUNDLESS HYPOTHESIS BECAME THE 263RD....

BUT OF COURSE IT'S IN THE GENES... NOT LONG AFTER HOMOLOGOUS CHROMOSOMES WERE DISCOVERED, SOMEBODY NOTICED AN EXCEPTION: HUMAN MALES HAVE ONE PAIR THAT IS *NOT* HOMOLOGOUS!!



THE LARGER OF THESE CHROMOSOMES WAS CALLED *X*; THE SMALLER, *Y*.

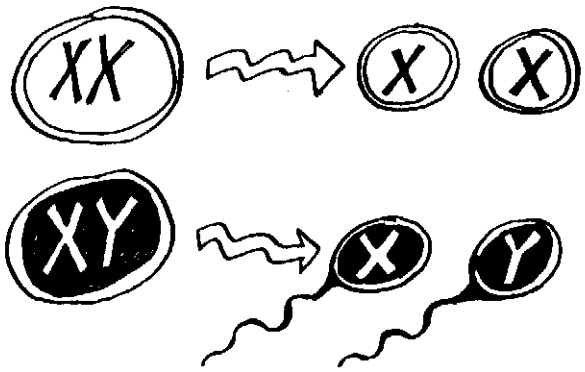
THE ONLY GENETIC DIFFERENCE BETWEEN (HUMAN) MALES AND FEMALES IS THIS:

FEMALES HAVE TWO *X* CHROMOSOMES:

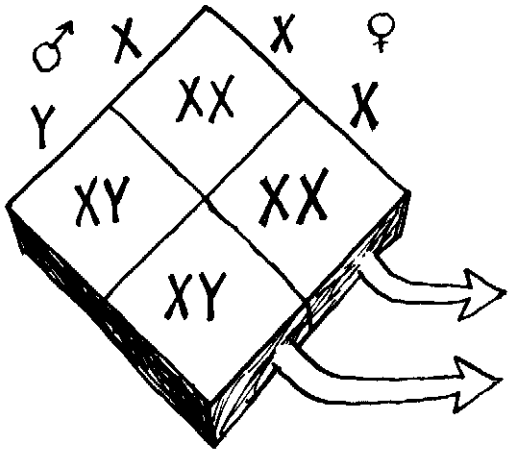
WHILE MALES HAVE ONE *X* AND ONE *Y*:

THE OTHER 22 OTHER PAIRS OF CHROMOSOMES ARE THE SAME.

LET'S JUST MAKE SURE THIS PRODUCES BOY AND GIRL BABIES IN THE RIGHT AMOUNTS.



MEIOSIS PRODUCES EGGS CARRYING THE X CHROMOSOME; SPERM ARE EQUALLY DIVIDED BETWEEN X AND Y—

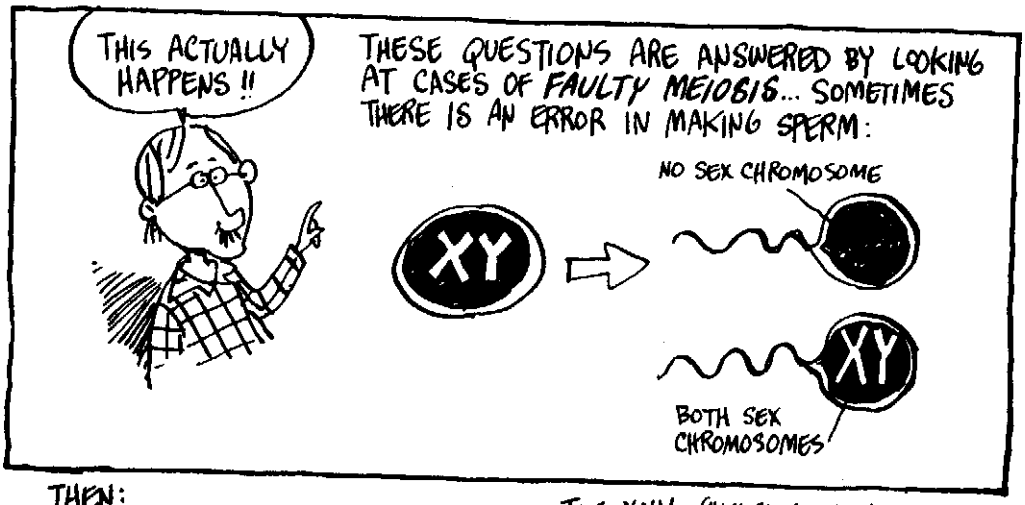


SO:

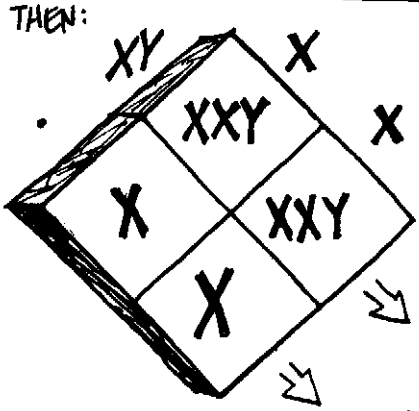
½ GIRLS

½ BOYS

HOWEVER, THE BASIC GENETIC QUESTION REMAINS: WHICH GENES ARE RESPONSIBLE FOR WHAT? IS IT THE Y CHROMOSOME THAT MAKES A MALE, OR DOES IT TAKE A DOUBLE DOSE OF X TO MAKE A FEMALE? WHAT WOULD HAPPEN TO SOMEBODY WITH *TWO* X CHROMOSOMES *AND* A Y ??



THEN:



"KLEINFELTER'S SYNDROME"

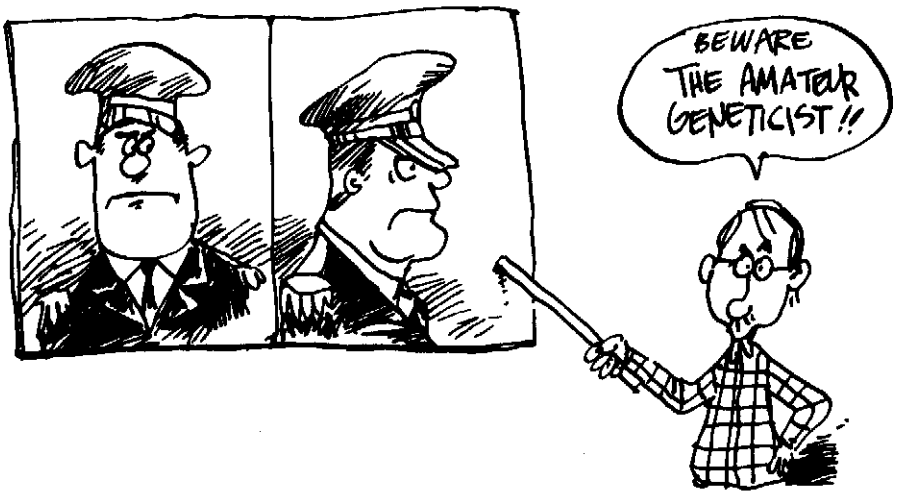
"TURNER'S SYNDROME"

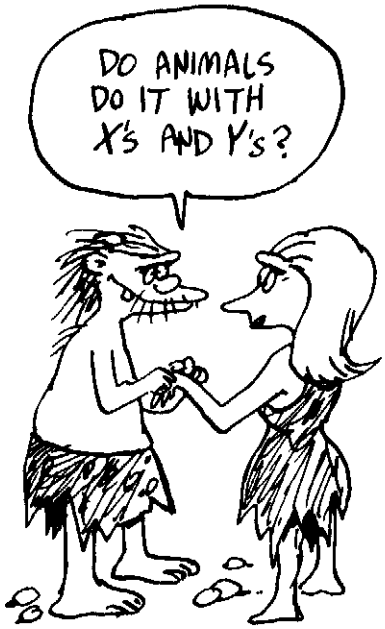
THE XXY ("KLEINFELTER'S SYNDROME") GROWS UP MALE. EVEN IN THE PRESENCE OF TWO X CHROMOSOMES, THE Y CAUSES MALENESS. THE SINGLE X GROWS UP FEMALE.

ANOTHER ABNORMALITY IS THE "SUPER MALE" COMBINATION **XYY**, WHICH OCCURS IN ABOUT ONE BIRTH IN A THOUSAND. XYY CHILDREN GROW UP TO BE NORMAL MALES — EXCEPT THAT THEY END UP IN ***PRISON*** ABOUT ***20 TIMES*** MORE OFTEN THAN THE REST OF THE POPULATION. ABOUT 5% OF ALL PRISONERS HAVE AN EXTRA Y CHROMOSOME. SOME SAY:

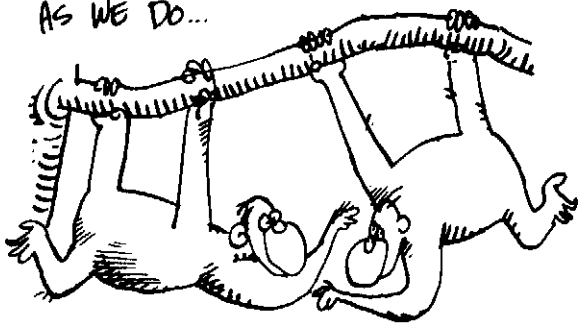
*KARYOTYPE = AN ORGANISM'S PATTERN OF CHROMOSOMES

MOST GENETICISTS WOULD BE MORE CAUTIOUS.. THE VAST MAJORITY (OVER 95%) OF XYY MALES ARE ***NOT*** IN PRISON... SO IT'S IMPOSSIBLE TO SAY THAT THE XYY KARYOTYPE CAUSES CRIMINALITY!

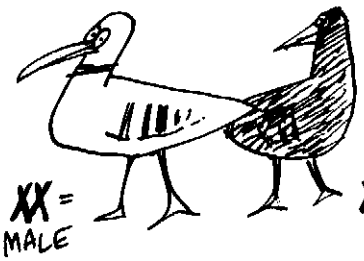




NOT NECESSARILY. SEX DETERMINATION IS HANDLED ALL SORTS OF WAYS, THOUGH MANY, MANY SPECIES HAVE THE SAME SYSTEM AS WE DO...



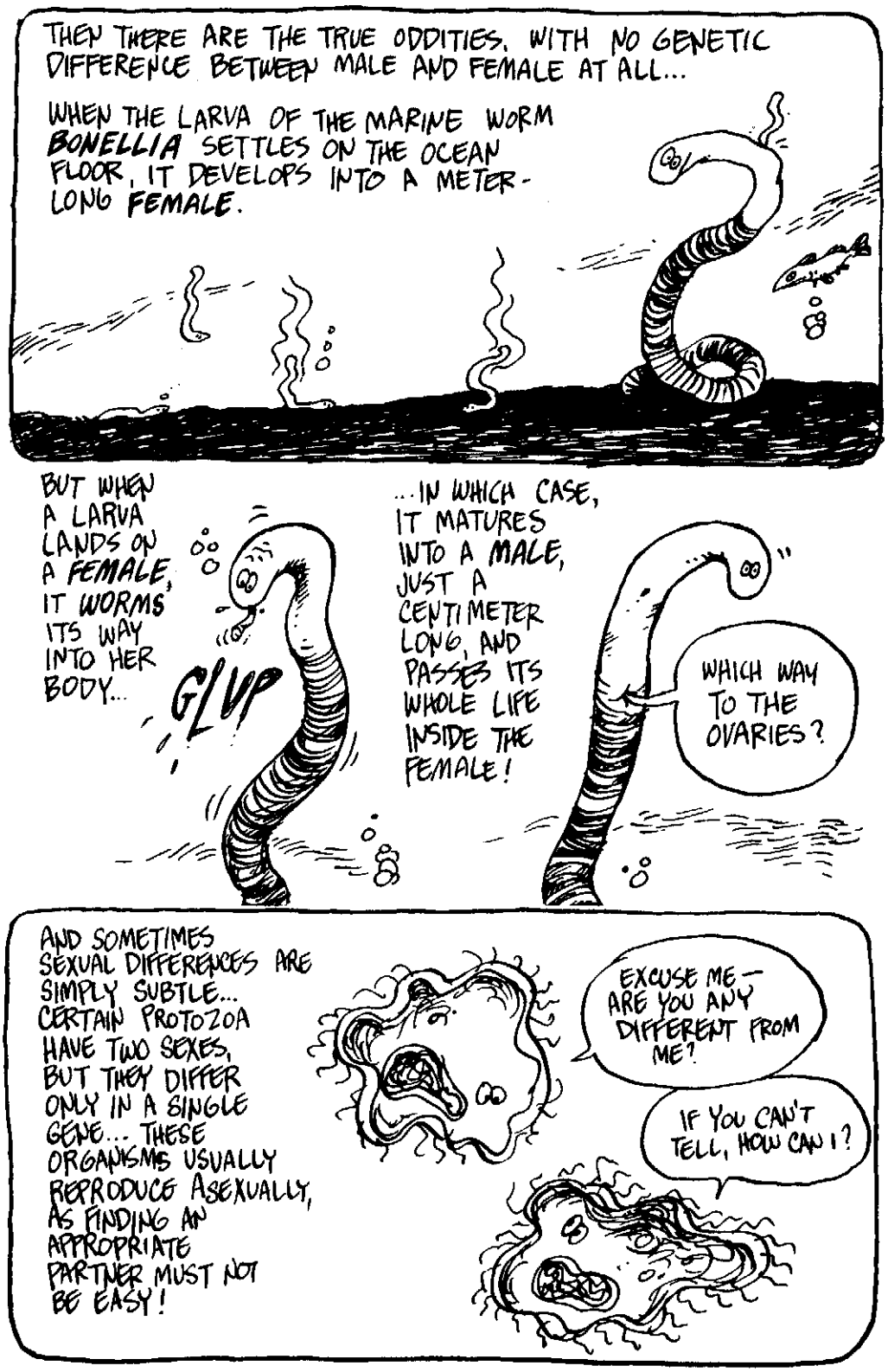
BUT AMONG BIRDS IT'S JUST THE *OPPOSITE* —



XX = MALE

XY = FEMALE

AND BEES ARE REALLY BEE-ZARRE: MALES DEVELOP FROM *UNFERTILIZED* EGGS. THEY'RE ALL *HAPLOID*, WHEREAS ALL *DIPLOIDS* ARE FEMALE (THE VAST MAJORITY OF THE HIVE). OTHERWISE, BEES HAVE NO SPECIFIC SEX CHROMOSOMES.


THEN THERE ARE THE TRUE ODDITIES, WITH NO GENETIC DIFFERENCE BETWEEN MALE AND FEMALE AT ALL...
WHEN THE LARVA OF THE MARINE WORM BONELLIA SETTLES ON THE OCEAN FLOOR, IT DEVELOPS INTO A METER-LONG FEMALE.
BUT WHEN A LARVA LANDS ON A FEMALE, IT WORMS ITS WAY INTO HER BODY...
GLUP
...IN WHICH CASE, IT MATURES INTO A MALE, JUST A CENTIMETER LONG, AND PASSES ITS WHOLE LIFE INSIDE THE FEMALE!
WHICH WAY TO THE OVARIES?
AND SOMETIMES SEXUAL DIFFERENCES ARE SIMPLY SUBTLE... CERTAIN PROTOZOA HAVE TWO SEXES, BUT THEY DIFFER ONLY IN A SINGLE GENE... THESE ORGANISMS USUALLY REPRODUCE ASEXUALLY, AS FINDING AN APPROPRIATE PARTNER MUST NOT BE EASY!
EXCUSE ME— ARE YOU ANY DIFFERENT FROM ME?
IF YOU CAN'T TELL, HOW CAN I?

X-RATED GENES

NOW BACK TO HUMANS... WE'VE SEEN THAT ALL THE GENES ACCOUNTING FOR PURELY SEX-RELATED MATTERS HAVE ACCUMULATED ON JUST TWO CHROMOSOMES, X FOR FEMALE, Y FOR MALE...

NOW WE MIGHT ASK THE FOLLOWING QUESTION:

ARE THERE ANY OTHER GENES ON THESE CHROMOSOMES ???

THERE'S A GOOD REASON TO ASK: HUMANS EXHIBIT SEVERAL DEFECTS THAT APPEAR TO BE *SEX-LINKED*...

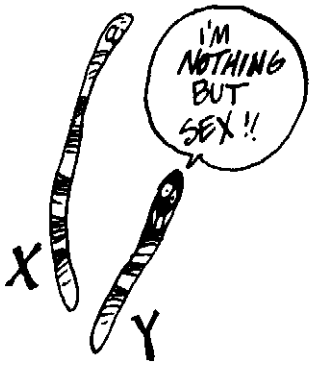
MOST **BALD** PEOPLE ARE **MEN**.

SO ARE MOST *COLOR-BLIND* PEOPLE.

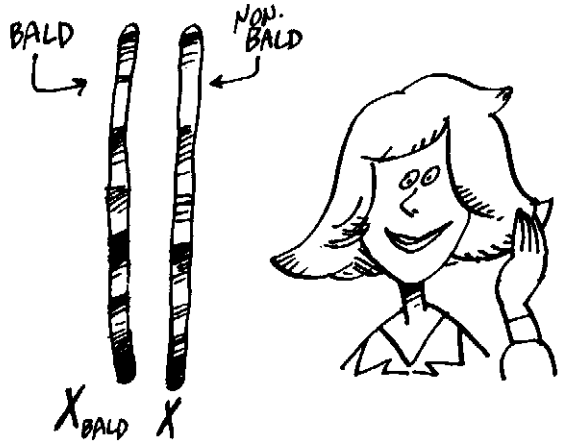
DITTO FOR *HEMOPHILIACS*.*

*HEMOPHILIA = A FAILURE OF THE BLOOD TO CLOT. HEMOPHILIACS CAN BLEED TO DEATH FROM A SMALL CUT.

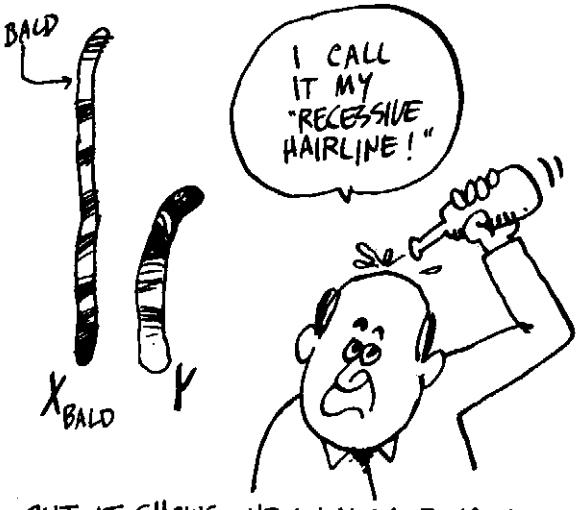
FROM THIS YOU MIGHT CONCLUDE THAT THESE GENES LIE ON THE Y CHROMOSOME— BUT YOU'D BE WRONG!! ACTUALLY, HEMOPHILIA, COLOR-BLINDNESS, AND HEREDITARY BALDNESS ARE ALL CAUSED BY **RECESSIVE** ALLELES LYING ON THE X CHROMOSOME!!



TAKE THE EXAMPLE OF BALDNESS:



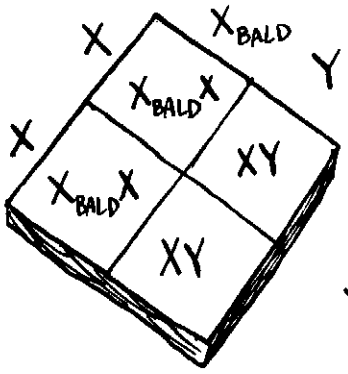
THE REASON WOMEN ARE RARELY BALD IS THAT, EVEN IF THEY HAVE THE BALDNESS ALLELE ON ONE X CHROMOSOME, THEY USUALLY HAVE THE DOMINANT **NON**-BALD ON THE OTHER.



BUT IT SHOWS UP IN MEN BECAUSE THE Y CHROMOSOME HAS NO ALLELE FOR THAT GENE AT ALL. IN THE ABSENCE OF A DOMINANT ALLELE, THE RECESSIVE IS EXPRESSED!!

LET'S SEE HOW THESE *SEX-LINKED* GENES ARE PASSED ALONG:

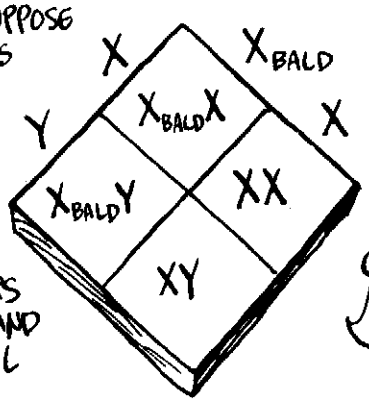
SUPPOSE A NORMAL WOMAN (XX) HAS CHILDREN BY A BALD MAN ($X_{BALD}Y$).



THE DAUGHTERS ($X_{BALD}X$) ARE ALL CARRIERS.... NOT BALD THEMSELVES, THEY STILL CARRY THE RECESSIVE GENE. THE SONS ARE NORMAL.

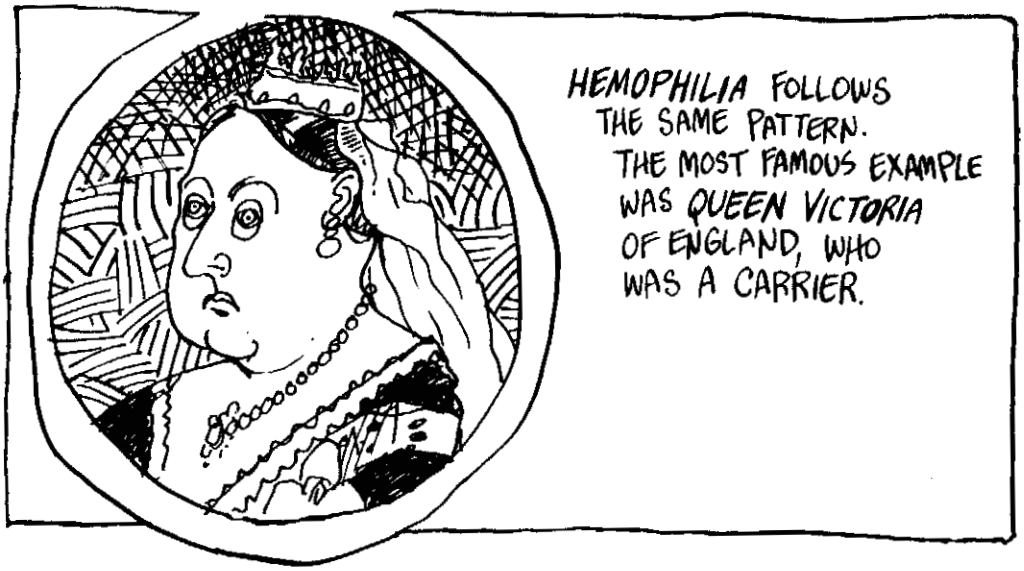
IF YOUR MOTHER IS NORMAL, YOU CAN'T INHERIT BALDNESS FROM YOUR FATHER!

NEXT GENERATION: SUPPOSE ONE OF THE CARRIERS MARRIES A NORMAL MAN.



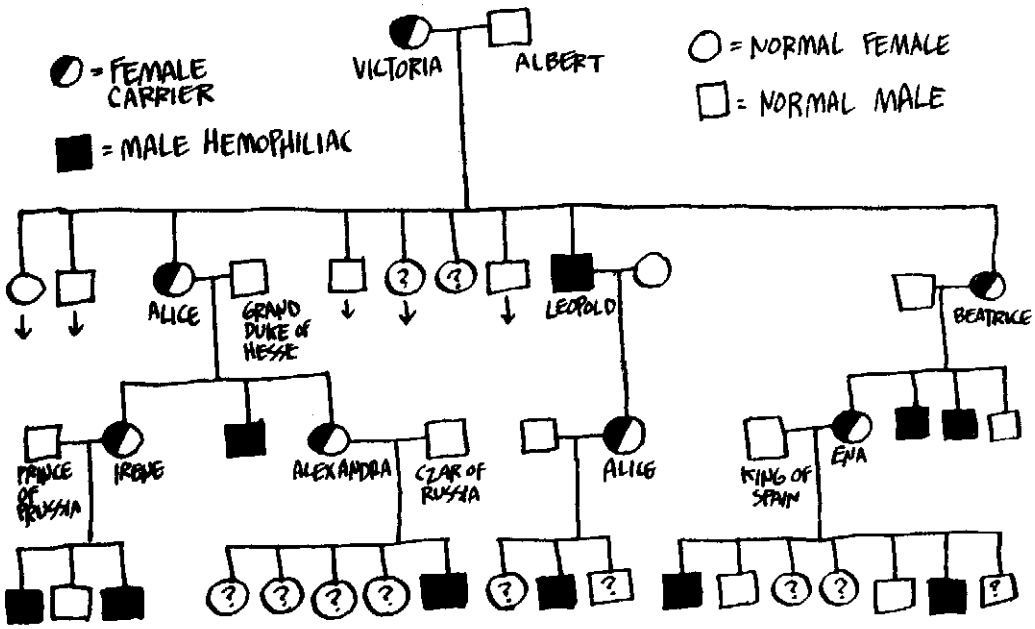
ON THE AVERAGE, HALF THE DAUGHTERS WILL BE CARRIERS, AND HALF THE SONS WILL BE BALD!

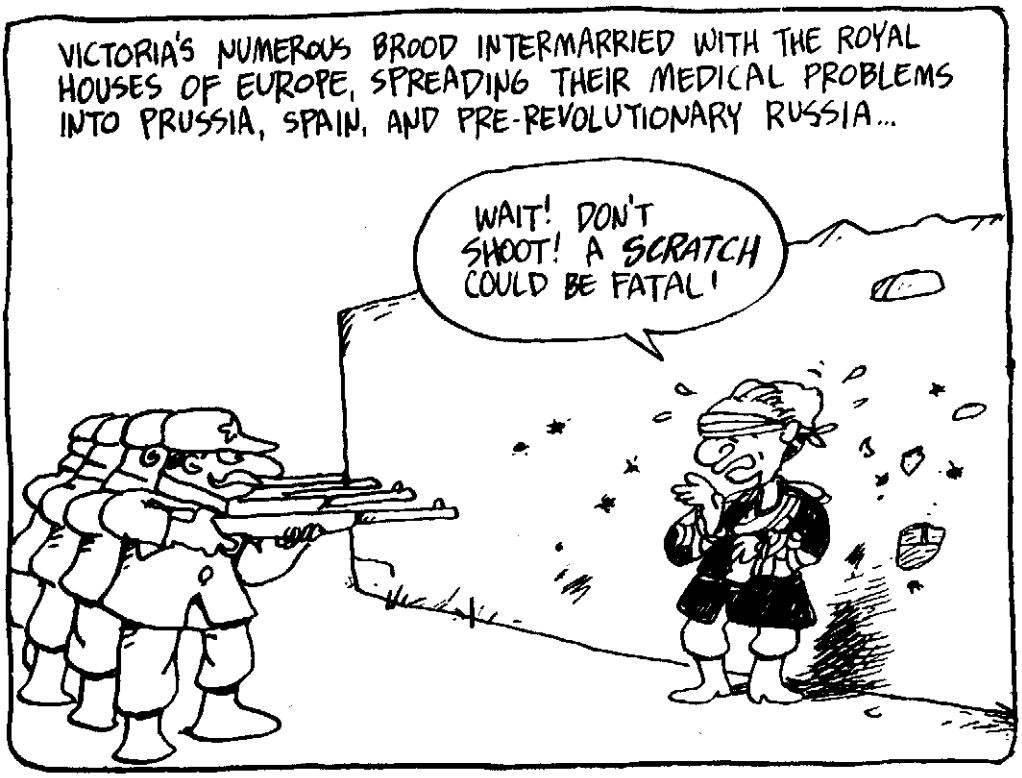
YOU CAN INHERIT BALDNESS FROM YOUR MATERNAL GRANDFATHER!!



THERE IS NO RECORD OF HEMOPHILIA IN VICTORIA'S ANCESTORS, SO WE MAY ASSUME THE DEFECT APPEARED IN HER GENES AS A SPONTANEOUS MUTATION. THIS HAPPENS WITH HEMOPHILIA IN AN ESTIMATED 1 CASE IN EVERY 50,000 PARENTS.

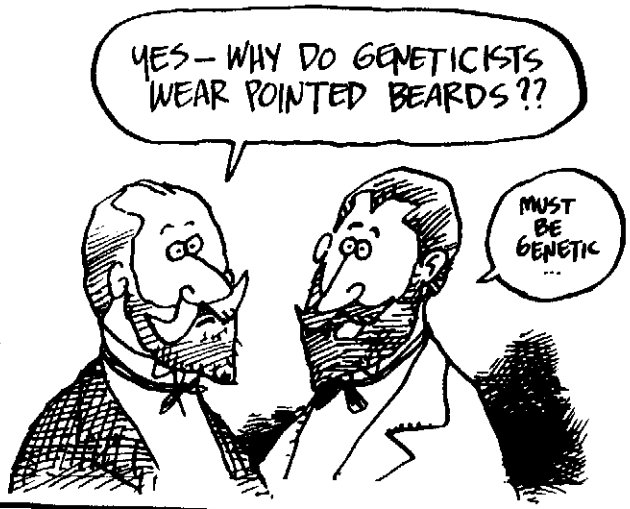
HEMOPHILIA IS PASSED ALONG JUST LIKE BALDNESS, AND YOU CAN SEE THE PATTERN IN VICTORIA'S FAMILY TREE





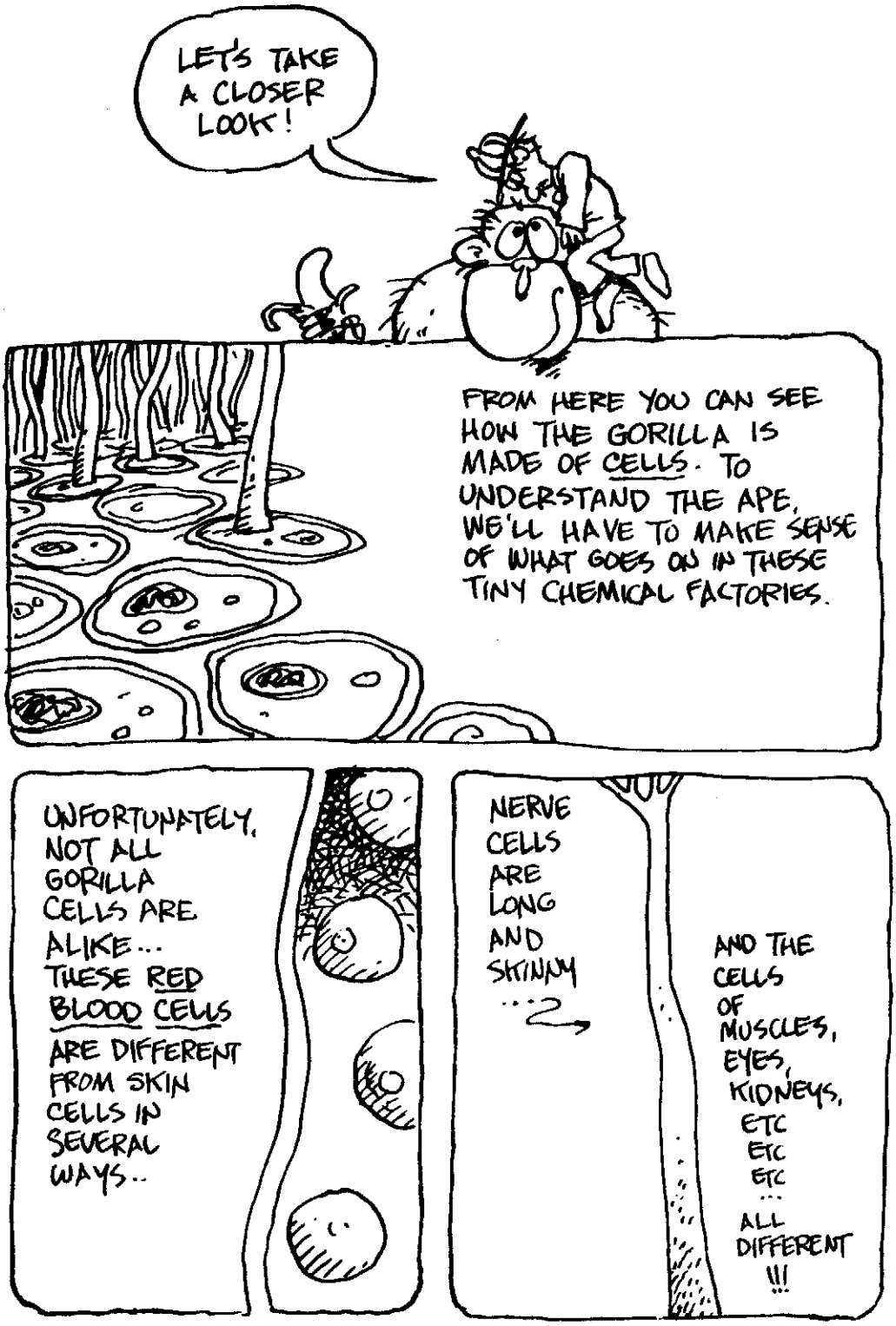
WELL, JUST LOOK HOW FAR SCIENCE HAD COME BY THE EARLY 19TH CENTURY: MENDEL AND HIS HEIRS HAD POLISHED OFF ALL THOSE OLD PUZZLES: THE ROLE OF MOTHER AND FATHER, THE NATURE OF HYBRIDS AND "SPORTS," WHAT DETERMINES SEX, AND EVEN WHAT CAUSES THE QUALITIES OF LIVING THINGS...

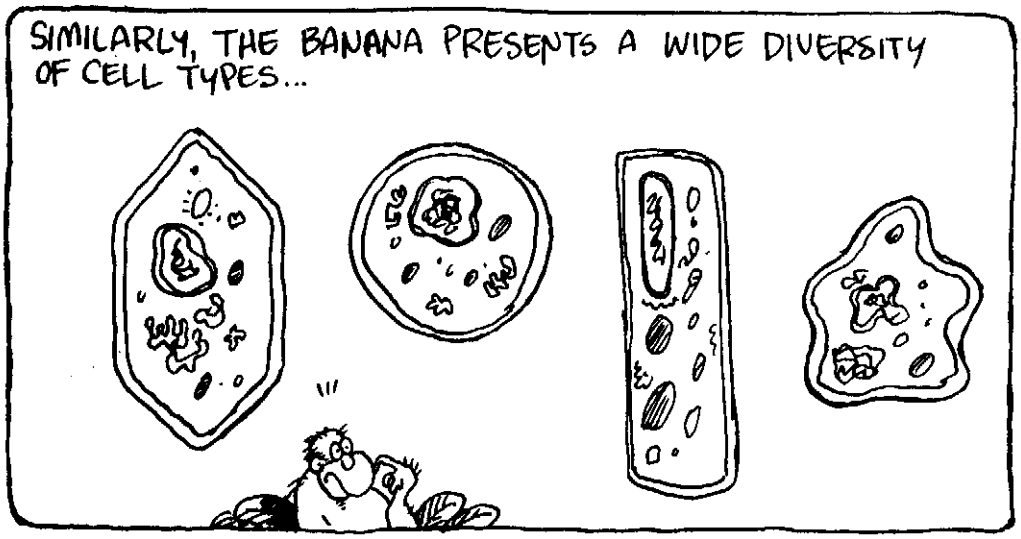
ALL THESE HAD BEEN EXPLAINED IN TERMS OF ***GENES***... GENES HAD BEEN LOCATED, MAPPED, AND THEIR PATTERNS OF INHERITANCE ANALYZED. NOW JUST ONE QUESTION REMAINED—.



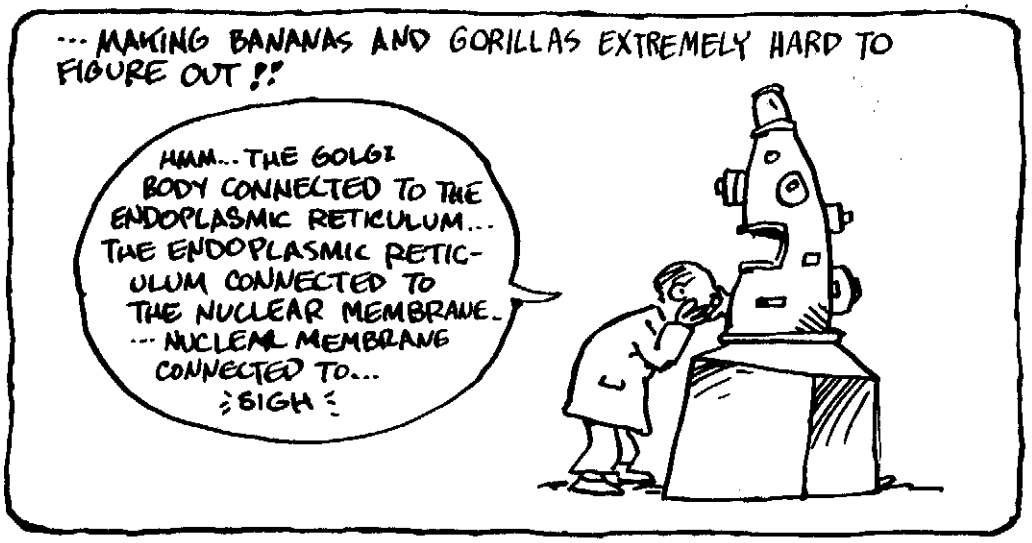
NO—THE QUESTION IS: WHAT *ARE* THE GENES, AND HOW DO THEY WORK??

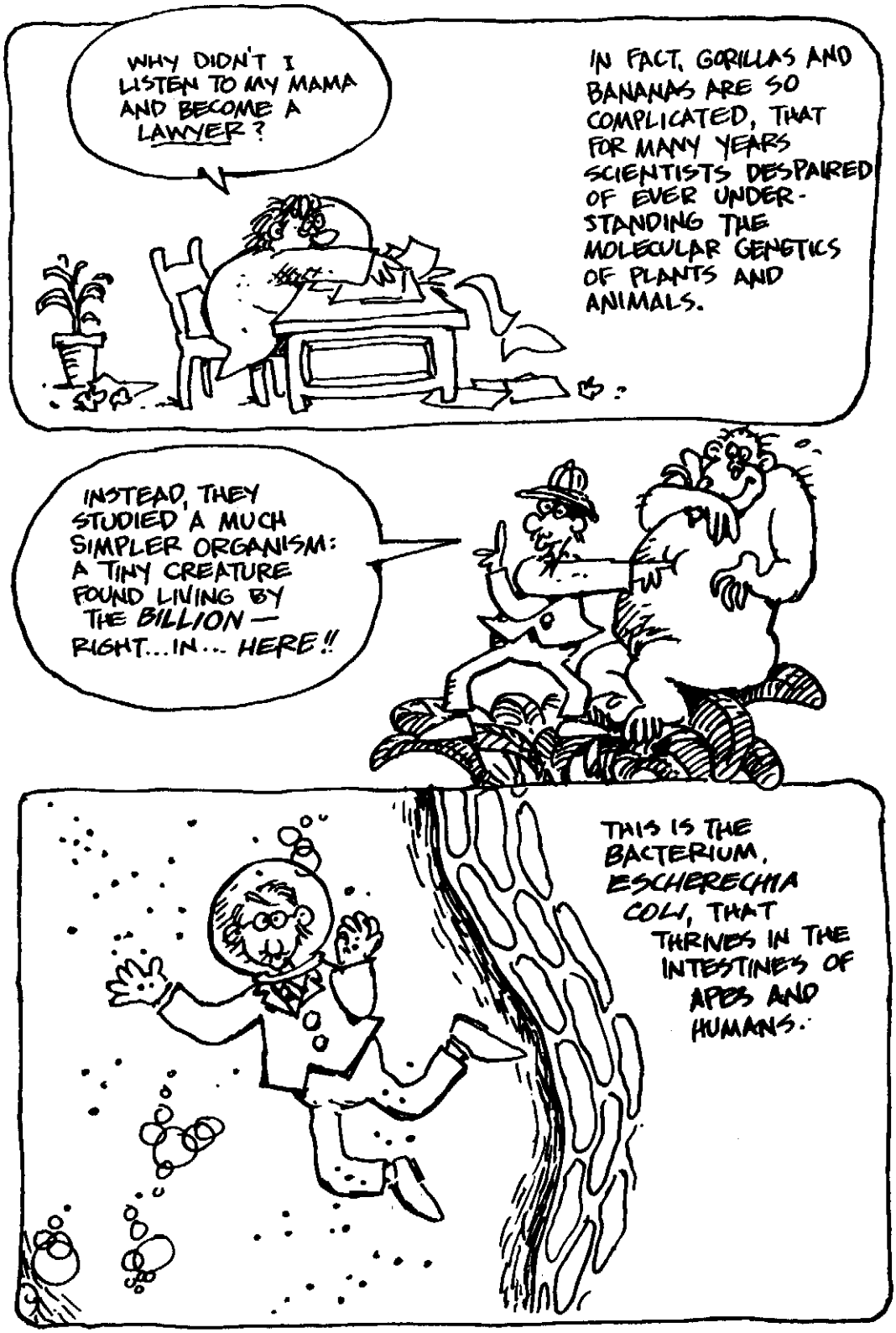
WHAT'S IN A CELL?


LET'S TAKE A CLOSER LOOK!
FROM HERE YOU CAN SEE HOW THE GORILLA IS MADE OF CELLS. TO UNDERSTAND THE APE, WE'LL HAVE TO MAKE SENSE OF WHAT GOES ON IN THESE TINY CHEMICAL FACTORIES.
UNFORTUNATELY, NOT ALL GORILLA CELLS ARE ALIKE... THESE RED BLOOD CELLS ARE DIFFERENT FROM SKIN CELLS IN SEVERAL WAYS..
NERVE CELLS ARE LONG AND SKINNY ...
AND THE CELLS OF MUSCLES, EYES, KIDNEYS, ETC ETC ETC ... ALL DIFFERENT !!!


SIMILARLY, THE BANANA PRESENTS A WIDE DIVERSITY OF CELL TYPES...


...EACH OF WHICH IS FILLED WITH ALL SORTS OF EVEN TINIER BODIES...

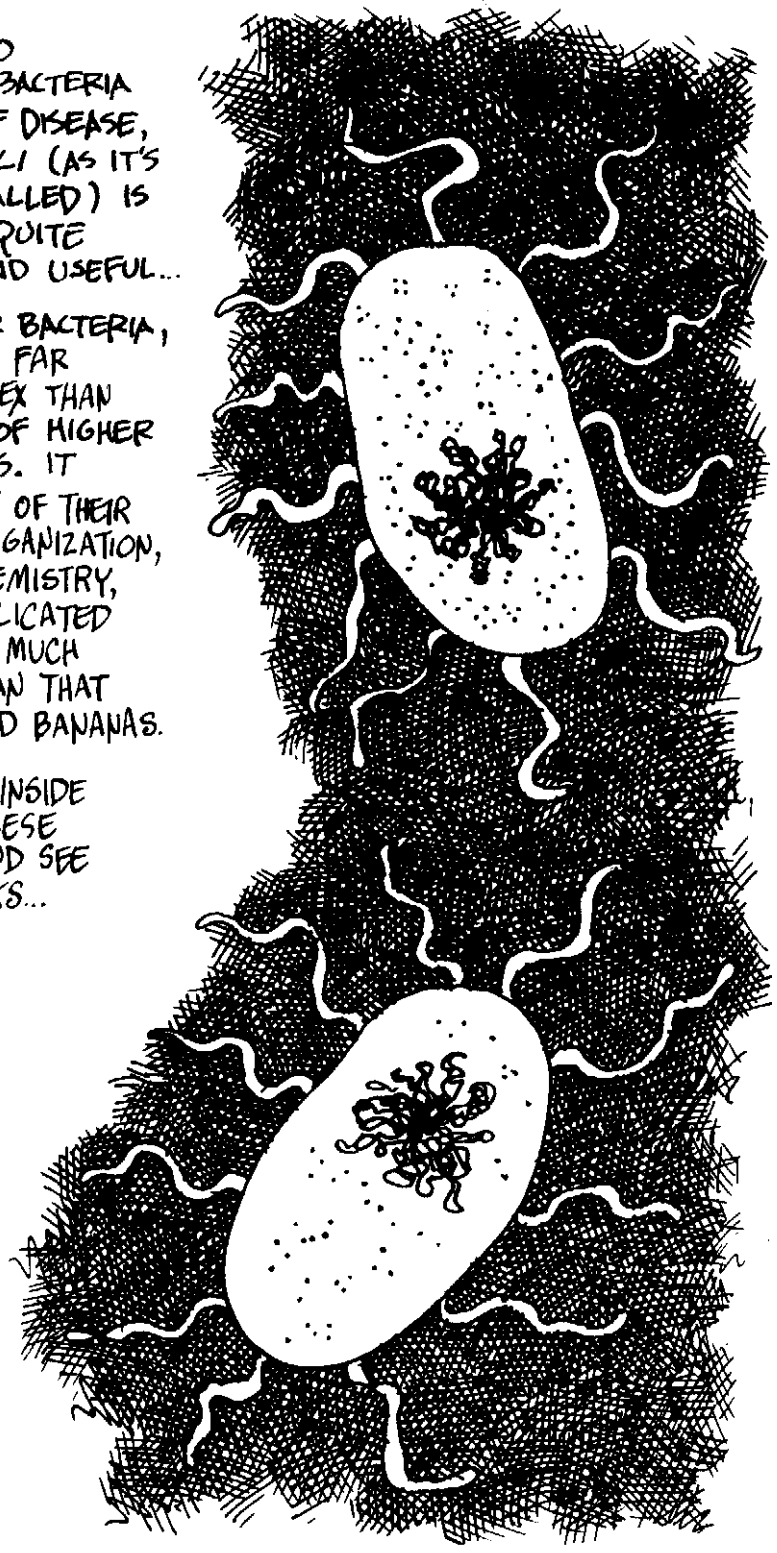

...MAKING BANANAS AND GORILLAS EXTREMELY HARD TO FIGURE OUT!!
HMM... THE GOLGI BODY CONNECTED TO THE ENDOPLASMIC RETICULUM... THE ENDOPLASMIC RETICULUM CONNECTED TO THE NUCLEAR MEMBRANE... NUCLEAR MEMBRANE CONNECTED TO...
SIGH

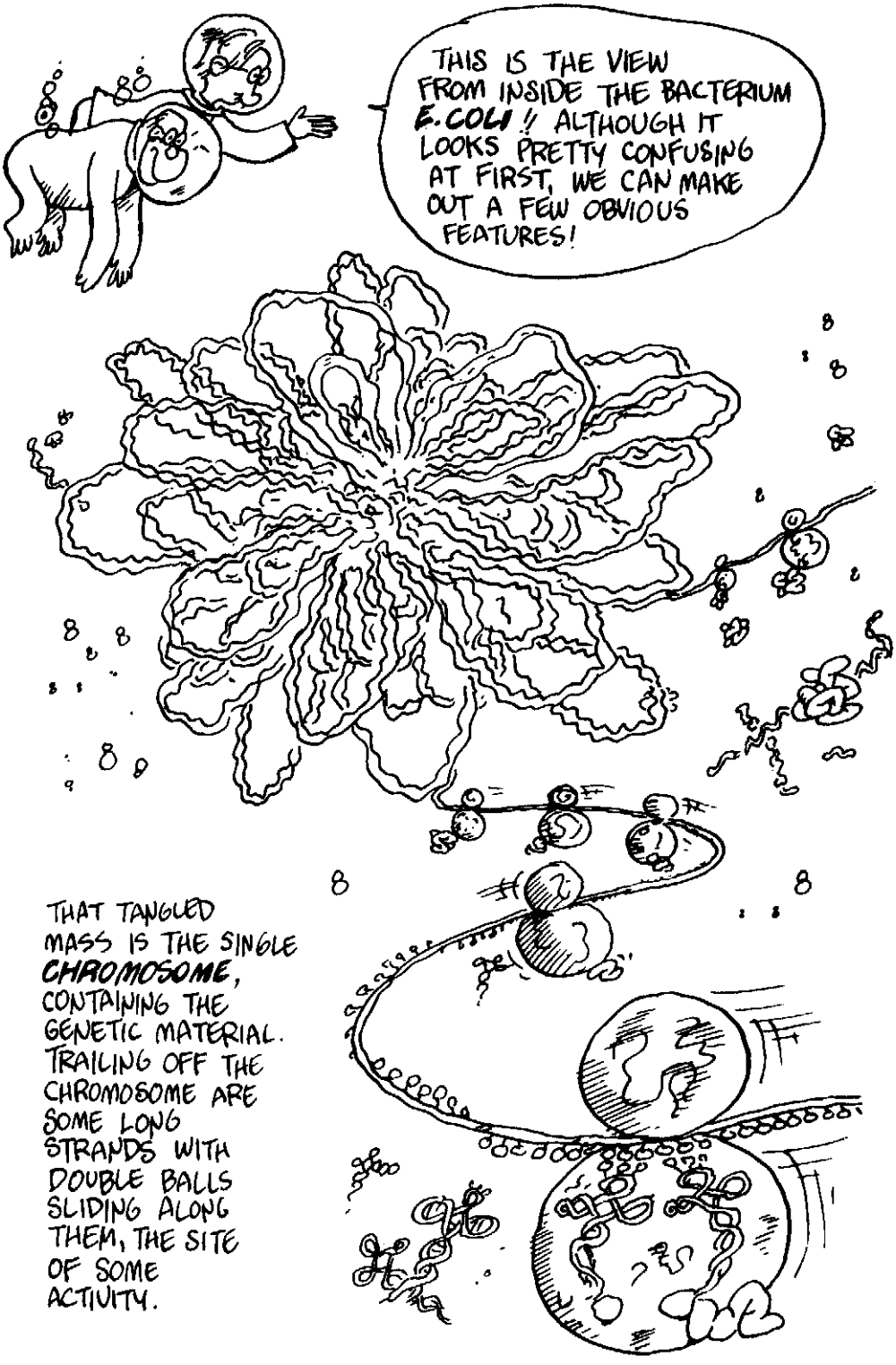

WHY DIDN'T I LISTEN TO MY MAMA AND BECOME A LAWYER?
IN FACT, GORILLAS AND BANANAS ARE SO COMPLICATED, THAT FOR MANY YEARS SCIENTISTS DESPAIRED OF EVER UNDERSTANDING THE MOLECULAR GENETICS OF PLANTS AND ANIMALS.
INSTEAD, THEY STUDIED A MUCH SIMPLER ORGANISM: A TINY CREATURE FOUND LIVING BY THE BILLION — RIGHT... IN... HERE!!
THIS IS THE BACTERIUM, ESCHERECHIA COLI, THAT THRIVES IN THE INTESTINES OF APES AND HUMANS.

