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# CHEMICAL GENETICS

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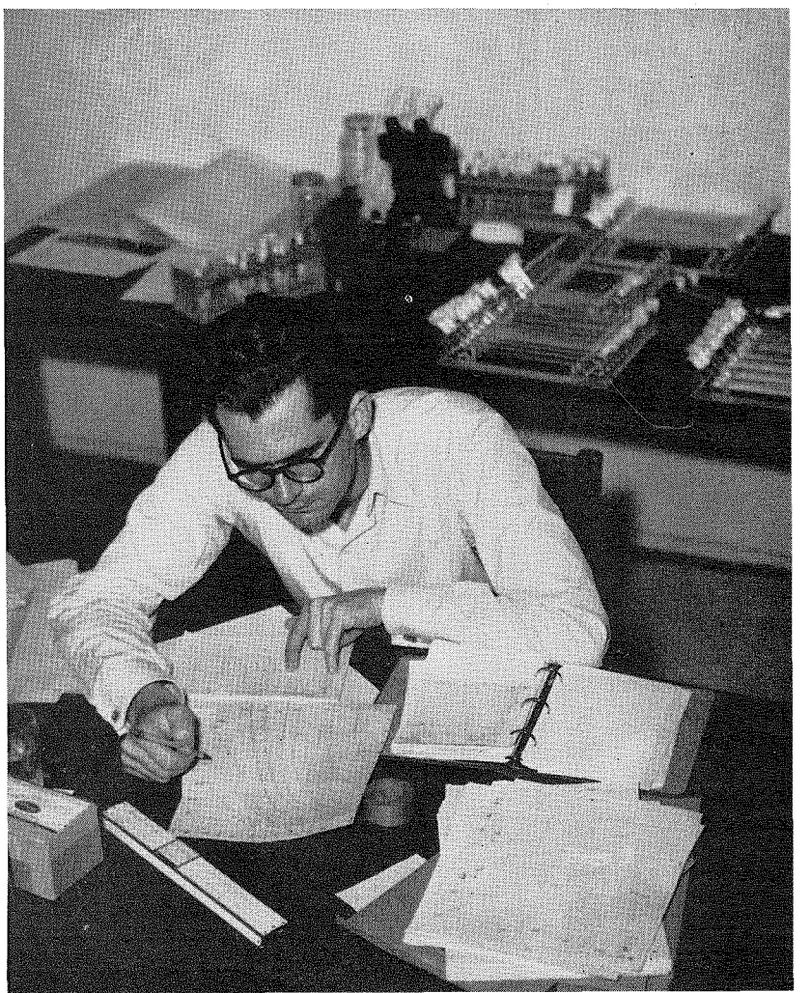
## HISTORICAL SKETCH

AS ALMOST everyone knows, the science of genetics was founded in his spare time by a monk named Gregor Mendel, who raised peas as a hobby in the monastery garden at Brünn, Austria (now Czechoslovakia). Mendel's great discovery, which went unnoticed for 35 years after it was first published, was, like most other important ideas, radical and simple. It was that the individual is made up of distinct hereditary qualities, and that these qualities, or characters, are transmitted independently of one another to future generations. In other words, hereditary characters are passed on as units, and they are distributed in families and populations according to the laws of independent events,—**i.e.,** the laws of probability.

Mendel's findings were published in 1865 and were promptly forgotten until their rediscovery in 1900. Subsequent research (since 1900) showed that for many characters the rule of independent inheritance is at best a first approximation. That is, when certain characters occur together in one parent—such as colorblindness and hemophilia in man—they tend to be transmitted to the progeny together, rather than independently. This finding, together with other evidence, led to the chromosome theory of inheritance and eventually to the theory of the gene. According to these theories, now universally accepted, the agents which are actually transmitted in the germ cells and which determine the inheritance of the individual are material elements in the chromosomes, called genes. Genes which lie in the same chromosome tend to be inherited together; the closer together they lie the more frequently they go together. Genes which are located on different chromosomes, or far apart on the same chromosome, are transmitted independently of one another. This generalization, which successfully correlated large amounts of biological data, was chiefly the creation of T. H. Morgan, A. H. Sturtevant, C. B. Bridges, and H. J. Muller of the **Drosophila** school of genetics. With the establishment of the gene concept, a new and more fundamental approach to the study of inheritance and evolution was opened—the investigation of the gene itself. Furthermore, by placing the whole problem on a physical basis, the gene theory made possible — or rather, invited — the introduction of chemistry and physics into the picture.

