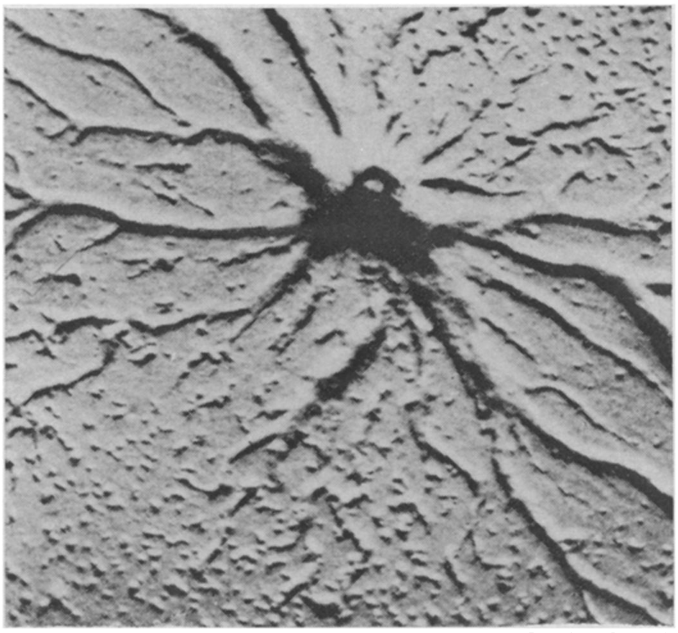
Theoretical ferment in embryology

Biologists from England and the U. S. are assembling a theoretical base to explain cell differentiation



When signaled by a pulse, amoebas move into streams aggregate in a slime cone (right) and emerge as a slug that moves as pulses force bulges in its body.

Gunther Gerisch

Cell differentiation is the central enigma of biology.

From what is known about genes, scientists understand that information coded in DNA is transcribed to RNA and leads to the synthesis of specific proteins. There is evidence that molecules known as repressors and derepressors play a role in turning genes, and protein synthesis, on and off.

In fact, the whole of the vast array of data accumulated in the last 15 years of molecular biology contributes peripheral bits and pieces to the understanding of cell differentiation. But none of it speaks effectively to the central question: How, from a single egg, do primordial cells emerge and differentiate to become flesh or blood or bone?

The missing ingredient has been a unifying theory.

Scientists know that specific genes control specific biochemical events. Yet the emergence of something like a hand is not the result of single gene action but the product of scores of specific influences coming together.

"The problem," Dr. Conrad H. Waddington, embryology's elder statesman says, "is to form laws to account for the fact that individual biological processes in a cell produce effects of a global nature." The English biologist is now at the State University of New York at Buffalo.

Approaching the question through the combined perspective of time and space, a small corps of embryologists is pursuing ideas that may provide at least a rudimentary framework. They are working toward a unifying theory into which emerging data can eventually be placed.

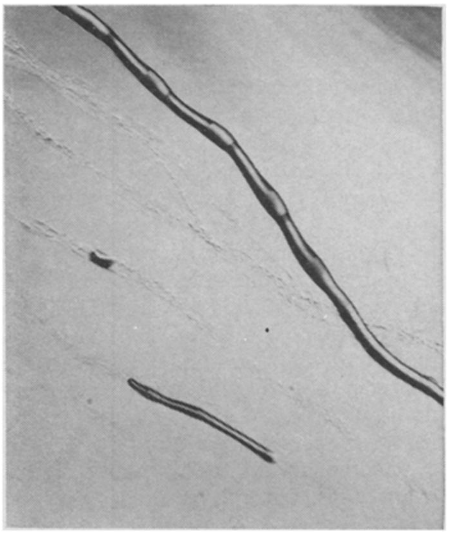
With the exception of a few pieces of experimental evidence, some developed only since December, the backbone of the new embryology is all theoretical. But growing interest in the field and the seeds of data to reinforce the theory indicate that embryology is about to break wide open, just as molecular biology did in the mid-1950's.

Much of the current excitement among the handful of researchers presently exploring the problems and laying the groundwork springs from a series of meetings initiated by Dr. Waddington. Held in Italy several times in the last three years and aptly called, "Toward a Theoretical Biology," they catalyzed new thinking.