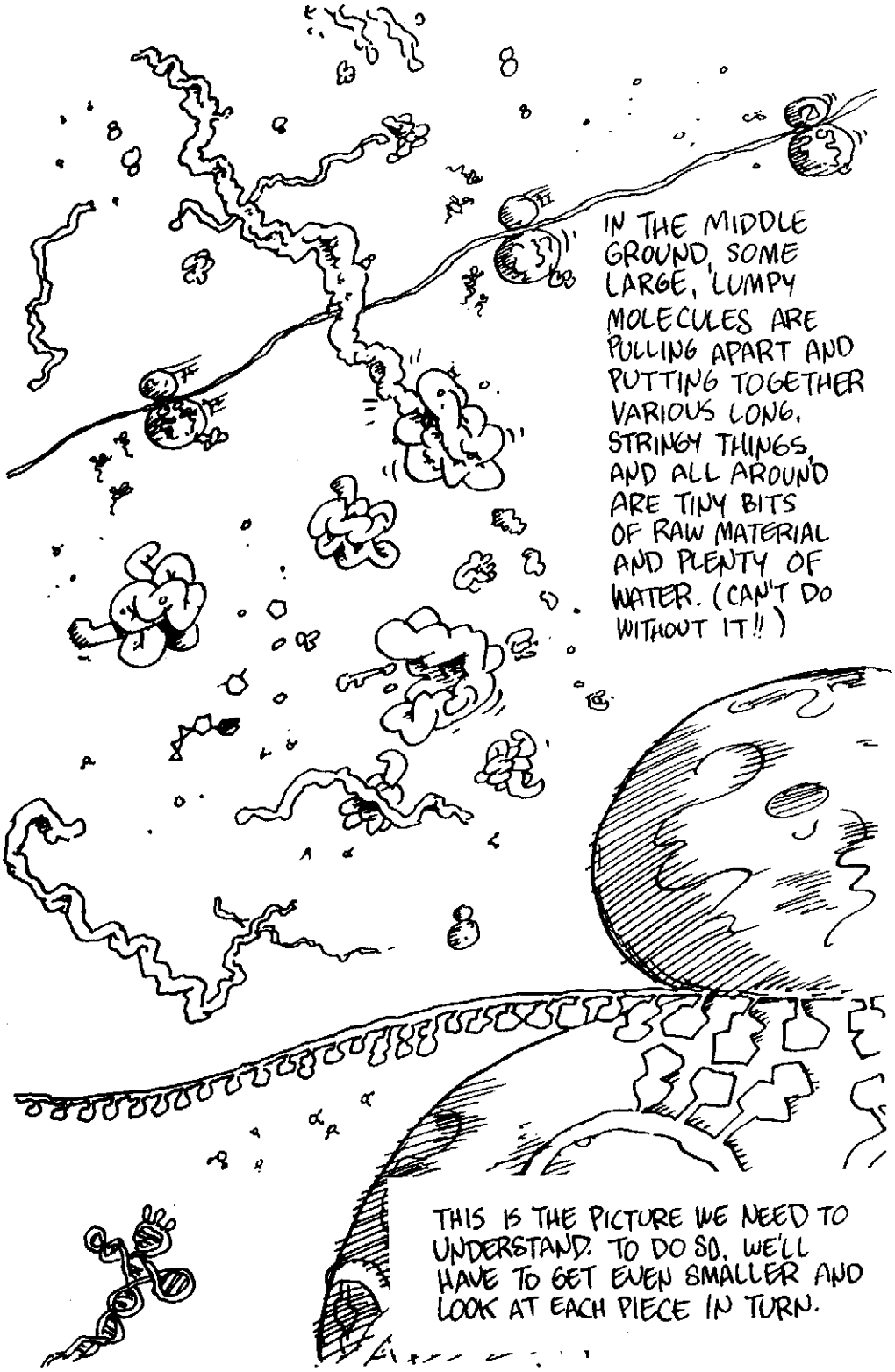
WE TEND TO THINK OF BACTERIA IN TERMS OF DISEASE, BUT *E. COLI* (AS IT'S USUALLY CALLED) IS ACTUALLY QUITE BENIGN AND USEFUL...

LIKE OTHER BACTERIA, *E. COLI* IS FAR LESS COMPLEX THAN THE CELLS OF HIGHER LIFE FORMS. IT LACKS MOST OF THEIR INTERNAL ORGANIZATION, AND ITS CHEMISTRY, WHILE COMPLICATED ENOUGH, IS MUCH SIMPLER THAN THAT OF APES AND BANANAS.

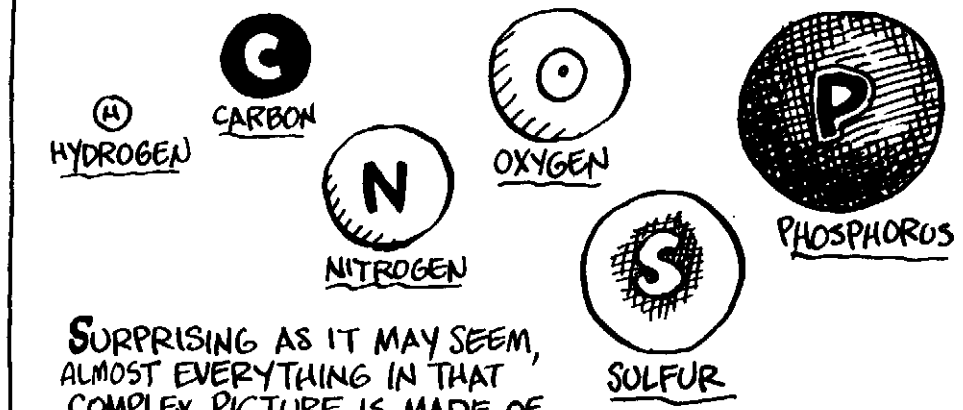
LET'S GET INSIDE ONE OF THESE *E. COLI* AND SEE HOW IT LOOKS...




THIS IS THE VIEW FROM INSIDE THE BACTERIUM E.COLI! ALTHOUGH IT LOOKS PRETTY CONFUSING AT FIRST, WE CAN MAKE OUT A FEW OBVIOUS FEATURES!
THAT TANGLED MASS IS THE SINGLE CHROMOSOME, CONTAINING THE GENETIC MATERIAL. TRAILING OFF THE CHROMOSOME ARE SOME LONG STRANDS WITH DOUBLE BALLS SLIDING ALONG THEM, THE SITE OF SOME ACTIVITY.

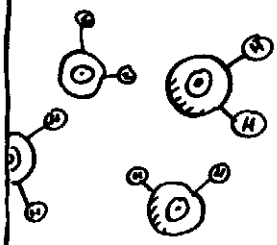

IN THE MIDDLE GROUND, SOME LARGE, LUMPY MOLECULES ARE PULLING APART AND PUTTING TOGETHER VARIOUS LONG, STRINGY THINGS, AND ALL AROUND ARE TINY BITS OF RAW MATERIAL AND PLENTY OF WATER. (CAN'T DO WITHOUT IT!!)
THIS IS THE PICTURE WE NEED TO UNDERSTAND. TO DO SO, WE'LL HAVE TO GET EVEN SMALLER AND LOOK AT EACH PIECE IN TURN.

MACROMOLECULES



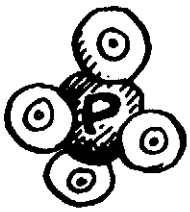
SURPRISING AS IT MAY SEEM, ALMOST EVERYTHING IN THAT COMPLEX PICTURE IS MADE OF JUST SIX DIFFERENT ELEMENTS.

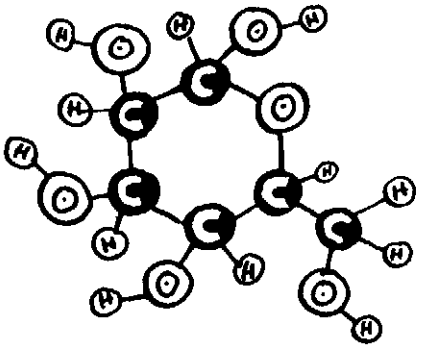
IN THE CELL THESE ATOMS ARE JOINED TOGETHER TO FORM ***MOLECULES***.



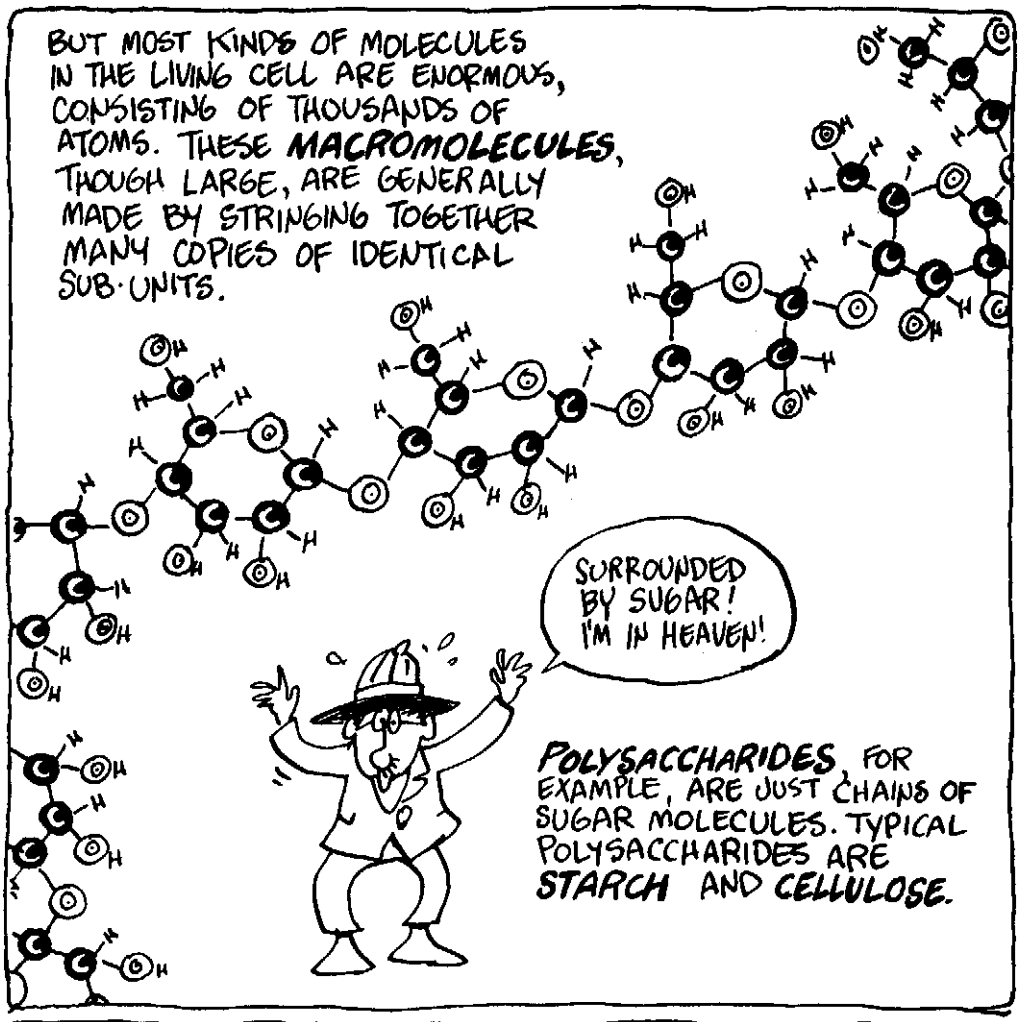
THE SIMPLEST AND MOST ABUNDANT BY FAR IS **WATER**, H_2O.

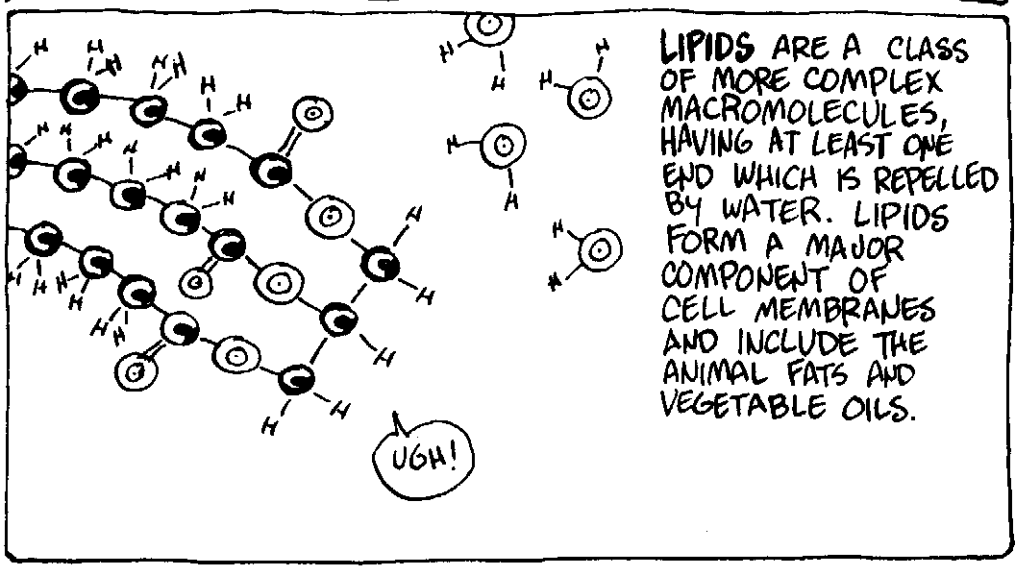
ANOTHER SMALL ONE IS THE PYRAMID-SHAPED ***PHOSPHATE***, PO_4.





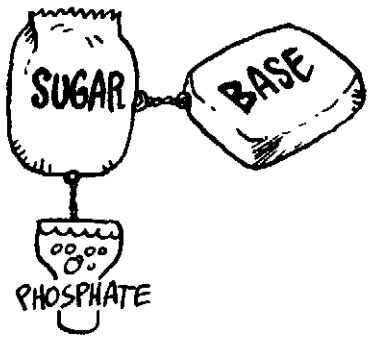
A BIT BIGGER ARE THE RING-SHAPED **SUGARS**. THIS ONE IS ***GLUCOSE***, $C_6H_{12}O_6$.


BUT MOST KINDS OF MOLECULES IN THE LIVING CELL ARE ENORMOUS, CONSISTING OF THOUSANDS OF ATOMS. THESE MACROMOLECULES, THOUGH LARGE, ARE GENERALLY MADE BY STRINGING TOGETHER MANY COPIES OF IDENTICAL SUB-UNITS.
SURROUNDED BY SUGAR! I'M IN HEAVEN!
POLYSACCHARIDES, FOR EXAMPLE, ARE JUST CHAINS OF SUGAR MOLECULES. TYPICAL POLYSACCHARIDES ARE STARCH AND CELLULOSE.

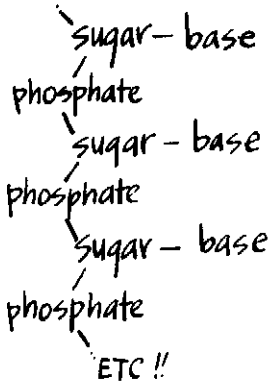

UGH!
LIPIDS ARE A CLASS OF MORE COMPLEX MACROMOLECULES, HAVING AT LEAST ONE END WHICH IS REPELLED BY WATER. LIPIDS FORM A MAJOR COMPONENT OF CELL MEMBRANES AND INCLUDE THE ANIMAL FATS AND VEGETABLE OILS.

STILL MORE COMPLEX, BUT MOST IMPORTANT IN GENETICS, ARE THE ***NUCLEIC ACIDS*** AND ***PROTEINS***... WATCH CLOSELY:

THE BUILDING BLOCKS FOR NUCLEIC ACIDS ARE CALLED ***NUCLEOTIDES***. AN INDIVIDUAL NUCLEOTIDE ITSELF HAS 3 COMPONENTS: A ***SUGAR***, A ***PHOSPHATE***, AND A ***BASE***, LIKE SO —

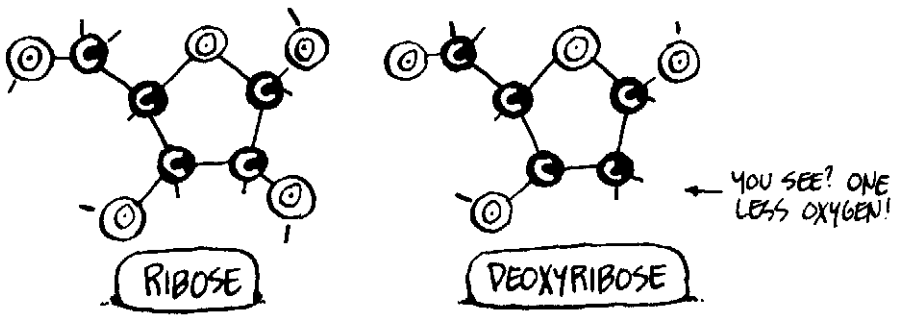


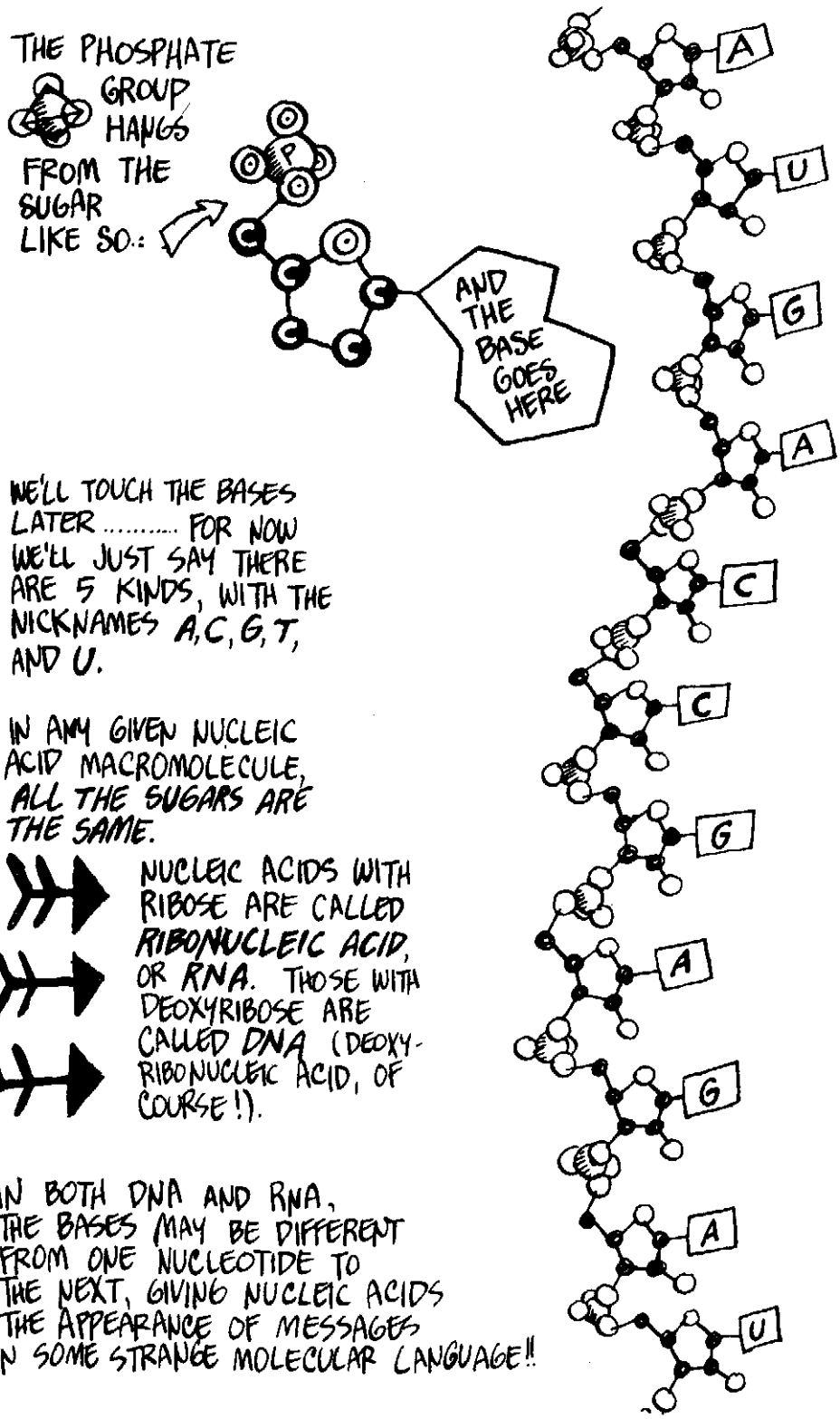
THESE ARE HOOKED TOGETHER TO MAKE A *LONNNNNNG* SUGAR-PHOSPHATE "BACKBONE" WITH A SEQUENCE OF BASES STICKING OFF:



THIS MAY GO ON FOR *MILLIONS* OF NUCLEOTIDES!

THE SUGAR MAY BE ONE OF TWO KINDS, WHICH WE ILLUSTRATE HERE WITHOUT ALL THEIR PESKY HYDROGEN ATOMS. (THEY JUST CLUTTER UP THE PICTURE!)





WE'LL TOUCH THE BASES LATER..... FOR NOW WE'LL JUST SAY THERE ARE 5 KINDS, WITH THE NICKNAMES *A, C, G, T,* AND *U.*

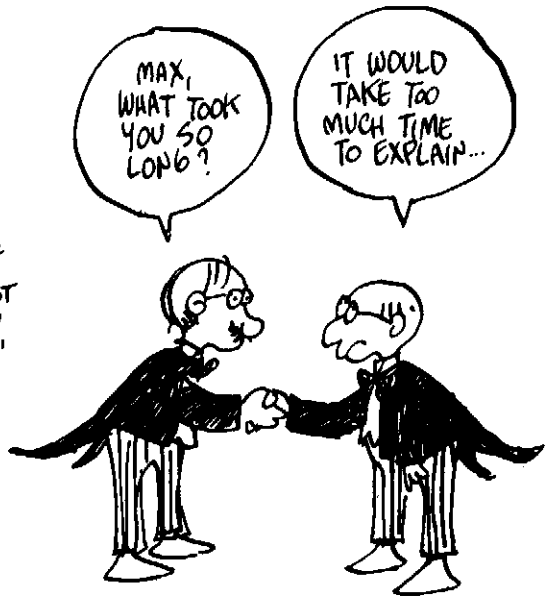
IN ANY GIVEN NUCLEIC ACID MACROMOLECULE, *ALL THE SUGARS ARE THE SAME.*

NUCLEIC ACIDS WITH RIBOSE ARE CALLED *RIBONUCLEIC ACID*, OR *RNA*. THOSE WITH DEOXYRIBOSE ARE CALLED *DNA* (DEOXY-RIBONUCLEIC ACID, OF COURSE!).

IN BOTH DNA AND RNA, THE BASES MAY BE DIFFERENT FROM ONE NUCLEOTIDE TO THE NEXT, GIVING NUCLEIC ACIDS THE APPEARANCE OF MESSAGES IN SOME STRANGE MOLECULAR LANGUAGE!!

PROTEINS

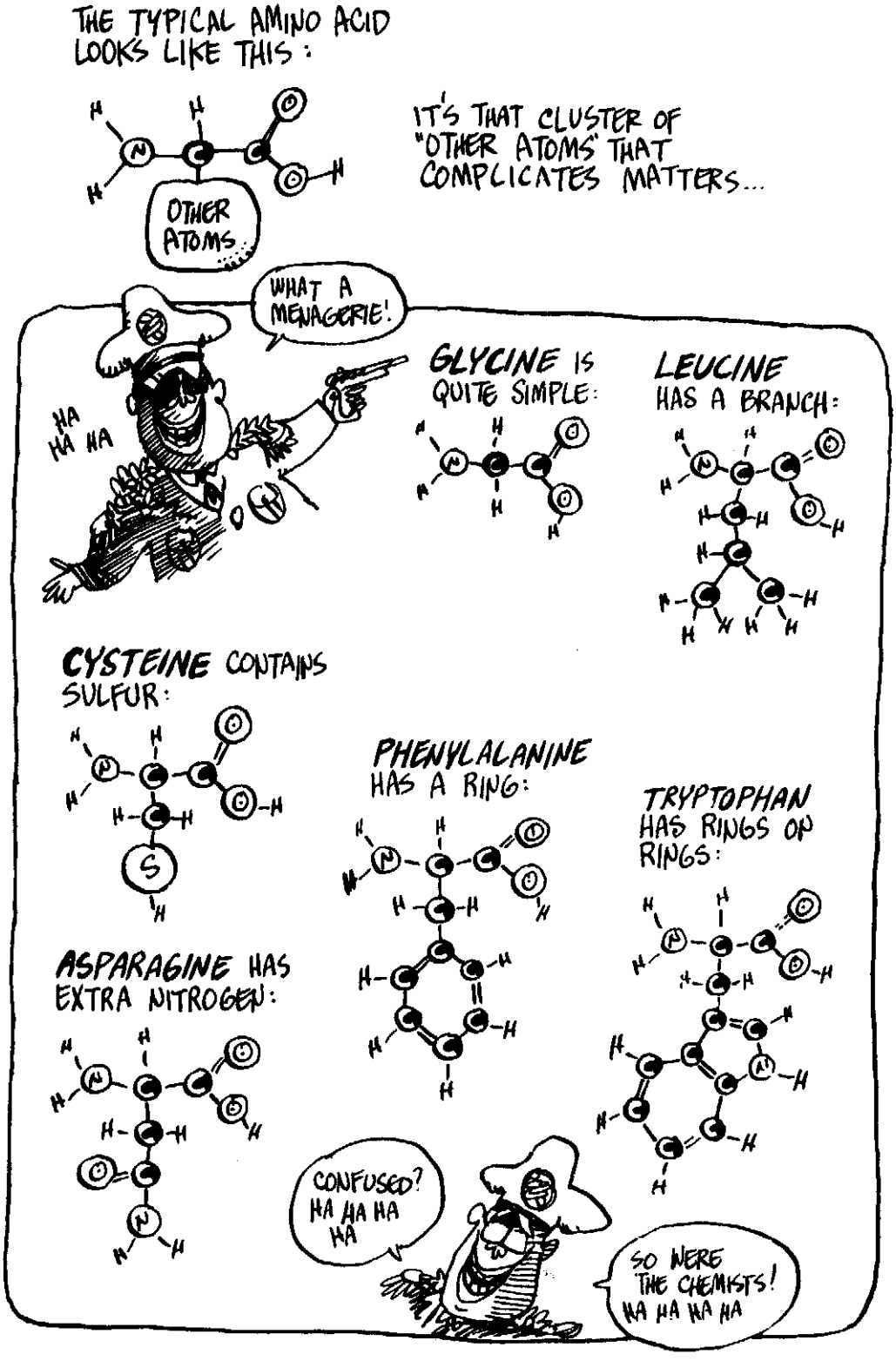
ARE THE MOST COMPLICATED MACROMOLECULES OF ALL. THE BIOLOGIST *MAX PERUTZ* SPENT 25 YEARS — MOST OF HIS CAREER — ANALYZING JUST *ONE* OF THEM: *HEMOGLOBIN*, THE PROTEIN THAT CARRIES OXYGEN THROUGH THE BLOODSTREAM. FOR THIS, PERUTZ RECEIVED THE NOBEL PRIZE IN 1962...



YET IN A CERTAIN SENSE, PROTEINS ARE SIMPLE, TOO: LIKE OTHER MACROMOLECULES, THEY ARE LONG CHAINS OF SMALLER SUBUNITS.

ACTUALLY, HEMOGLOBIN IS TWO PAIR OF SUCH CHAINS, WRAPPED UP IN A SYMMETRICAL TANGLE.

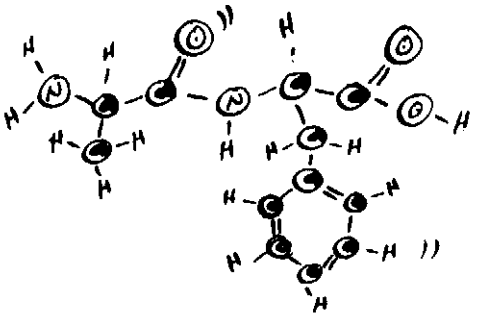
THE SUBUNITS OF PROTEIN MOLECULES ARE ***AMINO ACIDS***, WHICH ARE NOT NAMED AFTER **IDI AMIN**, THE FORMER DICTATOR OF UGANDA.


THE TYPICAL AMINO ACID LOOKS LIKE THIS:
OTHER ATOMS
IT'S THAT CLUSTER OF "OTHER ATOMS" THAT COMPLICATES MATTERS...
WHAT A MENAGERIE!
HA HA HA
GLYCINE IS QUITE SIMPLE:
LEUCINE HAS A BRANCH:
CYSTEINE CONTAINS SULFUR:
PHENYLALANINE HAS A RING:
TRYPTOPHAN HAS RINGS ON RINGS:
ASPARAGINE HAS EXTRA NITROGEN:
CONFUSED? HA HA HA HA
SO WERE THE CHEMISTS! HA HA HA HA

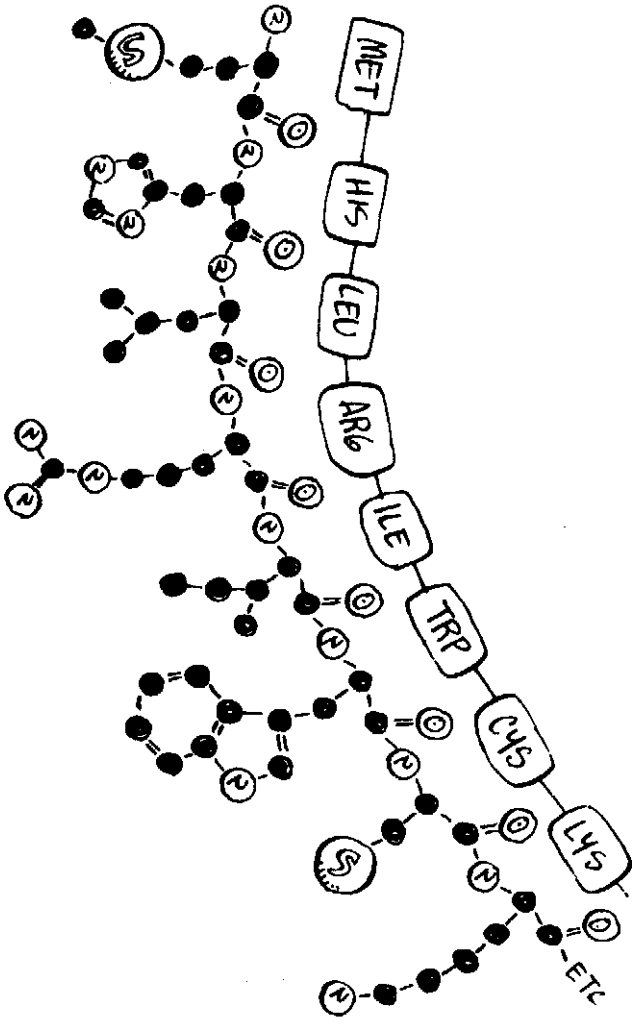
IN ALL, SOME 20 "STANDARD" AMINO ACIDS GO INTO PROTEINS:

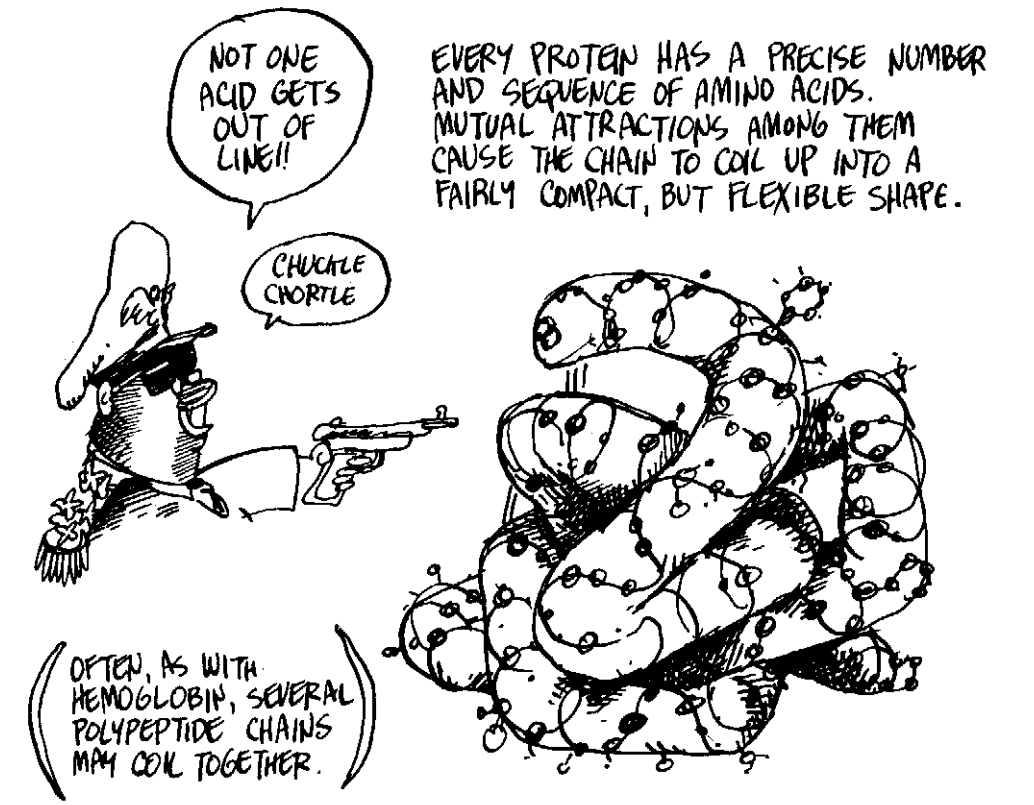
AMINO ACID	ABBREVIATED AS:
GLYCINE	GLY
ALANINE	ALA
VALINE	VAL
LEUCINE	LEU
ISOLEUCINE	ILE
SERINE	SER
THREONINE	THR
ASPARTIC ACID	ASP
GLUTAMIC ACID	GLU
LYSINE	LYS
ARGININE	ARG
ASPARAGINE	ASN
GLUTAMINE	GLN
CYSTEINE	CYS
METHIONINE	MET
PHENYLALANINE	PHE
TYROSINE	TYR
TRYPTOPHAN	TRP
HISTIDINE	HIS
PROLINE	PRO

(HYDROGENS OMITTED!)



ANY TWO OF THEM CAN JOIN TOGETHER TO FORM A ***PEPTIDE***... VERY PEPPY... ADD SOME MORE AND YOU GET A ***POLYPEPTIDE***, OR ***PROTEIN CHAIN***...




NOT ONE ACID GETS OUT OF LINE!!
CHUCKLE CHORTLE
EVERY PROTEIN HAS A PRECISE NUMBER AND SEQUENCE OF AMINO ACIDS. MUTUAL ATTRACTIONS AMONG THEM CAUSE THE CHAIN TO COIL UP INTO A FAIRLY COMPACT, BUT FLEXIBLE SHAPE.
OFTEN, AS WITH HEMOGLOBIN, SEVERAL POLYPEPTIDE CHAINS MAY COIL TOGETHER.


WHAT DO PROTEINS DO FOR A CELL? YOU PROBABLY THINK OF THEM AS SOMETHING THAT ENRICHES SHAMPOO... OR MAYBE YOU KNOW ABOUT THE PROTEIN IN FINGERNAILS, FEATHERS, AND HAIR... BUT ACTUALLY, MOST PROTEINS ARE SOMETHING ELSE AGAIN...
NEW!
PROTEIN-ENRICHED GLORP
AVOID HAIRY STOMACH — DO NOT DRINK!
MOST PROTEINS ARE ENZYMES!!
HA HA HA OUCH

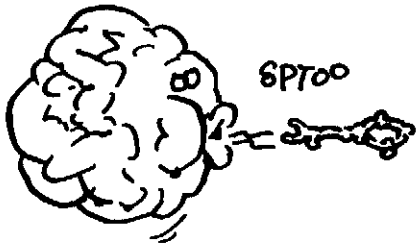
ENZYMES ARE PROTEINS WHICH TAKE APART OR PUT TOGETHER OTHER MOLECULES. EACH ENZYME IS RESPONSIBLE FOR JUST ONE SPECIFIC REACTION.

A TYPICAL ENZYME LIES IN WAIT FOR THE RIGHT MOLECULES TO COME AROUND.

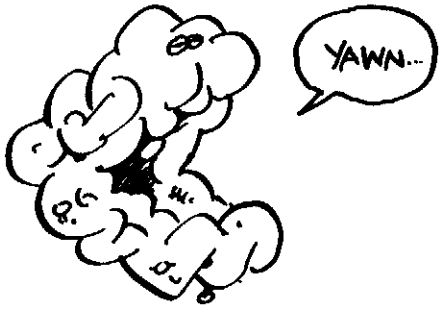
THE ENZYME BINDS TO THE SMALL MOLECULES...

...AND COMBINES THEM...

...INTO A NEW MOLECULE, WHICH IS RELEASED.



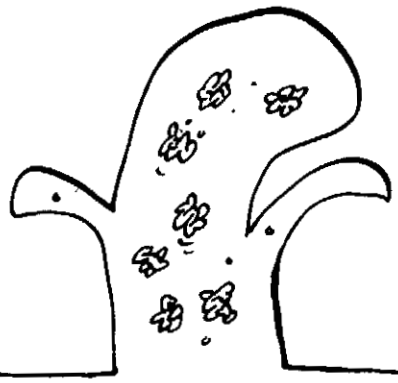
THE ENZYME ITSELF REMAINS UNCHANGED IN THE PROCESS.



IN A SIMILAR WAY, ***DIGESTIVE*** ENZYMES BREAK DOWN LARGE MOLECULES. SEVERAL KINDS, FOR EXAMPLE, CHOP SUGARS OFF POLYSACCHARIDES !!

THESE PROTEINS ARE SO IMPORTANT BECAUSE VIRTUALLY EVERY ONE OF LIFE'S CHEMICAL REACTIONS IS DRIVEN BY SOME ENZYME.

WHEN CHEMICALS COME UP THROUGH THE ROOTS OF THE BANANA TREE, THE PLANT'S ENZYMES CONVERT THEM INTO THE CONSTITUENTS OF A BANANA...

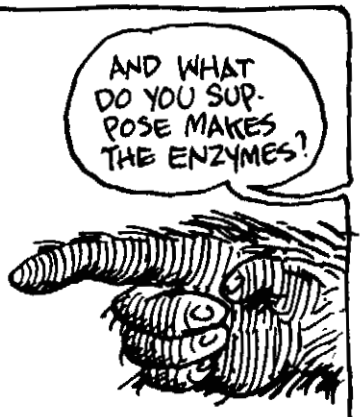


THEN, WHEN THE GORILLA EATS THE BANANA, THE APE'S ENZYMES DIGEST THE FRUIT AND TURN IT INTO AN APE...

...AND LIKEWISE FOR *E. COLI*, WHICH HAS ITS OWN ENZYMES..!

IN OTHER WORDS:

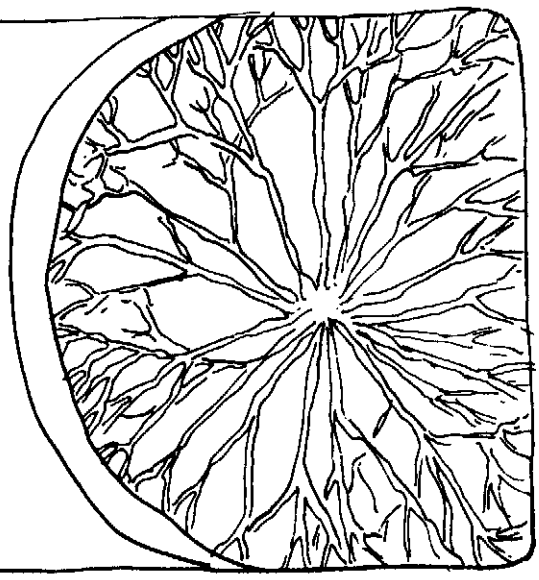
An organism is made by its enzymes.

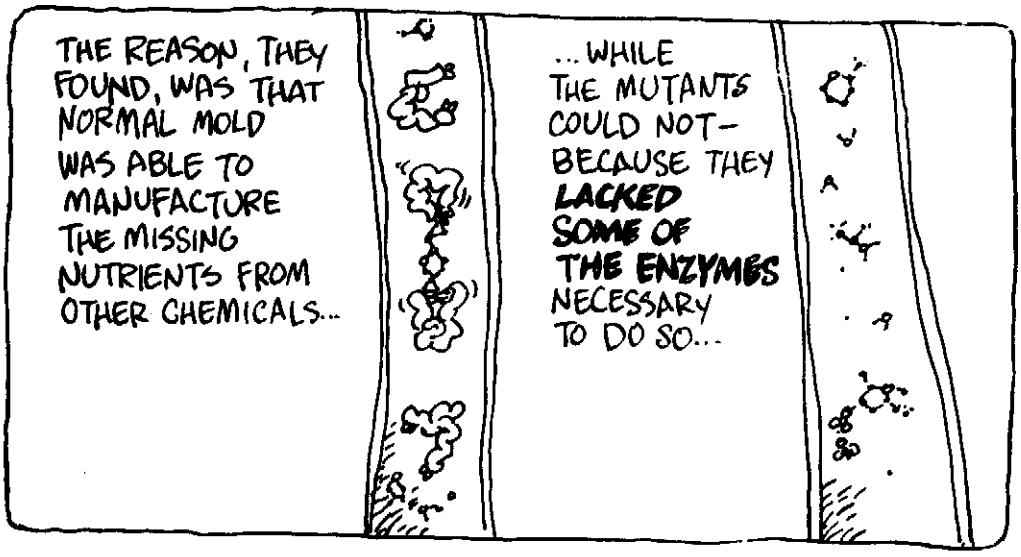


ONE GENE, ONE ENZYME

THE RELATIONSHIP BETWEEN GENES AND ENZYMES FIRST BECAME CLEAR IN THE 1940'S, THANKS TO EXPERIMENTS PERFORMED BY BIOLOGISTS **GEORGE BEADLE** AND **EDWARD TATUM**, WORKING WITH MUTANT STRAINS OF THE COMMON BREAD MOLD ***NEUROSPORA*** GROWN IN BATHS OF CHEMICAL NUTRIENTS.

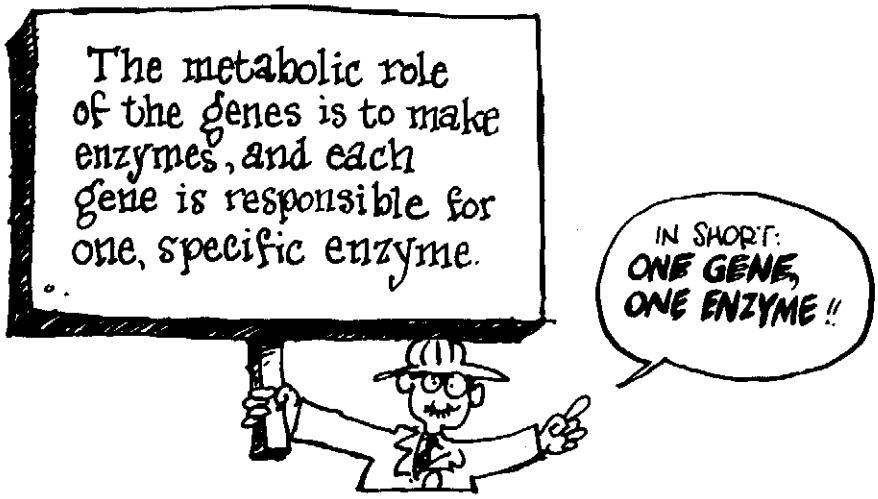
EACH MUTANT WAS FOUND TO REQUIRE **MORE CHEMICAL NUTRIENTS** IN ITS DIET THAN WERE NEEDED BY NORMAL MOLD FOR EXAMPLE, ONE MUTANT HAD TO BE FED AN EXTRA AMINO ACID, WHILE ANOTHER REQUIRED A CERTAIN VITAMIN.