## PROPERTIES OF THE GENE

The problem of chemical genetics is twofold: to describe the chemical nature of the gene and to investigate its relationship to the other components of



**Researcher Dr. Marco Zalokar plotting the growth rates of Neurospora inhibited by sulfanilamide (SA) in the presence of varying amounts of p-aminobenzoic acid (PAB). Rates are measured in the double-ended tubes in background. This research is attempting to determine the relations between SA and PAB in Neurospora.**

the cell. In a number of ways the gene is unique and without a counterpart in the physical universe. After considering the known properties of the gene in a recent book, the eminent physicist Erwin Schrodinger was led to remark that the science of genetics is "easily the most interesting of our day." Most geneticists concur in this opinion.

The genes are the basic self-reproducing units of the body. That is to say, every gene arises from a preceding gene through a process which insures that it will be an exact copy of its predecessor. With rare exceptions, the precision of the copying process is such that not more than once in a million duplications, at the outside, is there a detectable slip. Certain genes are known, such as those determining the blood groups in man, which have not changed perceptibly in centuries. Genes can and do change, however, and this is important, because it is these infrequent changes, or mutations, which make evolution possible. The essential point is that once the gene has mutated it reproduces itself in the new form. It is this property which distinguishes it from all simpler self-duplicating systems.

Indirect measurements of the size of the gene indicate it to be of the order of a large protein molecule. Spectral analysis as well as direct chemical isolation has shown that chromosomes contain nucleic acid. That the nucleic acid is contained in, or at least closely associated with, the genes is shown by the fact that maximum absorption of ultraviolet light by genes (as measured by its efficiency in causing mutations) occurs around 2600 Angstrom units.

## THE GENE AND THE METABOLISM OF THE CELL

The gene is also unique in the position it occupies in the economy of the cell. The cell, in the last analysis, is a highly complex chemical system adapted to the production of more cells like itself. It has a means for releasing the stored chemical energy of organic compounds and for utilizing the energy so liberated in the synthesis of new cell substance from simpler materials. To carry on its work, the cell is equipped with a large array of highly specific catalysts, called enzymes, which determine the course and the rate of these transformations. In a sense, there is nothing very novel in these arrangements, although nothing approaching the cell in complexity has ever been created in the laboratory. Catalysis is well known outside of living systems, and even in the cell mass and energy are conserved, and the second law of thermodynamics prevails. The distinctive feature of the cell as a chemical system lies in the fact that it contains certain key molecules, the alteration of a single one of which can radically change the course of the reactions which take place, or can even destroy the cell. The essential, irreplaceable molecules are the genes.

Consider a cell which in the course of its metabolism produces a characteristic pigment. It is possible, by the alteration or destruction of single gene, so to befuddle the cell that it can no longer synthesize the pigment, and all its descendants will be albinos. Restoration of the missing molecule also restores the missing synthesis, and from then on the line is normally pigmented. If, instead of a gene controlling pigment synthesis, we destroy a gene which controls the production of a substance essential to the operation of the cellular machinery—a vitamin, for example—then the cell cannot function and will die unless the vitamin is supplied from the outside. Again, restoration of the gene restores the capacity of the cell to carry on the synthesis.

The extraordinary thing here, from the chemist's point of view, is that we have a system whose structure rests on individual molecules. Yet the laws of physics and chemistry were not designed to describe the behavior of individual molecules, but only of statistical populations of molecules. They do not hold for small numbers. It is for this reason that physicists have concluded that life is not ultimately explainable in terms of ordinary physics and chemistry.

## CHEMICAL GENETICS OF NEUROSPORA

The work in chemical genetics being carried on in the Biology Division is concerned with the role of genes in controlling cellular chemistry. To what extent and by what means do the genes govern the rate and direction of biochemical reactions? The research centers around a mold, **Neurospora,** which has been found to be extraordinarily convenient for both genetical and biochemical investigations. As found in nature, **Neurospora** is capable of synthesizing all of its cell constituents, with the exception of one vitamin (biotin) from sugar and inorganic salts. Given carbohydrate, inorganic salts, and biotin, the organism grows without further assistance. By subjecting it to high energy radiations or mustard gas —agents known to produce gene mutations—it has been possible to obtain mutant types which are unable to carry on certain of the normal chemical activities of the wild strain. Mutant forms have been found which require the addition of a particular vitamin, amino acid, purine, or pyrimidine to the ordinary medium before growth can occur, showing that