There Dr. Lewis Wolpert of the Middlesex Hospital Medical School in London presented a theory that differentiation is related to a cell's position in time and space. There Dr. Brian Goodwin from England met Dr. Morrel Cohen from Chicago; the two have since collaborated on experiments inspired by Dr. Wolpert's ideas, and have made progress. The work of these three men, and that of others, spurred Sir Francis Crick's interest in the field, making him its newest disciple.

Dr. Wolpert's hypothesis for differentiation and embryological development holds that cells have access to, and can read, both a clock and a map. A cell differentiates because it is aware of its physical position in a developing line of cells—the consequence of a cyclic repetition of biochemical events —and it can make use of that information. To explain his theory that cells understand positional information, he makes an analogy to what he calls the French flag problem.

Regardless of whether it is four feet long or merely the size of a postage stamp, the French flag is invariably one-third blue, one-third white and one-third red. Suppose that it were made of cells instead of cloth and that before



David Francis

production begins its cells are undifferentiated as to color. Each cell would contain the genetic potential for expressing blue or white or red pigment; in order to make a French flag, each cell would have to know where it was positioned in relation to the whole line of cells. If there were 30 cells, the first 10 would differentiate to blue, the middle 10 to white and the last 10 to red. However, if 12 cells were deleted from the end, the cells would reorder themselves, so only the first six turned blue.

The cells of living organisms, Dr. Wolpert theorizes, behave in this way; by reading their position in a developing embryo they know what to become. Hence, he speculates, positional information precedes molecular differentiation.

Working within this theoretical framework, the challenge is to explain the nature and mechanisms of the chemical processes that are in effect the embryo's clock and map.

There are two postulates. Dr. Crick, a Nobel laureate from Cambridge University, writing in the Jan. 31 Nature, suggests that a simple diffusion mechanism may provide the necessary information about time and geographical location. During the initial stages of development, cells form embryonic fields, generally involving distances of less than 100 cells.

Dr. Crick's basic assumption is not new. As early as the 1930's, scientists suggested that a chemical diffuses through cells in a field, transmitting information as it goes.

Dr. Crick, by working the diffusion process out by what colleagues call "elegant mathematics," has revived the idea. An initial cell produces constant levels of an unidentified chemical called morphogen. It enters a line of cells at one end. As it diffuses through each cell in the line, it establishes a gradient of varying concentrations, which constitute positional information for the cells.

Dr. Crick's presentation may be too simplistic. "It is not his finest hour," says one English biologist. However, the simplicity may have been deliberate. According to Dr. Anthony Robertson of the University of Chicago, "Crick rightly holds that one should first look for the simplest explanation and discount it if necessary before concentrating on more complex phenomena. In a sense he's playing devil's advocate."

The second postulate, somewhat more complicated than Dr. Crick's but supported by preliminary evidence from experiments with the cellular slime mold and other extremely simple organisms, holds that time and place information is conveyed to cells by periodic pulses of chemical activity, initiated by a pacemaker cell. The pulses spread through an embryonic field to constitute an ephemeral map. This postulate is put forth by Dr. Goodwin, of the University of Sussex, and Dr. Cohen, of the University of Chicago. In papers soon to be published in Science, Nature and the Journal of Theoretical Biology, Dr. Cohen, with Dr. Robertson, will present data from slime mold studies and other work.

The Goodwin-Cohen model, like Dr. Crick's, states that positional information is conveyed by a gradient, but in this case it is a gradient of frequencies established by periodic events rather than one set up by concentrations of a specific chemical. "Its action is analogous," says Dr. Robertson, "to the nervous system that operates according to electrical pulses."

Time lapse photography, which Dr. Robertson calls "the basic new tool of embryology," was used to study the development of a slime mold, an organism that is an aggregation of single-celled amoebas encased in a slime sheath. An initiator cell puts out pulses of a signaling agent—in this case, cyclic–3′5′–adenosine monophosphate (AMP), a hormone involved in most types of cellular metabolism. In response to the signal, neighboring amoebas begin to move toward the source in long streams, while putting out their own cyclic AMP signals in a chain reaction.

