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T/25 remarks and slides for Biotechnology review in
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Prospects for Biotechnology

The scientific foundations for contemporary biotechnology were laid in 1944, with Avery's work at the Rockefeller Institute. But it is only within the last decade that this has borne important fruit in new products of the pharmaceutical and other major industries.

The principal technical insights and advances have included
1) the biochemistry of the genetic material, leading to gene (DNA) splicing
2) the biology and chemistry of immunity, leading to Monoclonal Antibodies (MAb's)
3) the structure and function of cell membranes, and the abundance of receptors involved in physiological signalling.

&) intricate combinations of all the above

Let me just say a few words about these principles; then I will turn to their implications for investment opportunities.

SLIDE 1. A slice through a typical cell.
All of its intricate machinery is controlled by the information in the nucleus.

SLIDE 2. From the dimensions of the cell to the scale of DNA -- another 10,000-fold magnification. Nucleus to chromosomes to DNA fibers (the double helix).

SLIDE 3. How DNA fragments are extracted from human cells and spliced into the chromosome of a bacterium, which can then be used for the large scale production of that DNA's specifications.

SLIDE 4. A closer look at the cell's surface membrane, and how it is studied with hundreds or thousands of receptor proteins. These are sensors of the external environment, and act as switches to regulate the function of the cell, whether to transmit a nerve impulse, encourage release of immune proteins, or be subverted to allow a virus to enter, or stimulate the cell's growth and multiplication. (I am sure Dr. Baulieu will be saying much more about this).

The net result is an enormous acceleration of discovery of these bioregulatory molecules, as well as the practical means of their production for diagnostic and therapeutic uses.

These technologies have already revolutionized every branch of biological and medical science -- "PCR" -polymerase chain reaction - used for copying DNA in the laboratory, was labelled the scientific discovery of 1989! They can also be applied to an unlimited range of economically significant applications. But I believe they have a unique place in making accessible the proteins of the human body -- proteins that for the most part we would have

difficulty in knowing about, and practically impossible to harvest.

SLIOE 5a and 5b. is a primer on the scale of the human genome (genome is the totality of the informational DNA in the chromosomes). There are at least 100,000 distinct entities (perhaps many times more if we take account of "alternative splicings" of constituent segments), of which so far only a few percent are known to us. So far from that cornucopia having been exhausted, we are just at the beginning of envisioning its scope. The numbers of options, mostly yet to be discovered, are truly unlimited. They wait mainly on the basic discoveries emerging from academic and other government- funded research laboratories, and on the fruitful connection of those discoveries with entrepreneurial development engines.