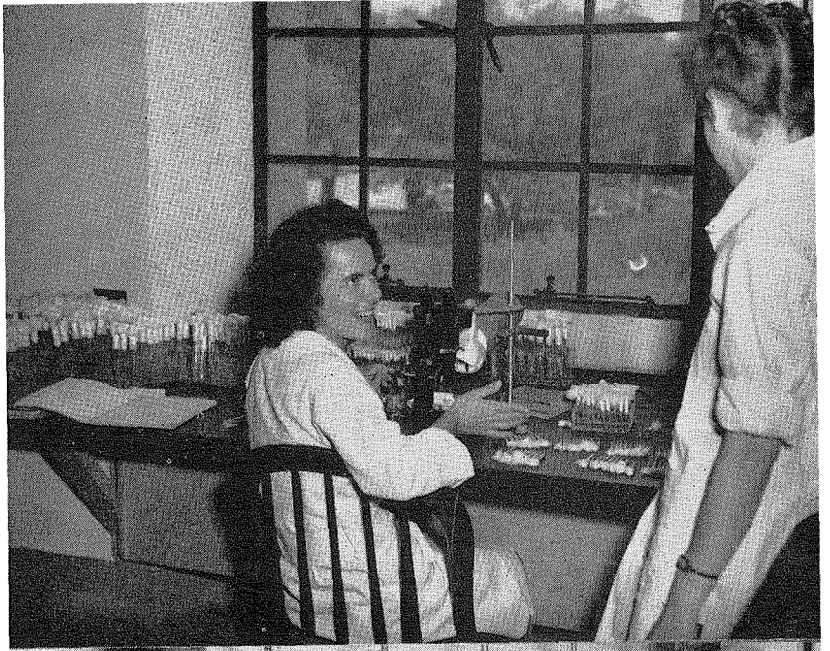
**Large scale cultures of Neurospora for the production and isolation of precursors and other metabolic products are maintained in Fernbach flasks and aerated carboys. These are being examined by David Regnery, graduate student in Genetics.**

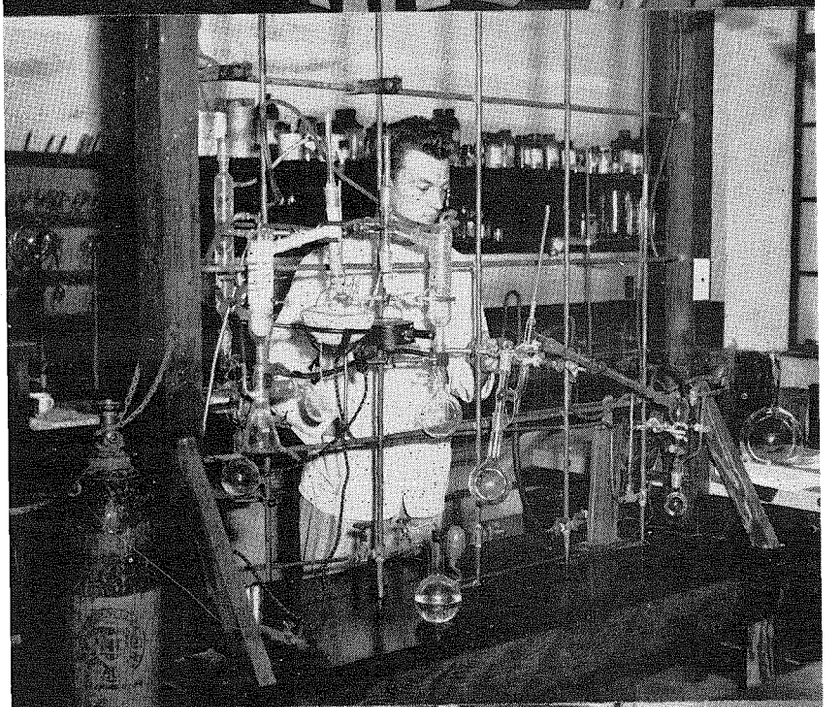
the mutants have lost the ability to synthesize these substances. In every case the loss of synthetic ability has been found to be inherited.