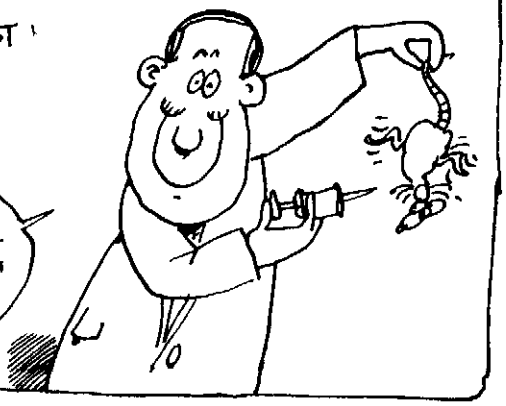
BY EXHAUSTIVE CROSS-BREEDING AND BIOCHEMICAL ANALYSIS, THE SCIENTISTS DISCOVERED THIS: **THE MUTATION OF A SINGLE GENE** LED TO THE **LACK OF A SINGLE ENZYME**...

* *

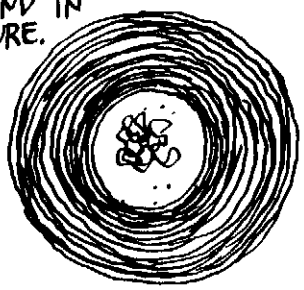


SO THAT'S WHAT GENES **DO**—MAKE ENZYMES—BUT STILL NOBODY UNDERSTOOD EXACTLY WHAT THEY **WERE**... THOUGH A FIRST STEP IN THAT DIRECTION HAD BEEN MADE IN THE 1920's BY **FRED GRIFFITH**...

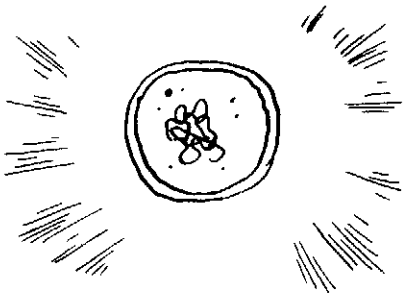
BY ACCIDENT, REALLY!



GRIFFITH WORKED WITH TWO STRAINS OF THE PNEUMONIA BACTERIUM ***PNEUMOCOCCUS***. ONE WAS THE VIRULENT "WILD TYPE" FOUND IN NATURE.



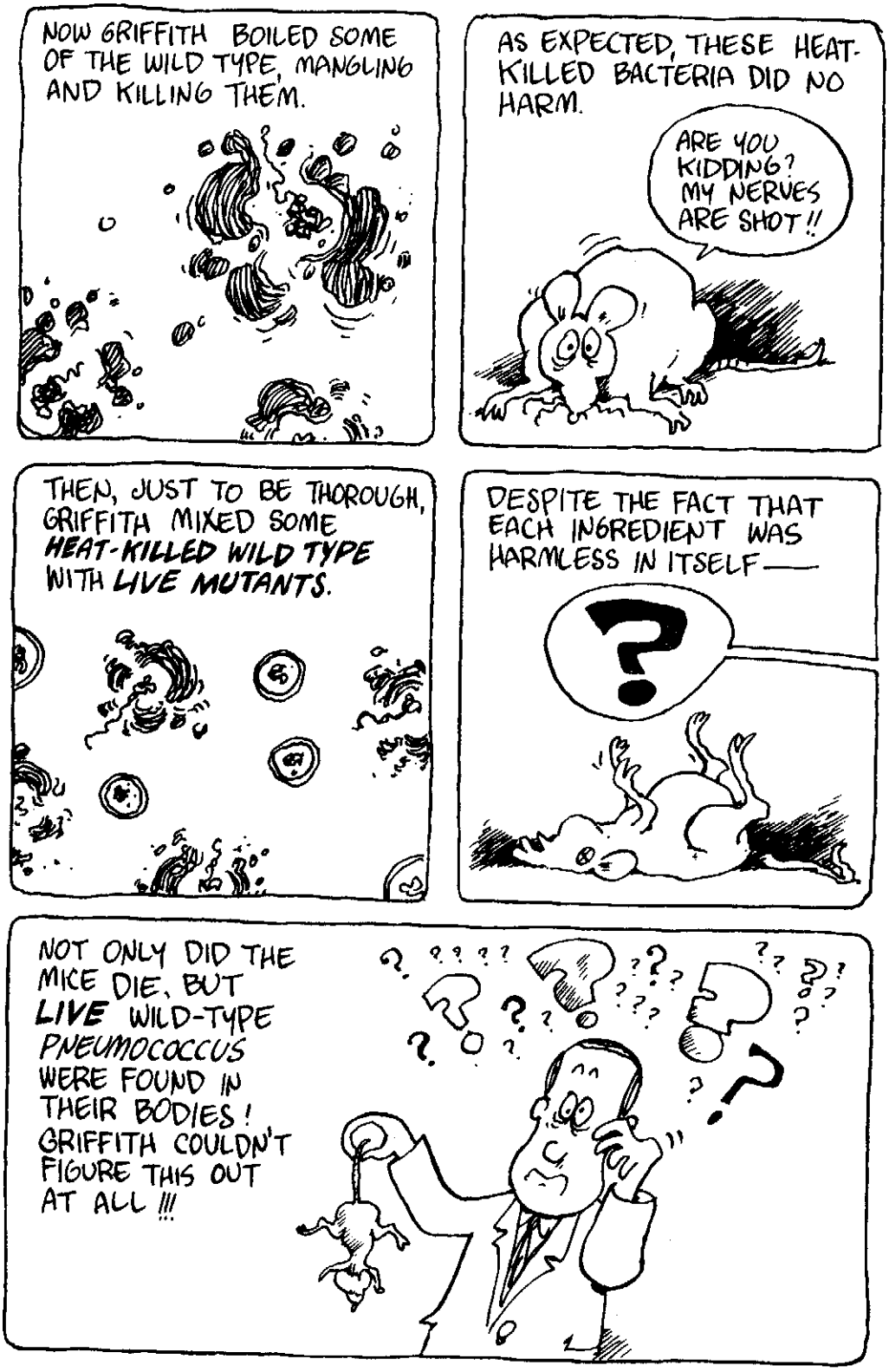
THE OTHER LACKED A CERTAIN ENZYME USED IN MAKING THE THICK OUTER CAPSULE SEEN IN THE WILD TYPE.



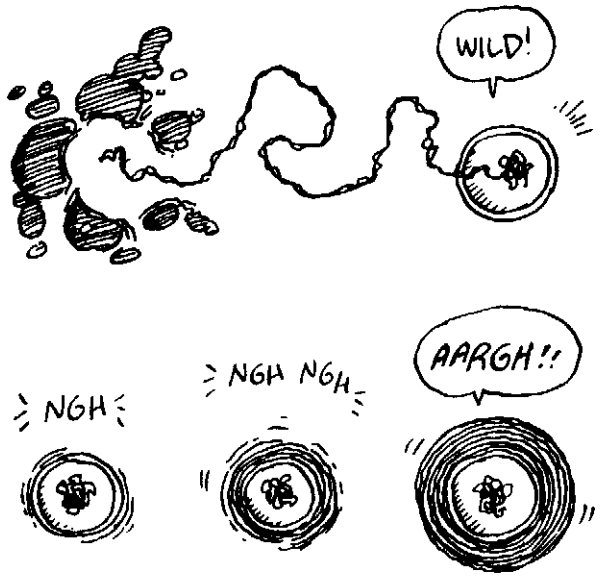
WHEN INJECTED INTO MICE, THE WILD TYPE INVARIABLY CAUSED DISEASE...

THE MUTANT ***PNEUMOCOCCUS***, ON THE OTHER HAND, HAD NO EFFECT.

WHEW!


NOW GRIFFITH BOILED SOME OF THE WILD TYPE, MANGLING AND KILLING THEM.
AS EXPECTED, THESE HEAT-KILLED BACTERIA DID NO HARM.
ARE YOU KIDDING? MY NERVES ARE SHOT!!
THEN, JUST TO BE THOROUGH, GRIFFITH MIXED SOME HEAT-KILLED WILD TYPE WITH LIVE MUTANTS.
DESPITE THE FACT THAT EACH INGREDIENT WAS HARMLESS IN ITSELF——
?
NOT ONLY DID THE MICE DIE, BUT LIVE WILD-TYPE PNEUMOCOCCUS WERE FOUND IN THEIR BODIES! GRIFFITH COULDN'T FIGURE THIS OUT AT ALL !!!

EVENTUALLY, IT WAS UNDERSTOOD THIS WAY:



THE **GENES** OF THE WILD TYPE HAD SURVIVED THE BOILING AND INFILTRATED THE LIVE MUTANTS, ***TRANSFORMING*** THE HARMLESS BACTERIA INTO THE DEADLY WILD TYPE!!

IN THE 1940'S, ***OSWALD AVERY*** SET OUT TO IDENTIFY THIS "TRANSFORMING FACTOR."

BOILING BACTERIA BY THE VATFUL, AVERY PRECIPITATED, EXTRACTED, CENTRIFUGED, ANALYZED, OVER AND OVER...

UNTIL HE HAD A THIMBLEFUL OF PURE GENETIC MATERIAL...

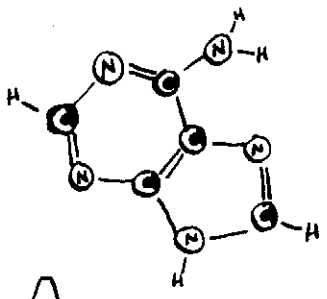

IT'S DNA.
WHEN AVERY ANNOUNCED HIS RESULTS IN 1940, FEW SCIENTISTS BELIEVED HIM!!

THE SPIRAL STAIRCASE

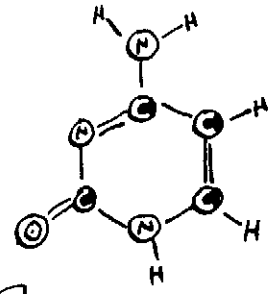
BEFORE AVERY, SCIENTISTS HAD PAID LITTLE ATTENTION TO DNA.

THEY KNEW IT CONTAINED THE SUGAR ***DEOXYRIBOSE***, PLENTY OF ***PHOSPHATE***, AND FOUR ***BASES***.

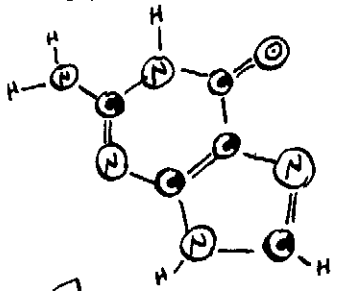
THE FOUR BASES ARE KNOWN AS **A**, **C**, **G**, AND **T**, WHICH ARE SHORT FOR:



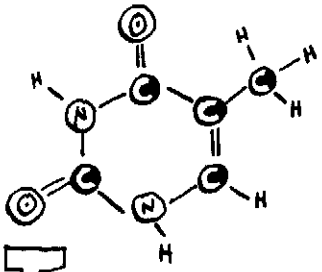
ADENINE



CYTOSINE



GUANINE



THYMINE

THESE WERE ASSUMED TO BE PRESENT IN EQUAL PROPORTIONS.

AFTER AVERY, HOWEVER, RESEARCHERS BEGAN TO LOOK MORE CLOSELY...

ERWIN CHARGAFF FOUND:

① THE COMPOSITION OF DNA VARIED FROM ONE SPECIES TO ANOTHER, IN PARTICULAR IN THE RELATIVE AMOUNTS OF THE BASES A, C, T, G.

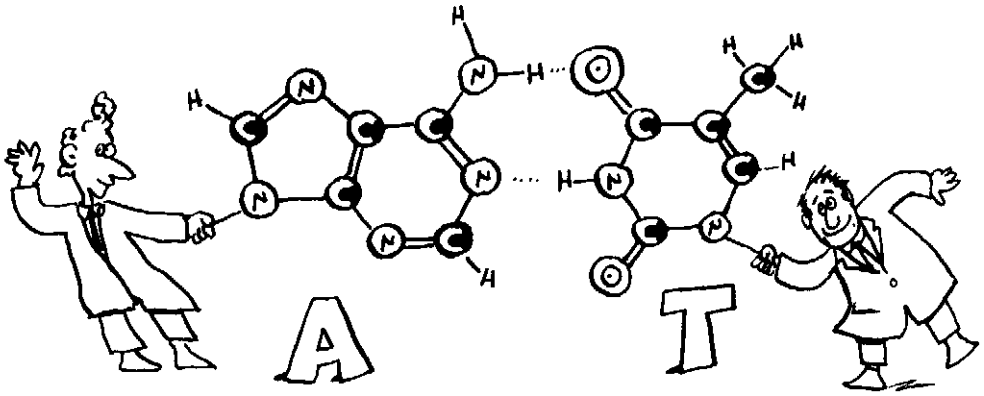
② IN ANY DNA, ***THE NUMBER OF A's WAS THE SAME AS THE NUMBER OF T's***; SIMILARLY, THE NUMBER OF **C's** WAS EQUAL TO THE NUMBER OF **G's**.

WHAT DID THIS MEAN? CHARGAFF COULDN'T SAY...

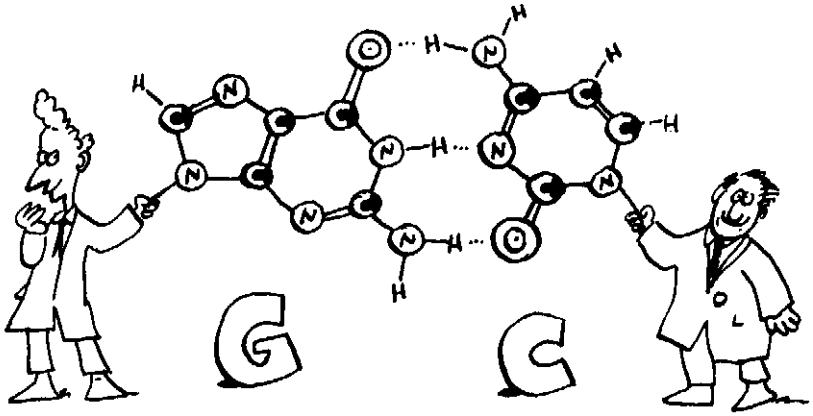
BY STUDYING X-RAY PICTURES OF DNA, ***ROSALIND FRANKLIN*** WAS ABLE TO SHOW THAT THE DNA MOLECULE PROBABLY HAD THE CORKSCREW SHAPE OF A ***HELIX*** WITH TWO OR THREE CHAINS...

BUT WAS IT TWO OR THREE...?

IN 1952 **JAMES WATSON** AND **FRANCIS CRICK** CRACKED THE PUZZLE.

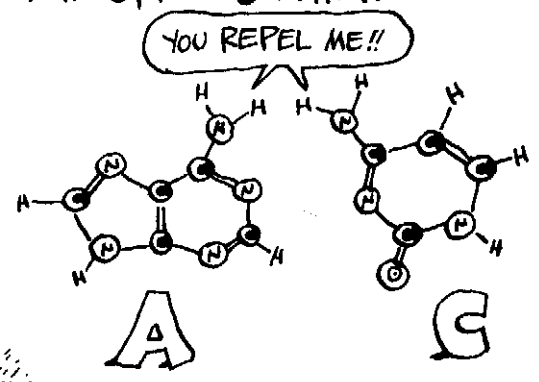


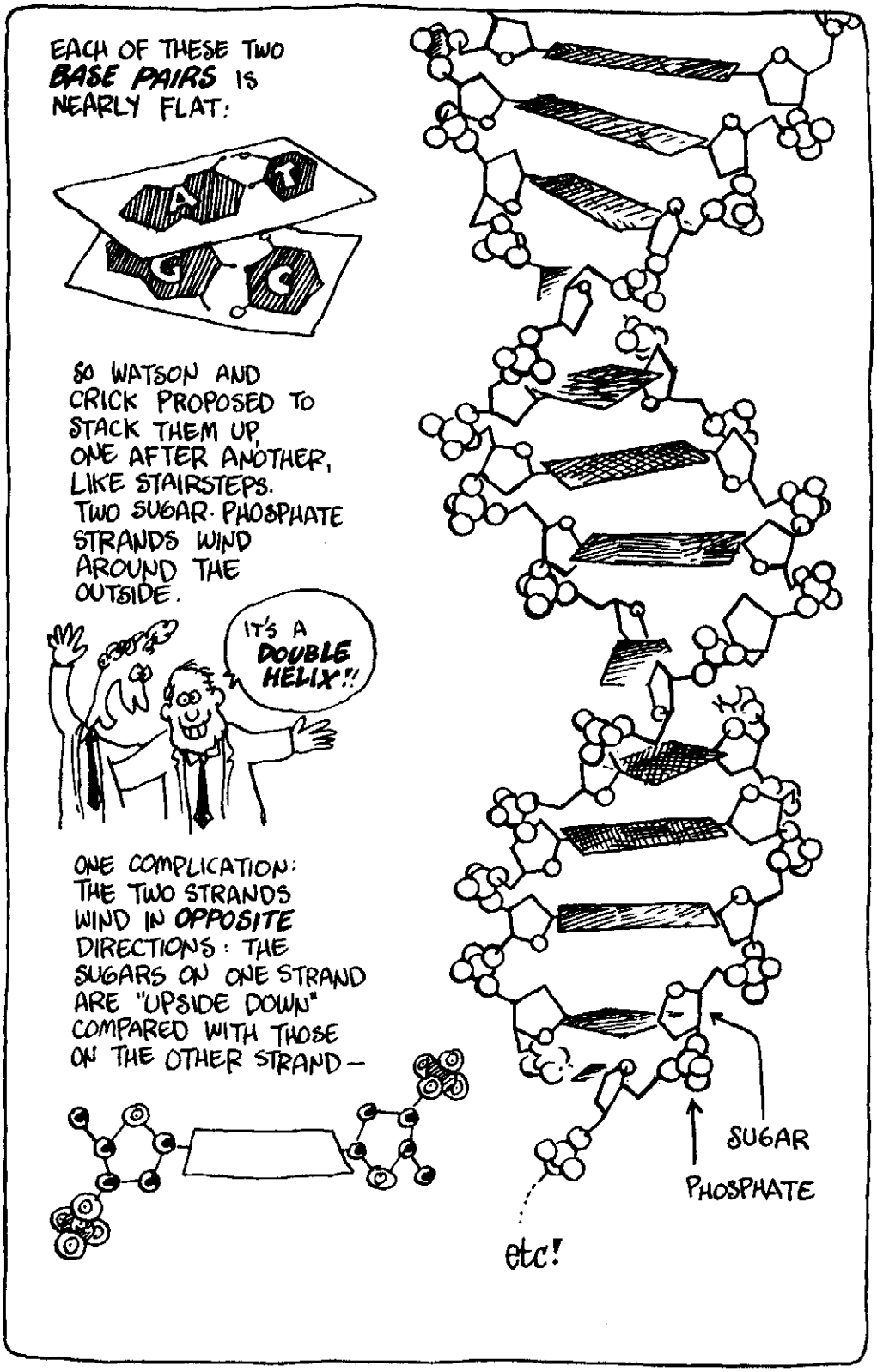
BY PLAYING WITH SCALE-MODEL ATOMS, THEY OBSERVED THAT **ADENINE** FITTED TOGETHER WITH **THYMINE**, WHILE **GUANINE** PAIRED NATURALLY WITH **CYTOSINE**.

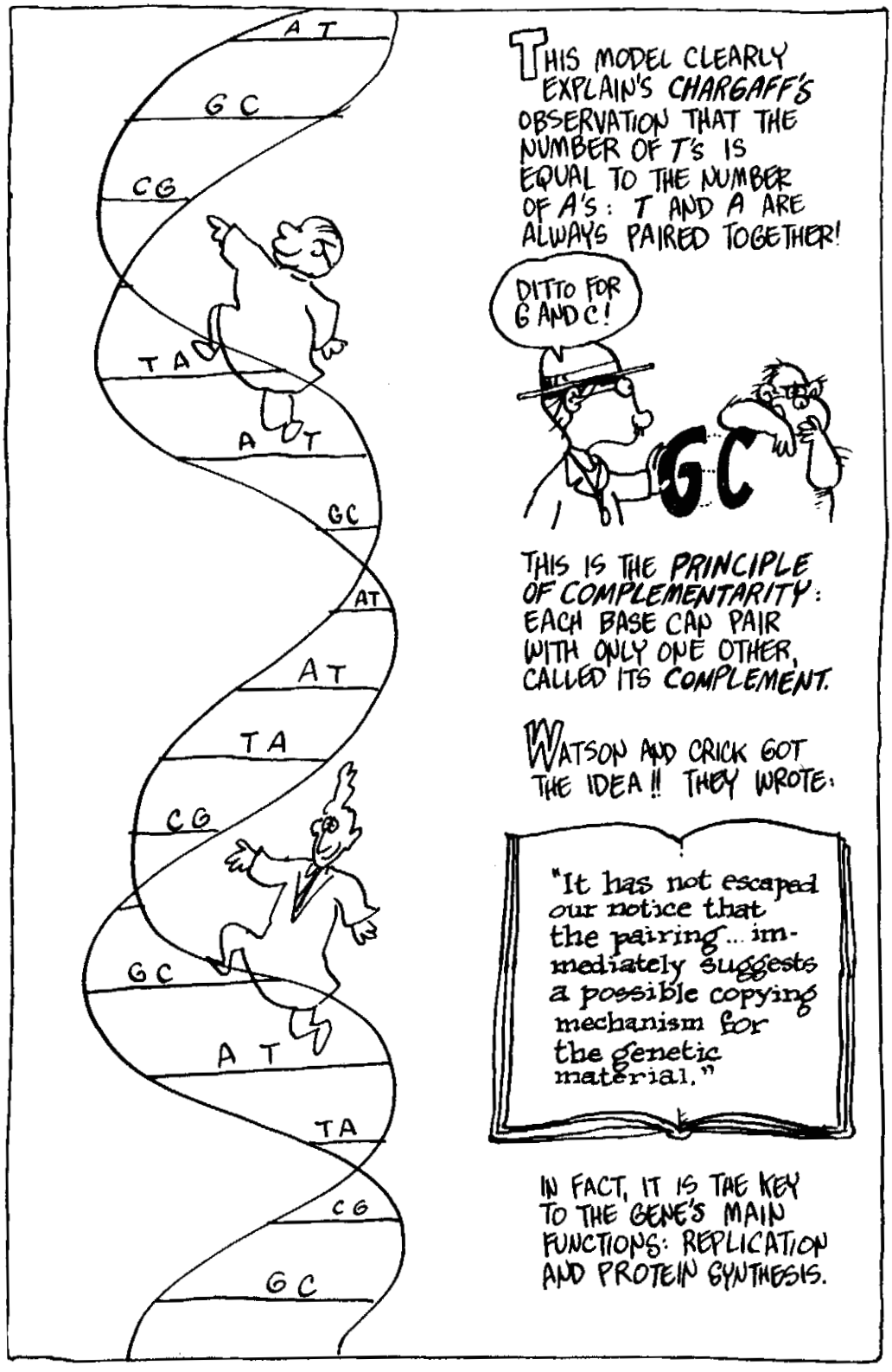


EACH BASE PAIR WOULD BE HELD TOGETHER BY **HYDROGEN BONDING**, A WEAK ATTRACTION THAT MAY OCCUR BETWEEN A HYDROGEN ON ONE MOLECULE AND A NON-HYDROGEN ATOM ON ANOTHER MOLECULE.

IT WAS ALSO CLEAR **A** DID NOT FIT WITH **C**, NOR **G** WITH **T**.



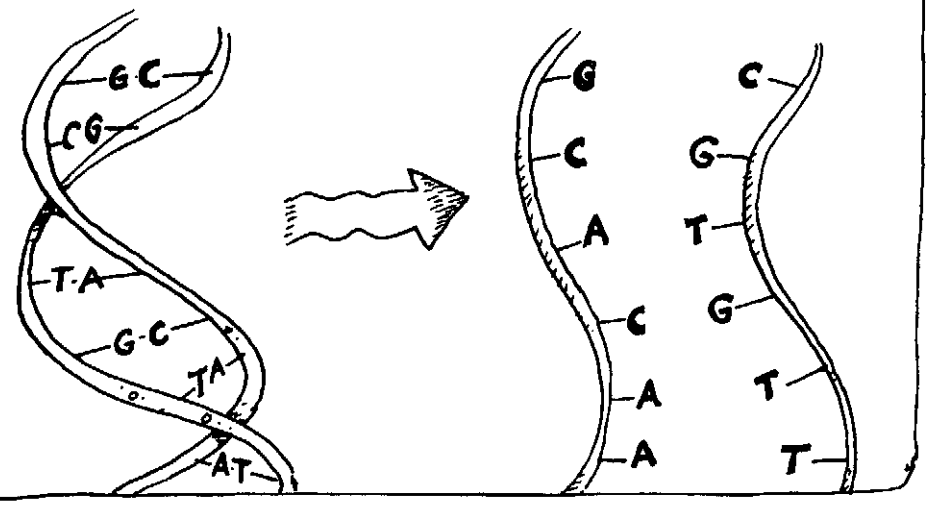

EACH OF THESE TWO BASE PAIRS IS NEARLY FLAT:
A
T
G
C
SO WATSON AND CRICK PROPOSED TO STACK THEM UP, ONE AFTER ANOTHER, LIKE STAIRSTEPS. TWO SUGAR-PHOSPHATE STRANDS WIND AROUND THE OUTSIDE.
IT'S A DOUBLE HELIX!!
ONE COMPLICATION: THE TWO STRANDS WIND IN OPPOSITE DIRECTIONS: THE SUGARS ON ONE STRAND ARE "UPSIDE DOWN" COMPARED WITH THOSE ON THE OTHER STRAND—
SUGAR
PHOSPHATE
etc!


A T
G C
C G
T A
A T
G C
A T
T A
C G
G C
A T
T A
C G
G C
THIS MODEL CLEARLY EXPLAIN'S CHARGAFF'S OBSERVATION THAT THE NUMBER OF T's IS EQUAL TO THE NUMBER OF A's: T AND A ARE ALWAYS PAIRED TOGETHER!
DITTO FOR G AND C!
G C
THIS IS THE PRINCIPLE OF COMPLEMENTARITY: EACH BASE CAN PAIR WITH ONLY ONE OTHER, CALLED ITS COMPLEMENT.
WATSON AND CRICK GOT THE IDEA!! THEY WROTE:
"It has not escaped our notice that the pairing... immediately suggests a possible copying mechanism for the genetic material."
IN FACT, IT IS THE KEY TO THE GENE'S MAIN FUNCTIONS: REPLICATION AND PROTEIN SYNTHESIS.

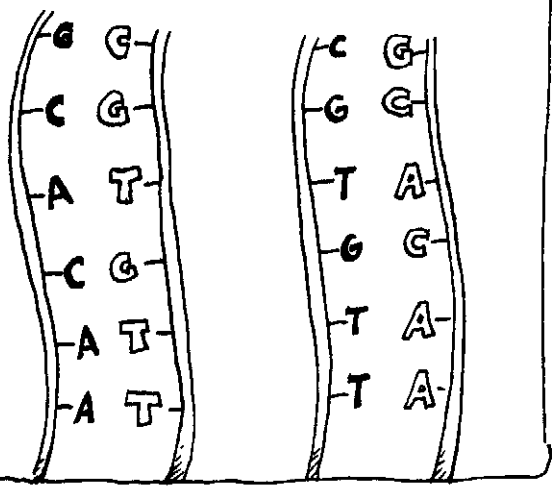
REPLICATION

GENE-COPYING, OR DNA *REPLICATION*, AS WATSON AND CRICK SAW, IS SIMPLE IN PRINCIPLE. *EACH STRAND OF THE DOUBLE HELIX CONTAINS THE INFORMATION NECESSARY TO MAKE ITS COMPLEMENTARY STRAND.*

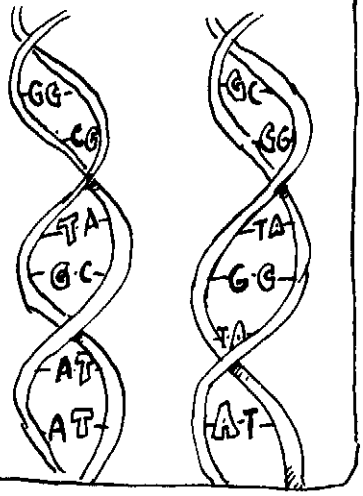
SCHEMATICALLY, IT WORKS LIKE THIS: WHEN THE DNA IS READY TO MULTIPLY, ITS TWO STRANDS PULL APART:

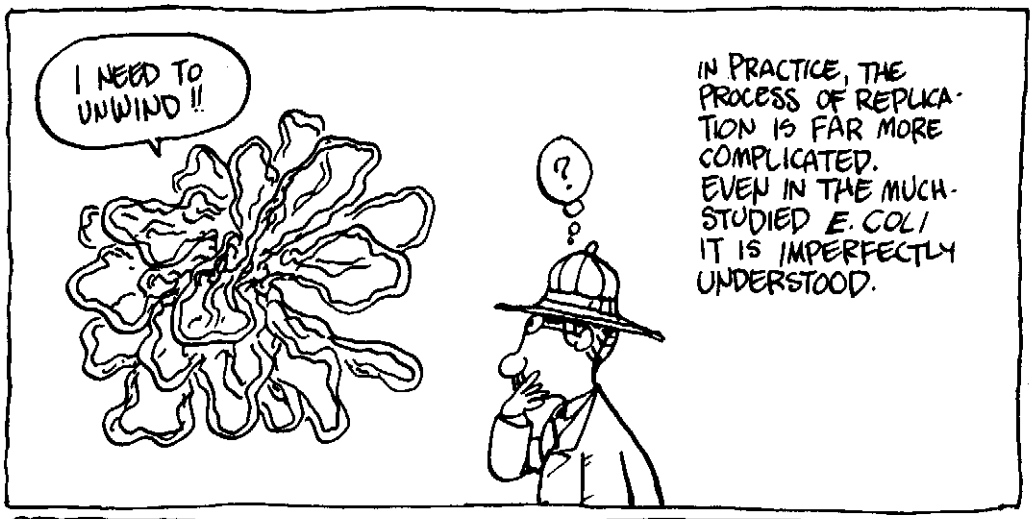


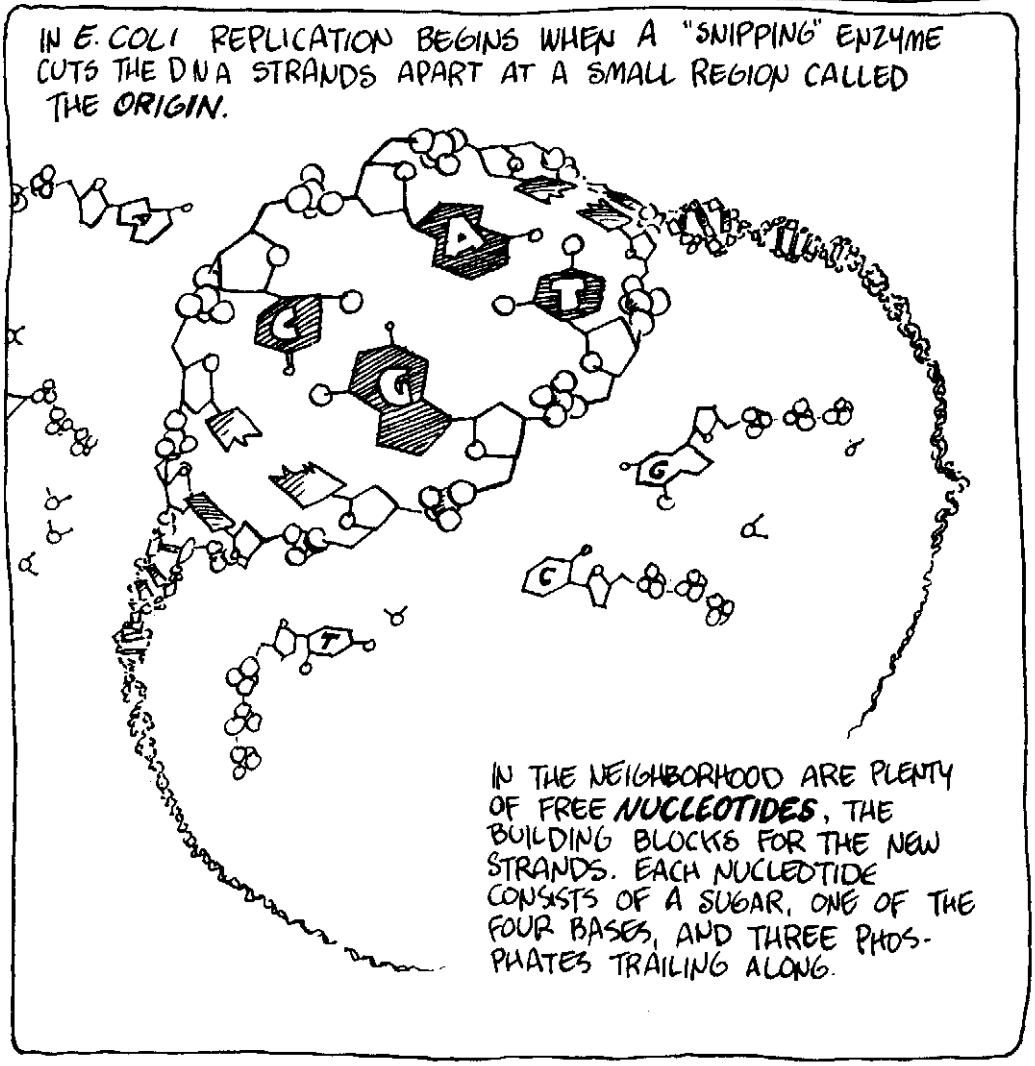
ALONG EACH ONE, A NEW STRAND FORMS IN THE ONLY POSSIBLE WAY:



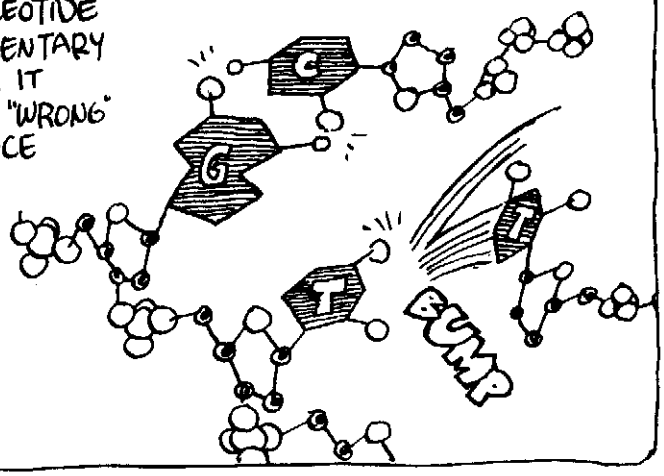
WE WIND UP WITH TWO COPIES OF THE ORIGINAL!



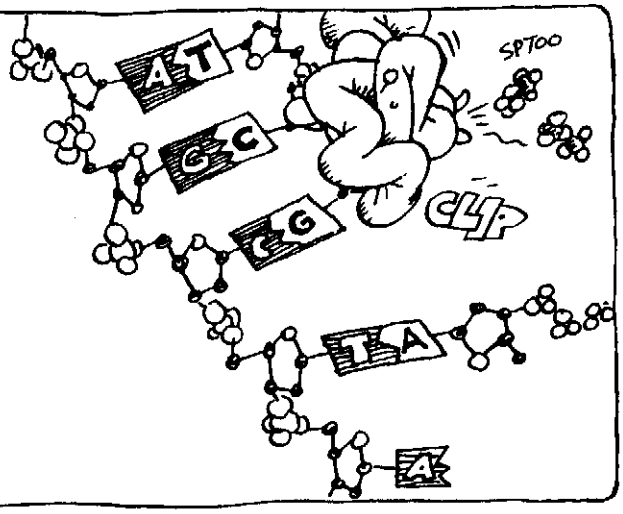

I NEED TO UNWIND!!
?
IN PRACTICE, THE PROCESS OF REPLICATION IS FAR MORE COMPLICATED. EVEN IN THE MUCH-STUDIED E. COLI IT IS IMPERFECTLY UNDERSTOOD.

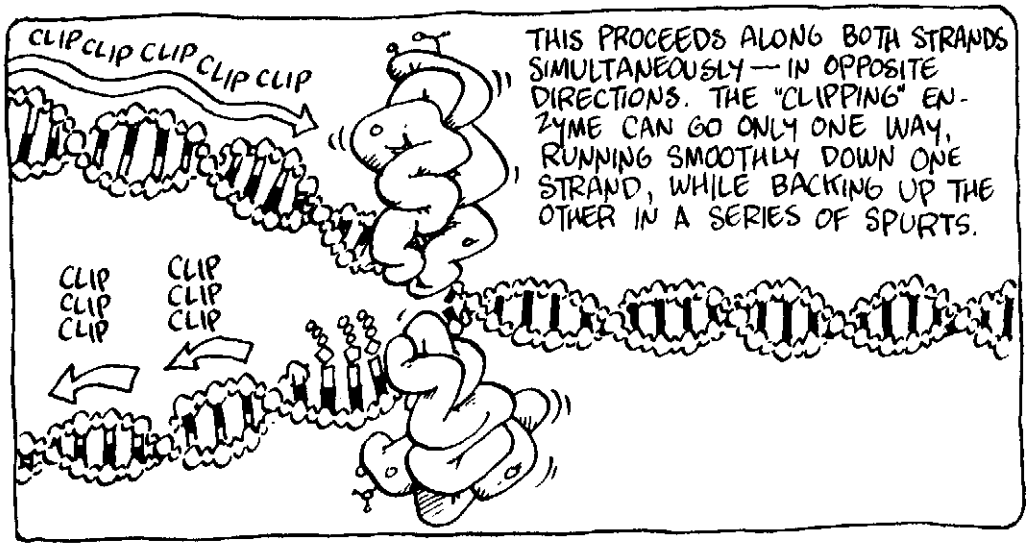

IN E. COLI REPLICATION BEGINS WHEN A "SNIPPING" ENZYME CUTS THE DNA STRANDS APART AT A SMALL REGION CALLED THE ORIGIN.
A
T
G
G
G
G
T
IN THE NEIGHBORHOOD ARE PLENTY OF FREE NUCLEOTIDES, THE BUILDING BLOCKS FOR THE NEW STRANDS. EACH NUCLEOTIDE CONSISTS OF A SUGAR, ONE OF THE FOUR BASES, AND THREE PHOSPHATES TRAILING ALONG.

WHEN A FREE NUCLEOTIDE MEETS ITS COMPLEMENTARY BASE ON THE DNA, IT STICKS, WHILE THE "WRONG" NUCLEOTIDES BOUNCE AWAY.



AS THE "SNIPPING" ENZYME OPENS THE DNA FURTHER, MORE NUCLEOTIDES ARE ADDED, AND A "CLIPPING" ENZYME PUTS THEM TOGETHER, KNOCKING OFF THE EXTRA PHOSPHATES.





THIS PROCEEDS ALONG BOTH STRANDS SIMULTANEOUSLY — IN OPPOSITE DIRECTIONS. THE "CLIPPING" ENZYME CAN GO ONLY ONE WAY, RUNNING SMOOTHLY DOWN ONE STRAND, WHILE BACKING UP THE OTHER IN A SERIES OF SPURTS.

ONCE REPLICATED, THE TWO NEW CHROMOSOMES HAVE TO BE DISENTANGLED SO THAT CELL DIVISION CAN OCCUR.

'BYE, NOW!

THE PICTURE WE HAVE OF DNA REPLICATION IS STILL SKETCHY. FOR EXAMPLE, UNWINDING THE TWO STRANDS OF THE DOUBLE HELIX INVOLVES ROTATIONS AT SPEEDS OVER *8000 RPM.* HOW THIS HAPPENS IS STILL NOT WELL UNDERSTOOD.

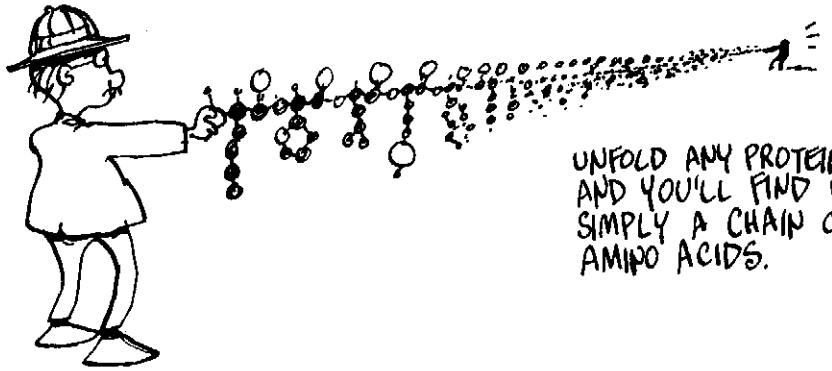
* *

WHATEVER THE DETAILS, THE PRINCIPLE OF COMPLEMENTARITY IS THE KEY TO REPLICATION, AS WELL AS TO THE GENE'S SECOND MAIN FUNCTION:

MAKING ENZYMES!

The MOLECULE is the MESSAGE

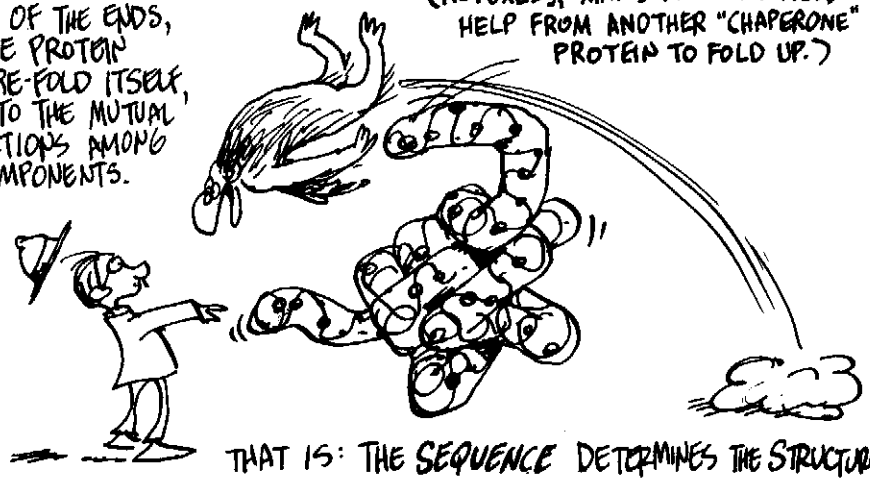
ENZYMES AND OTHER PROTEINS COME IN MANY SHAPES, BUT IN AN IMPORTANT RESPECT, THEY ARE ALL ALIKE.



UNFOLD ANY PROTEIN, AND YOU'LL FIND IT'S SIMPLY A CHAIN OF AMINO ACIDS.

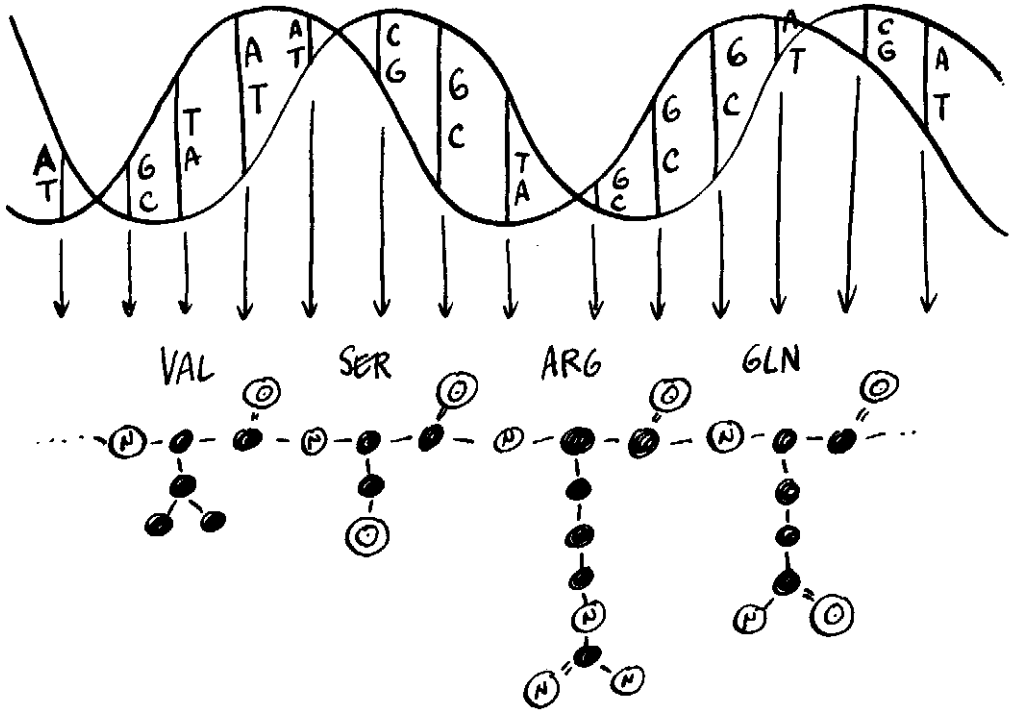
LET GO OF THE ENDS, AND THE PROTEIN WILL RE-FOLD ITSELF, OWING TO THE MUTUAL ATTRACTIONS AMONG THE COMPONENTS.

(ACTUALLY, MANY PROTEINS NEED HELP FROM ANOTHER "CHAPERONE" PROTEIN TO FOLD UP.)

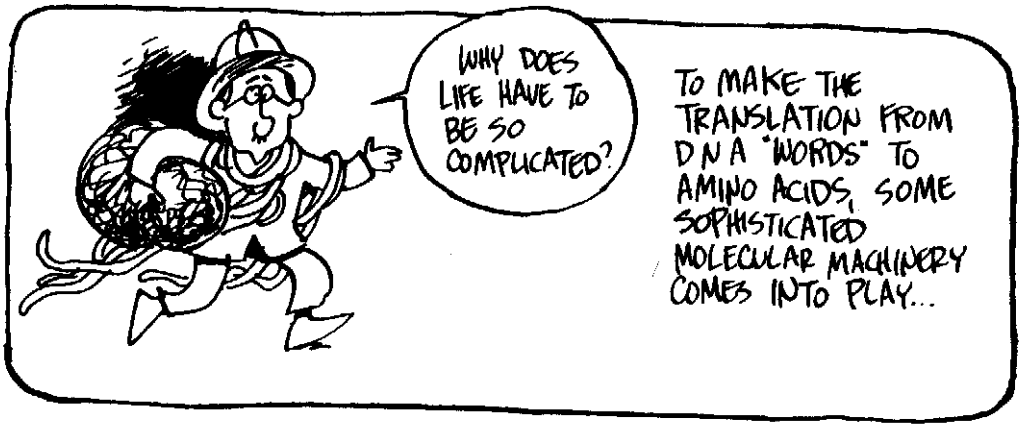


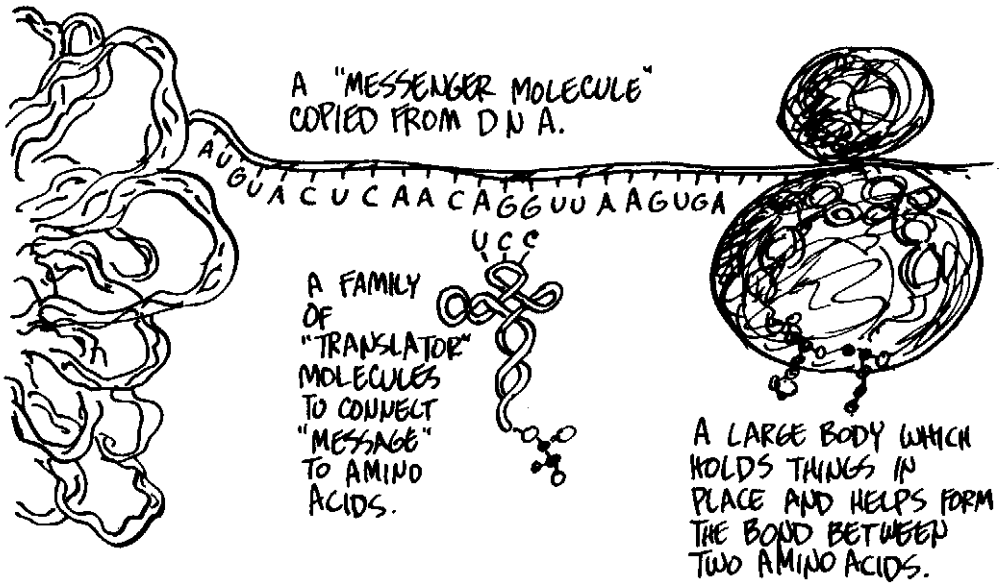
THAT IS: THE *SEQUENCE* DETERMINES THE STRUCTURE.