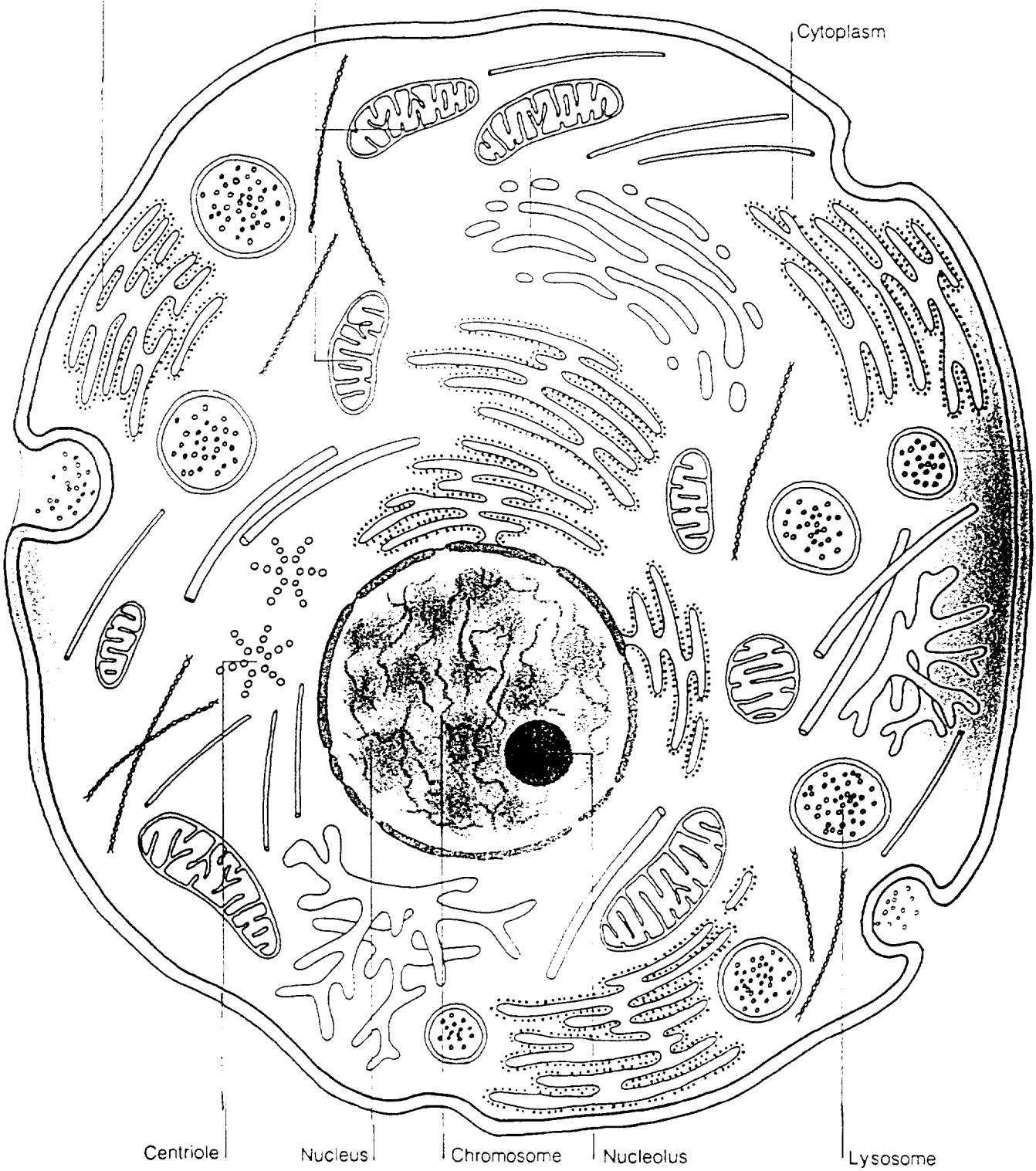
SLIDE 6 is a broader summary of opportunities. Human therapeutics offer the highest value added, and the most likely to recover the substantial costs and risks of development. They also entail all the usual and necessary delays and costs of pharmaceutical regulation. Diagnostics generally offer less risk and delay, and commensurately lower returns, in a competitive environment offering smaller assurance of proprietary protection.