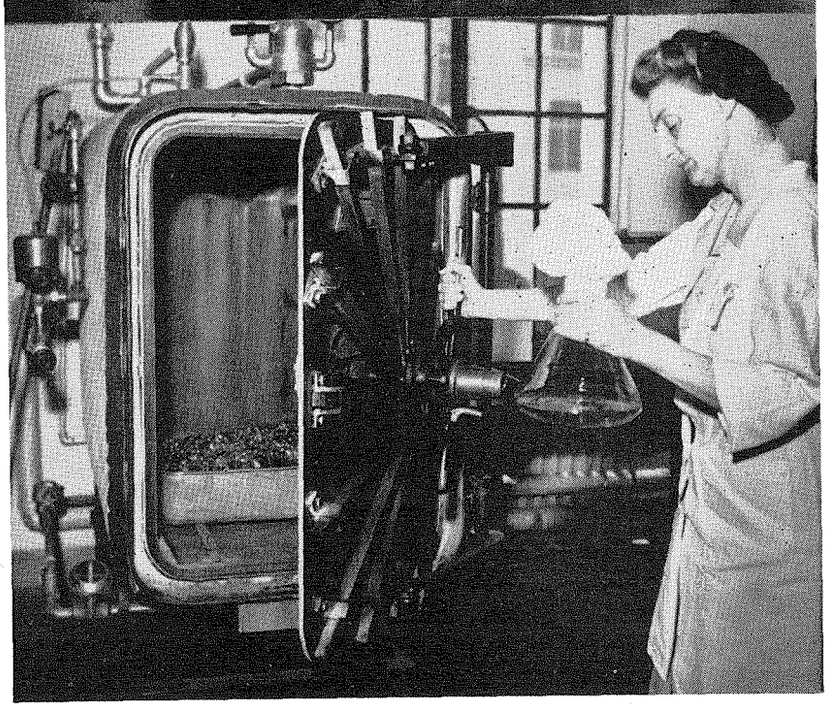
Closer study of the mutants has revealed that the synthesis of each vital substance is governed by a number of single genes, the mutation of any one of which abolishes the synthesis. It has been found that each gene controls a different step in the synthesis, and in numerous instances it has been possible to assign particular genes to particular biochemical reactions.

Aside from its genetic implications, the **Neurospora** work has a number of interesting biochemical aspects. The specific blocking of single reactions through gene mutations offers an unusually delicate method for probing the metabolic machinery of the cell. Through the use of **Neurospora** mutants it has been possible to ascertain the course of certain biological syntheses —**e.g.,** tryptophane, arginine, choline, methionine. One of the surprising results of these studies is the finding that the metabolic pathways so far uncovered in **Neurospora** are closely similar to, if not identical with, those of animals. This increases our confidence that findings made with this organism will have general application to living things. Another biochemical application of the mutants has been in the field of biological assay. The growth rate of mutants which have lost the ability to carry out a particular synthesis is a function of the concentration of the required growth factor. By measuring the growth rate of a mutant on an unknown material the amount of the particular growth substance contained therein can be determined. In this way, it is now possible by the use of **Neurospora** mutants to assay complex mixtures for such biologically important substances as leucine, lysine, choline, p-aminobenzoic acid, inositol, and pyridoxine.

While the lines of investigation described above have proven very fruitful of both fundamental and practical results, and are being actively pursued in the Biology Division, there is no doubt that the most interesting and exacting part of the road is still ahead. A number of basic questions remain to be answered. By what means do genes control the chemical activity of the cell, and how do they utilize cell materials for their reproduction? In answer to the first question it has been suggested that the genes act as templates, or patterns, on which the enzymes and other specific proteins of the cell are formed. Possible answers to the second question cannot be formulated in a few words, but the problem seems at least approachable in terms of quantum mechanics. Whatever the solutions to these problems may be, it is certain that they will be of the greatest consequence for biology and medicine.







**UPPER: Suzanne McLean, research assistant in Genetics explains the genetics of the red bread mold Neurspora to Margaret Campbell, research assistant in Embryology. The test tubes contain an agar medium on which the mold grows.**

**CENTER: Joseph Nyc, research fellow in Chemical Geneitcs, checking apparatus in which chemical compounds of biological importance are synthesized. In collaboration with Dr. H. K. Mitchell and Dr. G. W. Beadle, Dr. Nyc is attempting to determine how Neurospora converts the amino acid tryptophane into the vitamin niacin. Such a transformation, which apparently can be made by man, is of obvious importance in relation to pellagra, a deficiency disease that develops in the absence of sufficient niacin. LOWER: A large steam autoclave in which material is sterilized. For culturing various microorganisms such as Neurospora, it is necessary that all culture media be freed of extraneous bacteria and molds.**