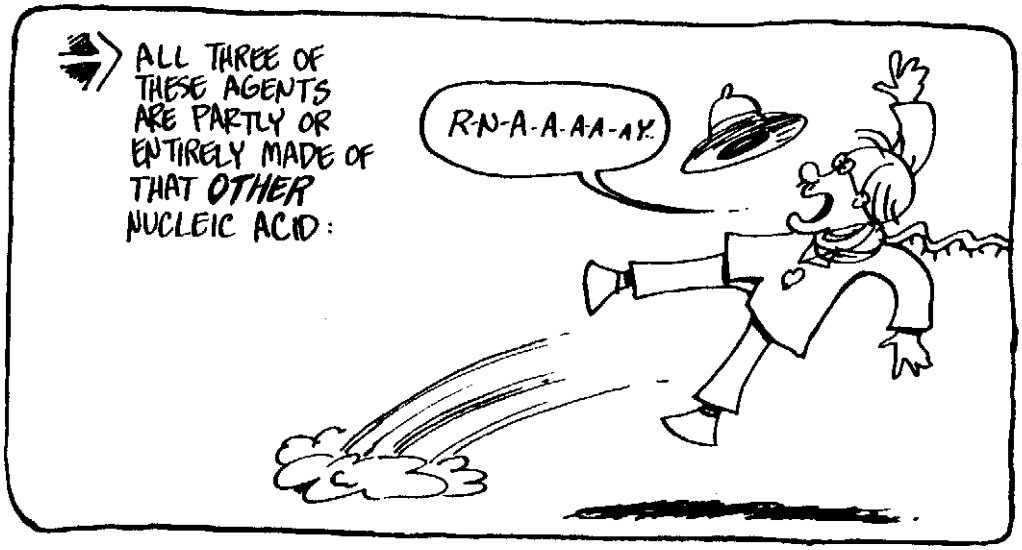
IN VIEW OF THE RELATIONSHIP BETWEEN GENES AND PROTEINS, THIS SUGGESTS THAT THE ***SEQUENCE*** OF DNA MUST SOMEHOW PARALLEL OR REFLECT THE ***SEQUENCE*** OF THE PROTEIN.



The sequence of base pairs may be thought of as a series of "words" specifying the order of amino acids in each protein.


WHY DOES LIFE HAVE TO BE SO COMPLICATED?
TO MAKE THE TRANSLATION FROM DNA "WORDS" TO AMINO ACIDS, SOME SOPHISTICATED MOLECULAR MACHINERY COMES INTO PLAY...

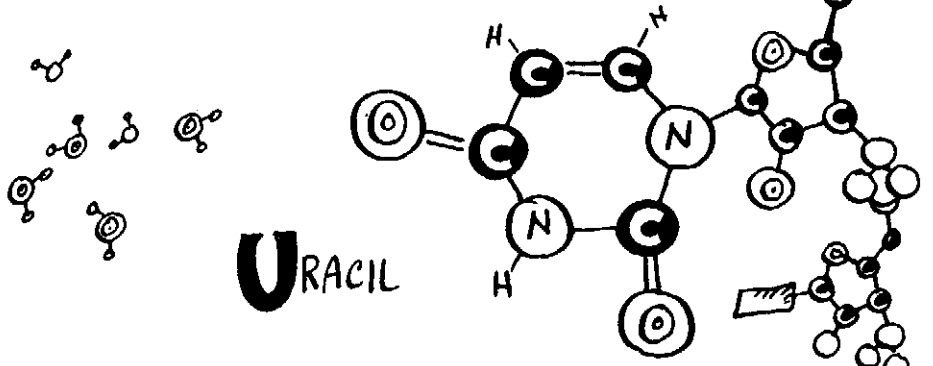

A "MESSENGER MOLECULE" COPIED FROM DNA.
AUGUACUCAACAGGUUAAGUGA
UCC
A FAMILY OF "TRANSLATOR" MOLECULES TO CONVERT "MESSAGE" TO AMINO ACIDS.
A LARGE BODY WHICH HOLDS THINGS IN PLACE AND HELPS FORM THE BOND BETWEEN TWO AMINO ACIDS.


ALL THREE OF THESE AGENTS ARE PARTLY OR ENTIRELY MADE OF THAT OTHER NUCLEIC ACID:
R-N-A-A-A-A-Y.

RNA — ***RIBO***NUCLEIC ACID — RESEMBLES DNA: A SUGAR-PHOSPHATE BACKBONE WITH A SERIES OF BASES ATTACHED.

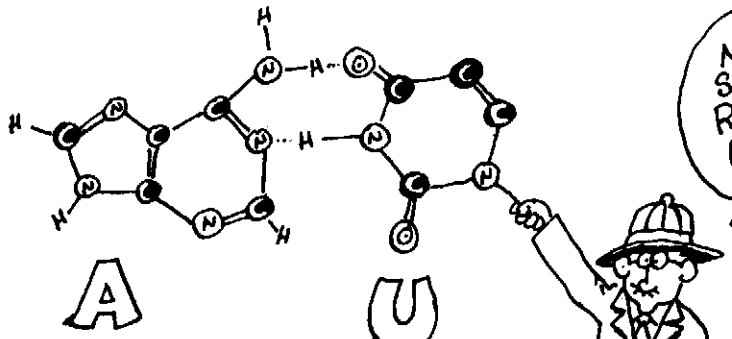
ITS SUGAR IS ***RIBOSE***, RATHER THAN DEOXYRIBOSE; RNA IS USUALLY ***SINGLE-STRANDED***; AND IT IS MUCH SHORTER — 50 TO 1000 NUCLEOTIDES, COMPARED WITH A MILLION OR MORE IN DNA!

AND FINALLY, WHILE THE BASES ***A***, ***C***, AND ***G*** ARE THE SAME AS IN DNA, RNA HAS IN PLACE OF ***T*** ANOTHER BASE CALLED ***URACIL*** ("***U***").



URACIL

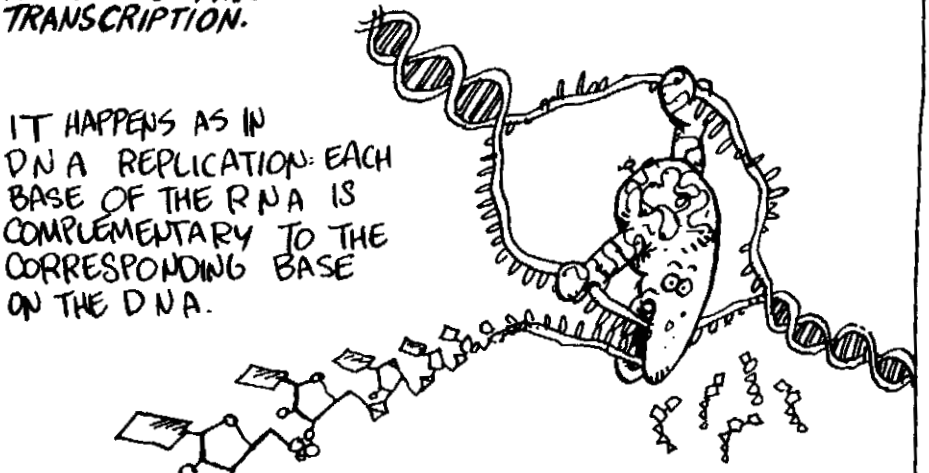
WHICH, LIKE ***THYMINE***, IS COMPLEMENTARY TO ***ADENINE***:



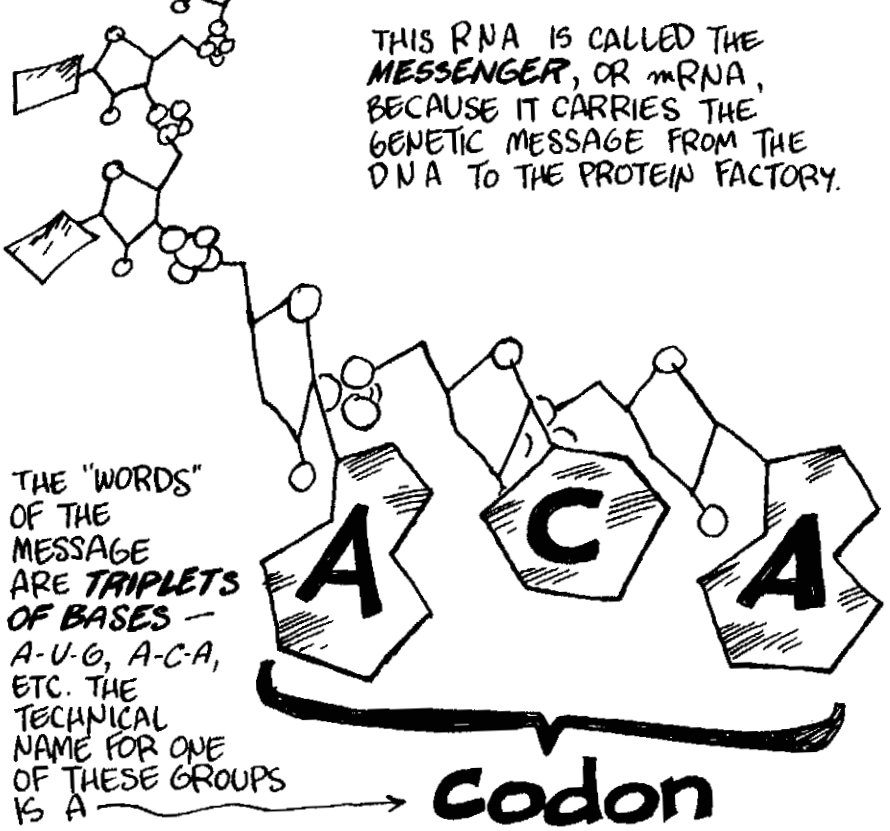
A U

PROTEIN SYNTHESIS BEGINS WHEN A REGION OF DNA IS TEASED APART AND A MOLECULE OF RNA IS BUILT ALONG ONE STRAND BY AN ENZYME CALLED ***RNA POLYMERASE.*** THIS PROCESS IS CALLED ***TRANSCRIPTION.***

IT HAPPENS AS IN DNA REPLICATION: EACH BASE OF THE RNA IS COMPLEMENTARY TO THE CORRESPONDING BASE ON THE DNA.



THIS RNA IS CALLED THE ***MESSENGER***, OR mRNA, BECAUSE IT CARRIES THE GENETIC MESSAGE FROM THE DNA TO THE PROTEIN FACTORY.

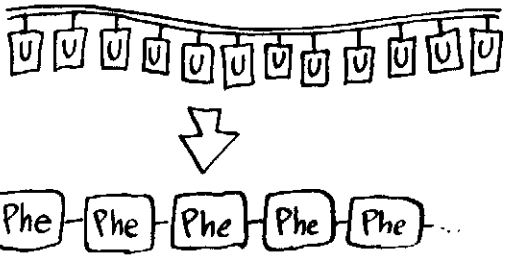


THE "WORDS" OF THE MESSAGE ARE ***TRIPLETS OF BASES*** — A-U-G, A-C-A, ETC. THE TECHNICAL NAME FOR ONE OF THESE GROUPS IS A

EACH 3-BASE CODON STANDS FOR A SINGLE AMINO ACID, AND THE WHOLE mRNA STRAND ENCODES A PROTEIN (OR SEVERAL PROTEINS). IT'S JUST LIKE A MESSAGE IN CODE—

THE GENETIC CODE!

CRACKING THIS CODE BEGAN IN 1961, WHEN **MARSHALL NIRENBERG** WAS ABLE TO MAKE A SPECIAL mRNA, WHOSE ONLY BASE WAS **URACIL**, REPEATED OVER AND OVER - "POLY-U."



FROM IT HE OBTAINED A PROTEIN CONSISTING ENTIRELY OF THE AMINO ACID **PHENYLALANINE**.

SO UUU WAS THE CODON FOR PHENYLALANINE...

NEXT THEY DECODED POLY-A, AND POLY-C, AND POLY-UG, POLY-UGU, ETC, ETC, ETC, UNTIL THE CODE WAS FINALLY BROKEN—

UUU → Phe
AAA → Lys
CCC →
UGU →
GUU →
UUG → Leu
GUG → Val

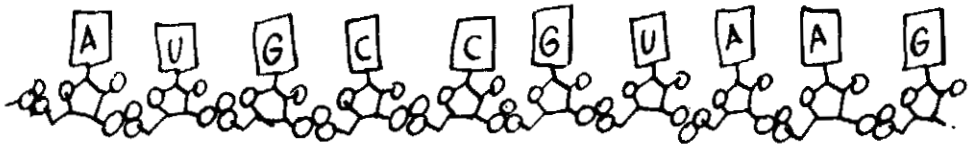
SECOND LETTER

FIRST LETTER	U	C	A	G	THIRD LETTER
U	UUU, UUC } PHE UUA, UUG } LEU	UCU, UCC, UCA, UCG } SER	UAU, UAC } TYR UAA, UAG } STOP	UGU, UGC } CYS UGA STOP UGG TRP	U C A G
C	CUU, CUC, CUA, CUG } LEU	CCU, CCC, CCA, CCG } PRO	CAU, CAC } HIS CAA, CAG } GLN	CGU, CGC, CGA, CGG } ARG	U C A G
A	AUU, AUC, AUA } ILE AUG MET	ACU, ACC, ACA, ACG } THR	AAU, AAC } ASN AAA, AAG } LYS	AGU, AGC } SER AGA, AGG } ARG	U C A G
G	GUU, GUC, GUA, GUG } VAL	GCU, GCC, GCA, GCG } ALA	GAU, GAC } ASP GAA, GAG } GLU	GGU, GGC, GGA, GGG } GLY	U C A G

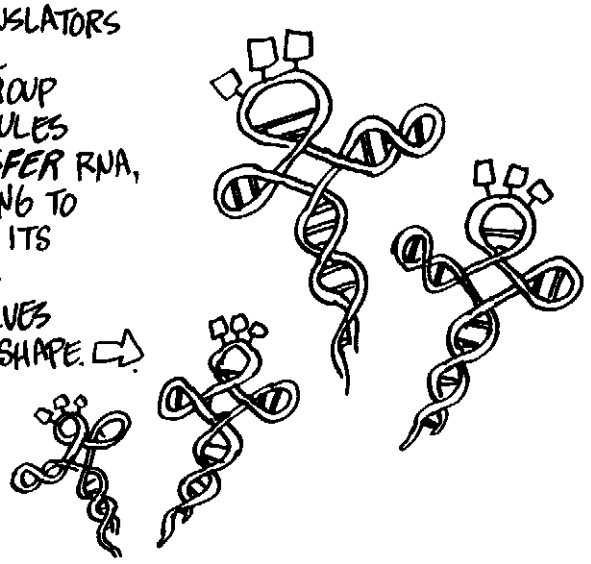
THE CODE IS ***REDUNDANT***: WITH 64 POSSIBLE CODONS, BUT ONLY 20 AMINO ACIDS, THERE MUST BE "SYNONYMS," DIFFERENT CODONS WHICH ENCODE THE SAME AMINO ACID.

THERE ARE "STOP" SIGNALS. THREE CODONS DO NOT ENCODE ANY AMINO ACID AT ALL. THESE SERVE TO TERMINATE MESSAGES.

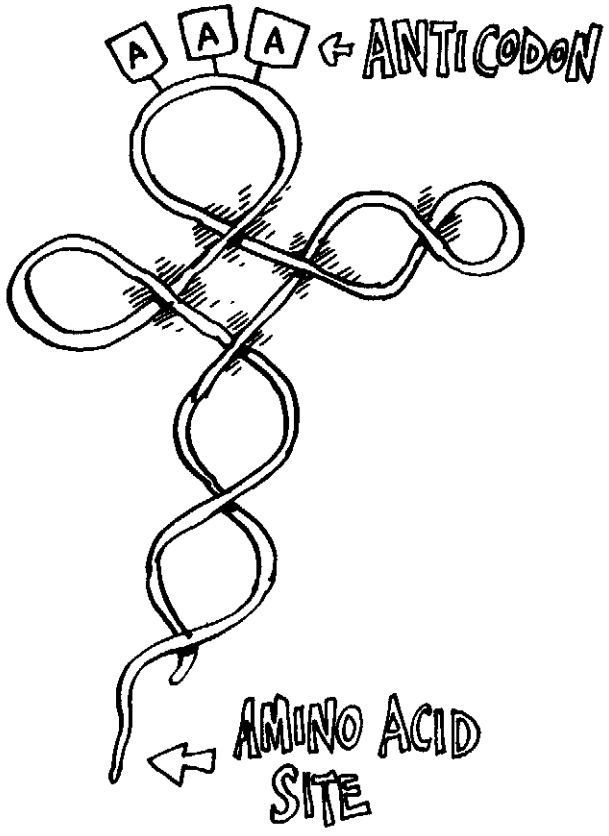
ALSO: THE CODE IS NON-OVERLAPPING. THE "WORDS" FOLLOW EACH OTHER WITHOUT GAPS OR OVERLAPS. WE'LL SEE SHORTLY HOW IT KNOWS WHERE TO START...



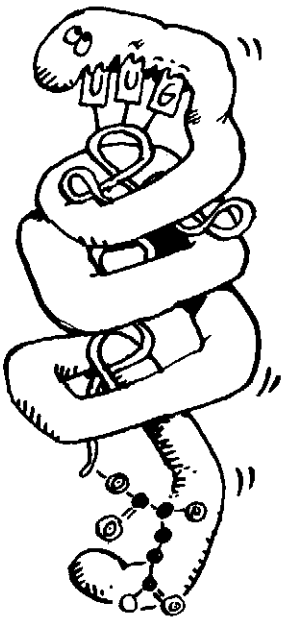
THE ACTUAL TRANSLATORS OF THE GENETIC CODE ARE A GROUP OF RNA MOLECULES CALLED *TRANSFER* RNA, OR tRNA. OWING TO PAIRING AMONG ITS BASES, tRNA's TWIST THEMSELVES INTO THIS KEY SHAPE. ⇨



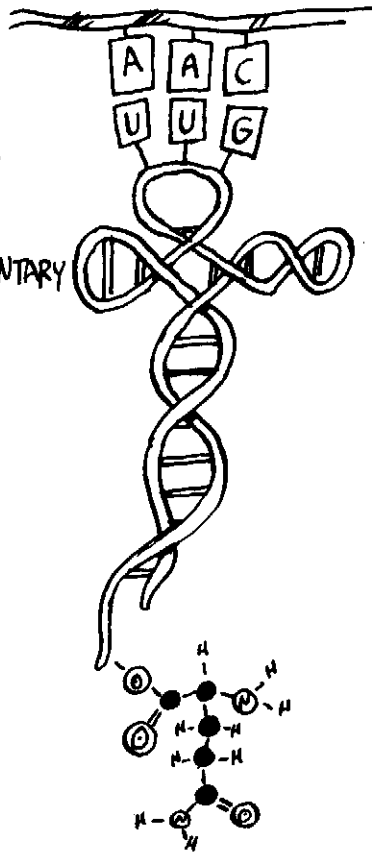
THE LOOP END OF tRNA HAS THREE UNPAIRED BASES. THIS "*ANTICODON*" MAY BIND WITH THE COMPLEMENTARY CODON OF mRNA. AT THE "TAIL" END OF tRNA IS A SITE FOR ATTACHING A SINGLE AMINO ACID.

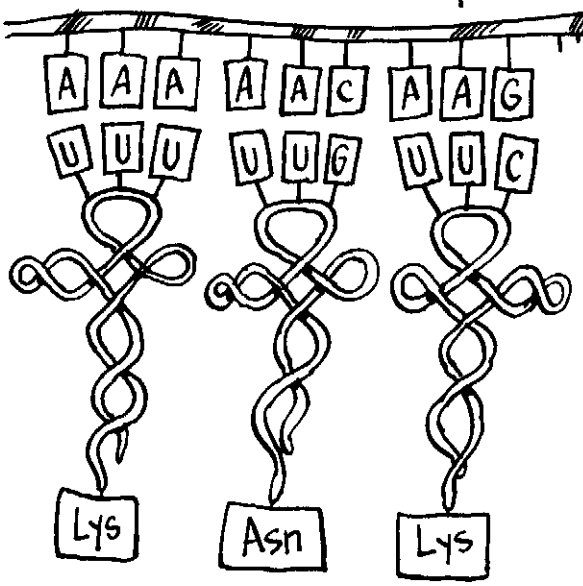


FOR EACH ANTICODON, THERE IS AN ENZYME WHICH RECOGNIZES IT AND ATTACHES THE APPROPRIATE AMINO ACID TO ITS tRNA.



ONCE THEY ARE LINKED, THE ANTICODON BINDS TO THE COMPLEMENTARY CODON OF MESSAGE.





SCHEMATICALLY, THIS IS THE WAY A STRING OF BASES IS TRANSLATED INTO A SEQUENCE OF AMINO ACIDS.

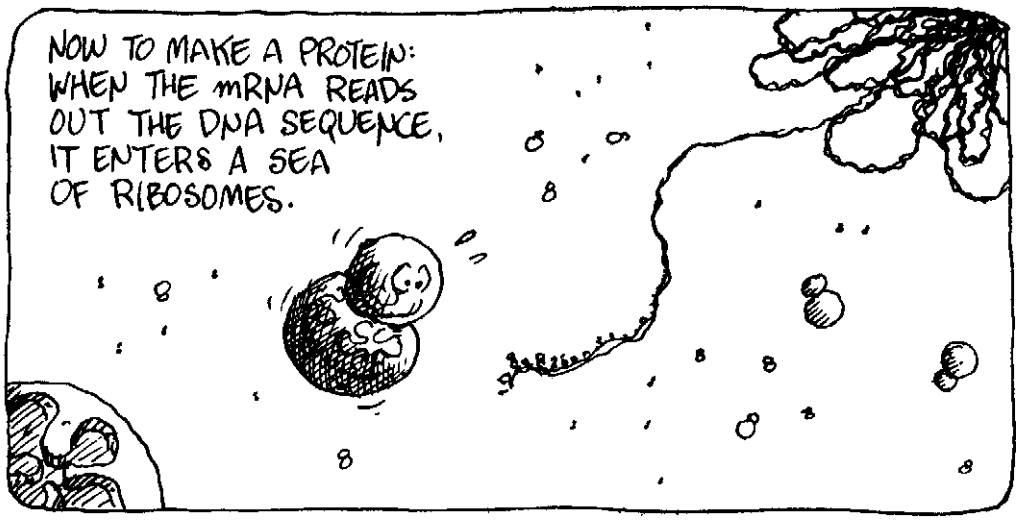
HOWEVER, THE CELL NEEDS ONE MORE PIECE OF EQUIPMENT TO MAKE IT WORK: THE *RIBOSOME*.

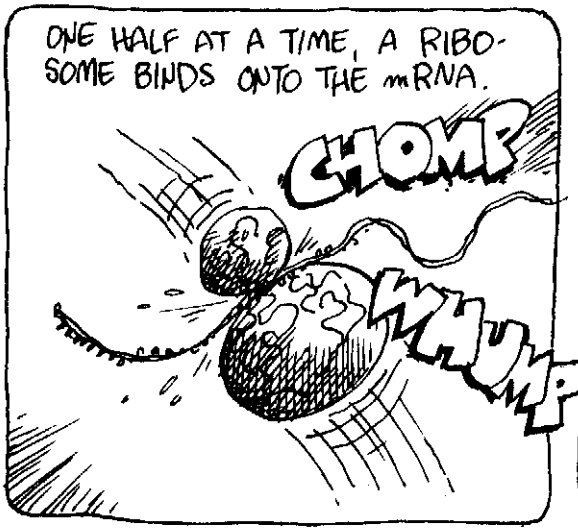
HOW PROTEINS ARE MADE

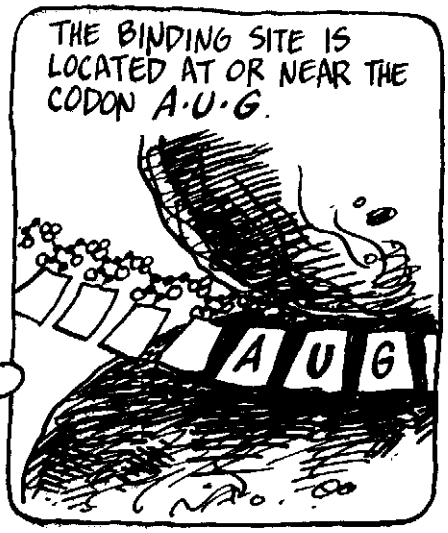
THE FINAL INGREDIENT IN THE PROTEIN-MAKING APPARATUS IS AN OBJECT THAT HOLDS EVERYTHING IN PLACE.

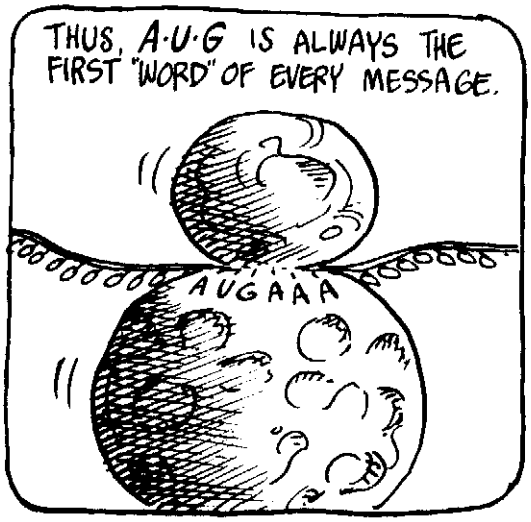
THIS IS THE ***RIBOSOME***, A DOUBLE BALL OF ABOUT 50 PROTEINS WRAPPED UP WITH RNA. THIS RNA IS CALLED ***RIBOSOMAL RNA***, rRNA FOR SHORT.

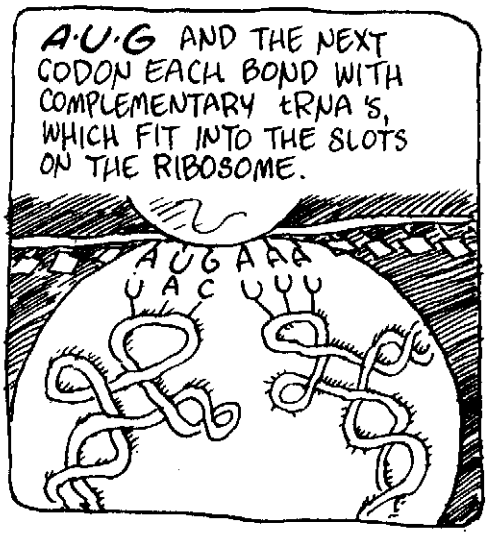
THE RIBOSOME HAS TWO SLOTS IN WHICH MOLECULES OF tRNA CAN FIT SNUGLY.

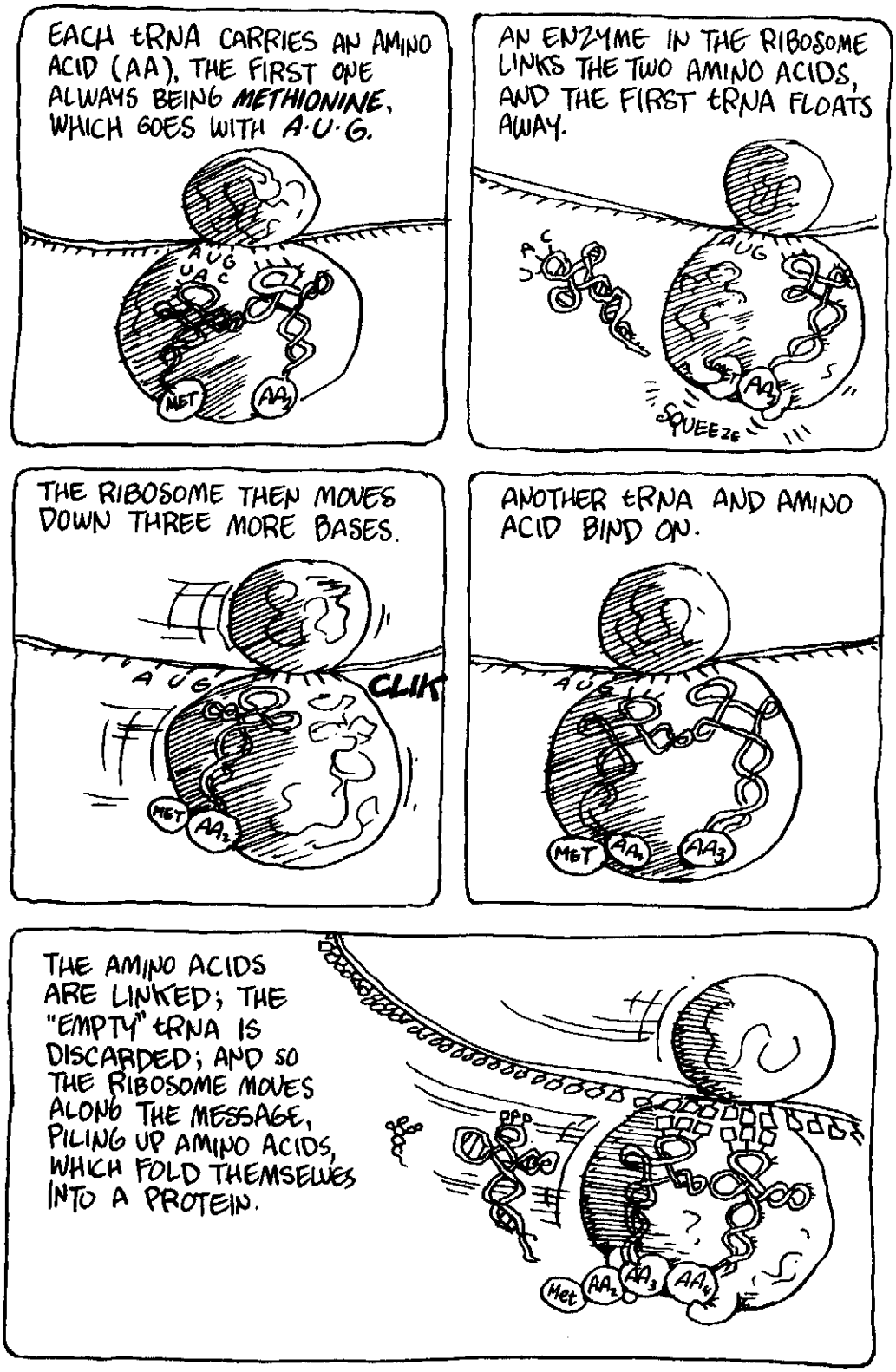

NOW TO MAKE A PROTEIN: WHEN THE mRNA READS OUT THE DNA SEQUENCE, IT ENTERS A SEA OF RIBOSOMES.

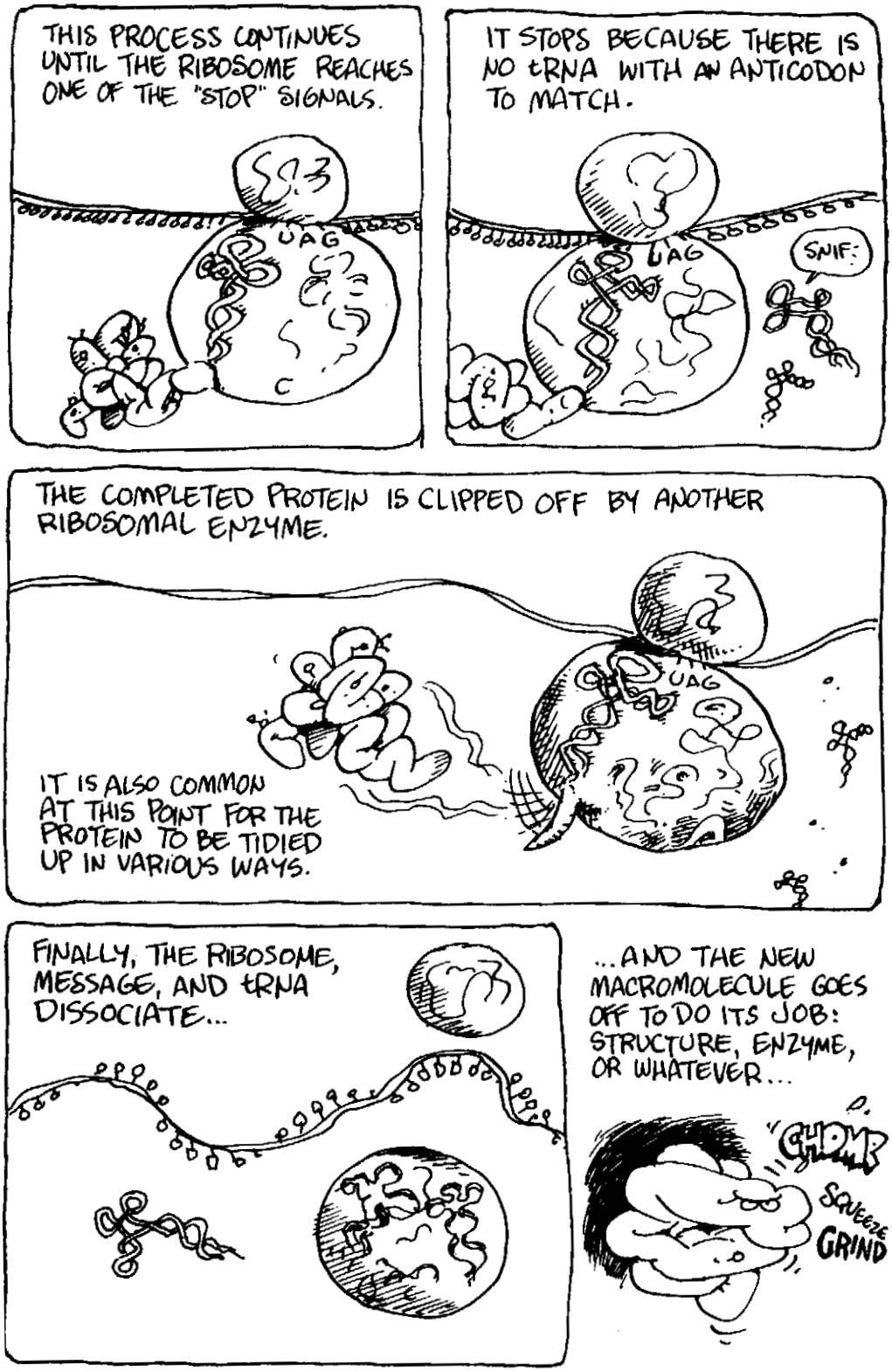

ONE HALF AT A TIME, A RIBOSOME BINDS ONTO THE mRNA.
CHOMP
WHUMP


THE BINDING SITE IS LOCATED AT OR NEAR THE CODON A·U·G.
A U G

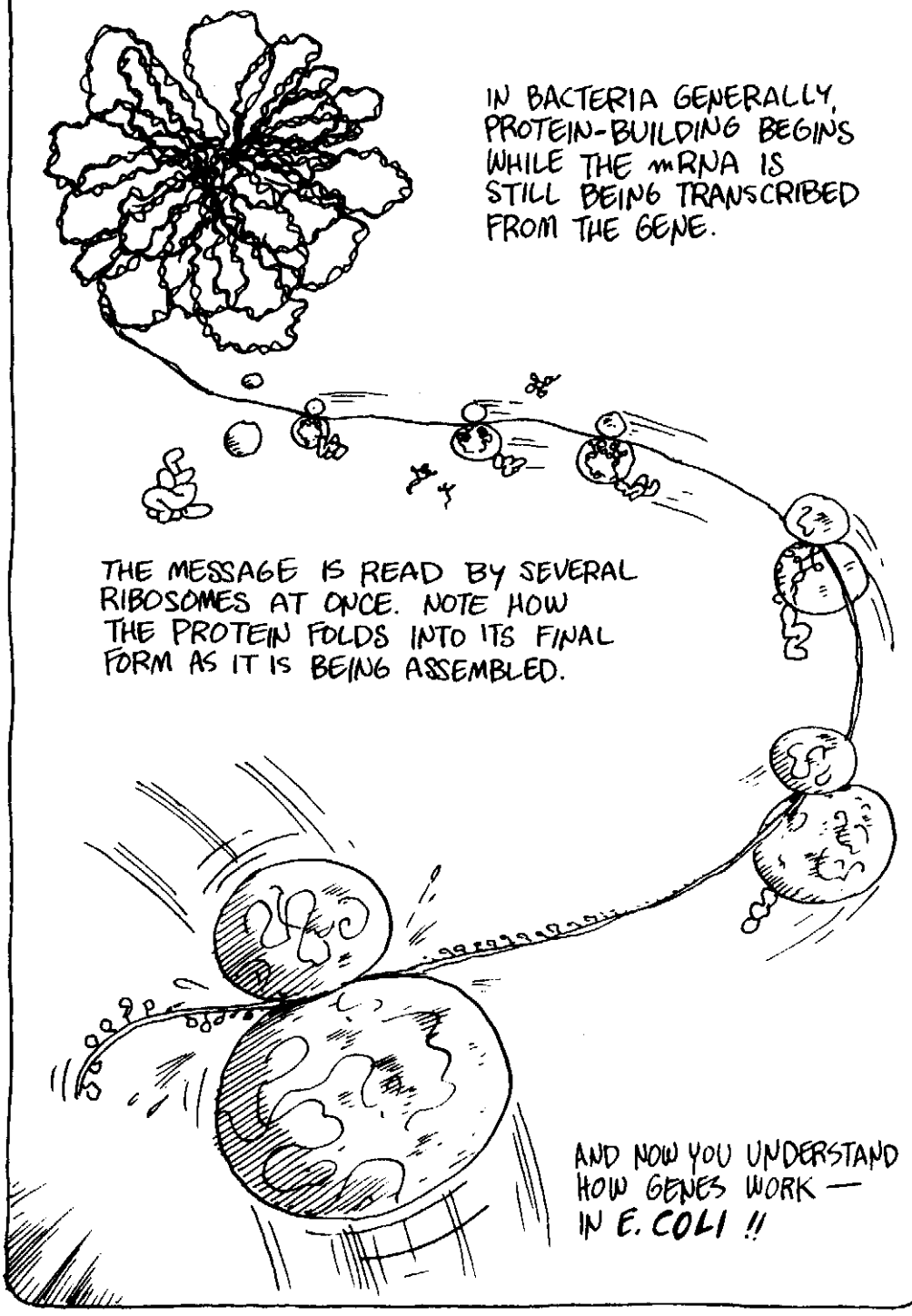

THUS, A·U·G IS ALWAYS THE FIRST "WORD" OF EVERY MESSAGE.
AUGAAA

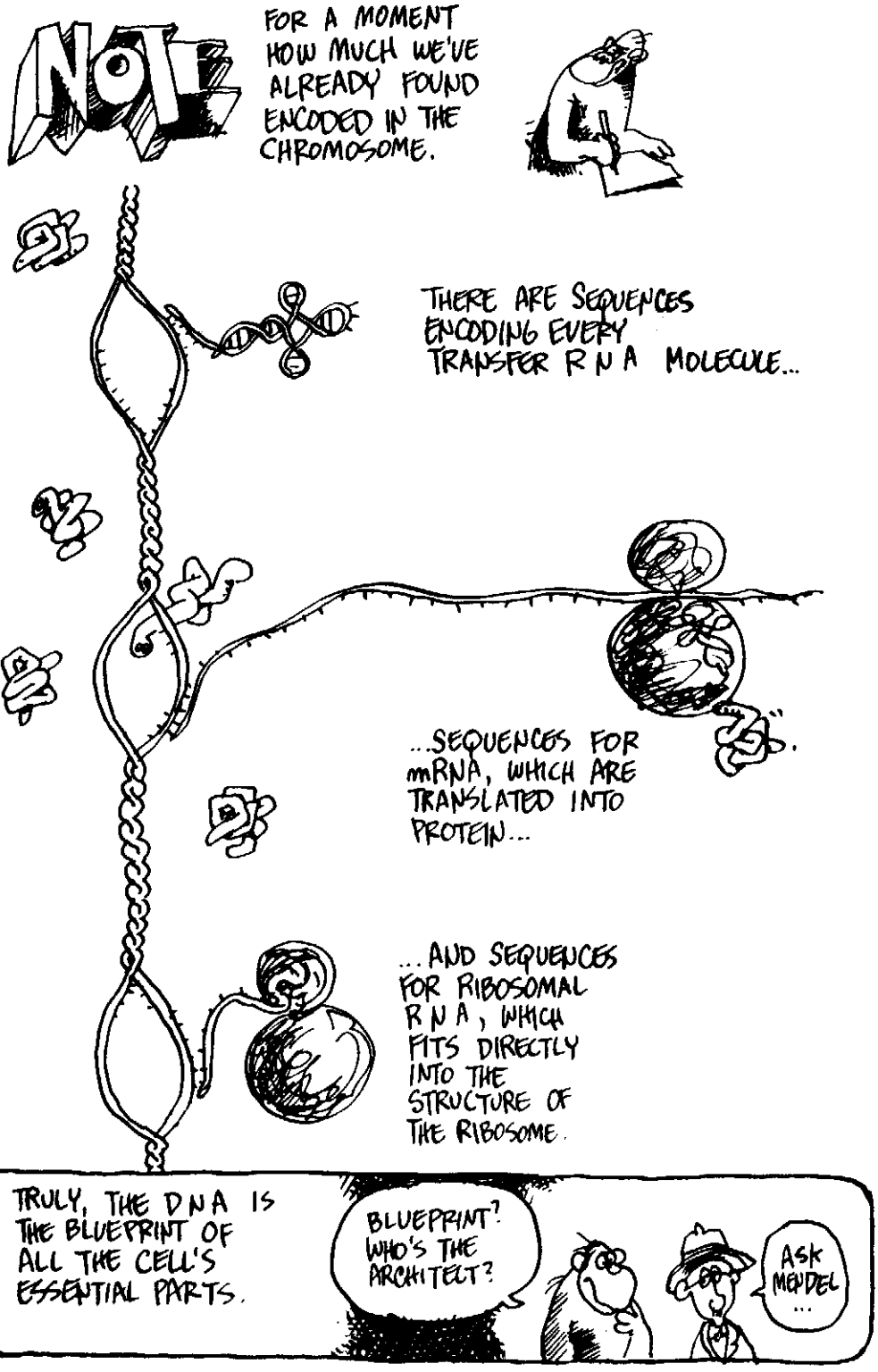

A·U·G AND THE NEXT CODON EACH BOND WITH COMPLEMENTARY tRNA'S, WHICH FIT INTO THE SLOTS ON THE RIBOSOME.
AUGAAA
UAC


EACH tRNA CARRIES AN AMINO ACID (AA), THE FIRST ONE ALWAYS BEING METHIONINE, WHICH GOES WITH A·U·G.
AUG
UAC
MET
AA2
AN ENZYME IN THE RIBOSOME LINKS THE TWO AMINO ACIDS, AND THE FIRST tRNA FLOATS AWAY.
AUG
MET
AA3
SQUEEZE
THE RIBOSOME THEN MOVES DOWN THREE MORE BASES.
AUG
CLIK
MET
AA2
ANOTHER tRNA AND AMINO ACID BIND ON.
AUG
MET
AA2
AA3
THE AMINO ACIDS ARE LINKED; THE "EMPTY" tRNA IS DISCARDED; AND SO THE RIBOSOME MOVES ALONG THE MESSAGE, PILING UP AMINO ACIDS, WHICH FOLD THEMSELVES INTO A PROTEIN.
Met
AA2
AA3
AA4


THIS PROCESS CONTINUES UNTIL THE RIBOSOME REACHES ONE OF THE "STOP" SIGNALS.
UAG
IT STOPS BECAUSE THERE IS NO tRNA WITH AN ANTICODON TO MATCH.
UAG
SNIF
THE COMPLETED PROTEIN IS CLIPPED OFF BY ANOTHER RIBOSOMAL ENZYME.
UAG
IT IS ALSO COMMON AT THIS POINT FOR THE PROTEIN TO BE TIDIED UP IN VARIOUS WAYS.
FINALLY, THE RIBOSOME, MESSAGE, AND tRNA DISSOCIATE...
...AND THE NEW MACROMOLECULE GOES OFF TO DO ITS JOB: STRUCTURE, ENZYME, OR WHATEVER...
GLOMP
SQUEEZE
GRIND

IN THE LIVING CELL, ALL THESE PROCESSES ARE GOING ON TOGETHER. THIS IS HOW IT LOOKS IN *E. COLI*.



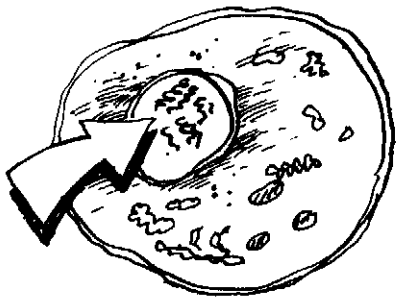

NOW
FOR A MOMENT HOW MUCH WE'VE ALREADY FOUND ENCODED IN THE CHROMOSOME.
THERE ARE SEQUENCES ENCODING EVERY TRANSFER RNA MOLECULE...
...SEQUENCES FOR mRNA, WHICH ARE TRANSLATED INTO PROTEIN...
...AND SEQUENCES FOR RIBOSOMAL RNA, WHICH FITS DIRECTLY INTO THE STRUCTURE OF THE RIBOSOME.
TRULY, THE DNA IS THE BLUEPRINT OF ALL THE CELL'S ESSENTIAL PARTS.
BLUEPRINT? WHO'S THE ARCHITECT?
ASK MENDEL ...

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?

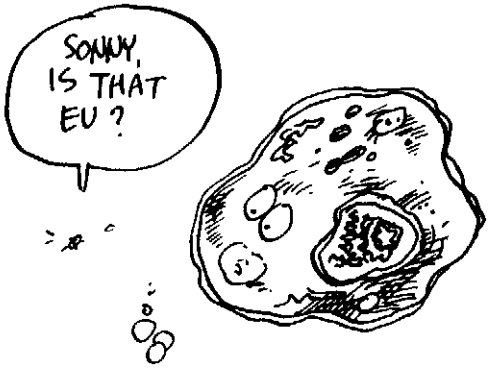
FIRST, SOME MORE ***JARGON***: THE CELLS OF PLANTS, ANIMALS, AND OTHER ADVANCED CREATURES — IN FACT, ANY CELL WITH A ***NUCLEUS*** — IS CALLED A ***EUCARYOTE*** ("YOU-CARRY-OAT"), MEANING "GOOD NUCLEUS" IN GREEK.

