In a laboratory at Rockefeller University, a cell surgeon goes about her extremely delicate task. Working with microinstruments and a stereoscopic microscope that magnifies up to 2,000 times, she performs surgery on a single somatic cell. Specifically, she is preparing to remove a pair of chromosomes while the cell goes through the process of replication.

The cell surgeon is Dr. Elaine G. Diacumakos, senior research associate. Dr. Diacumakos is part of a group working with Dr. Edward L. Tatum, who shared the 1958 Nobel prize in medicine with Drs. George Beadle and Joshua Lederberg. An abbreviated, simplified hypothesis underlying Dr. Tatum's work is that in every living organism, each gene controls the production, function, and specificity of a particular enzyme.

Every surgeon needs manual dexterity, but the need of the cell surgeon is acute. Her surgical field is limited to the area directly under the lens of the microscope. This minute operating area is surrounded with six microtools, forming a hexagon just within the circular optical field. Four very thin, rigid, tapering microneedles and two micropipettes surround the single living cell lying under the coverslip.

At a certain stage in mitosis, the cell surgeon inserts a microneedle through the cell matrix, just touching one pair of chromosomes. She has narrowed the general term "mitosis" into a more specific stage of the cell cycle. She uses "disjunction" to designate the sequence of events occurring when two single, living, replicate cells move away from each other.

At a certain stage in this disjunction, Dr. Diacumakos uses the microneedle to pro[d] the chromosomes, but not to impale them. She pulls the chromosomes out of the cell, pair by pair. But the living cell does not immediately surrender any of its parts. A thin, tough filament binds the chromosomes together in some type of a framework arrangement. As the tip of the needle brings one chromosome pair out of the cell,

the adjacent chromosomes follow it. If the needle is withdrawn, and a chromosome pair is left lying on the cell surface, the chromosome moves back into the cell, probably aided by this thin filament.

Dr. Diacumakos' research is more than merely an exercise in laboratory dexterity. One indication of this fact is that her work is supported by The National Foundation-March of Dimes, a voluntary health agency concerned with finding preventives for a variety of birth defects, particularly those known to be due to inborn errors of metabolism.

In recent years, about 2,000 of these inborn errors have been identified. Dr. Tatum's "one gene, one enzyme" theory has been shown to have more and more clinical implications for their eventual treatment or prevention.

These diseases were first described by Sir Archibald Garrod in 1908. In a series of lectures before the Royal College of Physicians, Sir Archibald explained how certain diseases could be caused by a mistake in metabolism resulting from an abnormal gene. He named four of these diseases--alcaptonuria, cystinuria, pentosuria, and albinism.

Drawing upon the principles of inheritance established by Gregor Mendel some 50 years earlier, Sir Archibald showed how these birth defects occurred: The patient received a defective gene from each parent. Although the parents were apparently normal, each was a carrier of a defective gene. He published all of this information in 1909, but his book remained essentially overlooked until Dr. Tatum's work in the 1940's.

This vast new area of medicine will almost certainly be influenced by the results of Dr. Diacumakos' in vitro micromanipulation of chromosomes within living cells. Already, these methods are recognized as potential means of obtaining transplantable genetic material, or of altering chromosome numbers, or of obtaining more detailed

analysis of chromosomes.

Working with somatic cells (not with germ cells), Dr. Diacumakos now is able to do specific microoperations on these cells. She can displace, extract, or add chromosomes from human cells in the disjunction ~~stage of mitosis~~. In order to do this, she has to enter the matrix of the cell without damaging the life processes going on.

Here again, Dr. Diacumakos makes minute distinctions between the matrix and the structural framework of a living cell, ~~which~~ she defines as the connections between and among the like and different parts.

She reports that the framework does not break when parts of one cell separate during disjunction. Rather, the framework determines the order and the movements during the separation of one into two: The two structural frameworks perform as a single entity within and against the matrix. The forces generated and exerted between the two frameworks are equal in magnitude and opposite in direction. Therefore, the movements are symmetrical. Matched parts move in the same way and for the same distance, but in opposite directions. Events in one cell occur in a mirror image in the other cell.