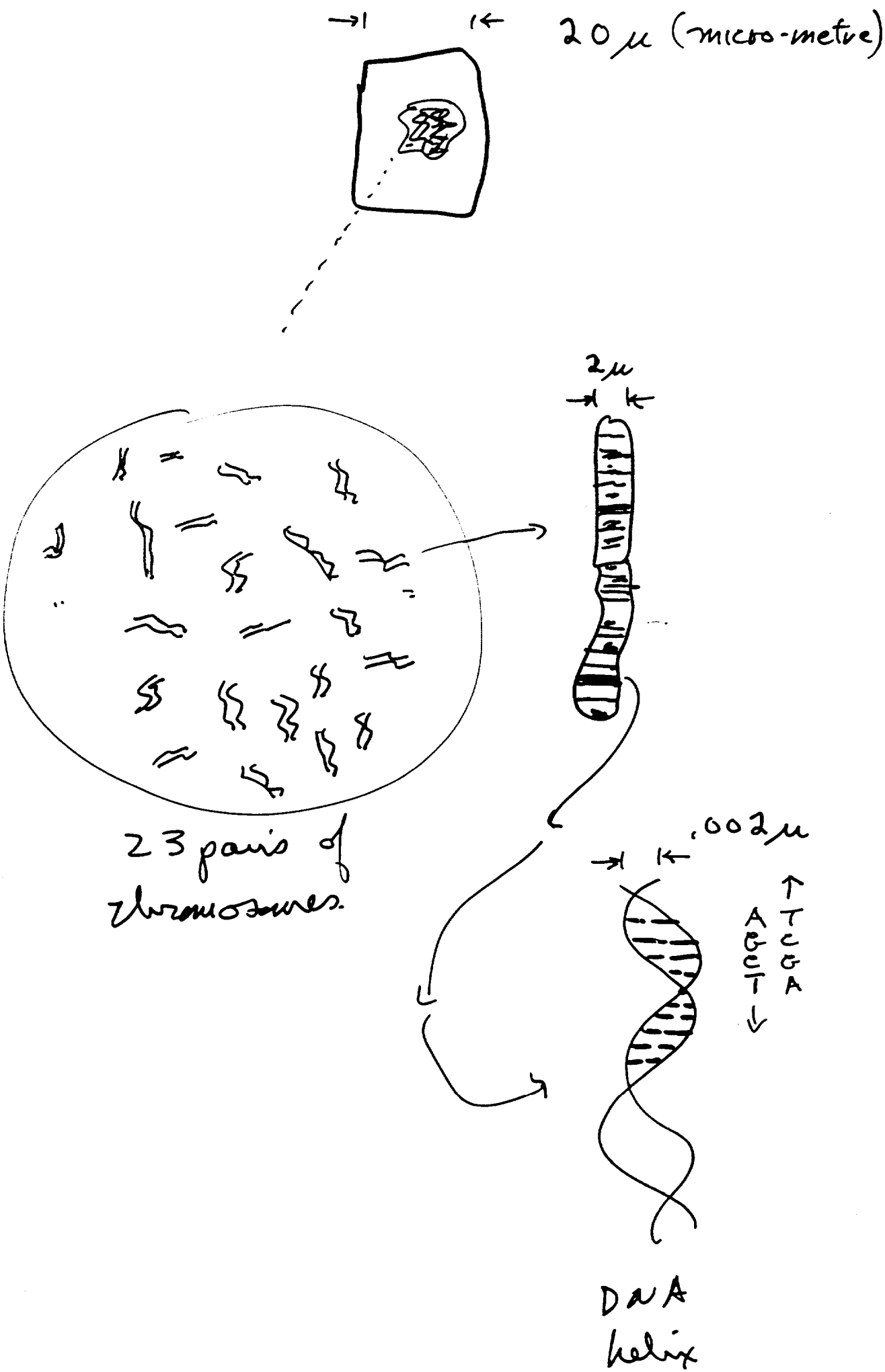
Veterinary therapeutics offer another short-circuit: paradoxically many of the most important drugs for the health of the Third World offer their developers a necessary return on investment primarily from veterinary sales.

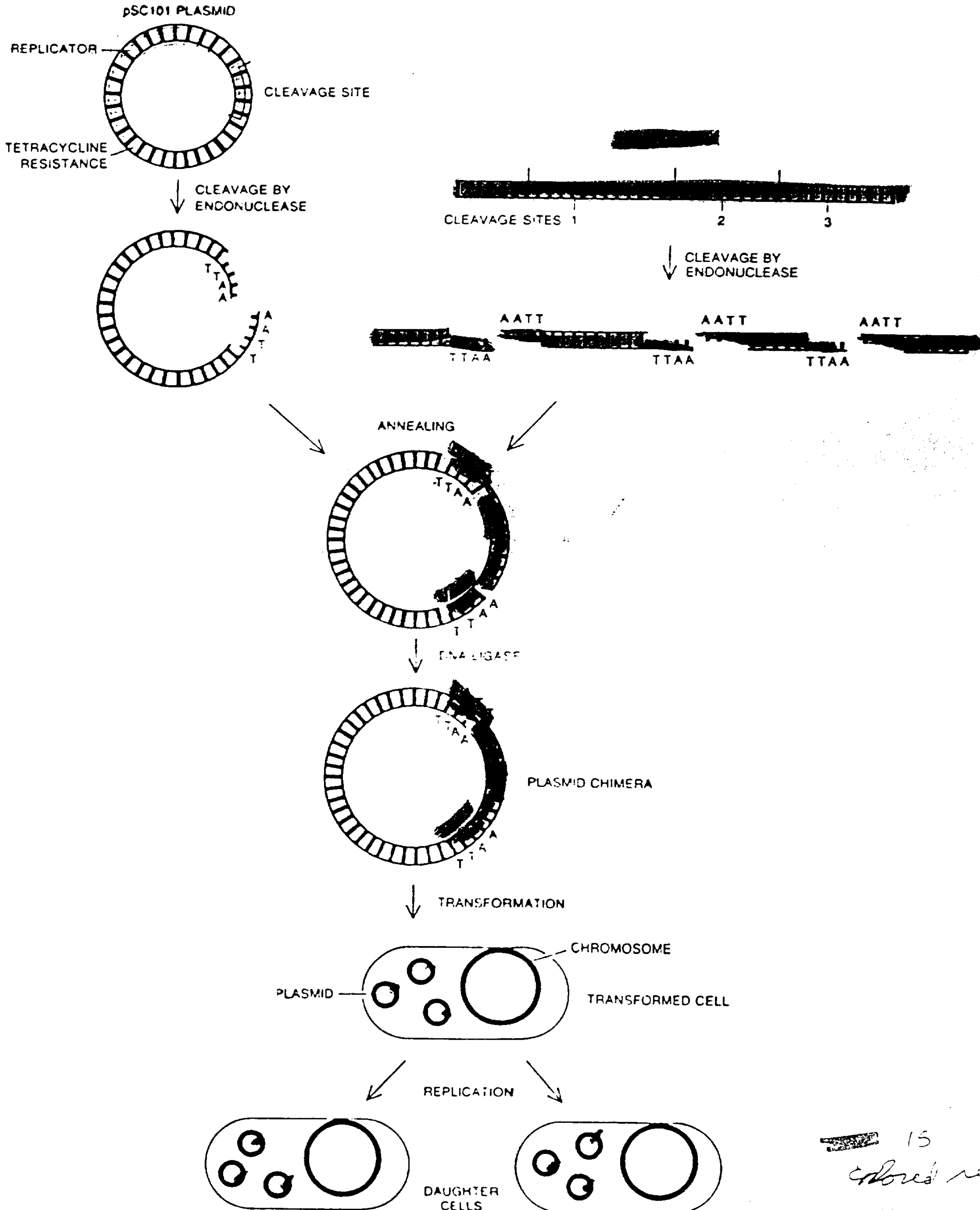
I have some skepticism about agricultural applications of biotechnology as an avenue of private investment. They may offer large enhancements of yield. But the market is ill-structured to recover an equitable part of that advantage for the genetic developer, and there is substantial governmental involvement and competition. Nevertheless, there are many specialized opportunities, though they must be chosen carefully.