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

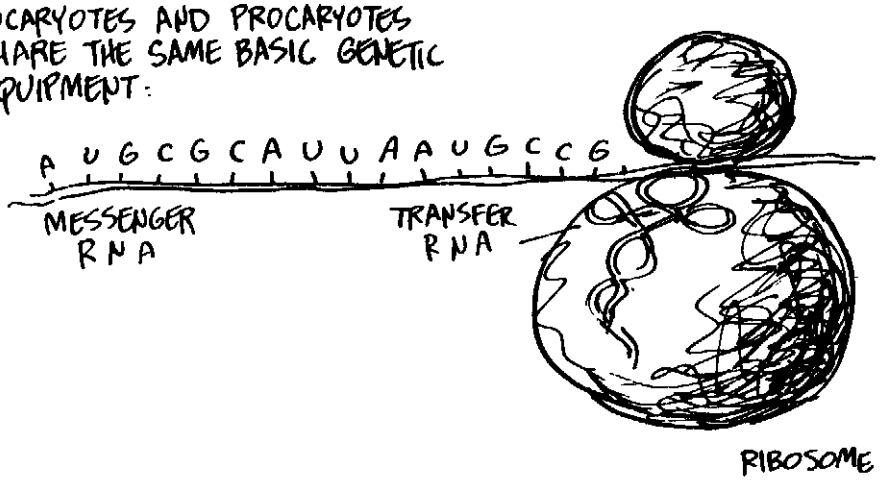


THE TINY BACTERIA, WITH THEIR SIMPLER STRUCTURE, ARE CALLED ***PROCARYOTES*** ("PRO-CARRY-OATS"), MEANING "BEFORE NUCLEUS" IN GREEK.

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



EUCARYOTES AND PROCARYOTES SHARE THE SAME BASIC GENETIC EQUIPMENT:

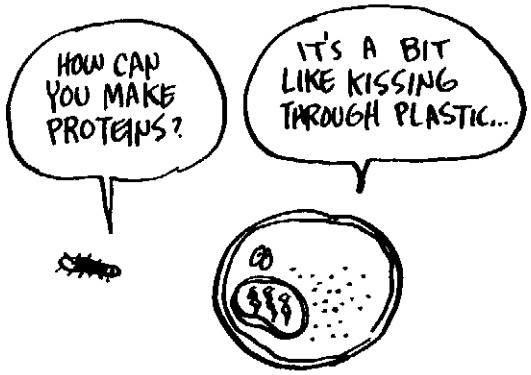


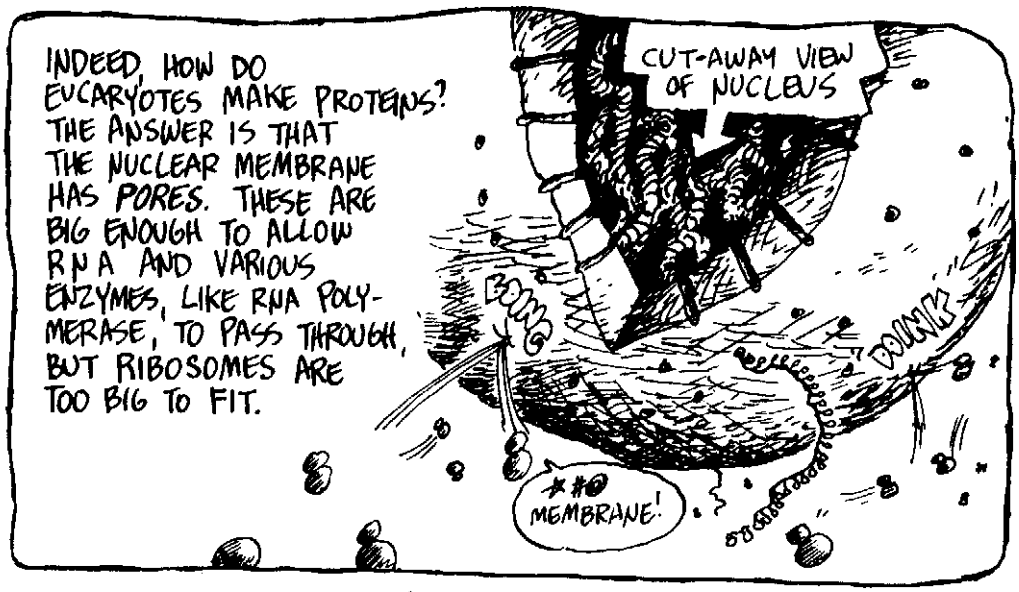
AND → **IN ALL LIFE, THE GENETIC CODE IS THE SAME —**

A FACT WHICH STRONGLY SUGGESTS THAT WE ALL COME FROM A COMMON ANCESTOR.

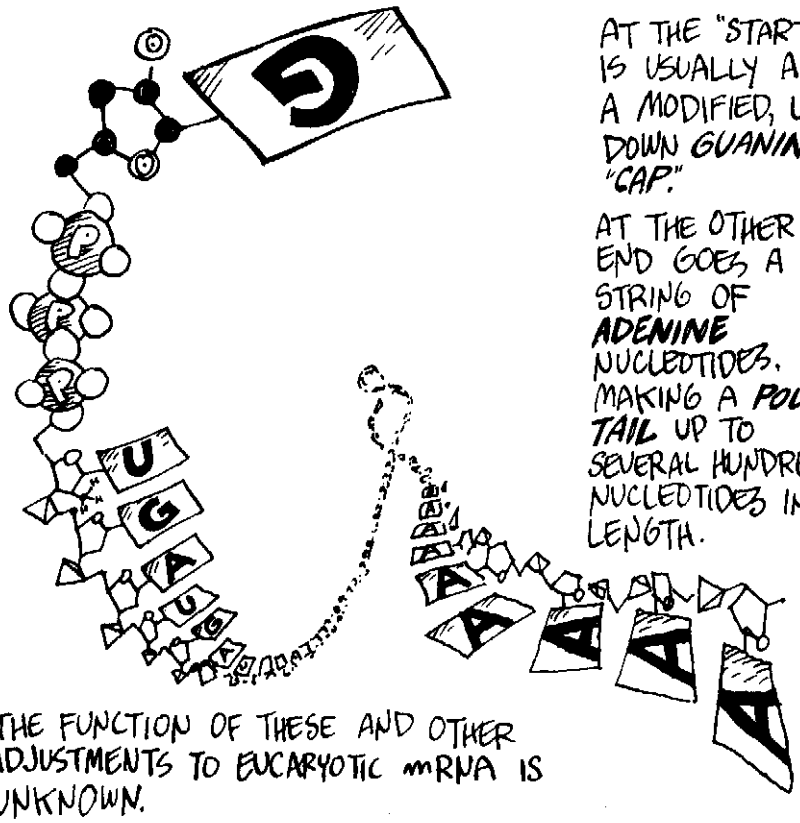
BUT → THERE ARE BIG DIFFERENCES BETWEEN PRO AND EU...

TO BEGIN WITH, EUCARYOTES HAVE ALL THEIR *RIBOSOMES* OUTSIDE THE NUCLEUS, SEPARATED FROM THE GENES BY A MEMBRANE.





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

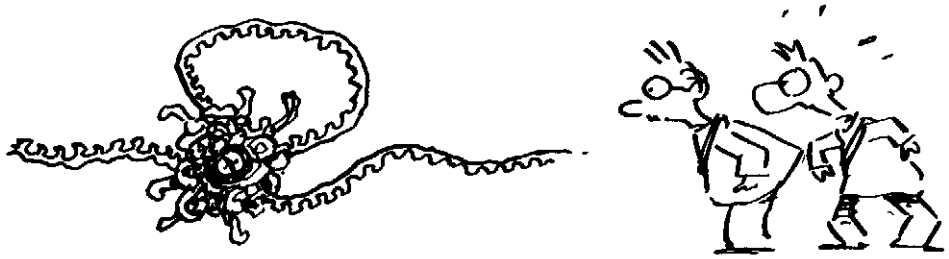


AT THE "START" END IS USUALLY ADDED A MODIFIED, UPSIDE-DOWN ***GUANINE "CAP."***

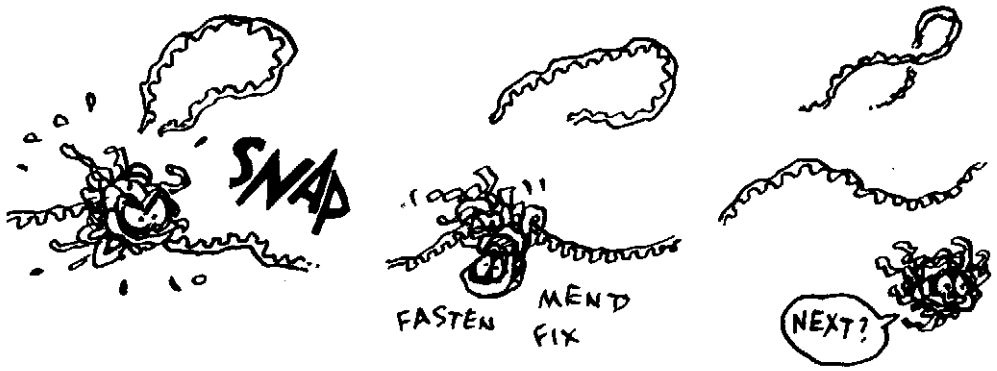
AT THE OTHER END GOES A STRING OF ***ADENINE*** NUCLEOTIDES, MAKING A ***POLY-A TAIL*** UP TO SEVERAL HUNDRED NUCLEOTIDES IN LENGTH.

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

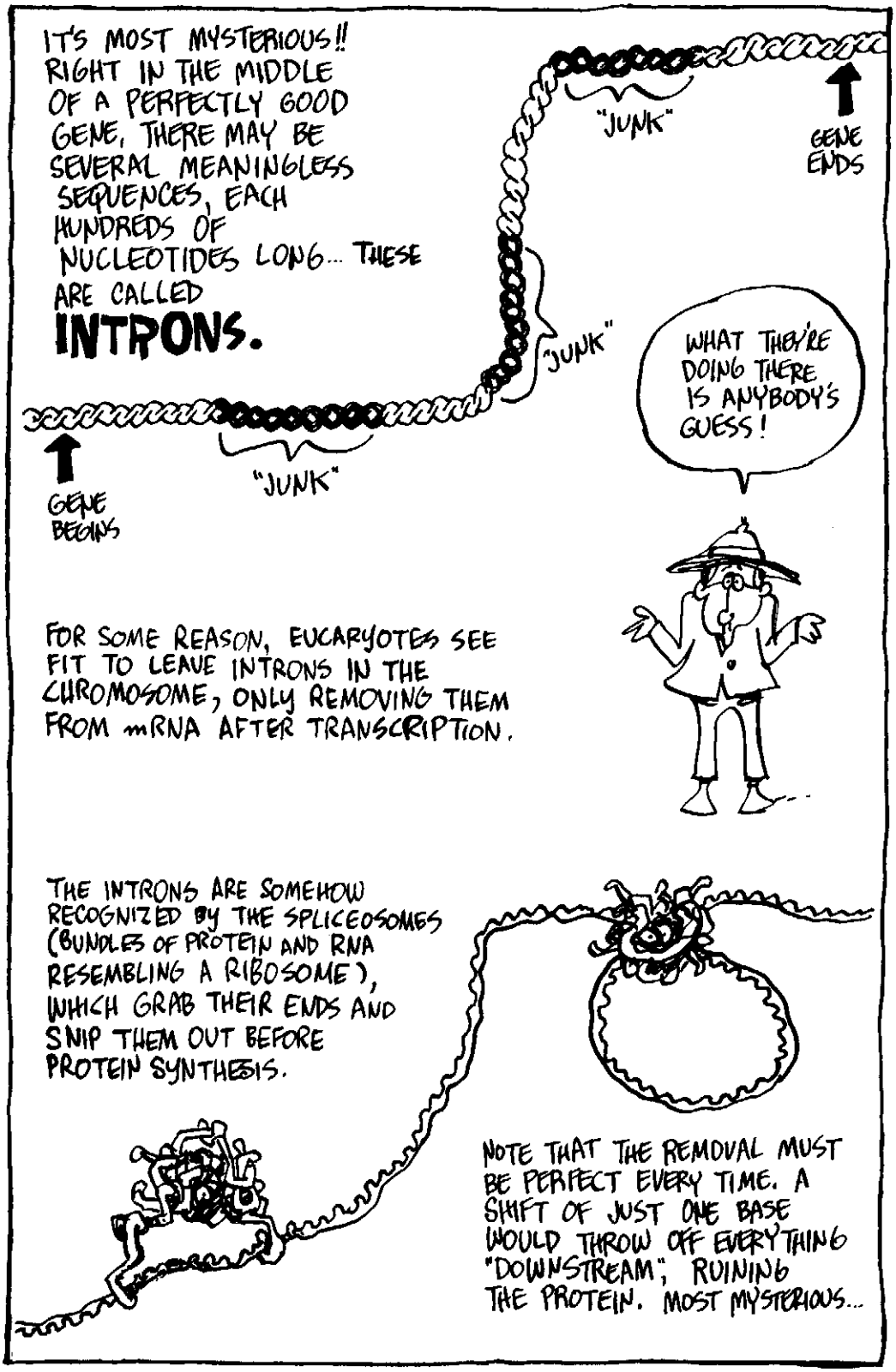
THE NEXT MOVE CAME AS A GREAT SURPRISE TO GENETICISTS: A COMPLEX OF PROTEIN AND RNA GRABS THE *mRNA*, FORMING LOOPS, LIKE THIS →

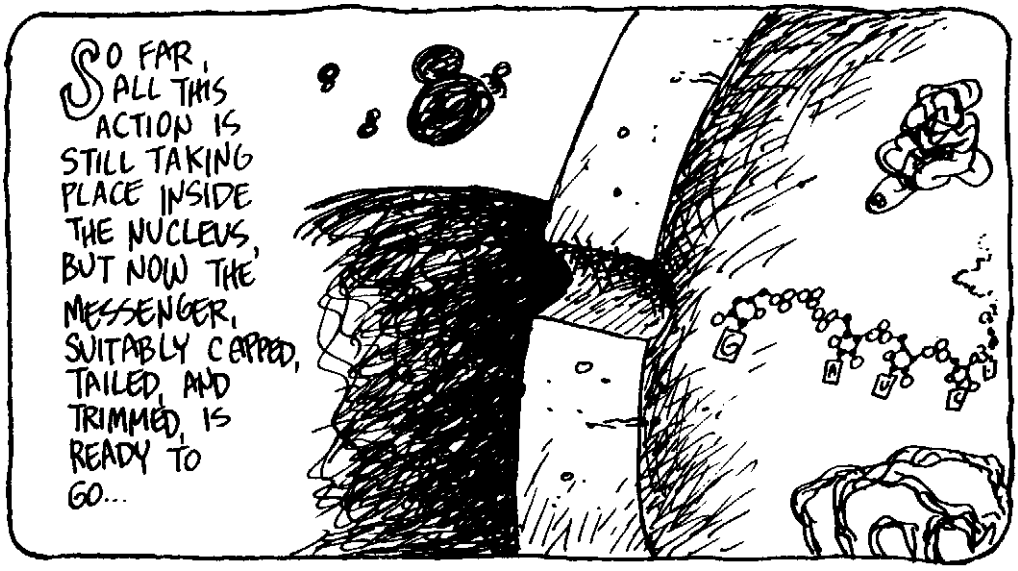


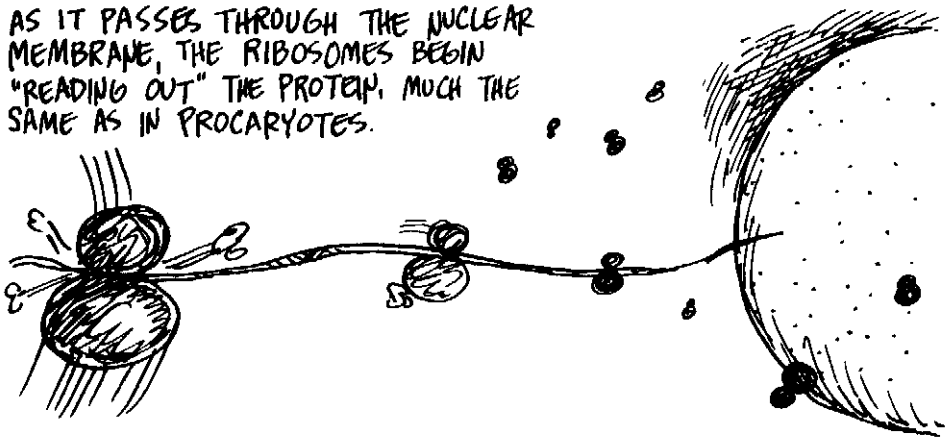
THE COMPLEX — CALLED A **SPLICEOSOME** — THEN SHEARS OFF THE LOOP, DISCARDS IT, SPLICES THE REMAINING PIECES TOGETHER, AND DEPARTS.

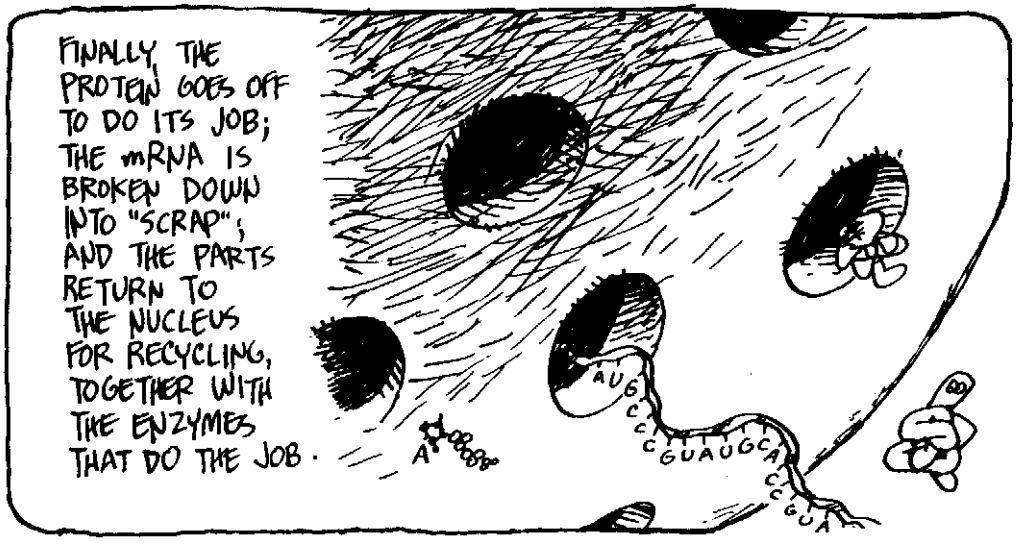


THIS IS BIZARRE! EUCARYOTIC GENES CONTAIN "**JUNK DNA**" — NON-CODING MESSAGE SEQUENCES THAT HAVE TO BE CUT OUT BEFORE THE GENE CAN BE EXPRESSED!!


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...

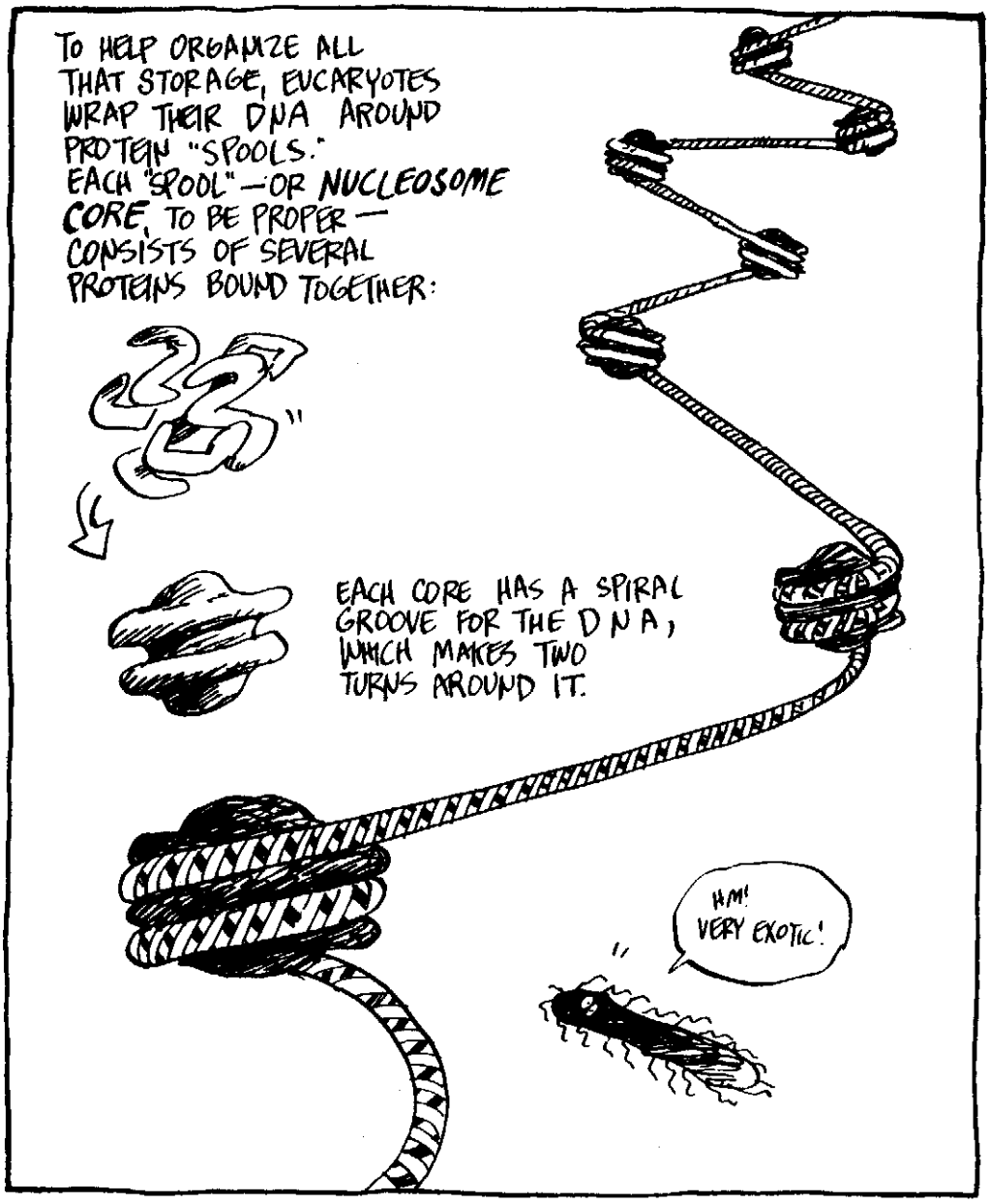

SO FAR, ALL THIS ACTION IS STILL TAKING PLACE INSIDE THE NUCLEUS, BUT NOW THE MESSENGER, SUITABLY CAPPED, TAILED, AND TRIMMED, IS READY TO GO...


AS IT PASSES THROUGH THE NUCLEAR MEMBRANE, THE RIBOSOMES BEGIN "READING OUT" THE PROTEIN, MUCH THE SAME AS IN PROCARYOTES.

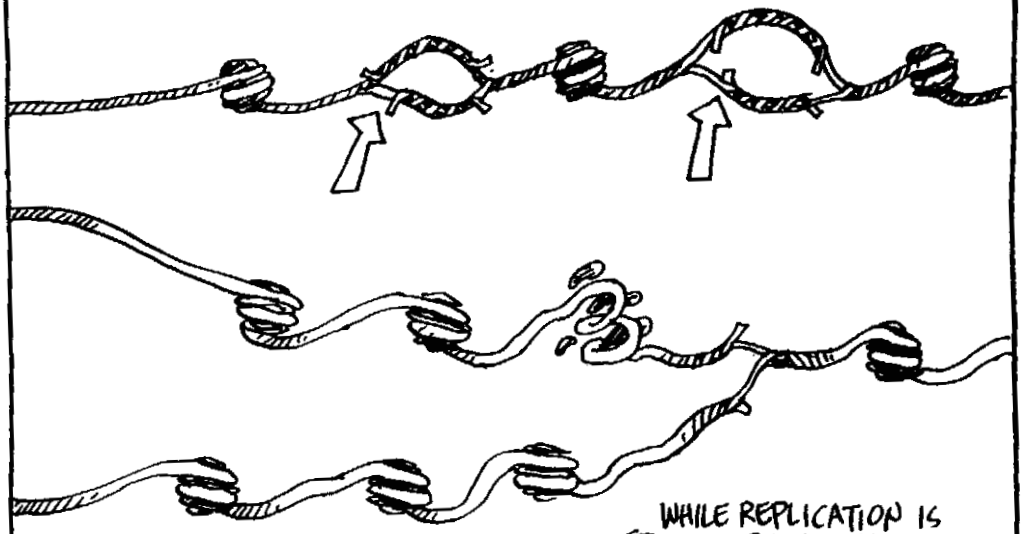

FINALLY, THE PROTEIN GOES OFF TO DO ITS JOB; THE mRNA IS BROKEN DOWN INTO "SCRAP"; AND THE PARTS RETURN TO THE NUCLEUS FOR RECYCLING, TOGETHER WITH THE ENZYMES THAT DO THE JOB.
A
AUG
C
C
C
GUAUGCA
C
C
GUA

ANOTHER

DIFFERENCE BETWEEN EU AND A BACTERIUM IS IN THE SHEER NUMBER OF GENES: 200,000 IN A HUMAN, 4000 IN E. COLI.

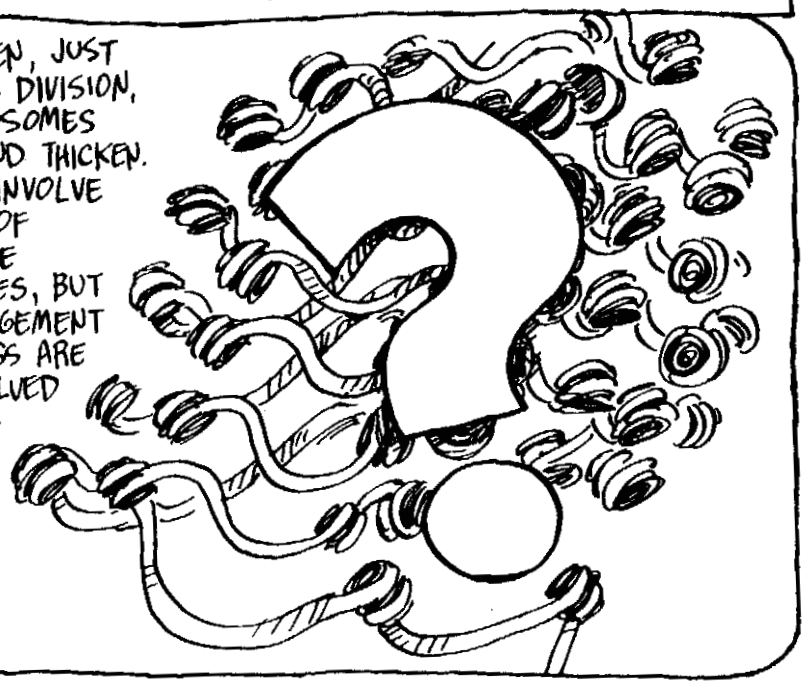


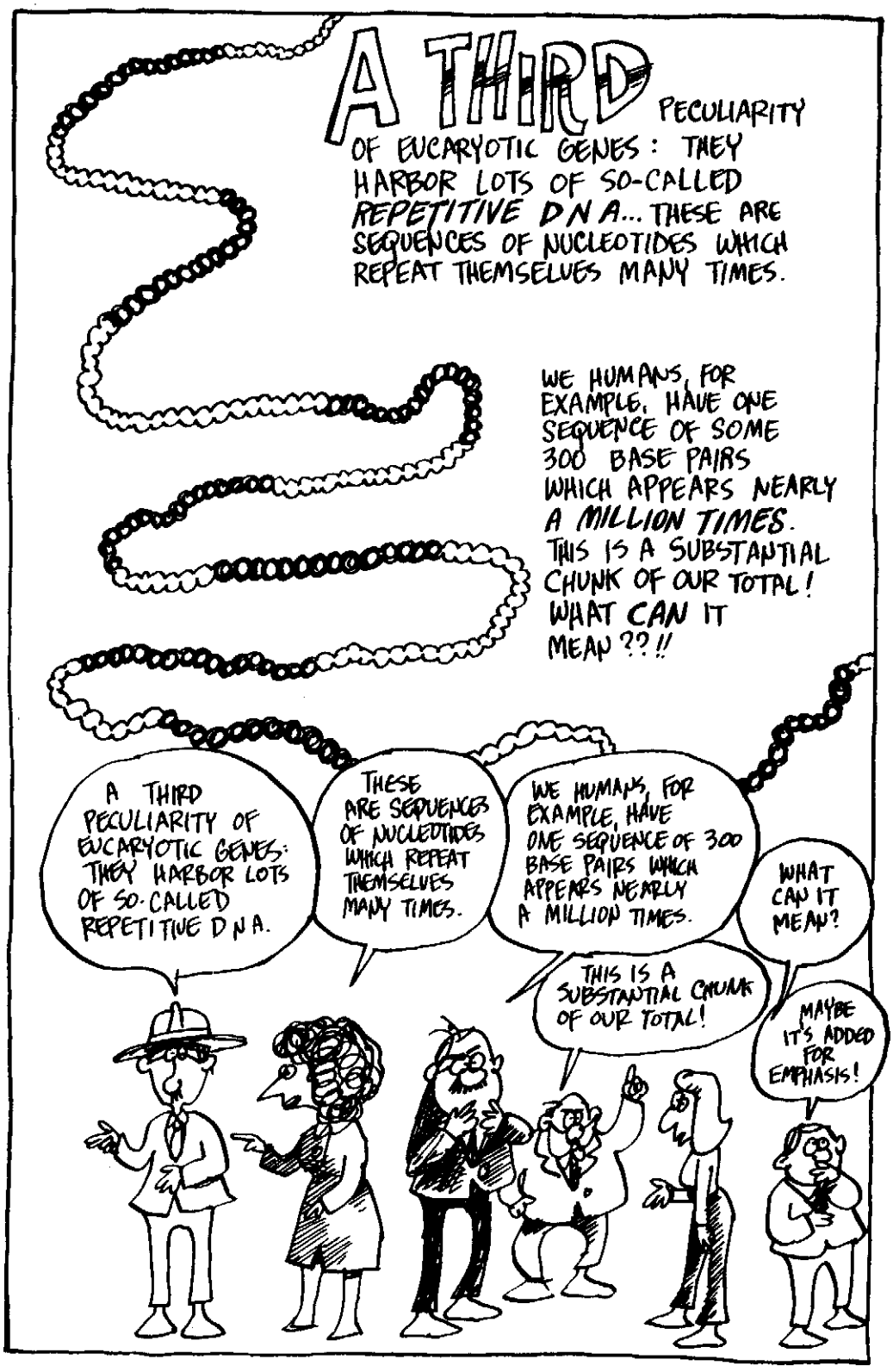
WHEN A EUCARYOTIC CELL WANTS TO DIVIDE, DNA REPLICATION BEGINS AT MANY SITES AT ONCE (UNLIKE IN *E. COLI*, WHERE IT BEGINS AT ONE SITE).

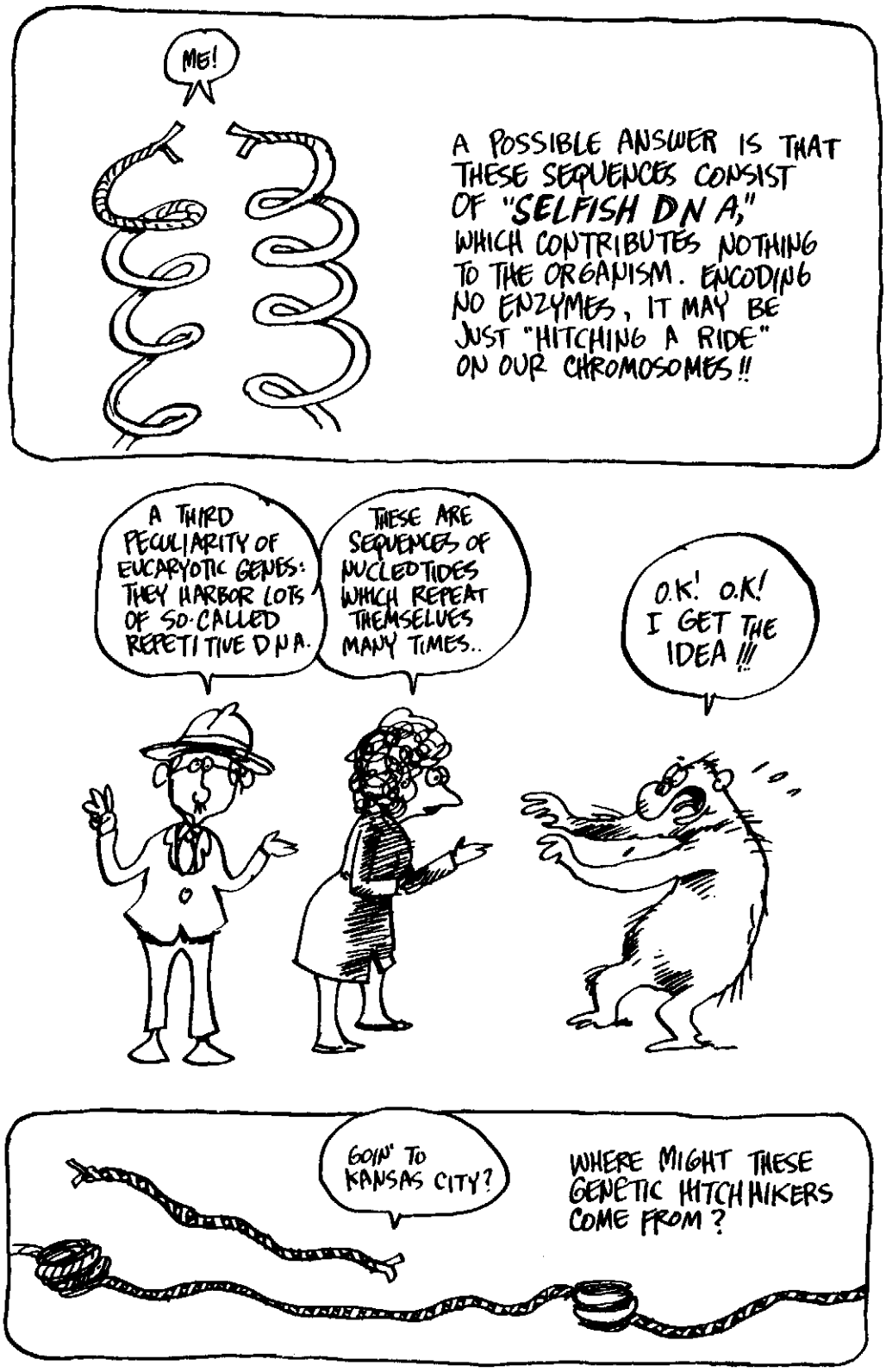


WHILE REPLICATION IS STILL IN PROGRESS, THE TWO NEW STRANDS ARE ALREADY WINDING ONTO NUCLEOSOME CORES. ONE STRAND INHERITS THE OLD CORES, AND THE OTHER GETS A NEW SET.

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.

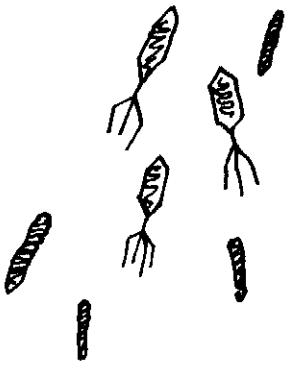



A THIRD PECULIARITY OF EUCARYOTIC GENES: THEY HARBOR LOTS OF SO-CALLED REPETITIVE DNA... THESE ARE SEQUENCES OF NUCLEOTIDES WHICH REPEAT THEMSELVES MANY TIMES.
WE HUMANS, FOR EXAMPLE, HAVE ONE SEQUENCE OF SOME 300 BASE PAIRS WHICH APPEARS NEARLY A MILLION TIMES. THIS IS A SUBSTANTIAL CHUNK OF OUR TOTAL!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

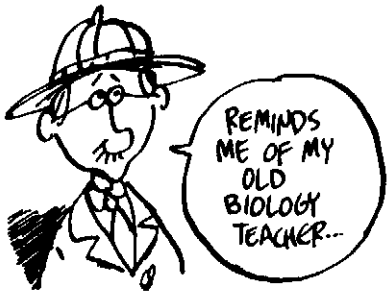

ME!
A POSSIBLE ANSWER IS THAT THESE SEQUENCES CONSIST OF "SELFISH DNA," WHICH CONTRIBUTES NOTHING TO THE ORGANISM. ENCODING NO ENZYMES, IT MAY BE JUST "HITCHING A RIDE" ON OUR CHROMOSOMES!!
A THIRD PECULIARITY OF EUCARYOTIC GENES: THEY HARBOR LOTS OF SO-CALLED REPETITIVE DNA.
THESE ARE SEQUENCES OF NUCLEOTIDES 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

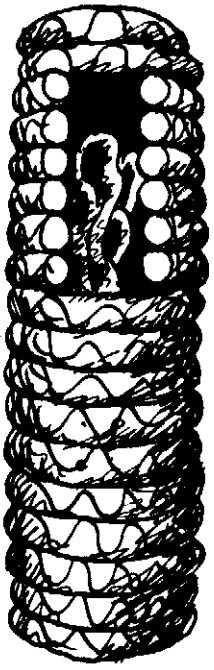
VIRUSES



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



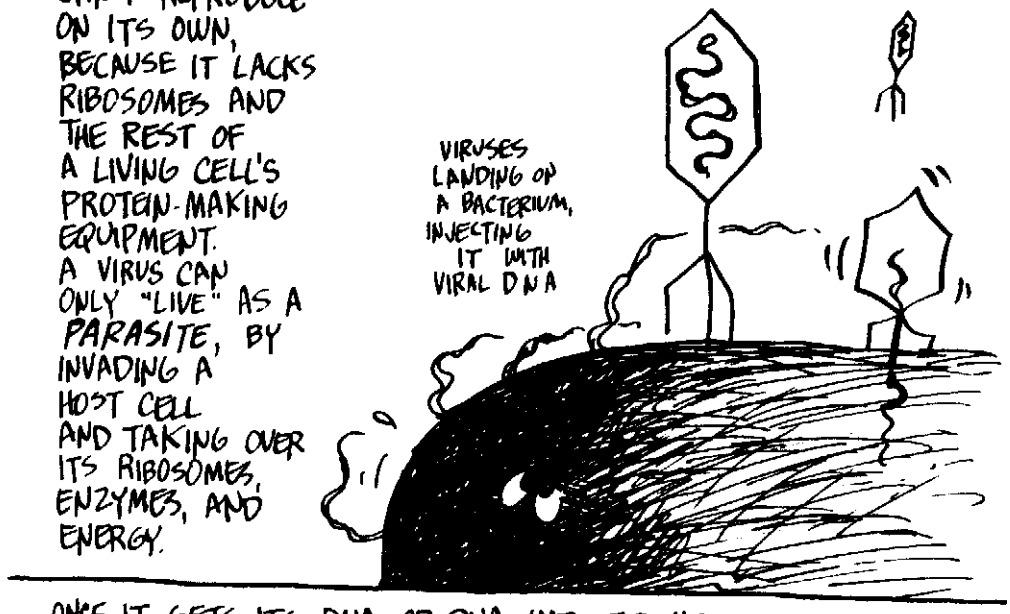
EVEN SIMPLER AND SMALLER THAN A BACTERIUM, A VIRUS HAS ONLY TWO PARTS: A BIT OF *NUCLEIC ACID* WRAPPED UP IN A *PROTEIN COAT*:



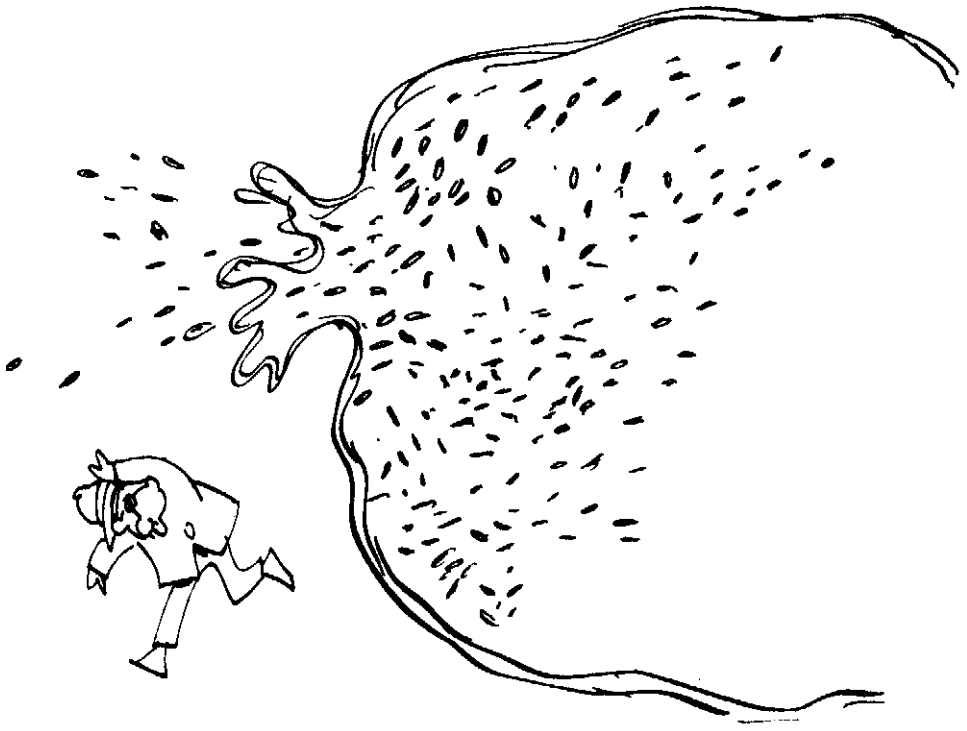
CUT-AWAY VIEW

THE NUCLEIC ACID, WHICH MAY BE D N A OR R N A, 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.

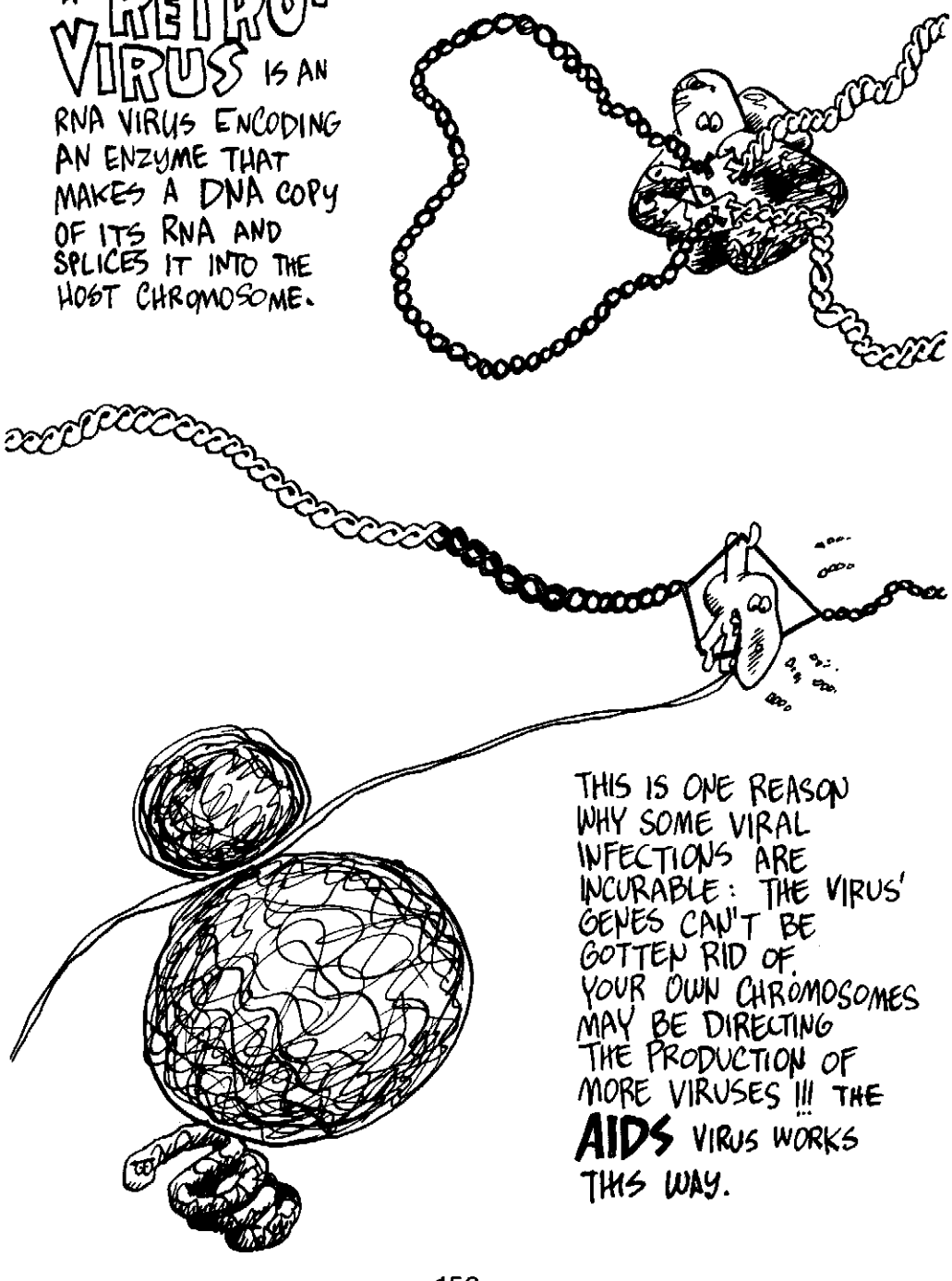


ONCE IT GETS ITS DNA OR RNA INTO THE HOST, THE VIRUS BEGINS TO REPRODUCE WILDLY, STRAINING THE CELL TO THE BURSTING POINT!