These frameworks perform this way because the hyaline cell matrix--made up entirely of submicroscopic parts which form its visible mass--is the more fluid entity. The matrix maintains the same viscosity throughout disjunction. Consequently, the same force mobilizes matrix more than it does the framework(s).

And it is at this crucial time, while the ~~parts~~ frameworks are separating, that the matrix can be moved, allowing material to be taken out of or put into a living cell. Dr. Diacumakos has evolved three ways of moving the matrix:

. Using a micropipette to put a fresh drop of silicone oil in contact with the matrix, just outside the separating cells. The volume of matrix moved is proportional to the size of the oil drop.

. Inserting a microneedle into the matrix and moving it around within the frameworks. To reduce the possibility that the medium bathing the cell will enter the cell, the needle is finely tapered.

. Introducing a micropipette into the cell, and injecting an aqueous solution within the cell's frameworks. The injection system must be free of air and air tight.

All three of these operations can be done without aborting cell disjunction, or without preventing cell reproduction.

After any of these operations, Dr. Diacumakos is able to take the treated cell and isolate it from all other cells. And then she is able to get new cell populations from these operated, isolated cells.

She is willing to draw some clinical implications of her work: "It is conceivable that if one could correct a damaged cell, and then grow some corrected cells in a test tube, it might even be possible to take these corrected cells and put them back into the individual from whom they were originally obtained. Hopefully, this might alleviate clinical symptoms, or restore the activity of an enzyme."

Can she name a date when these theories might be tested in patients? "Not yet. But we can say that our work goes smoothly. Nothing is holding us up. The process takes time. We are evolving ways that genetic information can be transferred from one living cell to another. Each step has to be worked out carefully, because the work has to be reproduced by other groups. Hopefully, some day, all of this will be easily reproducible on a mass basis."

Her work with cells, she says, is not too much different from the dialogue between physician and patient: "First, we have to find out what's wrong with the cell. Then we have to see if we can alleviate the condition. It's much like the dialogue between physician and patient, except that the dialogue between researcher and cell is nonverbal. Our dialogue is action. We do something. The cell responds. If we do the

right thing, the cell thrives. If we do something wrong, the cell dies."

The National Foundation is quite forthright in describing the eventual implications of Dr. Diacumakos' work, calling it an "attempt, through the use of microsurgical transplantation of genetic material from cell to cell, to develop successful genetic engineering by culturing the cells of a patient with inborn errors of metabolism, transforming the cells in a test tube, and transplanting the transformed cells back into the patient to restore metabolic capacity."

To some, this might seem a bit visionary, even for these days, when scientific accomplishments frequently surpass expectations. Others point out that parts of the Nobel lecture given in 1958 by Dr. Tatum may have seemed an imaginative flight of fancy at the time. But the rush of recent scientific events makes these predictions more prosaic and more practical with every year since then:

"It does not seem unrealistic to expect that as more is learned about control of cel machinery and heredity, we will see the complete conquering of many of man's ills, including hereditary defects in metabolism, and the momentarily more obscure conditions such as cancer and the degenerative diseases, just as diseases of bacterial and viral etiology are now being conquered.

"With a more complete understanding of the functioning and regulation of gene activi in development and differentiation, these processes may be more efficiently controlled and regulated, not only to avoid structural or metabolic errors in the developing organism, but also to produce better organisms.

"Perhaps within the lifetime of some of us here, the code of life processes tied up in the molecular structure of proteins and nucleic acids will be broken. This may permit the improvement of all living organisms by processes which we might call biological engineering.

"This might proceed in stages from the in vitro biosynthesis of better and more efficient enzymes, to the biosynthesis of the corresponding nucleic acid molecules,

and to the introduction of these molecules into the genome of organisms, whether via injection, viral introduction into germ cells, or via a process analogous to transformation. Alternatively, it may be possible to reach the same goal by a process involving directed mutation."

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