As to the chemical industry, biotechnology certainly has a place in vertically integrated companies, either for process improvements for commodity chemicals with huge markets, or for very high value specialties -- particularly those with optically active (chiral) centers -- molecules hard to synthesize by other routes. It will be difficult for biotech' entrepreneurship to reach its customary rate of return in dealing with that industry. However, growing environmental restrictions on many current products and processes will demand a reexamination of current practices, and should offer some new opprtunities for their displacement by microbiological methods.

Inside the nucleus, here shown in cross section, is the nucleolus (red) and threadlike chromosomes. Pores in the double membrane enveloping the nucleus allow substances to enter and leave it.




20 μ (micro-metre)
2μ
23 pairs of chromosomes.
.002μ
T C G A
A G C T
DNA helix



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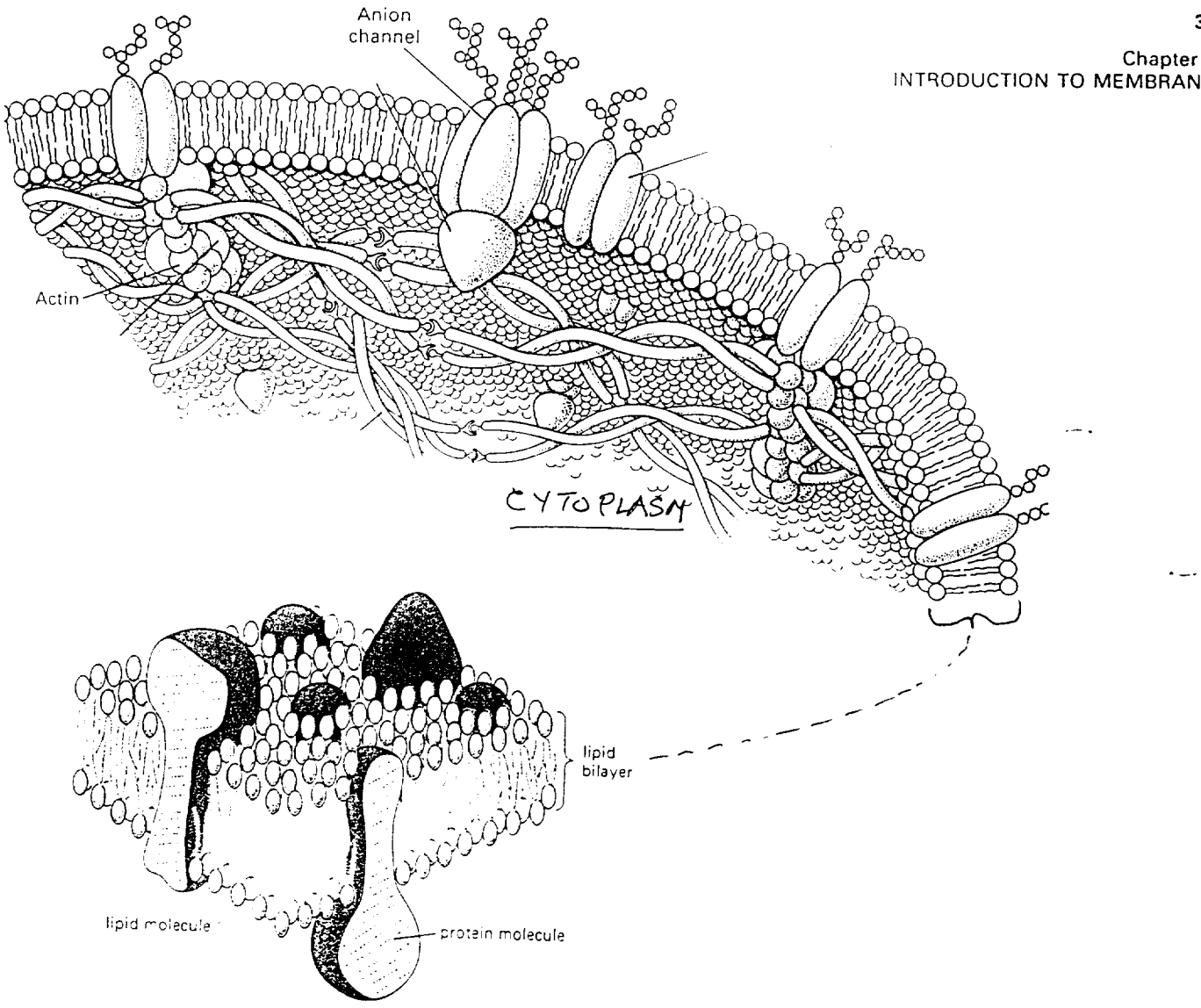

CELL MEMBRANE & RECEPTORS

A PRIMER ON HUMAN DNA

- 3 000 000 000 units in 2 meters
- 10 000 000 genes possible
  (= Encyclopedia Britannica)
- Only about 1% active (rest 'selfish'?)
- 100 000 proteins probably make up the constituents of the human body.
- About 5000 proteins have names AND can be guessed to be present in the body.
- About 500 proteins have been isolated and definitely characterized in human

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- If DNA were scaled to thickness of hair it would stretch from Paris to London
- Reasonable assumption: 10% or 10,000 potential use
- We've hardly reached 1% of the repertoire

- About 50 human proteins have medical uses today:

insulin, human growth hormone, ACTH, calcitonin
hemophilia replacement factors
immune globulins: anti-
  viral (hepatitis)
  cancer
  septic shock
  toxins
fibrin-lysing enzymes (TPA)
protease inhibitor
interferon, interleukins, other immunomodulators
tissue growth factors (erythropoietin, white cell)
gonadotropins; releasing hormones
collagen; proteases

forthcoming:

Many more growth factors (nerve, bone, skin, muscle)
HDL - apoliprotein - to clear cholesterol
Specific antibodies, receptors, ligands, inhibitors
Biosynthetic nutrients (milk)
Nonallergenic (humanized) enzymes

TARGETS FOR BIOTECHNOLOGY

- Basic Concepts and Methods:
  - Understanding genome
  - DNA splicing
  - Monoclonal antibodies
  - Receptors and ligands
  - Embryological knowledge

  - Many of these are merged, e.g:
    Antibodies and receptors grown in bacteria

- Economic targets - pharmaceutical (and veterinary):
  - Human proteins - most exotic
  - Vaccines - e.g. Hepavax, malaria
  - Bacterial Enzymes - streptokinase, hyaluronidase
  - Antibiotics - genetically engineered
  - Gene and Cell therapies
  - Production of "chiral" drugs
  - Diagnostics

- Economic targets - agricultural:
  - Specialty, high value plant or animal stocks
    - built in pesticides
    - adapt to marginal environments

- Economic targets - chemical industry:
  - Biochemical industrial production; enzymes
  - Synthetic nutrients (amino acids, vitamins)