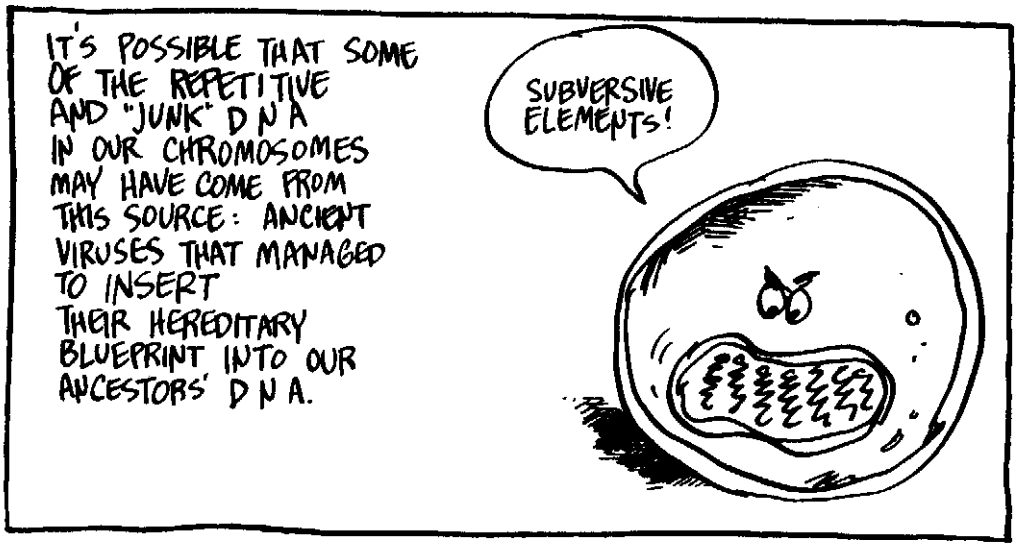


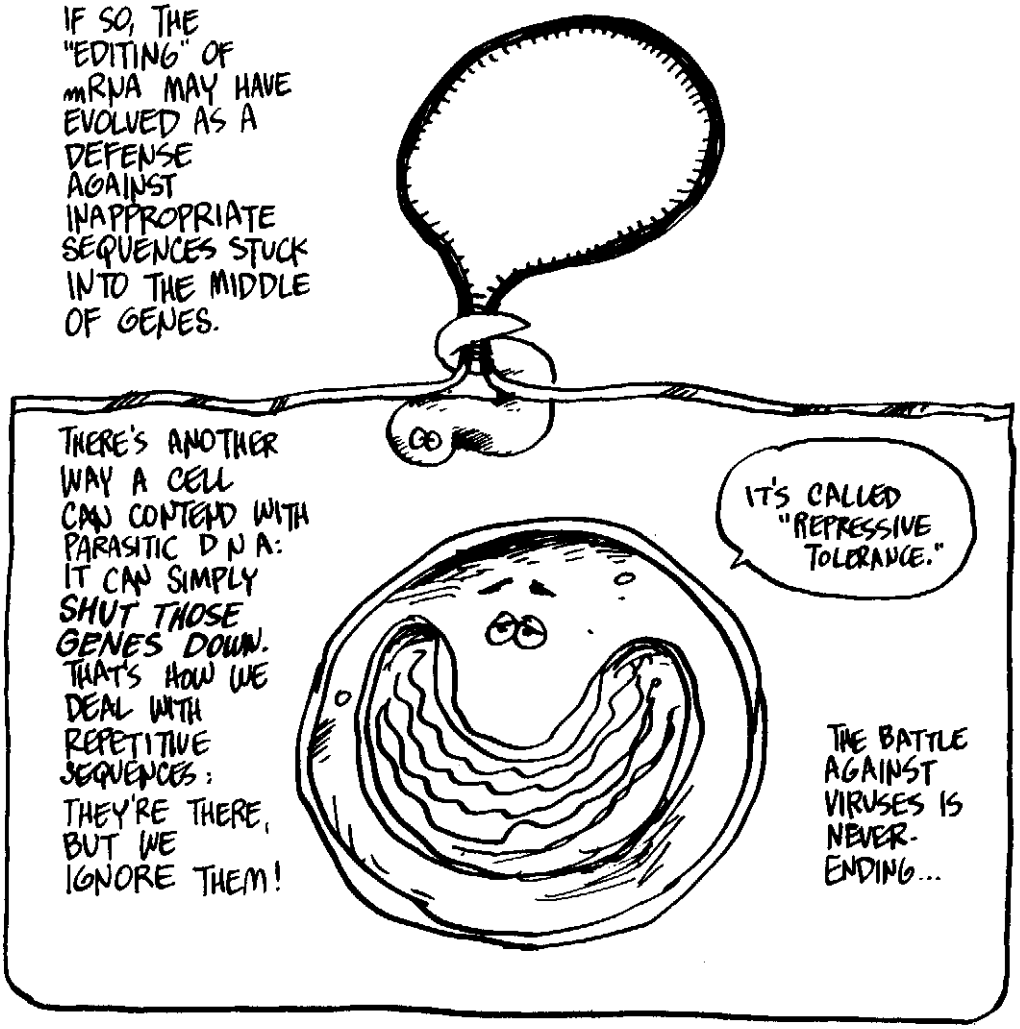
THAT'S A TYPICAL LIFE-STYLE (OR NON-LIFE-STYLE) FOR A VIRUS, BUT SOME VIRUSES ARE EVEN SNEAKIER: THEY ACTUALLY INSERT THEIR GENES INTO THE HOST CELL'S DNA.

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!

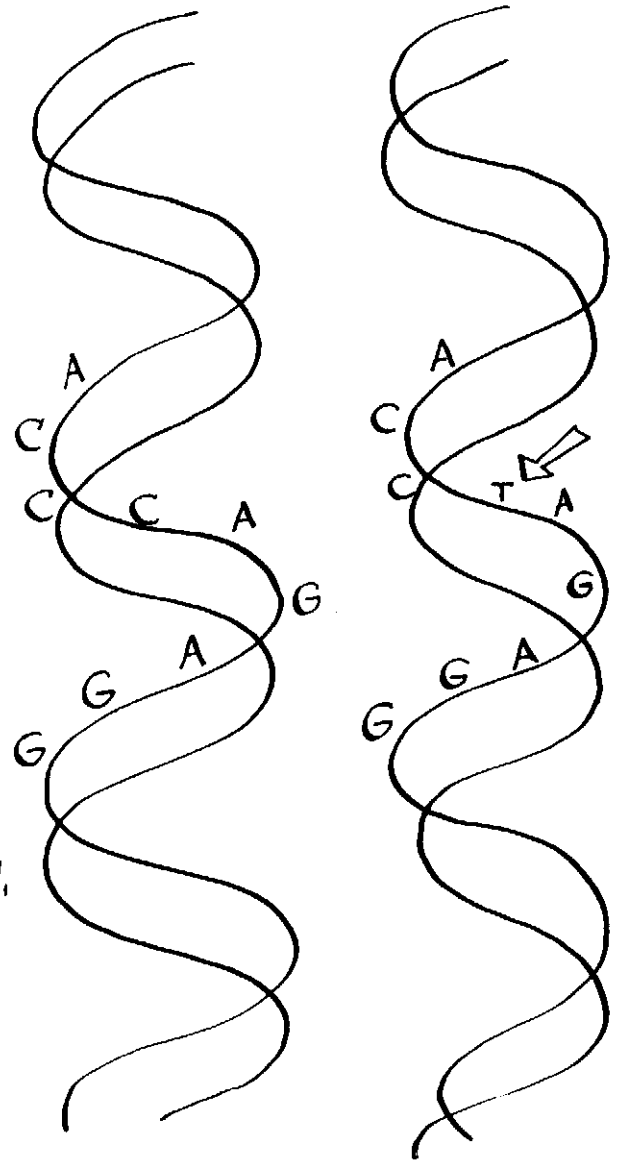

IF SO, THE "EDITING" OF mRNA MAY HAVE EVOLVED AS A DEFENSE AGAINST INAPPROPRIATE SEQUENCES STUCK INTO THE MIDDLE OF GENES.
THERE'S ANOTHER WAY A CELL CAN CONTEND WITH PARASITIC DNA: IT CAN SIMPLY SHUT THOSE GENES DOWN. THAT'S HOW WE DEAL WITH REPETITIVE SEQUENCES: THEY'RE THERE, BUT WE IGNORE THEM!
IT'S 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***.

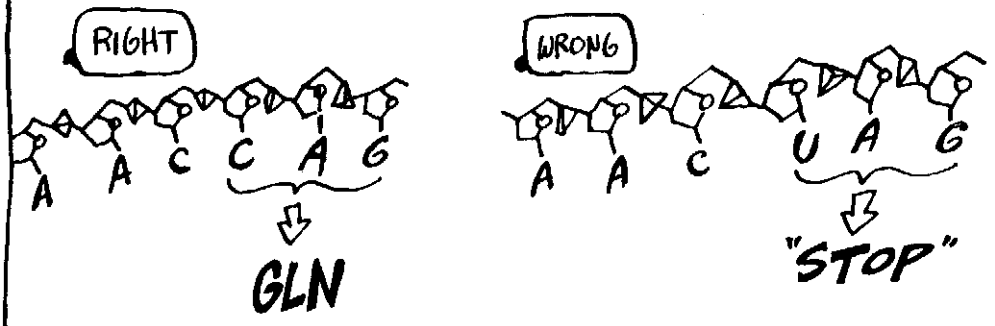
A MUTATION IN A GENE IS JUST A CHANGE IN THE DNA'S SEQUENCE OF NUCLEOTIDES. EVEN A MISTAKE AT JUST ***ONE POSITION*** CAN HAVE A PROFOUND EFFECT.

HERE IS A SMALL BUT DEVASTATING MUTATION IN THE GENE FOR ***HEMOGLOBIN***, THE PROTEIN WHICH CARRIES OXYGEN IN THE BLOOD.



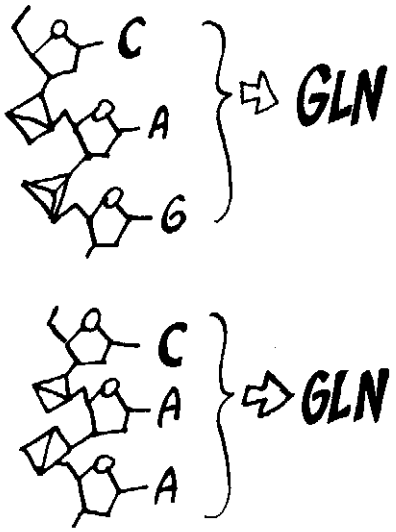
GOOD GENE MUTANT GENE

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).

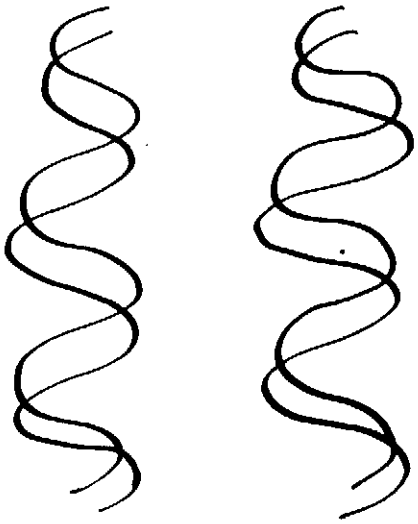
SOMETIMES — ONCE IN A BLUE MOON — THE PROTEIN MAY EVEN WORK *BETTER* THAN BEFORE.

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!!

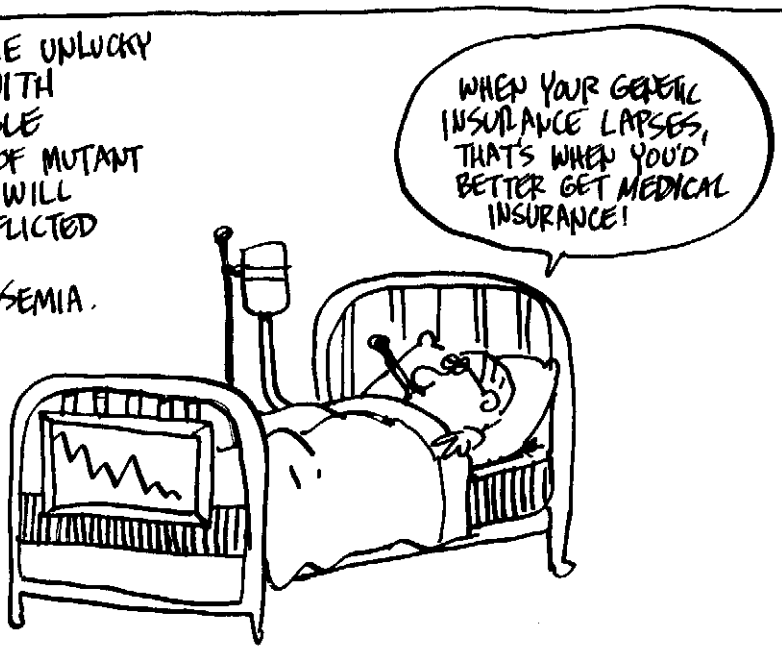
EARLIER (p. 81)

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.

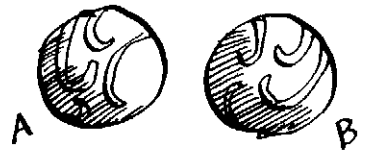


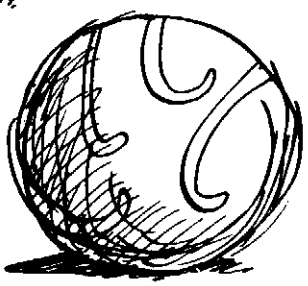
WE DIDN'T MENTION IT EARLIER, BUT SOME ALLELES CAN BE

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.



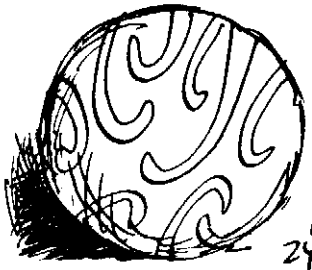


$I^A I^A$

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

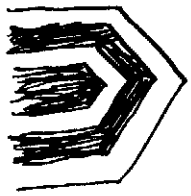
$I^B I^B$

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



$I^A I^B$

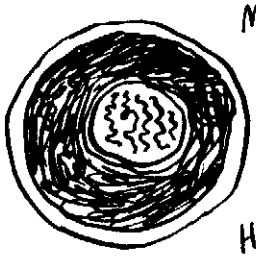
A HETERO-ZYGOTE MAKES BOTH SEQUENCES, AND HAS *TYPE AB BLOOD.*



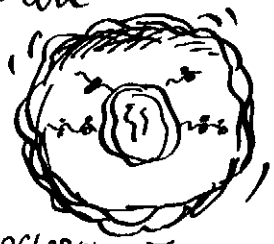
AND FINALLY, THERE IS A THIRD ALLELE, I^O, MAKING *NO* SUGAR SEQUENCE. *TYPE O* BLOOD IS *RECESSIVE.*

BLOOD CELLS ILLUSTRATE ANOTHER COMMON FACT OF LIFE: **ONE KIND OF CELL CAN TURN INTO ANOTHER KIND OF CELL.**

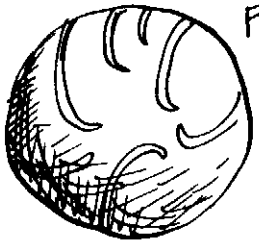
A RED BLOOD CELL BEGINS ITS EXISTENCE AS A BONE MARROW CELL, A PERFECTLY GOOD EUCARYOTE, BUT LACKING IN HEMOGLOBIN.



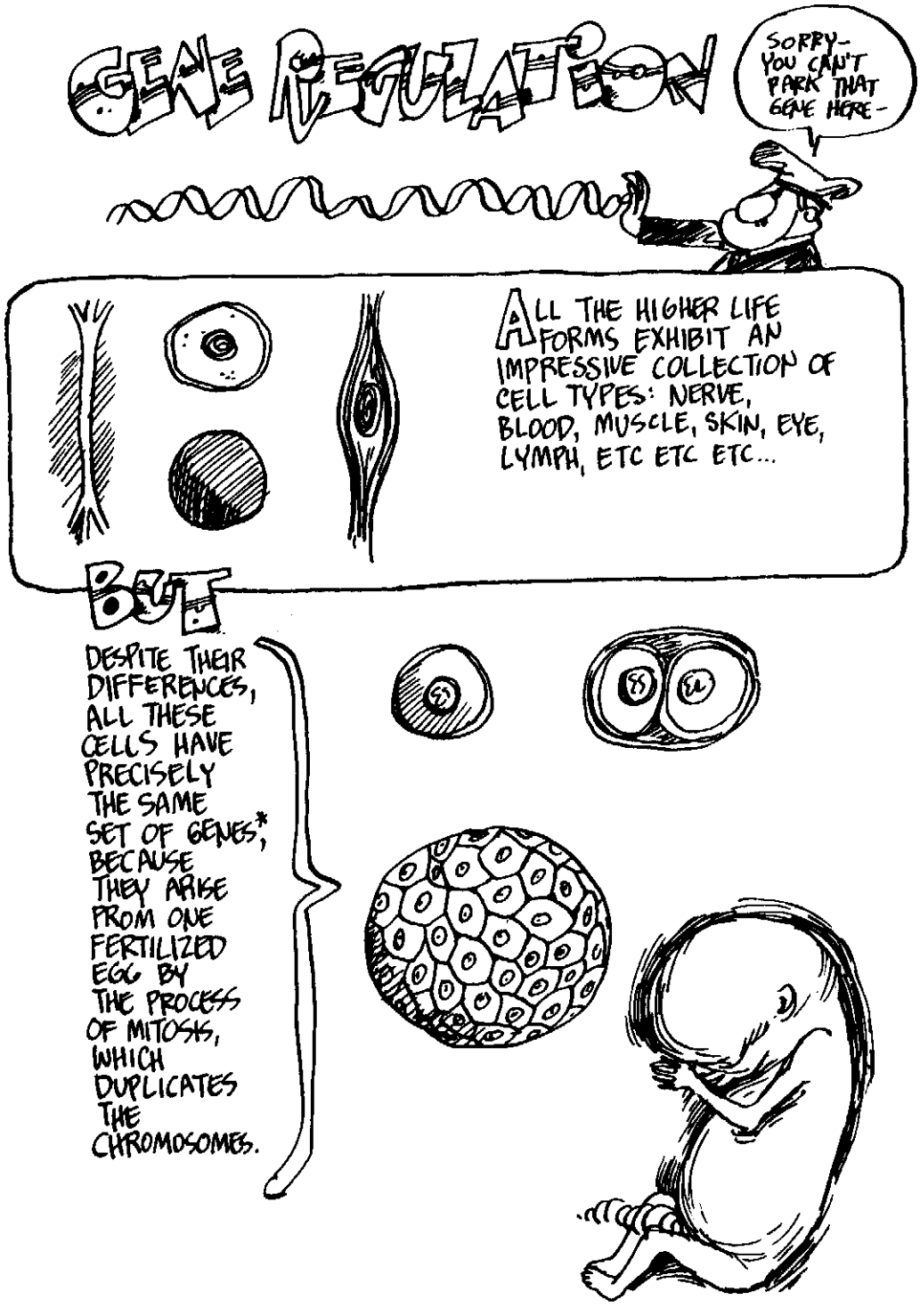
AT SOME POINT, A MARROW CELL BEGINS TO CHANGE... AMONG OTHER THINGS, IT BEGINS TO MAKE HEMOGLOBIN.



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...



*AS USUAL, THERE ARE EXCEPTIONS!!

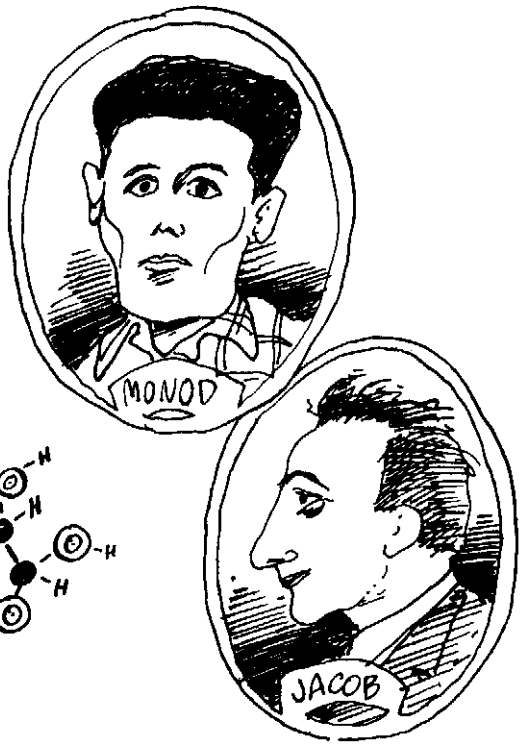
CLEARLY, DIFFERENT GENES COME INTO PLAY IN DIFFERENT CELLS... SO EACH CELL MUST HAVE WAYS OF "DECIDING" WHICH GENES TO "TURN ON" AND WHEN TO DO IT...

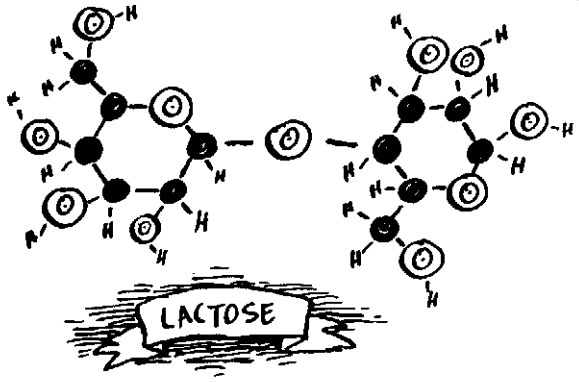
OTHERWISE, ONE DREADS THE RESULTS!

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...

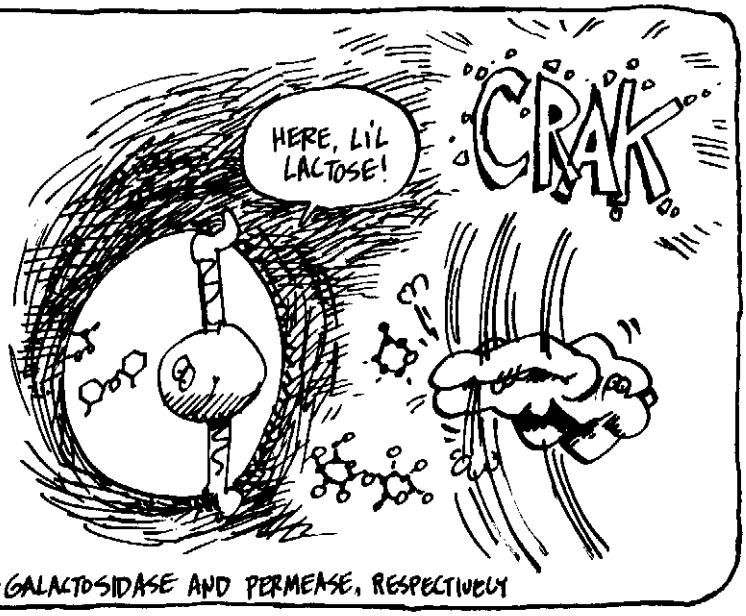
AS USUAL, THE QUESTION HAS BEEN MOST THOROUGHLY STUDIED IN *E. COLI*.

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**.

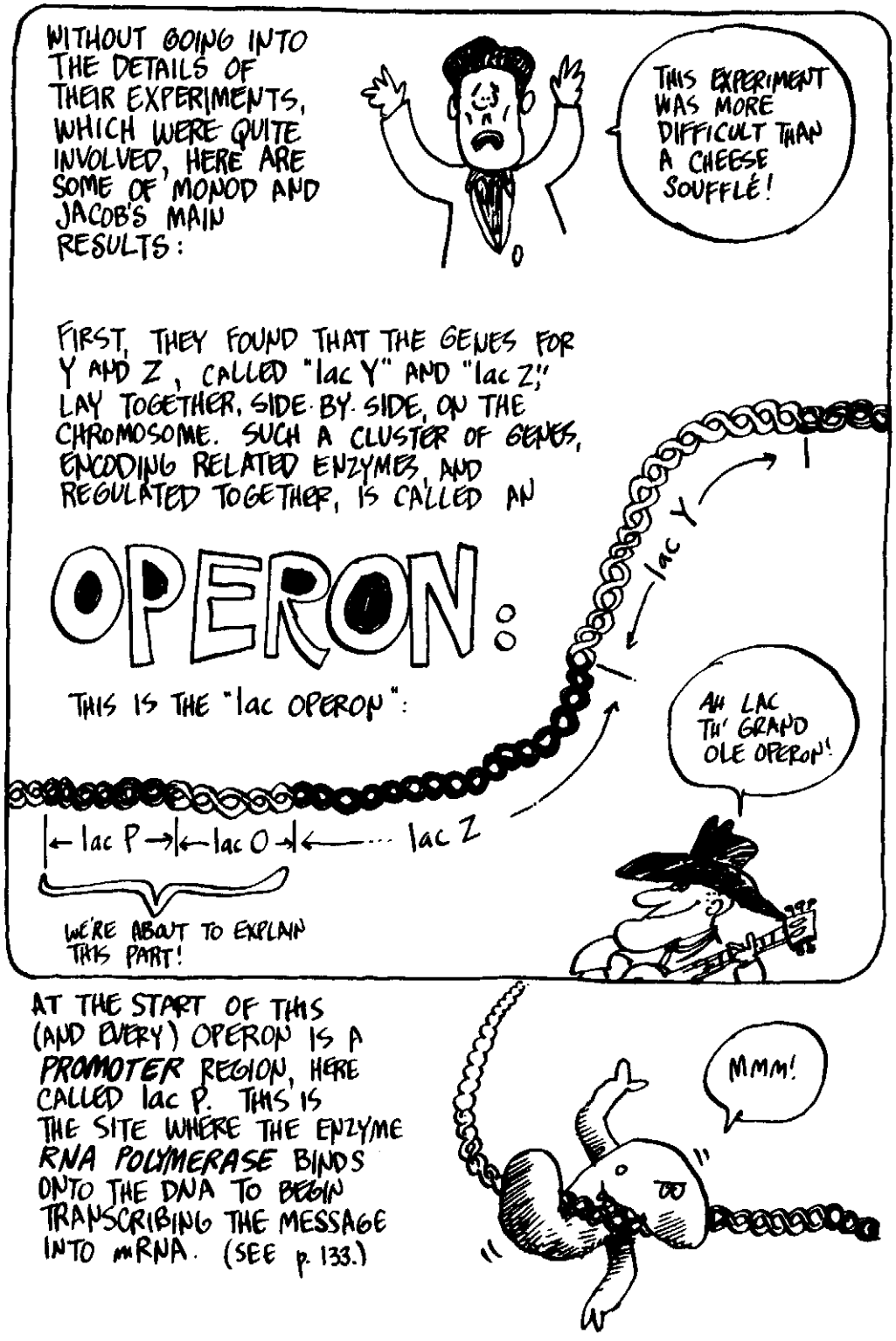




IN THE PRESENCE OF LACTOSE, *E. COLI* PRODUCES TWO ENZYMES, CALL THEM **Y** AND **Z***. **Z** OPENS THE CELL WALL TO LACTOSE, AND **Y** BREAKS THE SUGAR IN HALF.



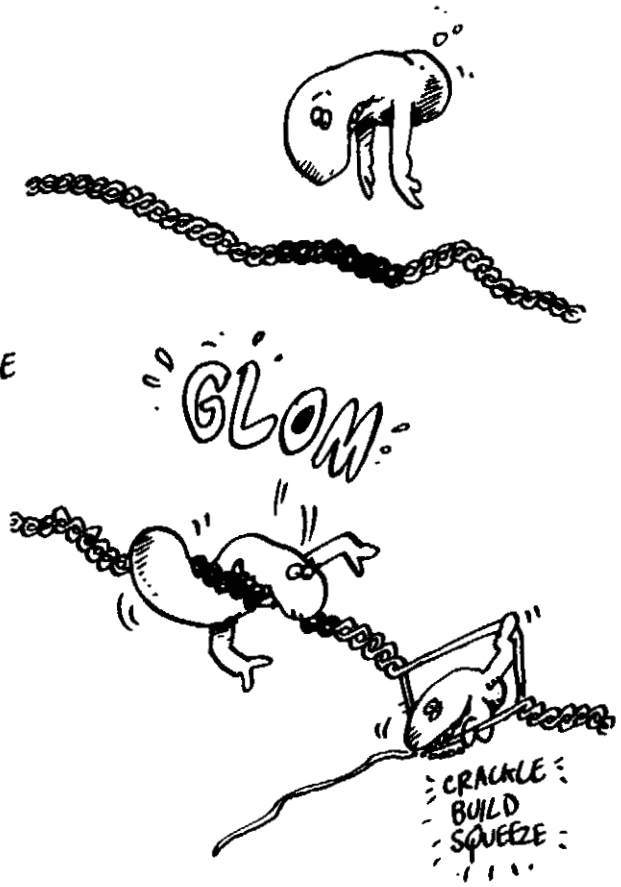
*REAL NAMES: BETA-GALACTOSIDASE AND PERMEASE, RESPECTIVELY


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":
lac Y
lac P
lac O
lac Z
WE'RE ABOUT TO EXPLAIN THIS PART!
AH LAC TH' GRAND OLE 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.)
MMM!

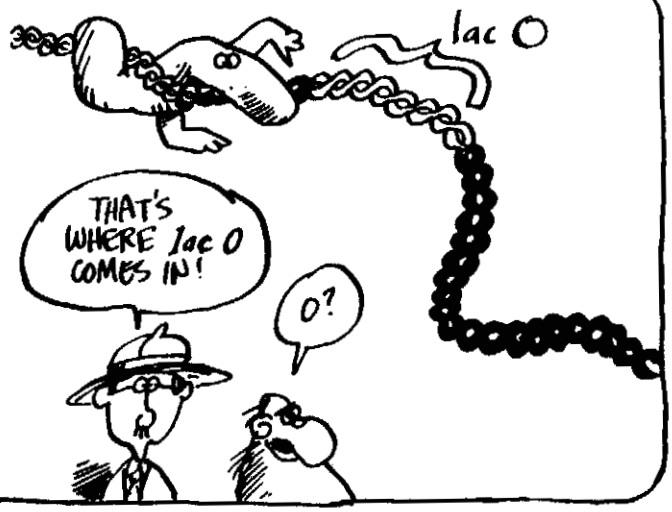
The first

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 ??

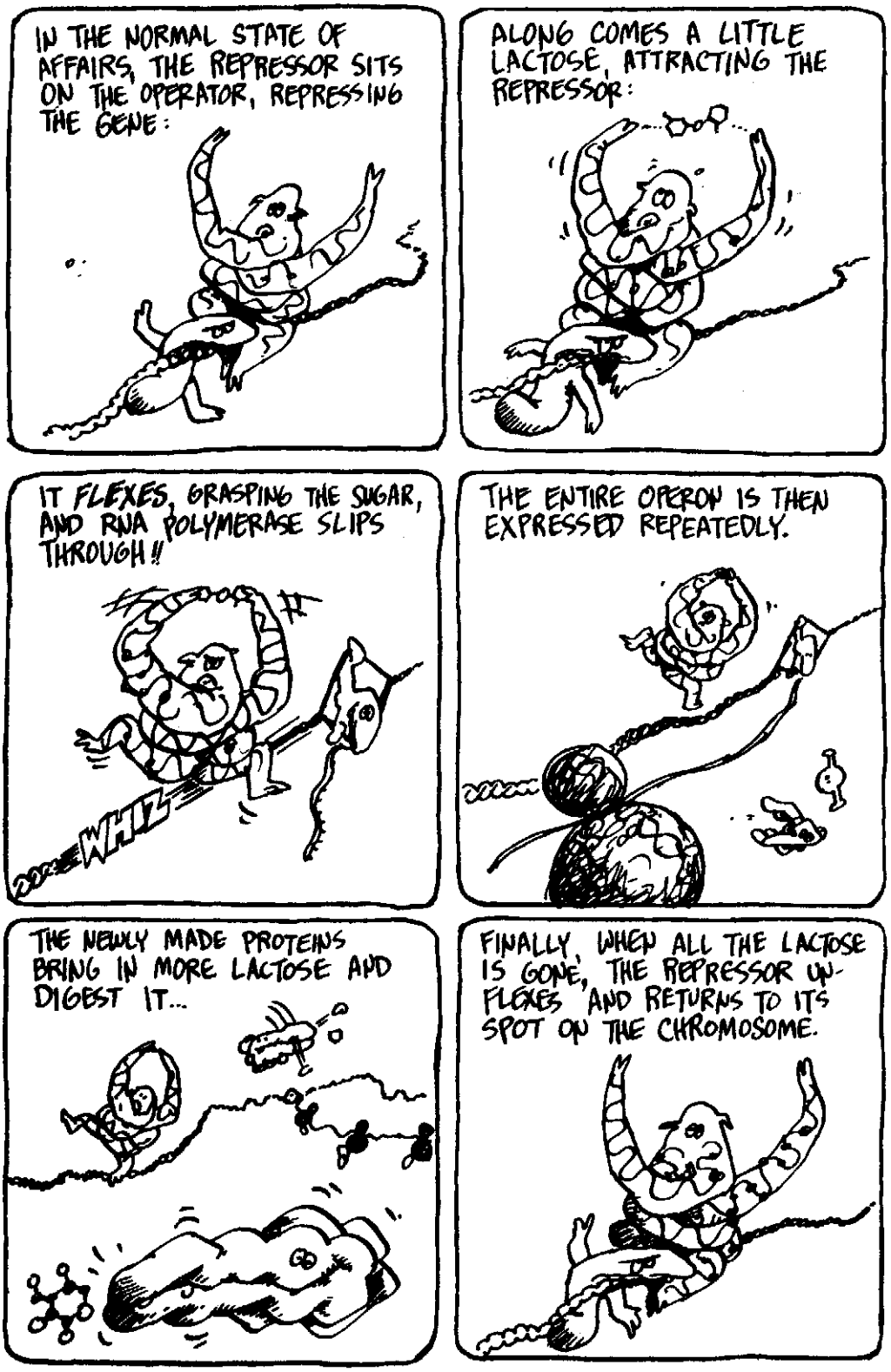


MONOD + JACOB'S IDEA:
THERE IS A PROTEIN,
THE REPRESSOR,
WHICH SITS ON THE DNA
AT A SPOT BETWEEN
THE PROMOTER AND
THE FIRST GENE, lacZ.
THIS SPOT IS CALLED
THE OPERATOR,
lac O.

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!!
WHIZ
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.

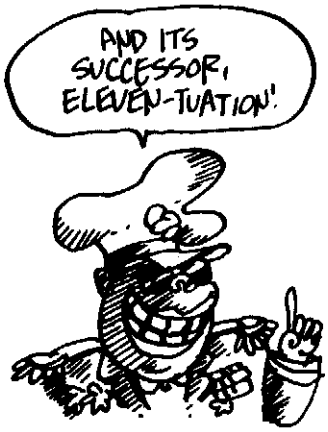
REPRESSORS TURN OUT TO BE A COMMON WAY TO REGULATE "INDUCIBLE" ENZYMES— I.E., ENZYMES WHICH ARE MADE IN RESPONSE TO A CHEMICAL-LIKE LACTOSE... BUT DESPITE THIS BRILLIANT IDEA, MONOD AND JACOB COULD NEVER ACTUALLY FIND A REPRESSOR. IT REMAINED A THEORETICAL POSSIBILITY...

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

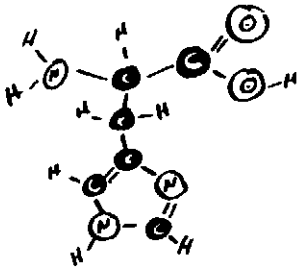
THEIR RESULTS MADE PLAIN WHY IT HAD BEEN SO HARD TO FIND THEM: A SINGLE *E. COLI* BACTERIUM HAS ONLY *FIVE* TO *TEN* MOLECULES OF LAC REPRESSOR. LATER, GILBERT MANAGED TO BREED MUTANT *E. COLI* THAT PRODUCED IT IN MUCH LARGER AMOUNTS....

ANOTHER METHOD OF GENE REGULATION GOES BY THE NAME OF:

ATTENUATION

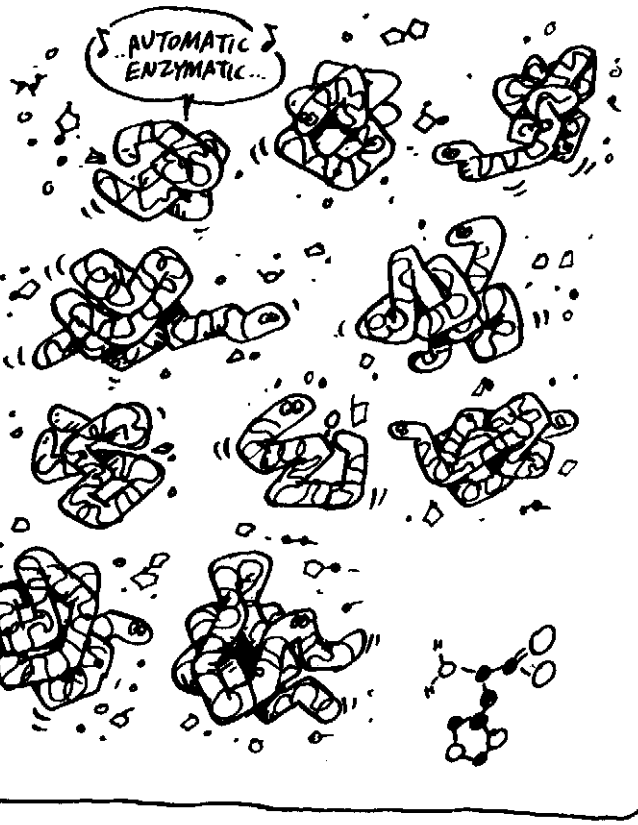


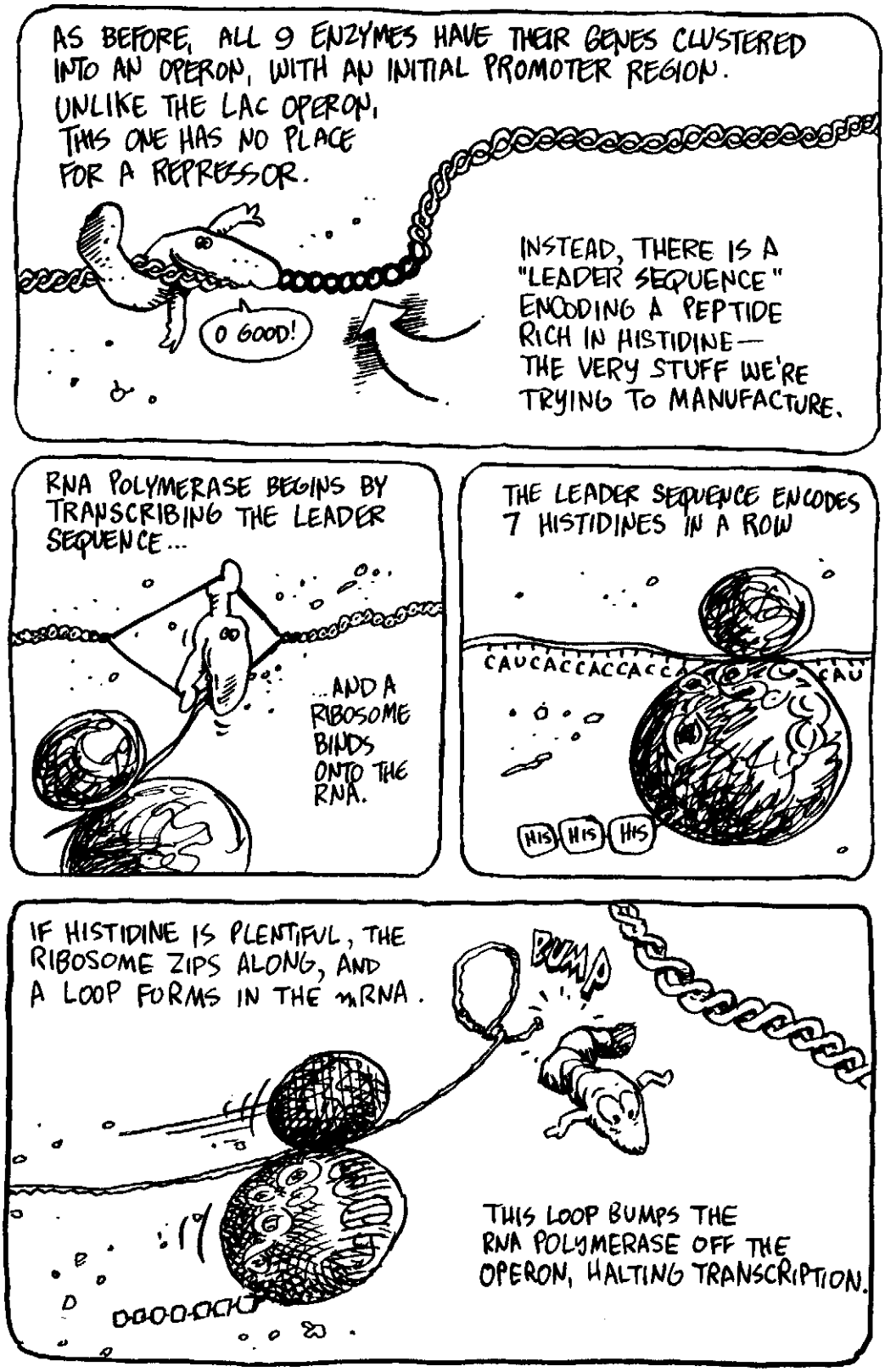
THIS GOVERNS AN E. COLI OPERON RESPONSIBLE FOR CONSTRUCTING THE AMINO ACID *HISTIDINE*.

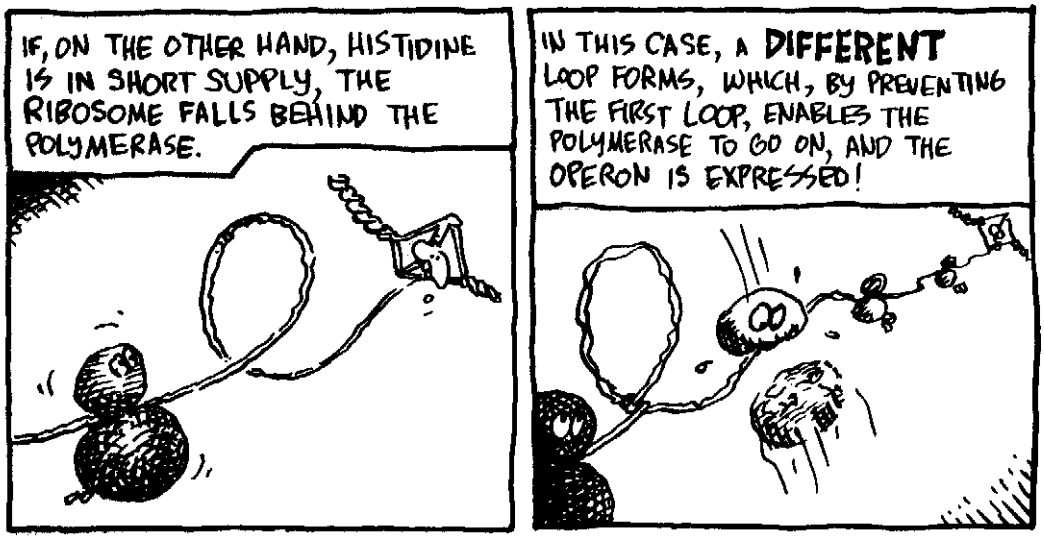


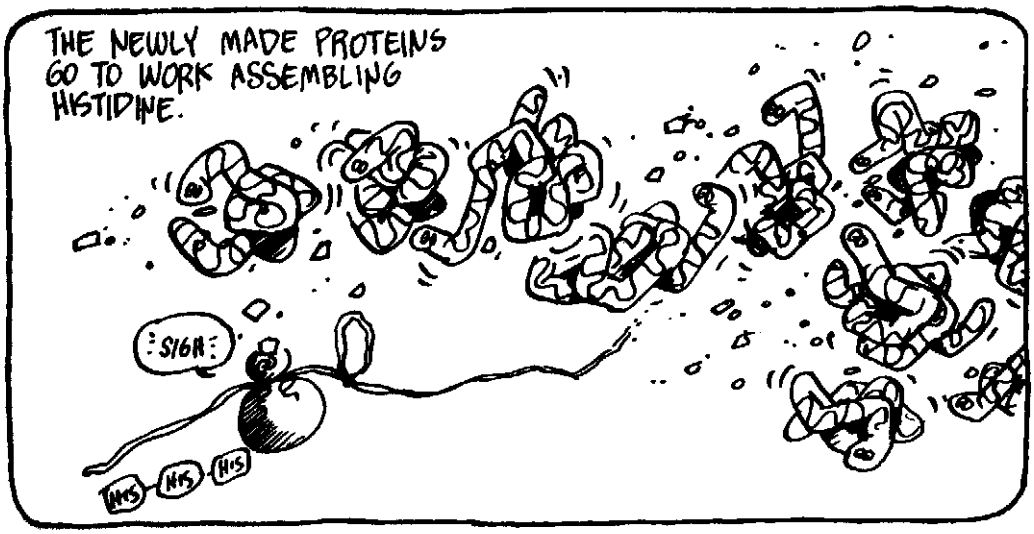
WHEN E. COLI RUNS LOW ON THIS ESSENTIAL STUFF, THE BACTERIUM PRODUCES A GROUP OF *NINE* PROTEINS, WHICH CAN BUILD HISTIDINE MOLECULES FROM SCRATCH.

AN ENZYMATIC ASSEMBLY LINE!



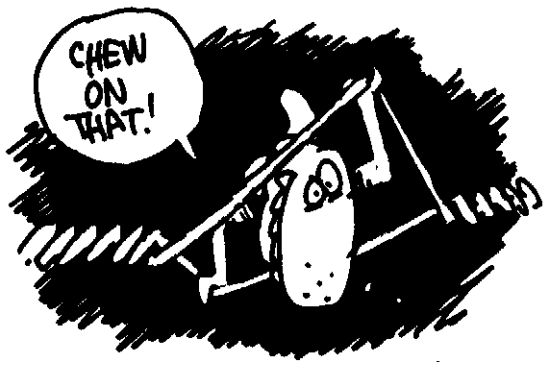

AS BEFORE, ALL 9 ENZYMES HAVE THEIR GENES CLUSTERED INTO AN OPERON, WITH AN INITIAL PROMOTER REGION.
UNLIKE THE LAC OPERON, THIS ONE HAS NO PLACE FOR A REPRESSOR.
O GOOD!
INSTEAD, THERE IS A "LEADER SEQUENCE" ENCODING A PEPTIDE RICH IN HISTIDINE— THE VERY STUFF WE'RE TRYING TO MANUFACTURE.
RNA POLYMERASE 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.