Streams of amoebas continue to migrate toward the source, piling up and pushing through a cone of slime until the developing mass falls over. The fallen mass is a slug with a body and a distinct tip or pacemaker region. That region, as in the aggregation process, continues to emit pulses from periodic cyclic AMP activity. These pulses move through the slug in waves causing bulges, followed by a phase of relaxation; in this way the organism moves.

If the pacemaker tip is removed experimentally, no movement occurs until a new region, somehow sensitive to the fact that its position in relation to the whole has changed, takes over to form a new tip and emit pulses.

Thus, the amoeba cells, once in the body of the slug, respond to their new position.

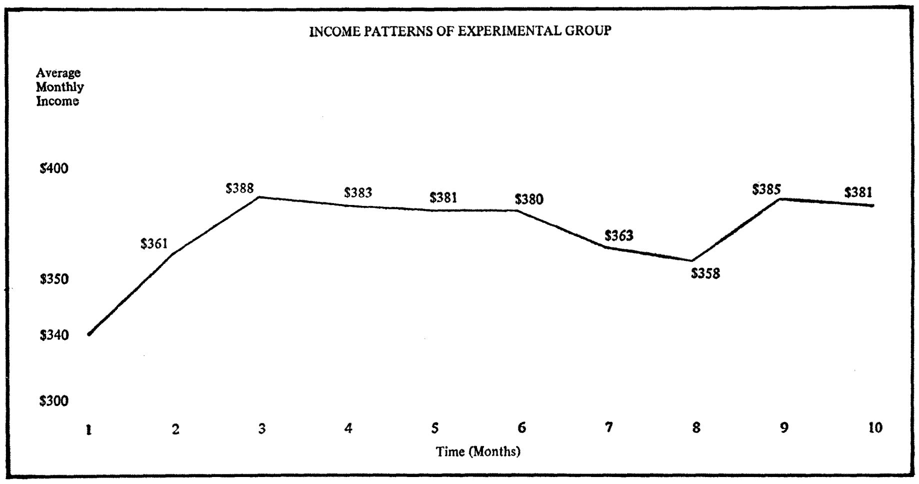
The essence of this theory of embryological development rests on the idea that biochemical events in cells and throughout tissues occur in rhythmic and periodic cycles that, in themselves, convey information.

It demands a complete reorientation for researchers steeped in molecular biology, which focuses primarily on events occurring within single cells more than on interactions among them. As Dr. Waddington points out, molecular biology has had its breakthrough. A similar breakthrough in the theory of embryology could lead to the same shifting of gears and an emphasis on cell behavior in time and space.

"Molecular biology and biochemistry," say Drs. Goodwin and Cohen, "tend to reinforce the deep-seated prejudice that differences of cell state are due to differences in the permanent, as distinct from the transient, biochemical composition of cells. . . . Our model makes clear the fact that, whereas at some stage of differentiation it is necessary for cell-specific substances to be synthesized, it is perfectly possible that the initial stage of the differentiation process involves differences of cell state which are strictly temporal." □

INCOME MAINTENANCE

Trying out the new plan



OEO

On the new welfare plan, families increased their average work earnings.

Although reforming the current welfare system is a project high on President Nixon's list of domestic priorities, the Administration's reform proposals have been in the House Ways and Means Committee since summer.

The committee is promising now to report out a welfare reform bill by April 1. And last week the President's proposals were given a boost when the Office of Economic Opportunity released the results of a study of a model income maintenance project that has been in operation—with input from several teams of university-based social scientists—since 1968.

The OEO project has been tried by researchers from the University of Wisconsin and Mathematica, a Princeton, N. J., research corporation, in Scranton, Pa., and in four New Jersey cities. It resembles Mr. Nixon's proposed welfare system in that the recipient families are guaranteed a set annual income. The 1,359 families involved in the OEO experiment were selected as representative welfare families: The average family contained five or six members.

The income-guarantee payment these families have been receiving has been set as a percentage of the poverty-line income of $3,300 per year. On the