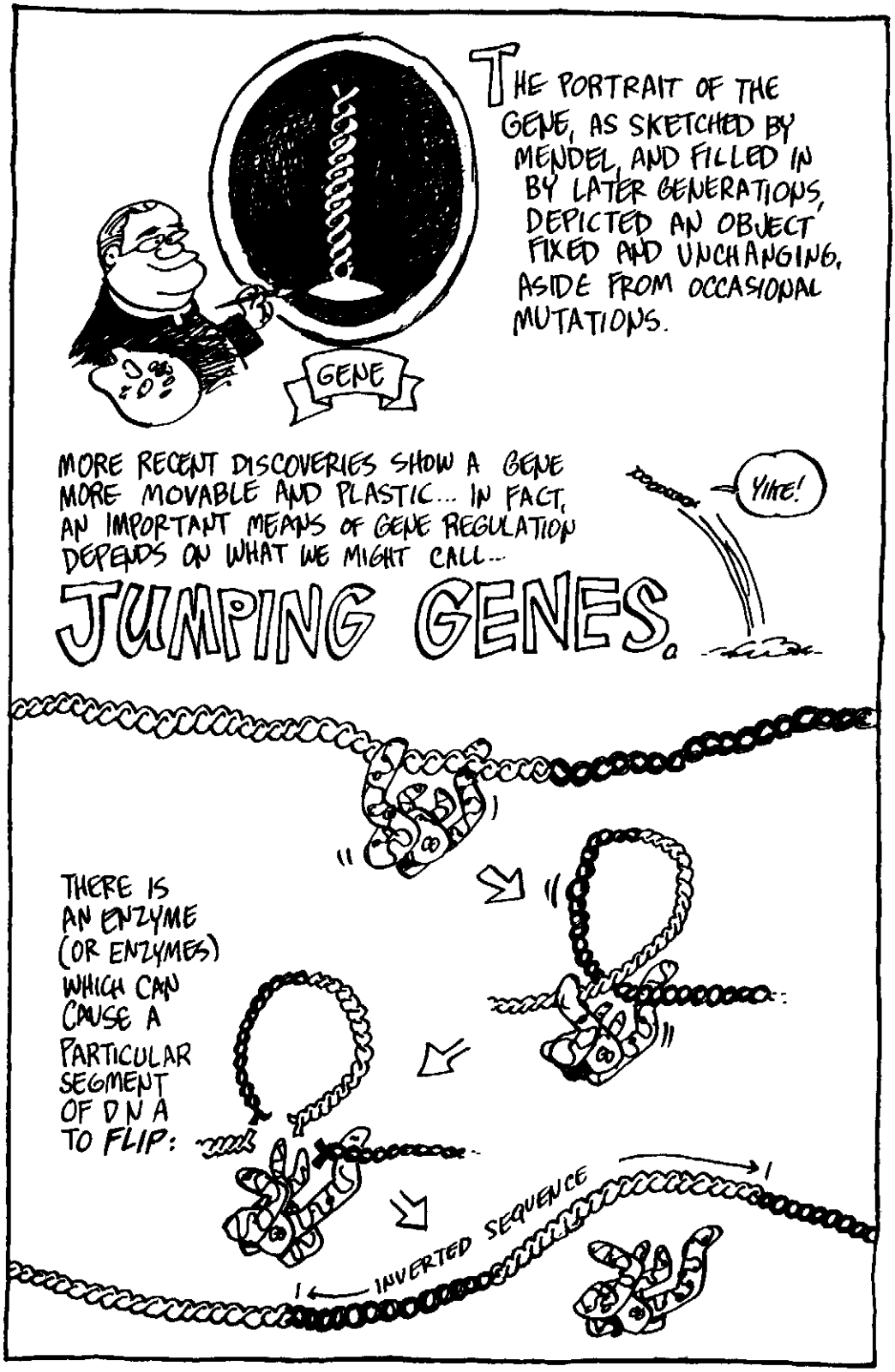


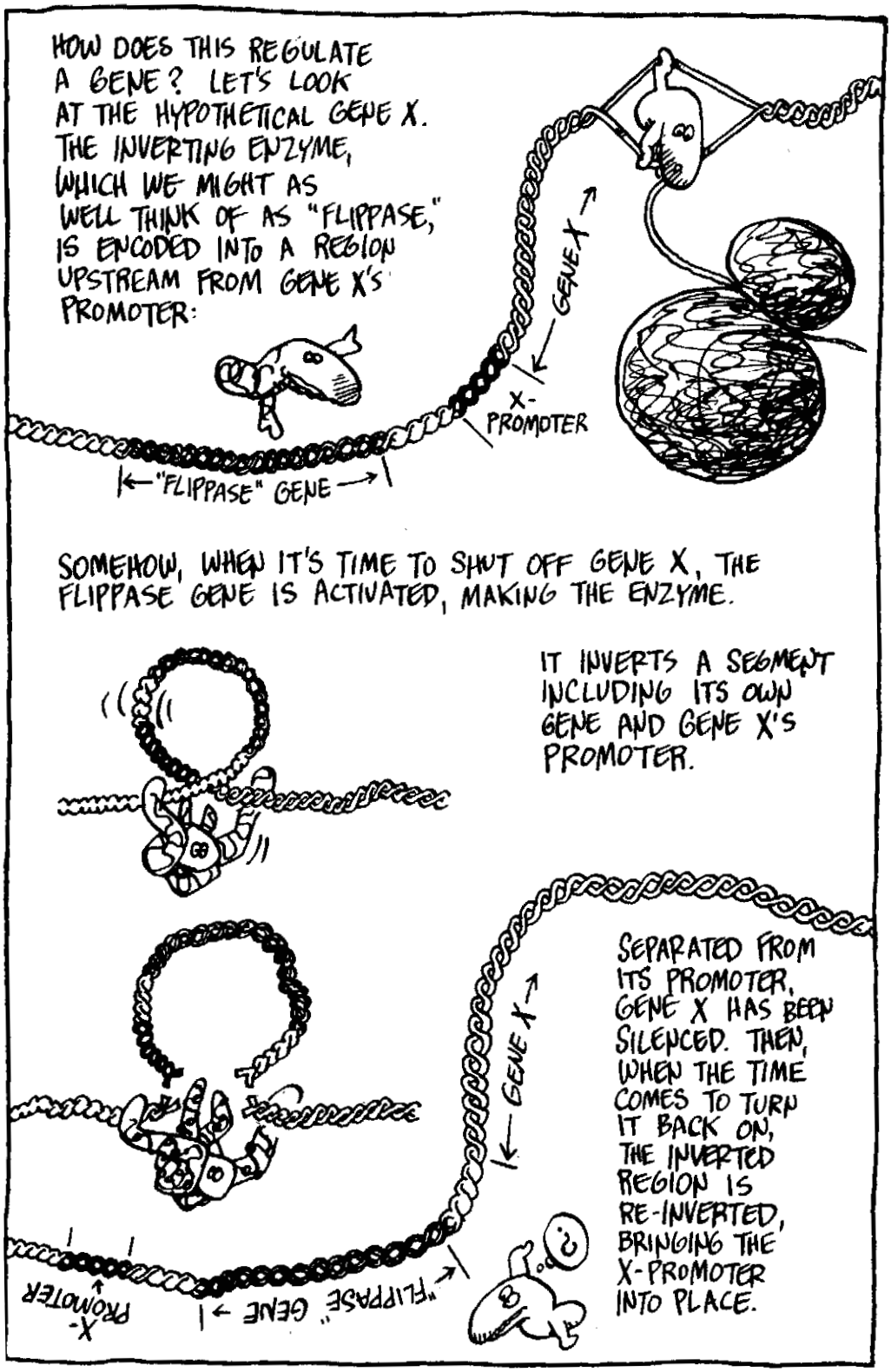


RESULT?

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

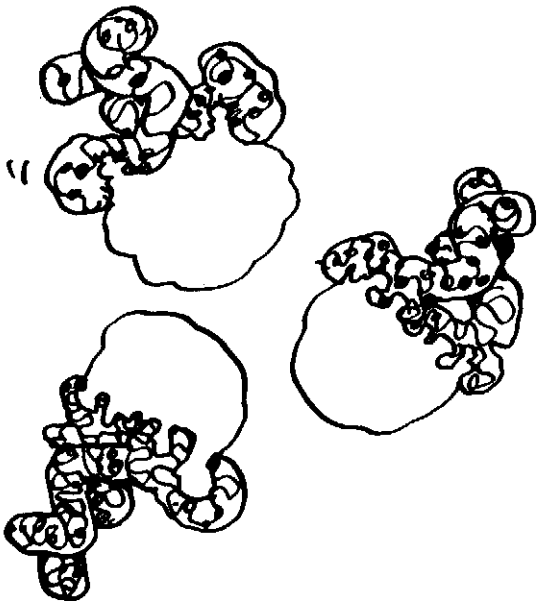



GENE
THE PORTRAIT OF THE GENE, AS SKETCHED BY MENDEL, AND FILLED IN BY LATER GENERATIONS, DEPICTED AN OBJECT FIXED AND UNCHANGING, ASIDE FROM OCCASIONAL MUTATIONS.
MORE RECENT DISCOVERIES SHOW A GENE MORE MOVABLE AND PLASTIC... IN FACT, AN IMPORTANT MEANS OF GENE REGULATION DEPENDS ON WHAT WE MIGHT CALL...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

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?

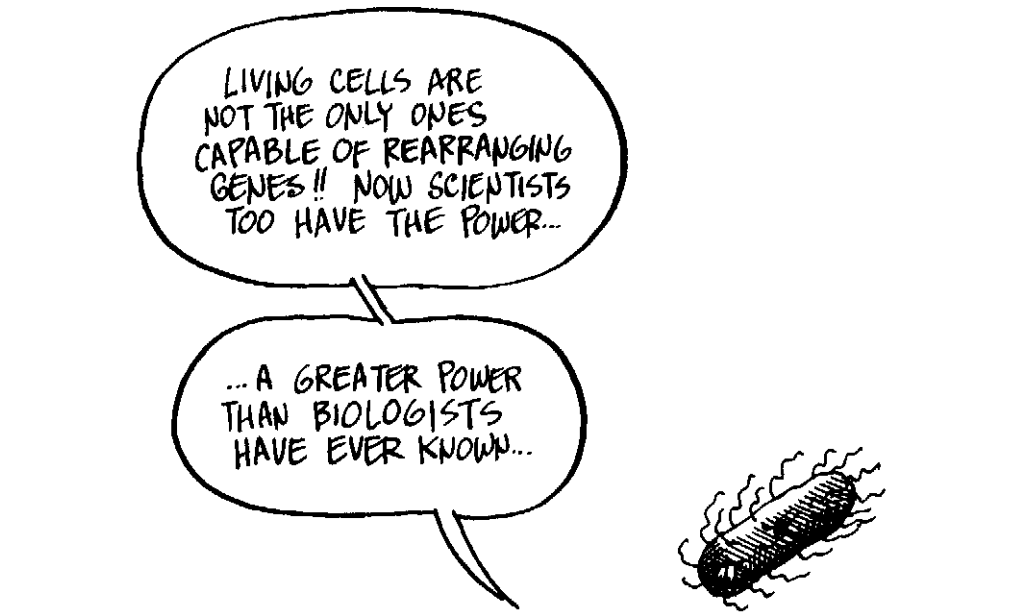
RATHER THAN HAVING BILLIONS OF GENES FOR ANTIBODIES, THE CHROMOSOMES CARRY A "TOOL KIT" OF A FEW HUNDRED *PARTIAL GENES*.

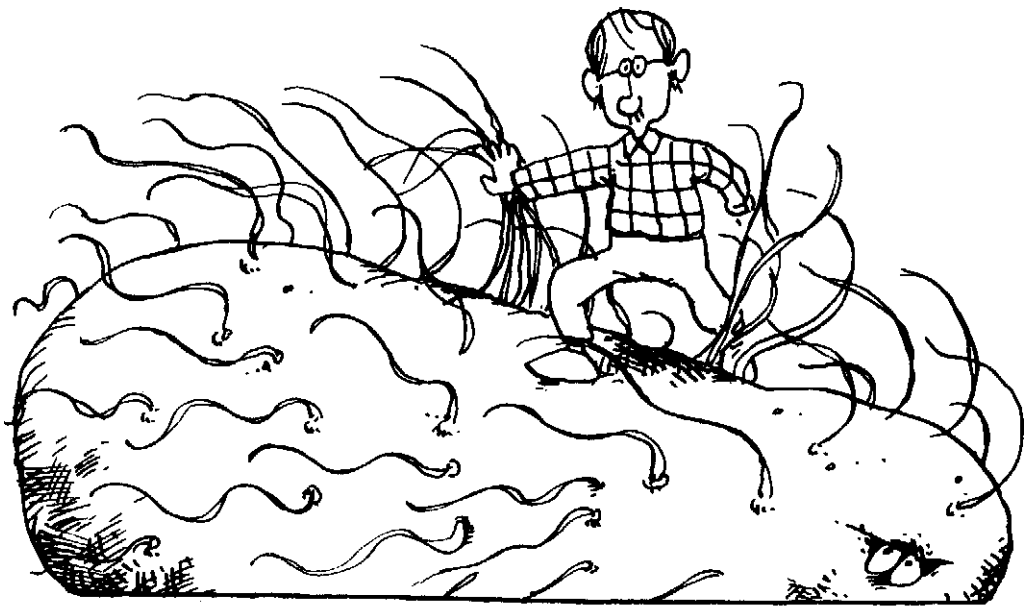
IN CERTAIN CELLS, THESE BITS OF DNA ARE CUT UP AND REARRANGED, EACH RECOMBINATION SPELLING OUT THE GENE OF A PARTICULAR ANTIBODY.

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.

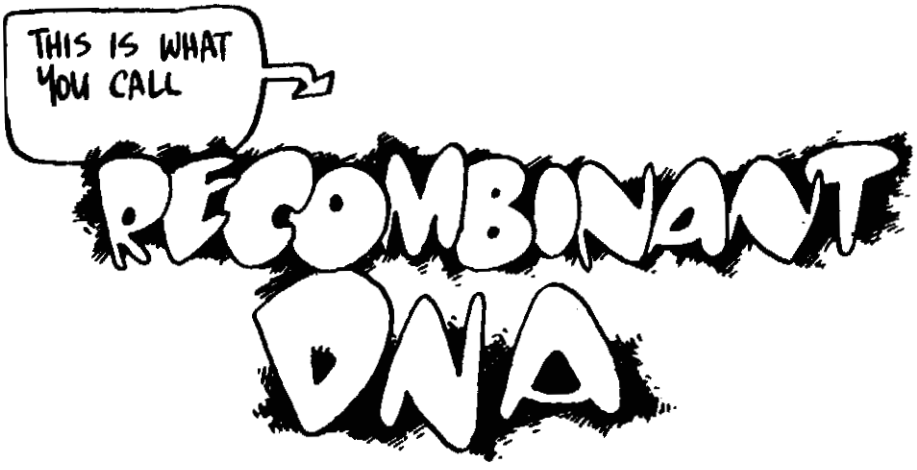
IT'S CLEAR THAT THE FLEXIBLE GENES OF EUCARYOTES WILL BE AN ACTIVE AREA OF RESEARCH IN YEARS TO COME.

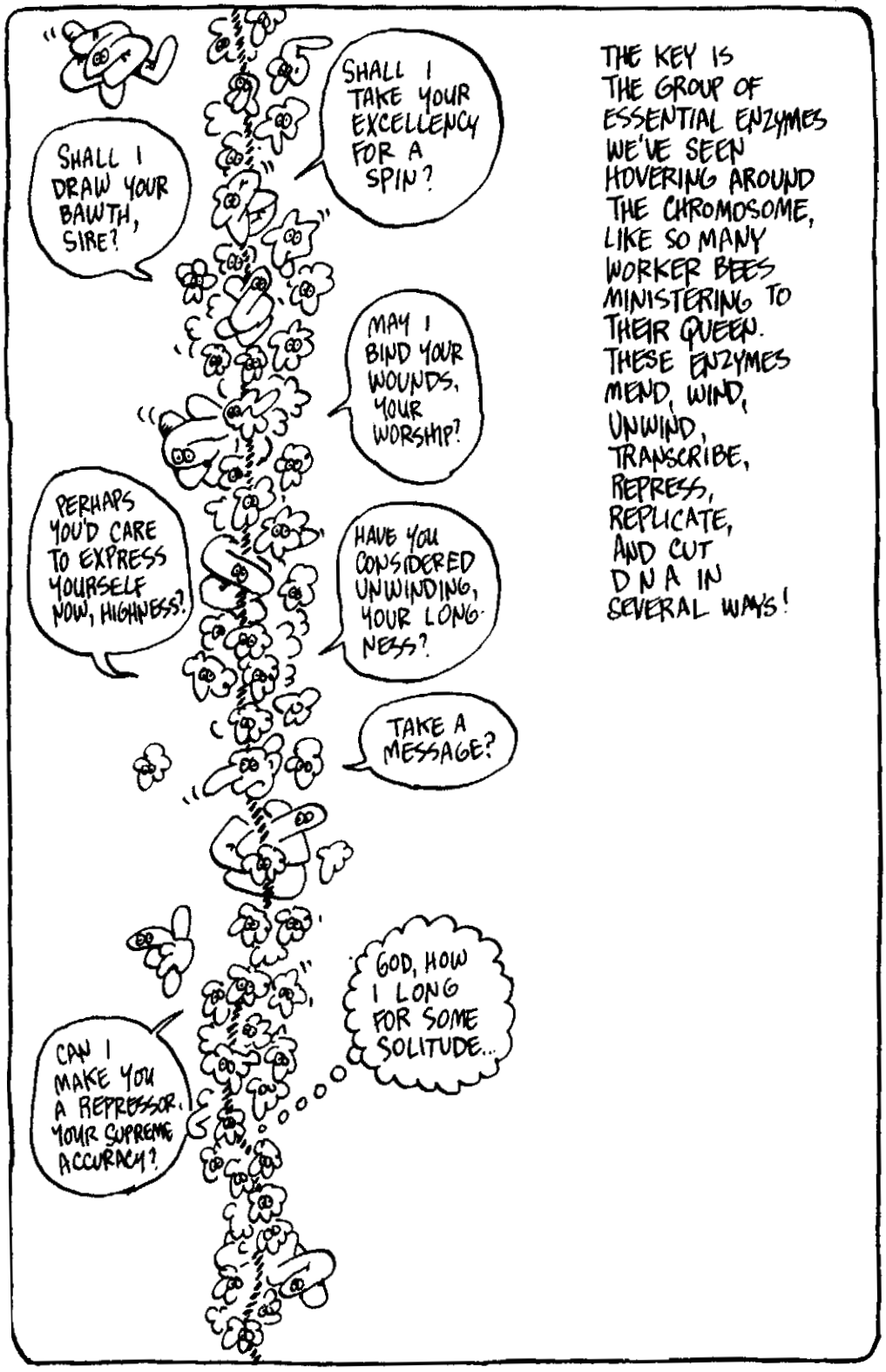
GENETIC ENGINEERING





THE COMBINATIONS CAN BE PRETTY BIZARRE: MOST COMMONLY, HUMAN GENES ARE ATTACHED TO THOSE OF A BACTERIUM, LIKE *E. COLI*...



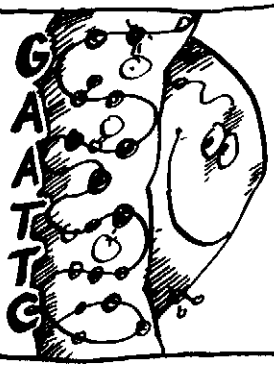

SHALL I DRAW YOUR BAWTH, SIRE?
SHALL I TAKE YOUR EXCELLENCY FOR A SPIN?
MAY I BIND YOUR WOUNDS, YOUR WORSHIP?
PERHAPS YOU'D CARE TO EXPRESS YOURSELF NOW, HIGHNESS?
HAVE YOU CONSIDERED UNWINDING, YOUR LONGNESS?
TAKE A MESSAGE?
GOD, HOW I LONG FOR SOME SOLITUDE...
CAN I MAKE YOU A REPRESSOR, YOUR SUPREME ACCURACY?
THE KEY IS THE GROUP OF ESSENTIAL ENZYMES WE'VE SEEN HOVERING AROUND THE CHROMOSOME, LIKE SO MANY WORKER BEES MINISTERING TO THEIR QUEEN. THESE ENZYMES MEND, WIND, UNWIND, TRANSCRIBE, REPRESS, REPLICATE, AND CUT DNA IN SEVERAL WAYS!

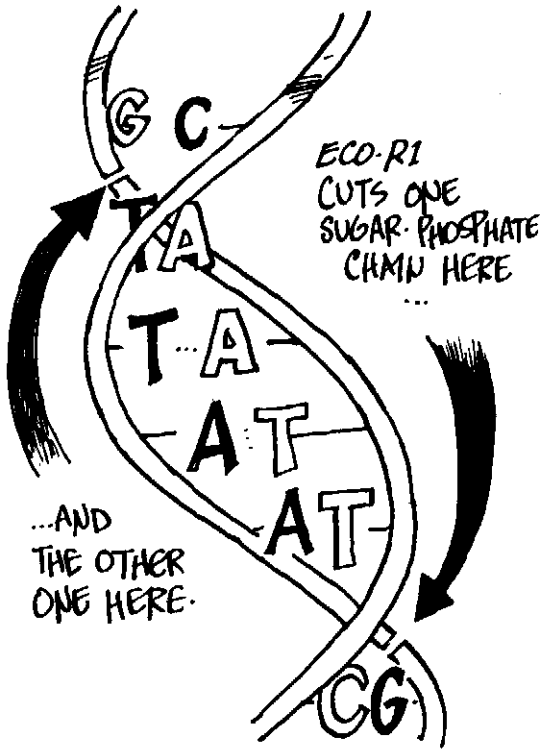
GENE SPLICING DEPENDS ON A SPECIAL TYPE OF CUTTING ENZYME CALLED A *RESTRICTION ENDONUCLEASE*, OR RESTRICTION ENZYME FOR SHORT.

A RESTRICTION ENZYME MAKES A "STAGGERED NICK" IN DNA AT A SPECIFIC SEQUENCE OF BASES.

THE ENZYME *ECO·R1*, FOR EXAMPLE, RECOGNIZES ONLY THE SEQUENCE

-G-A-A-T-T-C-
-C-T-T-A-A-G-

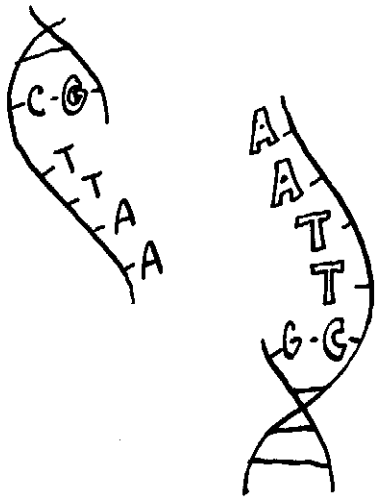


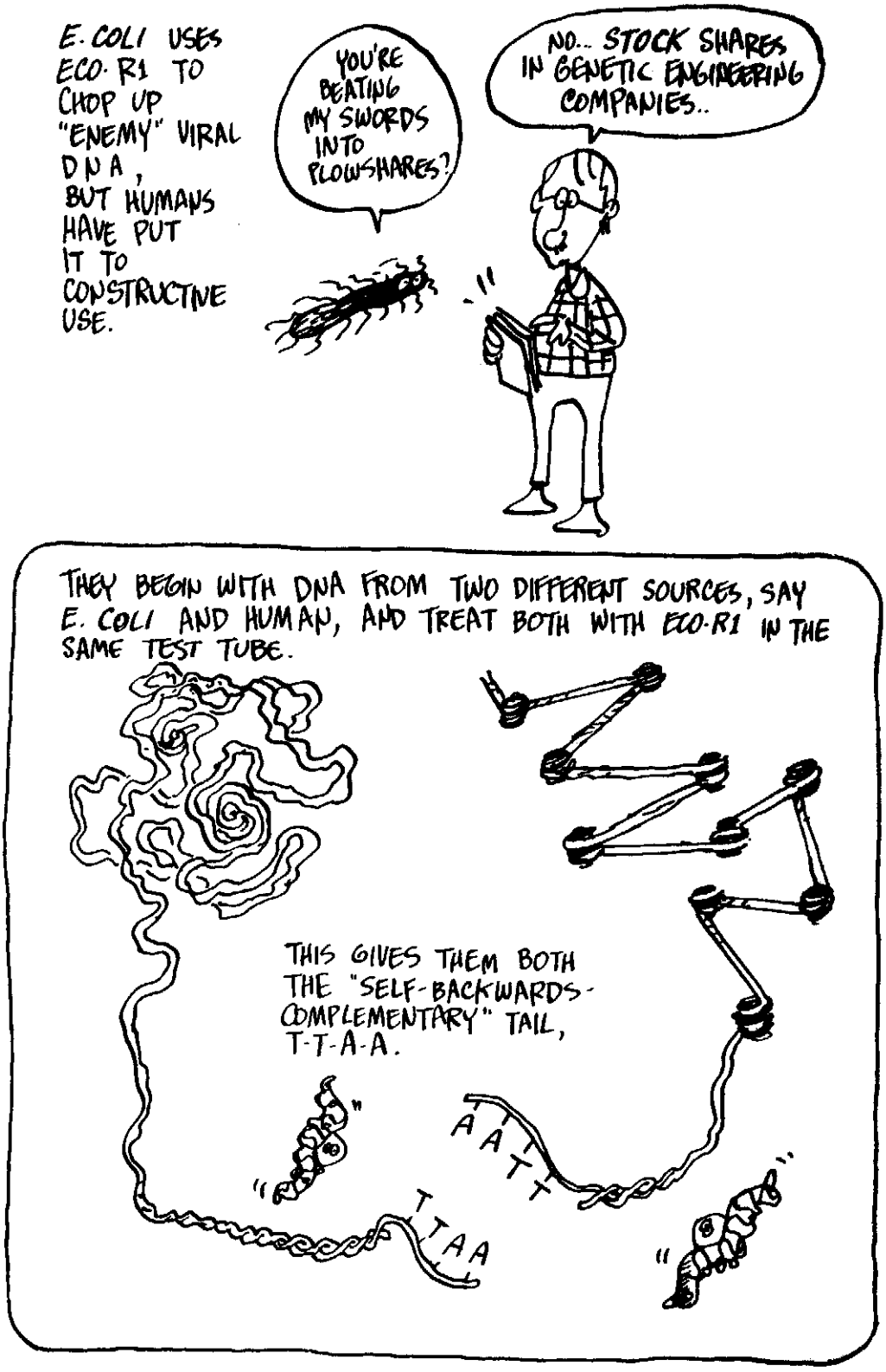


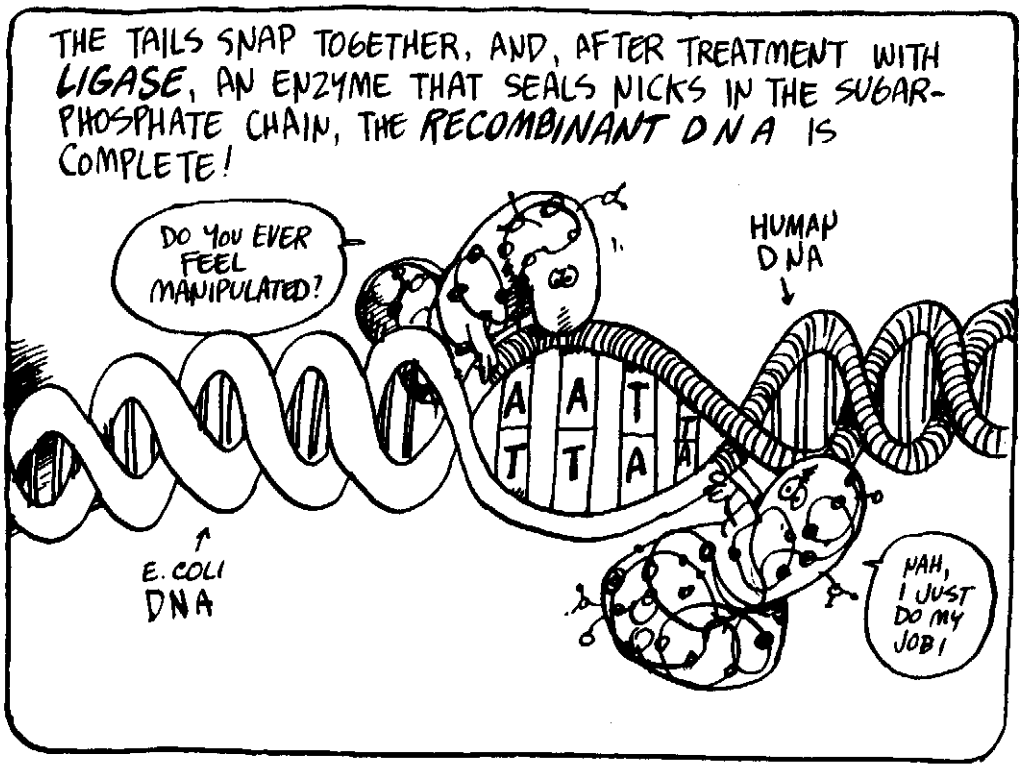
ECO·R1 CUTS ONE SUGAR·PHOSPHATE CHAIN HERE ...

...AND THE OTHER ONE HERE.

THIS CREATES TWO PIECES OF DNA WITH IDENTICAL T-T-A-A "TAILS." (BECAUSE C-T-T-A-A-G IS THE SAME AS ITS COMPLEMENT READ BACKWARDS!)




E. COLI USES ECO·R1 TO CHOP UP "ENEMY" VIRAL DNA, BUT HUMANS HAVE PUT IT TO CONSTRUCTIVE USE.
YOU'RE BEATING MY SWORDS INTO PLOWSHARES?
NO... STOCK SHARES IN GENETIC ENGINEERING COMPANIES..
THEY BEGIN WITH DNA FROM TWO DIFFERENT SOURCES, SAY E. COLI AND HUMAN, AND TREAT BOTH WITH ECO·R1 IN THE SAME TEST TUBE.
THIS GIVES THEM BOTH THE "SELF-BACKWARDS-COMPLEMENTARY" TAIL, T-T-A-A.
A A T T
T T A A


THE TAILS SNAP TOGETHER, AND, AFTER TREATMENT WITH LIGASE, AN ENZYME THAT SEALS NICKS IN THE SUGAR-PHOSPHATE CHAIN, THE RECOMBINANT DNA IS COMPLETE!
DO YOU EVER FEEL MANIPULATED?
HUMAN DNA
A
T
A
T
T
A
A
T
E. COLI DNA
NAH, I JUST DO MY JOB!

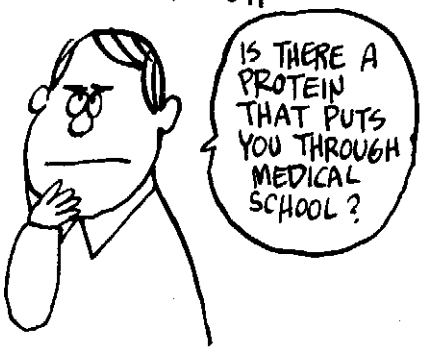

WHAT CAN YOU DO WITH THIS HYBRID MOLECULE? WHAT HAPPENS WHEN RECOMBINANT DNA IS INSERTED INTO A LIVING SYSTEM?
UNDER SOME CONDITIONS, IT TURNS OUT THAT GENE SPLICING CAN BE USEFUL IN PRACTICE...
USEFUL?
IN PRACTICE?
HOW QUAINT!

THE TECHNIQUE IS CALLED

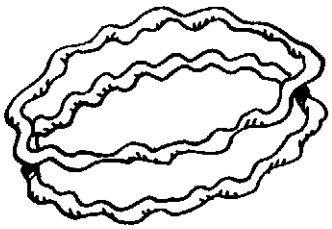
GENE CLONING,

AND IT WORKS LIKE THIS:

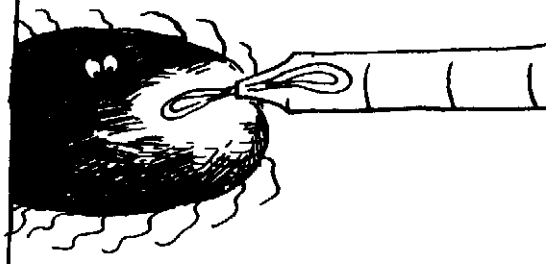
FIRST, CHOOSE A HUMAN GENE ENCODING SOME USEFUL PROTEIN.



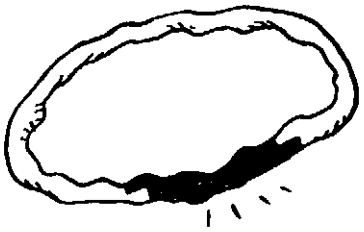
FOR YOUR BACTERIAL DNA, YOU NEED SOMETHING THAT WILL BE REPLICATED ONCE IT'S RETURNED TO THE CELL — A "*VECTOR*," SO-CALLED.



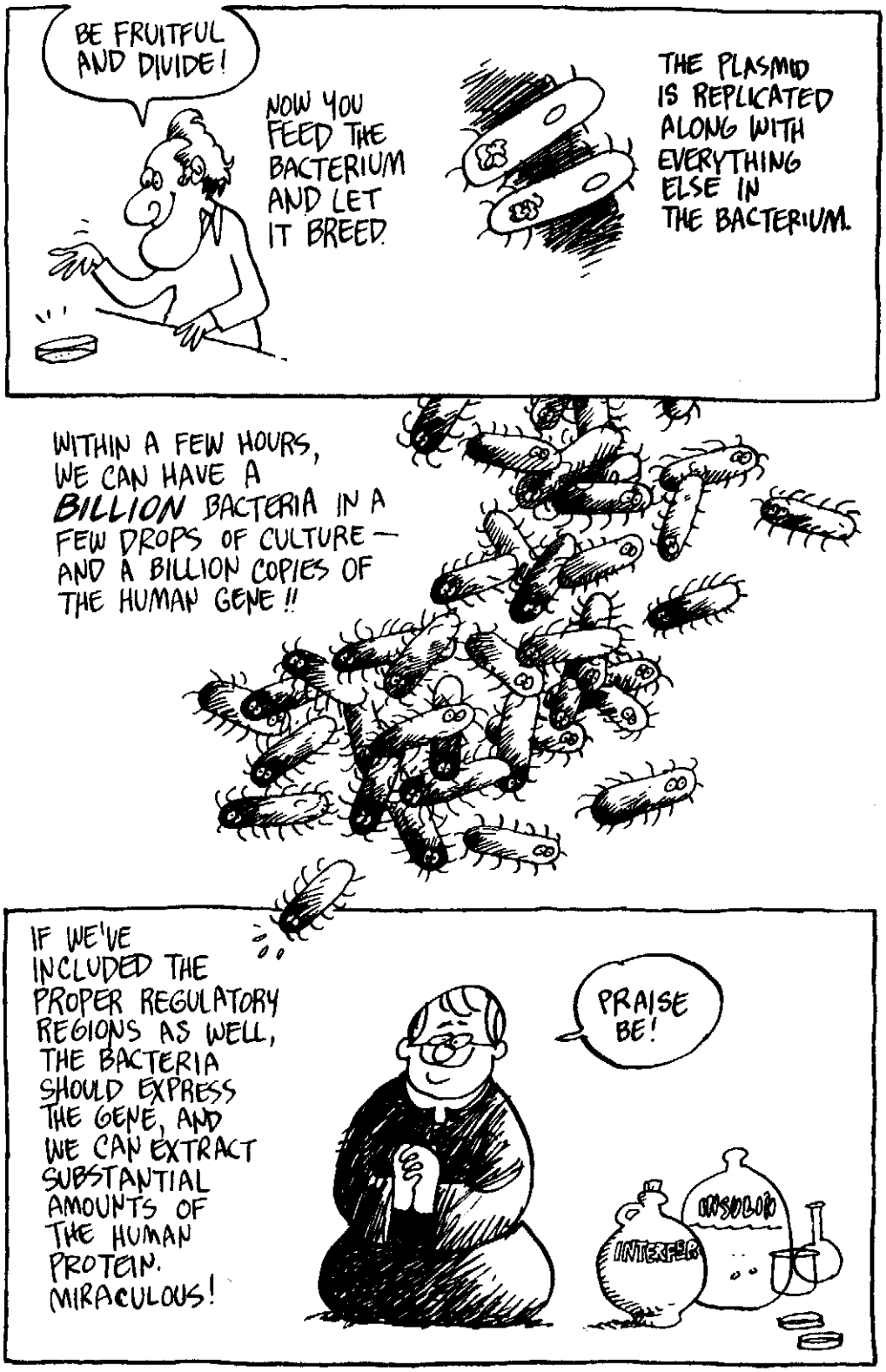
LUCKILY, *E. COLI* HAS SMALL RINGS OF DNA CALLED *PLASMIDS*, SEPARATE FROM THE CHROMOSOME. YOU CHOOSE (OR ENGINEER!) A PLASMID CONTAINING THE SEQUENCE *G·A·A·T·T·C*, AND REMOVE IT FROM THE BACTERIUM.



JUST AS ABOVE, YOU *SPLICE* THE HUMAN GENE INTO THE PLASMID —



AND PUT IT BACK INTO *E. COLI*.

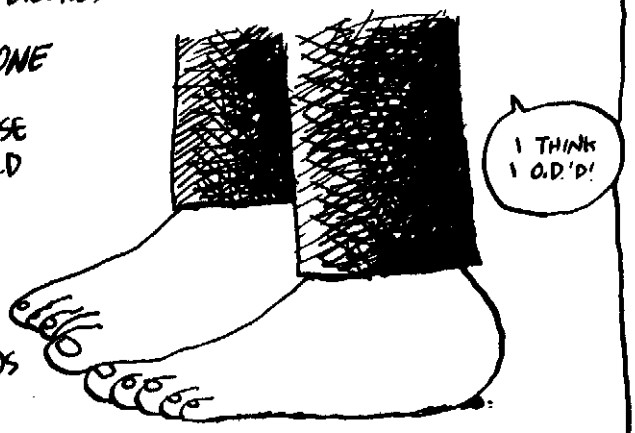

BE FRUITFUL AND DIVIDE!
NOW YOU FEED THE BACTERIUM AND LET IT BREED
THE PLASMID IS REPLICATED ALONG WITH EVERYTHING ELSE IN THE BACTERIUM.
WITHIN A FEW HOURS, WE CAN HAVE A BILLION BACTERIA IN A FEW DROPS OF CULTURE — AND A BILLION COPIES OF THE HUMAN GENE!!
IF WE'VE INCLUDED THE PROPER REGULATORY REGIONS AS WELL, THE BACTERIA SHOULD EXPRESS THE GENE, AND WE CAN EXTRACT SUBSTANTIAL AMOUNTS OF THE HUMAN PROTEIN. MIRACULOUS!
PRAISE BE!
INTERFER

THE PROCEDURE SOUNDS SIMPLE — AND, IN PRINCIPLE, IT IS. IN PRACTICE IT CAN BE MOST COMPLICATED, BUT THE FOLKS IN THE LABS HAVE SOLVED MOST OF THOSE PRACTICAL PROBLEMS. WE CAN NOW CLONE JUST ABOUT ANY GENE WE WANT... USUALLY IN *E. COLI*, BUT OTHER FAST-GROWING ORGANISMS WORK, AS WELL, EVEN EUCARYOTES LIKE *YEAST* —

IT'S EVEN POSSIBLE TO CLONE GENES INTO HUMAN CELLS, BUT SO FAR IT ONLY WORKS IN A DISH, NOT IN A REAL PERSON...

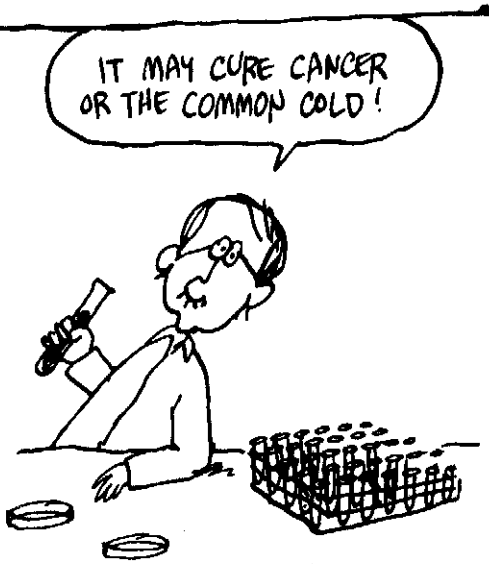
AT LEAST 3 PROTEINS NOW PRODUCED BY RECOMBINANT DNA HAVE MEDICAL POSSIBILITIES...

HUMAN GROWTH HORMONE PREVENTS ONE TYPE OF DWARFISM. PEOPLE WHOSE GENETIC MAKE-UP WOULD OTHERWISE LEAVE THEM A BIT "SHORT," CAN GROW NORMALLY IF GIVEN ADEQUATE DOSES. SO FAR, DEMAND STILL EXCEEDS SUPPLY, BUT NOT FOR "LONG"!



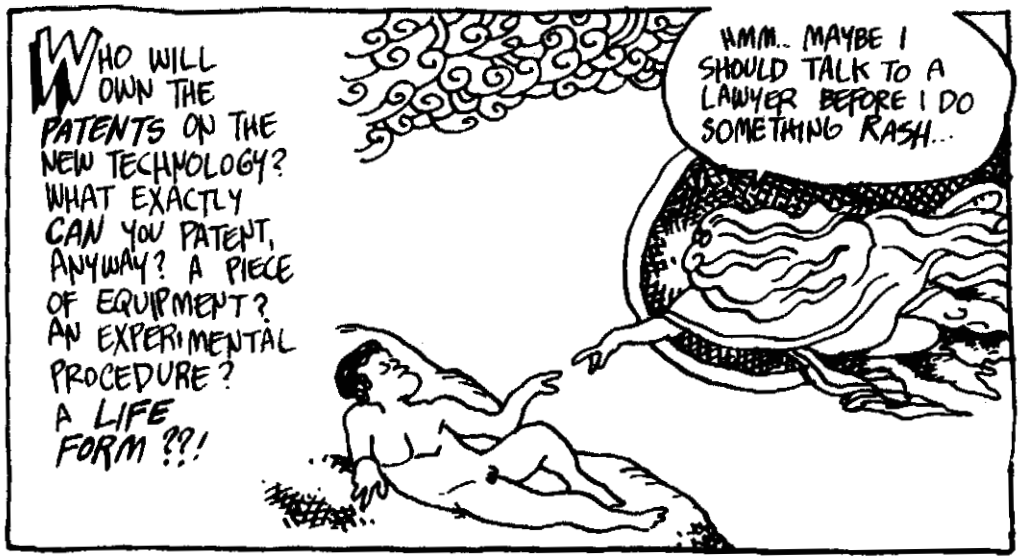
INSULIN, WHICH BREAKS DOWN SUGAR IN THE BLOOD, HAS LONG BEEN MADE BY OTHER MEANS... BUT SHOULD NOW BECOME MORE PLENTIFUL, AND POSSIBLY CHEAPER, MAKING LIFE EASIER FOR DIABETICS —

INTERFERON, THE VIRUS-FIGHTER, USED TO BE SO SCARCE IT COST A ***TRILLION DOLLARS*** AN OUNCE — BUT NOW IT'S MADE BY THE VATFUL BY TRILLIONS OF *E. COLI*. UNFORTUNATELY, NO ONE KNOWS EXACTLY WHAT TO DO WITH IT, THOUGH CLINICAL TRIALS CONTINUE AMID HIGH HOPES...

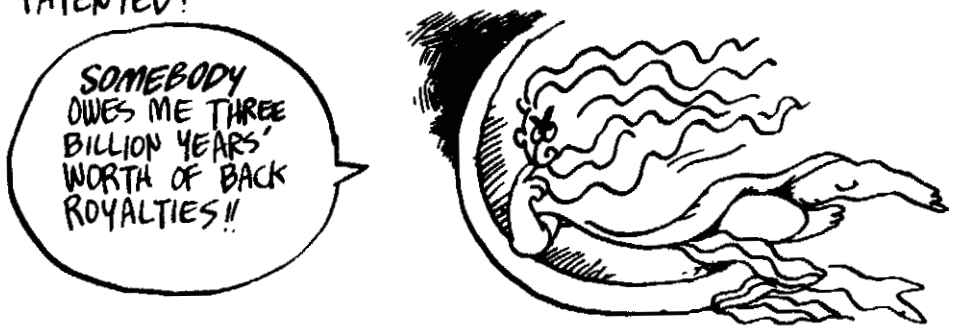



SUDDENLY, GENE-SPLICING HAS BECOME
BIG BUSINESS!
IT'S THE AMERICAN WAY!
ZOOM-ZYME
A GROWTH INDUSTRY
LURED BY THE PROSPECT OF PROFITS FROM PROTEINS, VENTURE CAPITALISTS HAVE BEEN ENTICING BIOLOGY PROFESSORS INTO A NEW SORT OF ENTERPRISE: THE GENETIC ENGINEERING COMPANY.
YOU'RE OUR KIND OF FOLKS, PROF-
YOU MAKE HUMAN PROTEIN FROM TINY BACTERIA - WE MAKE FORTUNES FROM MICROSCOPIC INVESTMENTS...
BACK IN THE UNIVERSITY, THIS IS THE CAUSE OF SOME CONCERN...
IS FREE INQUIRY POSSIBLE IF OUR DISCOVERIES BECOME TRADE SECRETS?
CAN OPEN RESEARCH BE GUIDED BY THE PROFIT MOTIVE?
DO WE WANT TO DIRTY OUR HANDS WITH MERE MONEY?


... WHICH HASN'T SLOWED THE GROWTH OF INDUSTRY AT ALL!!
WHERE DO I GET MY HANDS DIRTY??
THIS RAISES QUESTIONS OUTSIDE THE UNIVERSITY, TOO...
YES... WHERE'S THE AMBULANCE?



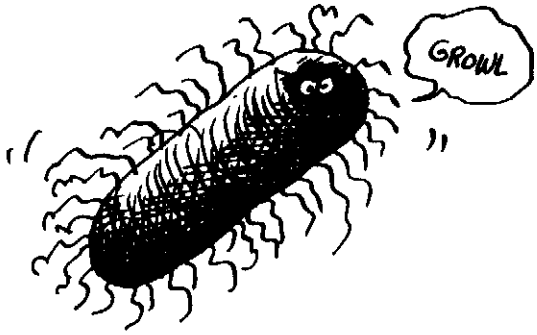
THIS QUESTION HAS ALREADY GONE TO THE SUPREME COURT, WHICH RULED THAT *NEWLY INVENTED LIFE FORMS* MAY BE PATENTED!



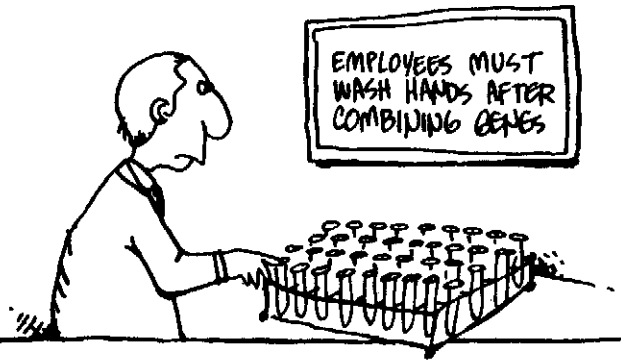
BUT FORGET ABOUT *MONEY*... WHAT ABOUT OUR *HEALTH*?? FROM THE FIRST DAYS OF GENETIC ENGINEERING, PEOPLE HAVE WORRIED ABOUT BREEDING *MONSTERS* IN THE LAB!!

THE FEAR WAS THAT TAMPERING WITH *E. COLI*'S DNA MIGHT CREATE A SUPER-DEADLY GERM BY ACCIDENT.

REMEMBER, *E. COLI* LIVES IN THE HUMAN INTESTINE — IF A VIRULENT STRAIN SHOULD ESCAPE FROM THE LAB, THERE MIGHT BE NO STOPPING IT!! WHO'D HAVE THOUGHT FRANKENSTEIN'S MONSTER WOULD LOOK LIKE THIS?



ACCORDINGLY, SCIENTISTS VOLUNTARILY ADOPTED GUIDELINES TO LIMIT POTENTIAL HAZARDS...



THE MOST ENCOURAGING THING IS THIS: THE STRAIN OF E. COLI USUALLY USED FOR CLONING GENES HAS GROWN SO "DOMESTICATED" DURING ITS YEARS IN THE LAB, THAT IT CAN NO LONGER SURVIVE IN THE HUMAN GUT!!

SO MAYBE THERE'S NOTHING TO WORRY ABOUT... THOUGH IT'S TRUE THAT THE SAFEGUARDS ADOPTED BY UNIVERSITIES DON'T GENERALLY APPLY TO PRIVATE COMPANIES!!!


WHAT'S MUCH MORE LIKELY IS THAT SOMEONE WILL MAKE A DEADLY GERM ON PURPOSE. AND WHO WOULD WANT TO DO THAT, YOU ASK?
I CAN'T IMAGINE!!!


THE GENERALS HAVE BEEN KNOWN TO TURN NEW TECHNOLOGY TO MILITARY USE, AND THEY USUALLY FIND SCIENTISTS TO OBLIGE...
REPEAT AFTER ME: "IT'S PURE RESEARCH!"
IT'S... PURE...
CONTRACT

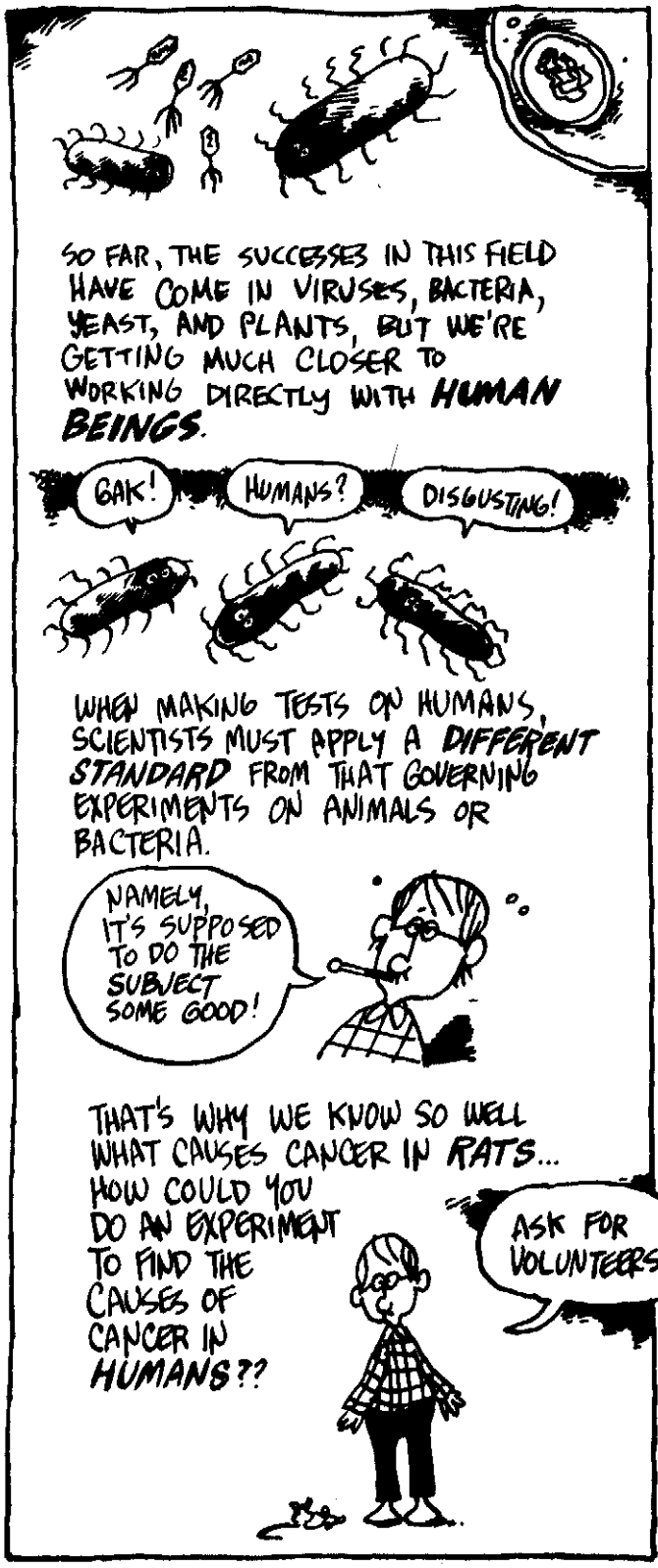
WE CAN TAKE SOME COMFORT FROM THE FACT THAT BIOLOGICAL WARFARE IS BANNED BY INTERNATIONAL TREATY, BUT YOU NEVER KNOW...

IT'S A POLITICAL QUESTION RAISED BY A SCIENTIFIC ADVANCE—A FAMILIAR FACT OF 20TH CENTURY LIFE.

DOES THIS POTENTIAL FOR HARM MEAN THAT GENE SPLICING SHOULD BE STOPPED?? ALMOST WITHOUT EXCEPTION, THE BIOLOGISTS SAY "NO." WHY REJECT THE MEDICAL ADVANCES ALONG WITH THE MILITARY USES??

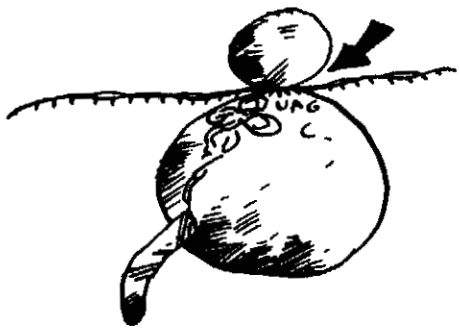
BESIDES, THE POISONS THAT COULD BE MADE THIS WAY ARE PROBABLY NO WORSE THAN THE ONES THAT ALREADY EXIST, WHILE MEDICAL ADVANCES PROMISE TO BE TRULY *REVOLUTIONARY*.

ON THE VERGE

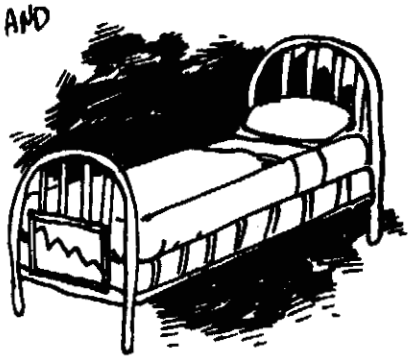

SO FAR, THE SUCCESSES IN THIS FIELD HAVE COME IN VIRUSES, BACTERIA, YEAST, AND PLANTS, BUT WE'RE GETTING MUCH CLOSER TO WORKING DIRECTLY WITH HUMAN BEINGS.
GAK!
HUMANS?
DISGUSTING!
WHEN MAKING TESTS ON HUMANS, SCIENTISTS MUST APPLY A DIFFERENT STANDARD FROM THAT GOVERNING EXPERIMENTS ON ANIMALS OR BACTERIA.
NAMELY, IT'S SUPPOSED TO DO THE SUBJECT SOME GOOD!
THAT'S WHY WE KNOW SO WELL WHAT CAUSES CANCER IN RATS... HOW COULD YOU DO AN EXPERIMENT TO FIND THE CAUSES OF CANCER IN HUMANS??
ASK FOR VOLUNTEERS?

..WHICH IS TO SAY, EXPERIMENTS ON HUMANS STIR UP CONTROVERSY, A GOOD EXAMPLE BEING RECENT ATTEMPTS TO TREAT *THALASSEMIA*.

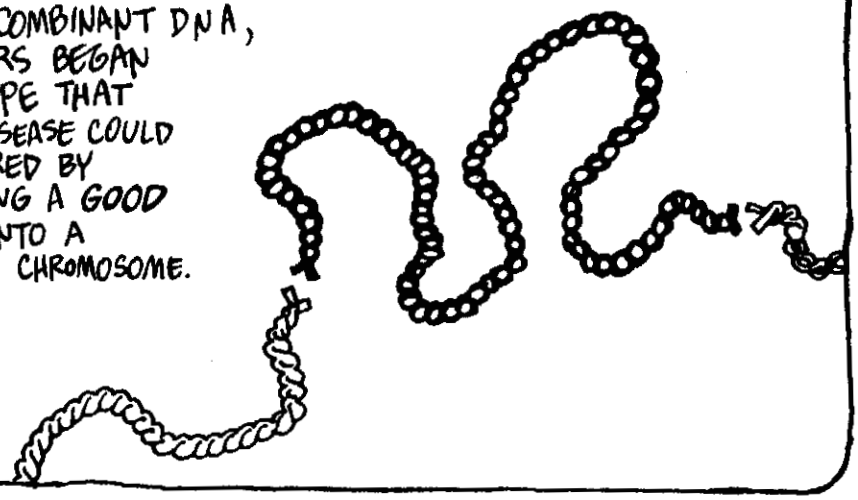
AS YOU RECALL, THIS CONDITION IS AN INABILITY TO MAKE ***HEMOGLOBIN***, CAUSED BY A MISTAKEN "STOP" CODON IN THE MIDDLE OF THE GENE FOR ONE OF ITS CHAINS.

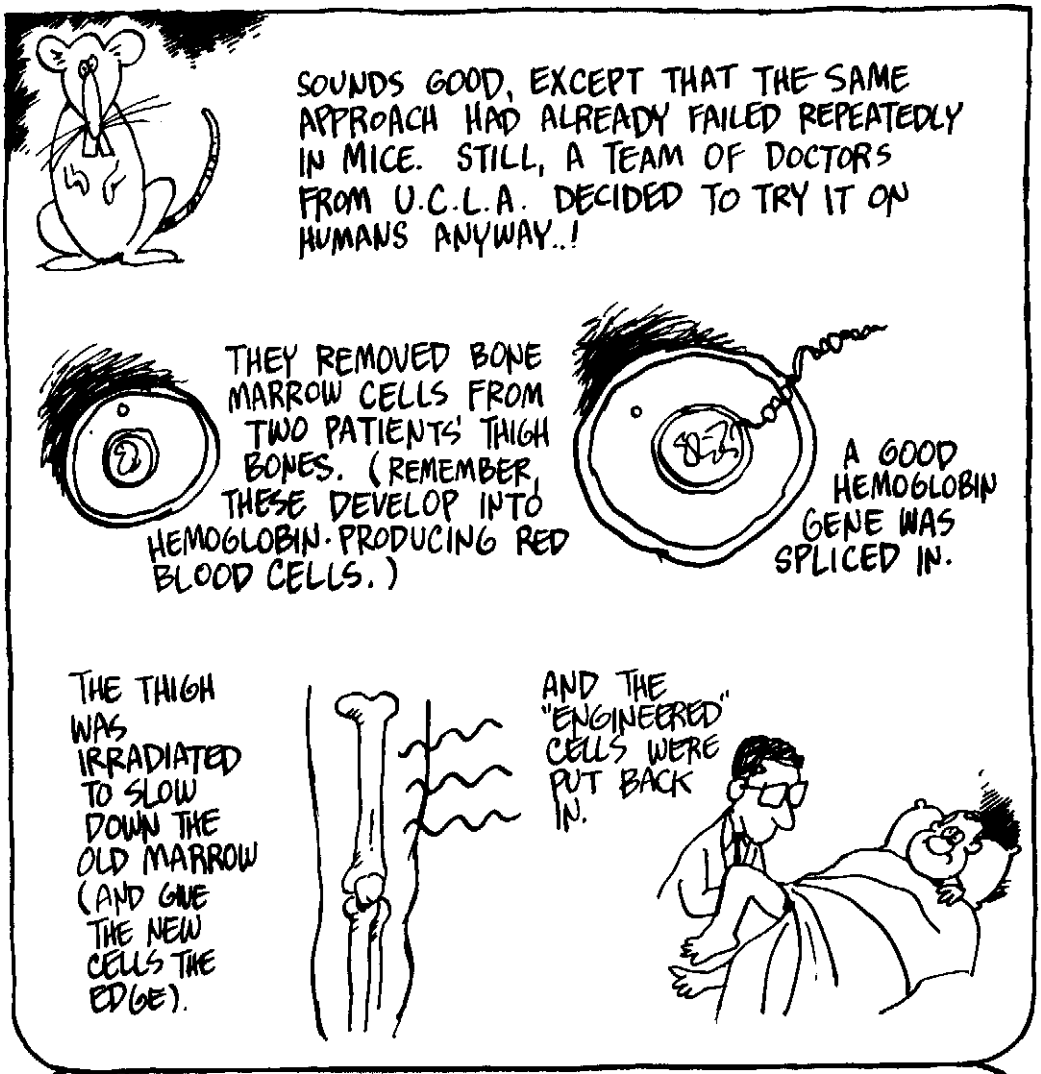


THALASSEMIA VICTIMS CAN SUFFER FROM ANEMIA, BONE DEFORMITIES, AND HEART PROBLEMS. THEY REQUIRE FREQUENT BLOOD TRANSFUSIONS TO SURVIVE, AND EVEN THEN THEY DON'T LIVE LONG.

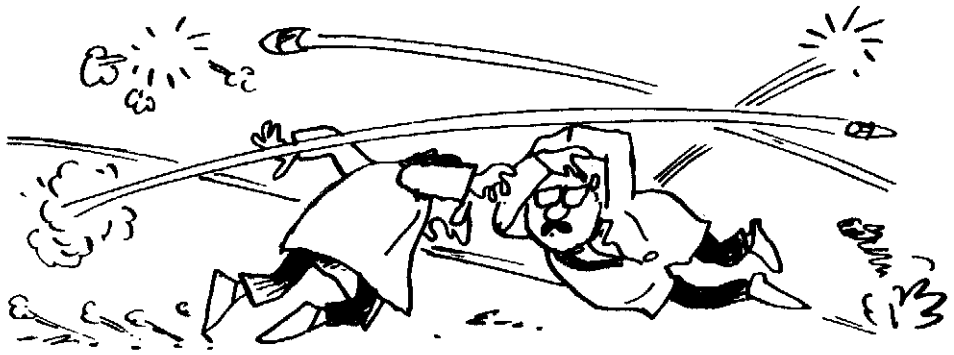


WITH THE SUCCESS OF RECOMBINANT DNA, DOCTORS BEGAN TO HOPE THAT THE DISEASE COULD BE CURED BY SPLICING A *GOOD* GENE INTO A HUMAN CHROMOSOME.

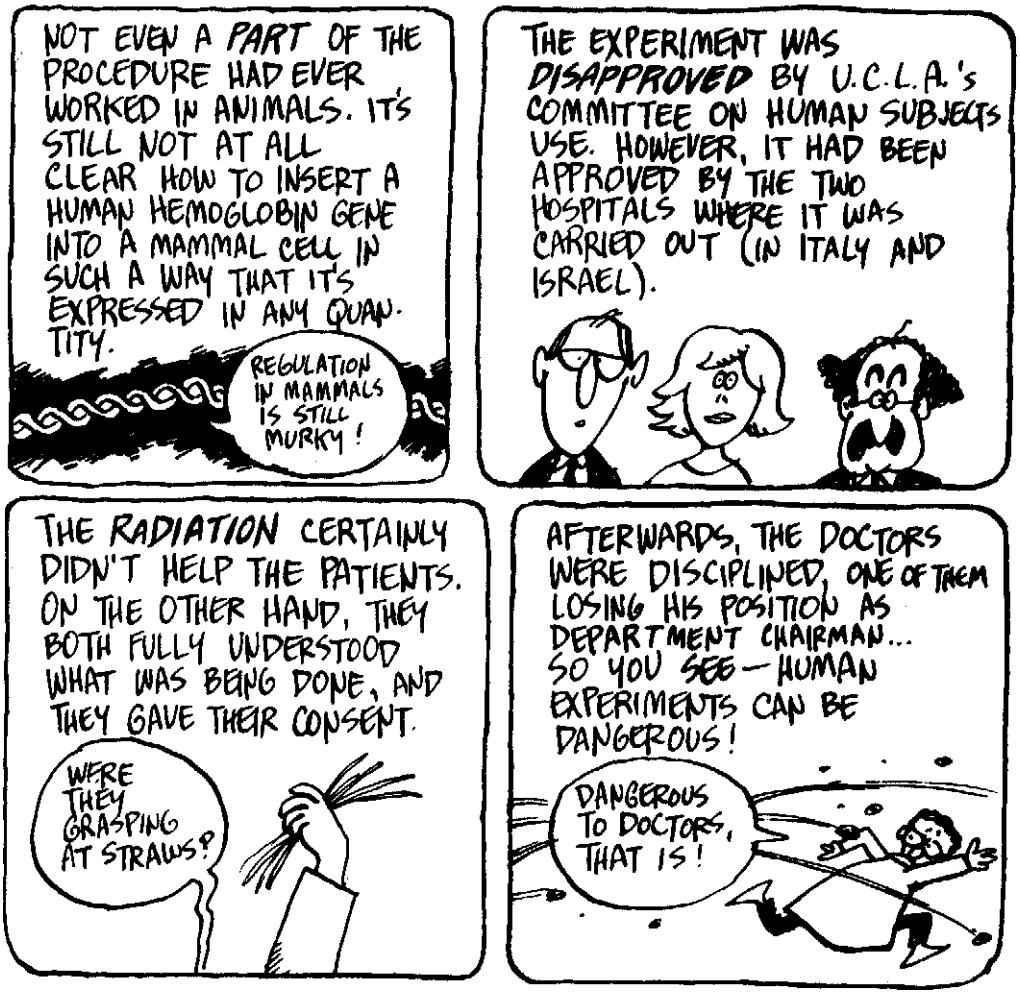



SOUNDS GOOD, EXCEPT THAT THE SAME APPROACH HAD ALREADY FAILED REPEATEDLY IN MICE. STILL, A TEAM OF DOCTORS FROM U.C.L.A. DECIDED TO TRY IT ON HUMANS ANYWAY..!
THEY REMOVED BONE MARROW CELLS FROM TWO PATIENTS' THIGH BONES. (REMEMBER, THESE DEVELOP INTO HEMOGLOBIN-PRODUCING RED BLOOD CELLS.)
A GOOD HEMOGLOBIN GENE WAS SPLICED IN.
THE THIGH WAS IRRADIATED TO SLOW DOWN THE OLD MARROW (AND GIVE THE NEW CELLS THE EDGE).
AND THE "ENGINEERED" CELLS WERE PUT BACK IN.
AND THE RESULT?
ABSOLUTELY NOTHING!
(SINCE THEN, THE EXPERIMENT HAS WORKED — IN MICE.)
:SIGH: THERE GOES THE EXPERIMENT...
AND THE PATIENT...

THE DOCTORS TOOK A LOT OF FLAK FOR THIS EXPERIMENT.



SEVERAL OBJECTIONS WERE RAISED:

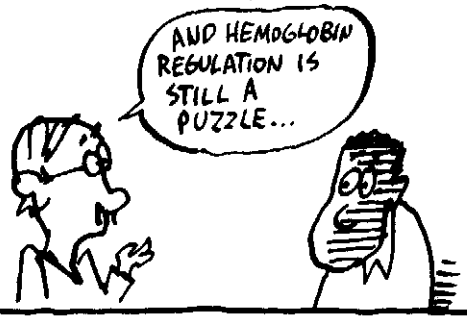


NEVERTHELESS, THIS IS PROBABLY THE WAY THE FIRST GENETIC THERAPIES WILL BE DONE, BECAUSE BONE MARROW IS THE EASIEST TISSUE TO TRANSPLANT.

THERE ARE SEVERAL DISEASES THAT MIGHT BE TREATED THIS WAY:

THALASSEMIA, OF COURSE, ALTHOUGH THE UCLA EXPERIENCE SHOWS IT WON'T BE EASY.

SICKLE-CELL ANEMIA IS A HEMOGLOBIN ABNORMALITY AFFECTING MAINLY BLACK PEOPLE. THIS WILL BE EVEN HARDER BECAUSE THE MUTANT GENE IS CODOMINANT, NOT RECESSIVE.



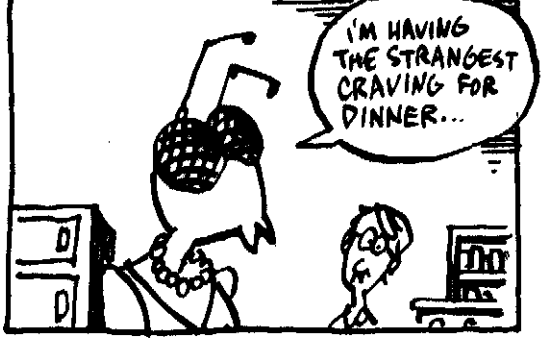
HEMOPHILIA, DUE TO THE LACK OF A BLOOD PROTEIN, MIGHT BE THE EASIEST TO CURE!

AND THERE ARE **IMMUNO-DEFICIENCY** DISEASES CAUSED BY RECESSIVE GENES IN BONE MARROW. AT PRESENT, PEOPLE WITH THESE DISEASES HAVE TO LIVE IN GERM-FREE ISOLATION CHAMBERS.

OF COURSE, THERE ARE FEWER RESTRICTIONS ON PLANT AND ANIMAL EXPERIMENTS THAN ON HUMANS. (THIS BOTHERS SOME PEOPLE, BY THE WAY.)

SO PROGRESS HAS BEEN MORE RAPID AMONG PLANTS AND ANIMALS. ALREADY THERE ARE BREEDS OF COTTON, TOMATO, AND TOBACCO WITH AN ADDED BACTERIAL GENE THAT MAKES THEM POISONOUS TO INSECTS.

SCIENTISTS ARE EXCITED ABOUT TRANSGENIC ANIMALS — ANIMALS THAT CONTAIN A FEW GENES FROM ANOTHER SPECIES.

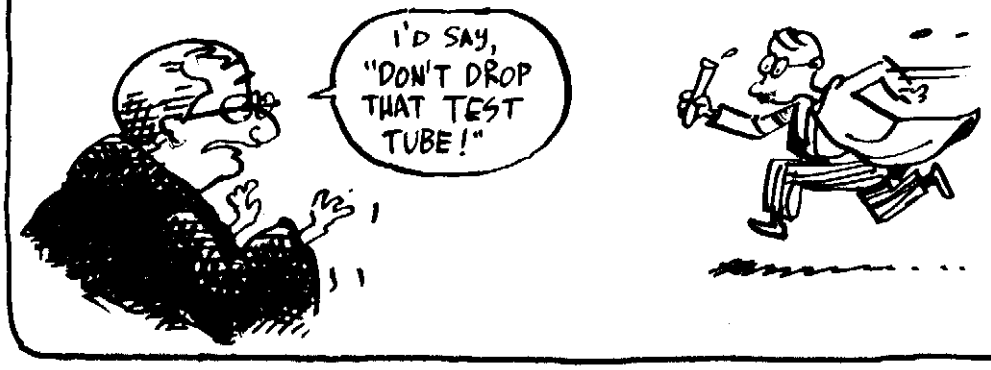


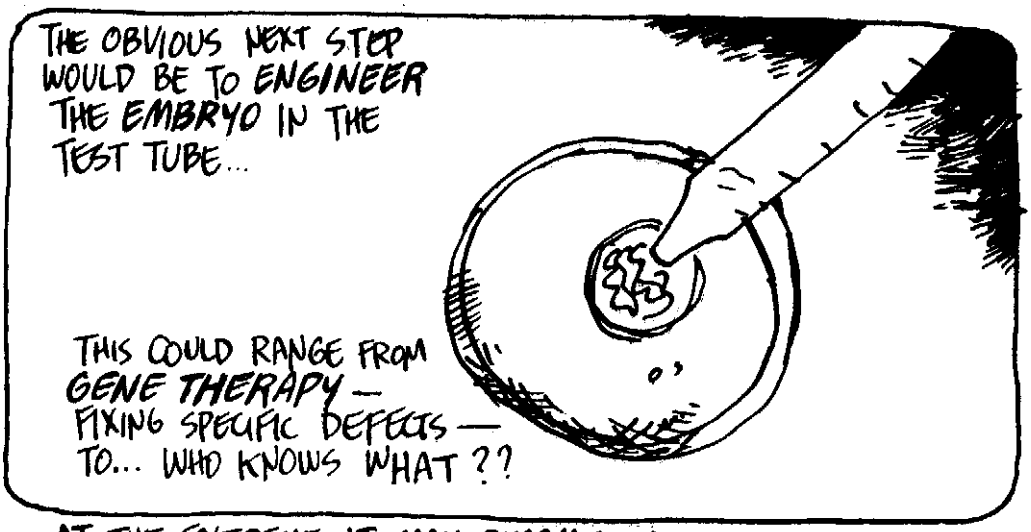
ONE EXAMPLE ARE PIGS WITH BOVINE GROWTH HORMONE. THEY GROW FASTER AND LEANER, BUT ALSO HAVE OTHER PROBLEMS, LIKE ULCERS AND ARTHRITIS — SO YOU'LL HAVE TO WAIT FOR THAT "BORK" CHOP.

TRANGENIC PLANTS AND ANIMALS CAN PASS ON THEIR NEW GENES TO THEIR OFFSPRING, BECAUSE THE GENES ARE INSERTED AT A VERY EARLY STAGE OF DEVELOPMENT, ALLOWING THEM TO GET INTO SPERM AND EGG CELLS. PERFORMING THESE EXPERIMENTS ON HUMANS WOULD THEREFORE RAISE SOME HARD ETHICAL ISSUES.

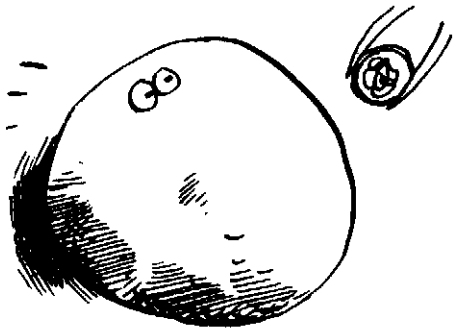
BUT WE'RE GETTING CLOSER. THERE ARE ALREADY LIVING "TEST TUBE BABIES" — FERTILIZED IN A TEST TUBE AND THEN, AFTER A FEW DIVISIONS, IMPLANTED IN THE MOTHER'S WOMB, WHERE THEY DEVELOPED NATURALLY.

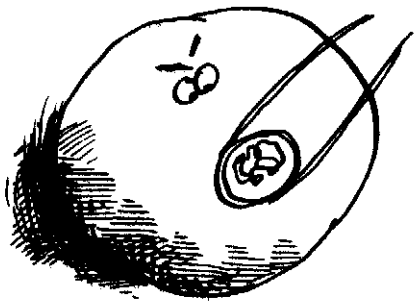
WHAT WOULD THE MONK MENDEL HAVE TO SAY ABOUT **THIS?**





AT THE EXTREME, IT MAY BECOME POSSIBLE TO **CLONE PEOPLE.** THE EGG'S NUCLEUS WOULD BE REMOVED ALTOGETHER AND REPLACED WITH A NUCLEUS FROM ANOTHER PERSON.



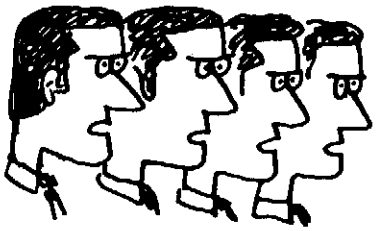


THIS EGG WOULD BE IMPLANTED IN A "MOTHER," TO WHOM IT WOULD BE GENETICALLY UNRELATED.

INSTEAD, THE LITTLE TYKE WOULD BE GENETICALLY *IDENTICAL* TO WHOEVER— OR WHATEVER— DONATED THE NUCLEUS.

SOUND FAR-FETCHED? WELL, SCIENTISTS HAVE ALREADY SUCCEEDED IN CLONING MICE AND FROGS...

THE TECHNIQUE MAKES IT POSSIBLE TO MAKE MULTIPLE COPIES OF LIVING INDIVIDUALS! IS THIS WHAT WE WANT TO BECOME, A WORLD OF CLONES??



WE SEE NOTHING WRONG WITH IT!

YOU MIGHT WELL ASK: WHO WILL BE CLONED? WHO WILL DECIDE? WILL IT BE BASED PURELY ON MONEY? WILL IT BE LEGAL? WILL THERE BE *PEOPLE-BREEDERS* SELECTING THE MOST "FIT" FOR REPRODUCTION?

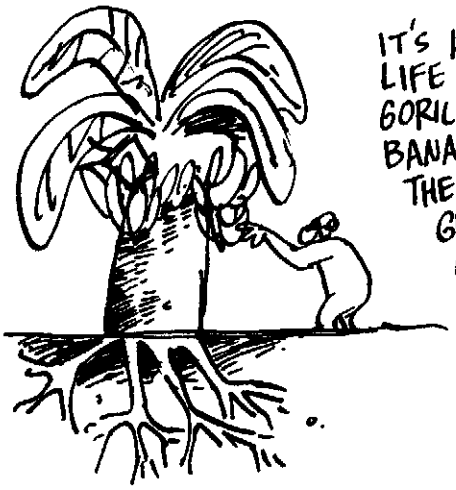
STAND ASIDE, WEAKLINGS!

THE LAST TIME ANYONE TRIED TO BREED A MASTER RACE, IT WAS AN UNHAPPY EXPERIENCE, TO SAY THE LEAST...

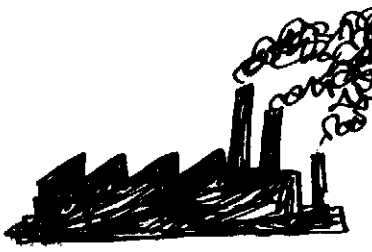
OR MAYBE WE'RE BEING TOO **GLOOMY**... MAYBE THE FUTURE WILL BE A GLORIOUS TIME WHEN PEOPLE WILL BE ENGINEERED TO FIT CLOTHES INSTEAD OF VICE VERSA!!

MAYBE WE CAN EVEN BE CLONED TO RESIST ECOLOGICAL DISASTER, LIKE THE DEPLETION OF ATMOSPHERIC OZONE!!

IT'S NOT ONLY OUR OWN GENES WE NEED TO WORRY ABOUT... THERE IS ALSO THE *GENETIC DIVERSITY* OF THE ENTIRE PLANET... (IT LOOKS SOMETHING LIKE A GIANT CELL, DOESN'T IT?)

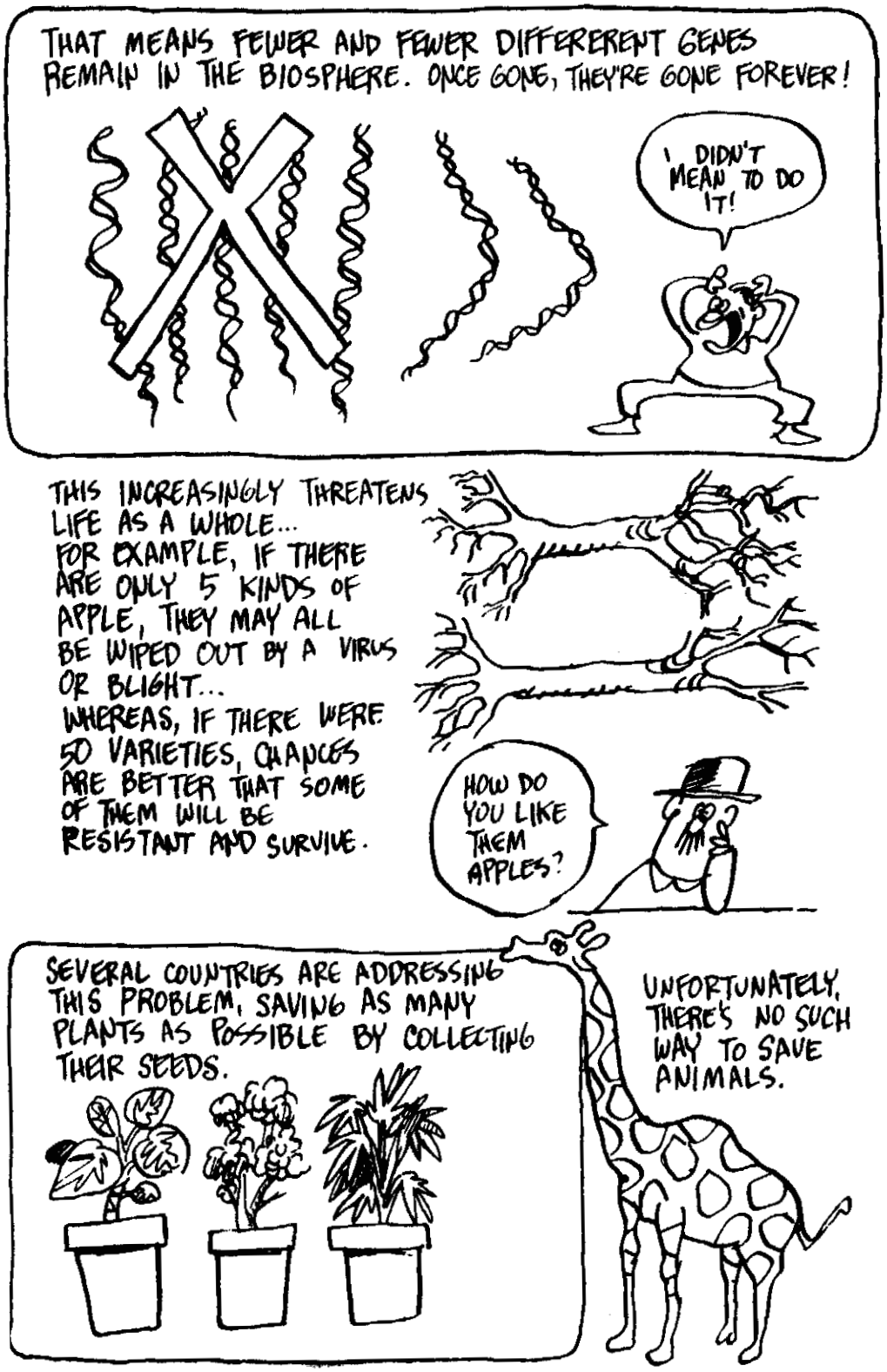


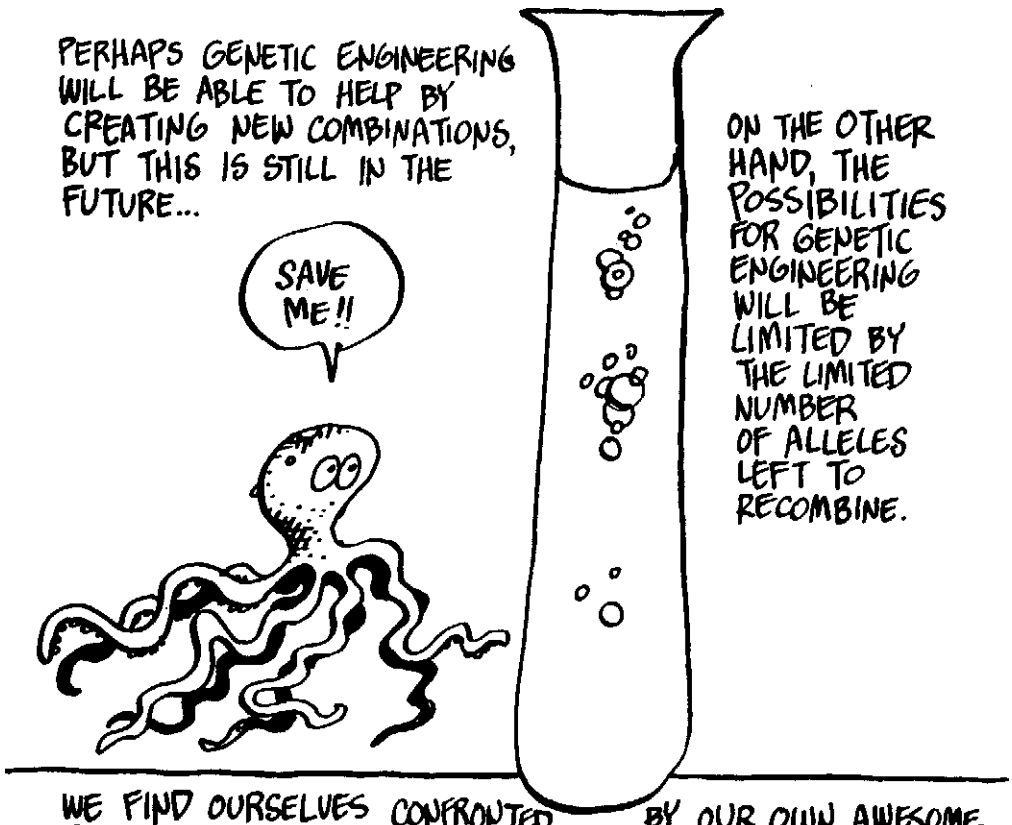
IT'S HARDLY NEWS THAT ALL LIFE IS INTERDEPENDENT... GORILLA EATS BANANA; BANANA EATS CHEMICALS FROM THE SOIL; SOME OF THE CHEMICALS GET THERE FROM BACTERIAL ACTION; OTHER BACTERIA AID THE APE'S DIGESTION; STILL OTHERS BREAK DOWN ITS WASTE PRODUCTS, ETC ETC ETC...



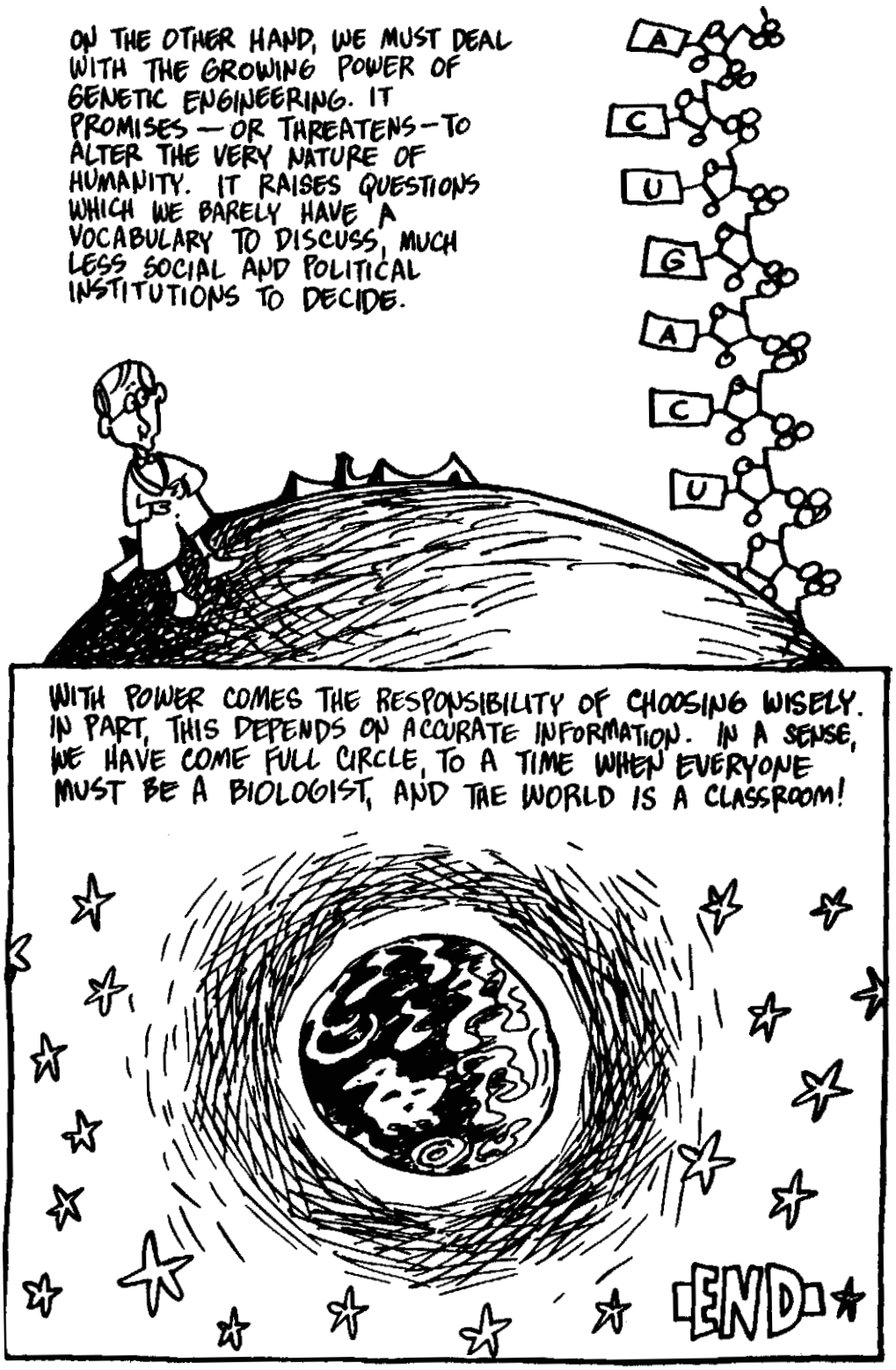
BUT WE HUMANS

WITH OUR EXPLODING POPULATION, RESOURCE-HOGGING, MODERN AGRICULTURE, AND POLLUTION, ARE CHANGING THE ENVIRONMENT SO DRASTICALLY THAT HUNDREDS OF PLANT AND ANIMAL SPECIES GO EXTINCT EVERY YEAR.


THAT MEANS FEWER AND FEWER DIFFERERENT GENES REMAIN IN THE BIOSPHERE. ONCE GONE, THEY'RE GONE FOREVER!
I DIDN'T MEAN TO DO IT!
THIS INCREASINGLY THREATENS LIFE AS A WHOLE... FOR EXAMPLE, IF THERE ARE ONLY 5 KINDS OF APPLE, THEY MAY ALL BE WIPED OUT BY A VIRUS OR BLIGHT... WHEREAS, IF THERE WERE 50 VARIETIES, CHANCES ARE BETTER THAT SOME OF THEM WILL BE RESISTANT AND SURVIVE.
HOW DO YOU LIKE THEM APPLES?
SEVERAL COUNTRIES ARE ADDRESSING THIS PROBLEM, SAVING AS MANY PLANTS AS POSSIBLE BY COLLECTING THEIR SEEDS.
UNFORTUNATELY, THERE'S NO SUCH WAY TO SAVE ANIMALS.



WE FIND OURSELVES CONFRONTED BY OUR OWN AWESOME POWERS.


ON THE OTHER HAND, WE MUST DEAL WITH THE GROWING POWER OF GENETIC ENGINEERING. IT PROMISES — OR THREATENS — TO ALTER THE VERY NATURE OF HUMANITY. IT RAISES QUESTIONS WHICH WE BARELY HAVE A VOCABULARY TO DISCUSS, MUCH LESS SOCIAL AND POLITICAL INSTITUTIONS TO DECIDE.
A
C
U
G
A
C
U
WITH POWER COMES THE RESPONSIBILITY OF CHOOSING WISELY. IN PART, THIS DEPENDS ON ACCURATE INFORMATION. IN A SENSE, WE HAVE COME FULL CIRCLE, TO A TIME WHEN EVERYONE MUST BE A BIOLOGIST, AND THE WORLD IS A CLASSROOM!
END

BIBLIOGRAPHY

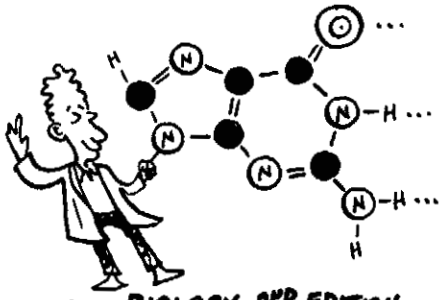
STUBBE, H., **HISTORY OF GENETICS FROM PRE-HISTORIC TIMES TO THE REDISCOVERY OF MENDEL'S LAWS**, M.I.T. PRESS, 1972. HARD TO FIND, BUT A FINE SCHOLARLY HISTORY OF GENETICS TO 1900.

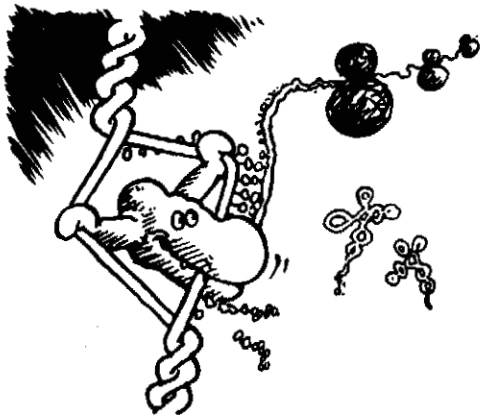
DUNN, L.C., **A SHORT HISTORY OF GENETICS**, McGRAW-HILL, 1965. MORE PRE-1959 GENETICS. GOOD PIX.

JUDSON, H.F., **THE EIGHTH DAY OF CREATION**, SIMON & SCHUSTER, 1979. READABLE HISTORY OF MOLECULAR BIOLOGY.

WATSON, J.D., **THE DOUBLE HELIX**, ATHANEUM, 1968. ONE OF THE DISCOVERERS OF DNA'S STRUCTURE TELLS HIS STORY. FLIPPANT AND SEXIST, BUT FASCINATING.

SAYRE, A., **ROSALIND FRANKLIN AND DNA**, NORTON, 1978. AN ANTIDOTE TO WATSON'S BIAS.





CURTIS, H., **BIOLOGY, 2ND EDITION**, WORTH, 1975. A GOOD GENERAL BIO TEXT, FOR MORE ON MOLECULES AND CELLS.

AYALA, F.J., & KEIGER, J.A., **MODERN GENETICS**, BENJAMIN CUMMINGS, 1980. ONE OF MANY UP-TO-DATE TEXTS.

STENT, G. & CALENDAR, R. **MOLECULAR GENETICS, 2ND EDITION**, FREEMAN, 1978. ALL THE DETAILS. (THE FIRST EDITION, BY STENT ALONE, IS A CLASSIC, THOUGH DATED.)

WATSON, J.D., **MOLECULAR BIOLOGY OF THE GENE, 3RD EDITION**, W.A. BENJAMIN, 1976. MORE DETAILS.

CAVALIERI, L.F., **THE DOUBLE-EDGED HELIX**, COLUMBIA U. PRESS, 1981; SUBTITLED "SCIENCE IN THE REAL WORLD".

CHARGAFF, E., **HERACLITEAN FIRE**, ROCKEFELLER U. PRESS, 1978. A CRANKY MEMOIR, BUT MAYBE WE SHOULD LISTEN TO HIM!

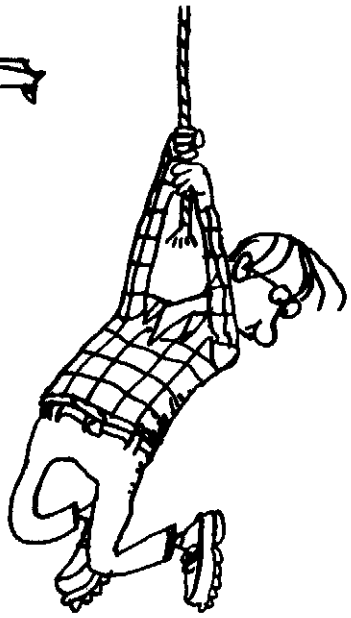
WADE, N., **THE ULTIMATE EXPERIMENT: MAN-MADE EVOLUTION**, WALKER & Co, 1977. RECOMBINANT DNA, BY ONE OF OUR BEST SCIENCE WRITERS.

ALSO: **SCIENTIFIC AMERICAN** MAGAZINE REGULARLY PRINTS ARTICLES ON RECENT DEVELOPMENTS, AND SO DOES YOUR DAILY NEWSPAPER!

INDEX

ABOUT THE AUTHORS:

LARRY GONICK IS THE AUTHOR OR CO-AUTHOR OF MANY BOOKS OF GRAPHIC NON-FICTION ON SCIENTIFIC AND HISTORICAL SUBJECTS. A GRADUATE OF HARVARD IN MATH, HE DROPPED OUT OF GRADUATE SCHOOL TO PURSUE SOMETHING REALLY DIFFICULT: RENDERING INFORMATION IN LITTLE PICTURES. HE LIVES WITH HIS FAMILY IN SAN FRANCISCO.



MARK WHEELIS, WHEN NOT CLIMBING ROCKS OR RAFTING RIVERS, IS SENIOR LECTURER IN MICROBIOLOGY AT THE UNIVERSITY OF CALIFORNIA AT DAVIS. BESIDES TEACHING NUMEROUS BIOLOGY COURSES, HE HAS WRITTEN MANY RESEARCH PAPERS AND IS CO-AUTHOR OF THE STANDARD TEXTBOOK ***THE MICROBIAL WORLD.*** HE LIVES IN DAVIS WITH HIS WIFE, CHILDREN, DOG, AND MICROBES.

REFERENCE/SCIENCE

THE CARTOON GUIDE TO GENETICS
LARRY GONICK AND MARK WHELLIS

Have you ever asked yourself:

Are spliced genes the same as mended Levis?
Watson and Crick? Aren't they a team of British detectives?
Plant sex? Can they do that?
Is Genetic Mutation the name of one of those heavy metal bands?
Asparagine? Which of the four food groups is that in?

Then you need *The Cartoon Guide to Genetics* to explain the important concepts of classical and modern genetics—it's not only educational, it's funny too!

"If you can't learn Mendelian genetics from this text,
I guess you never will."
—*NEW SCIENTIST*

"It puts textbooks to shame."
—MATTHEW MESELSON,
PROFESSOR OF BIOLOGY, HARVARD UNIVERSITY

HarperPerennial
A Division of HarperCollins*Publishers*
http://www.harpercollins.com

USA	$15.00
CANADA	$21.50

ISBN 0-06-273099-1
51500>
9 780062 730992