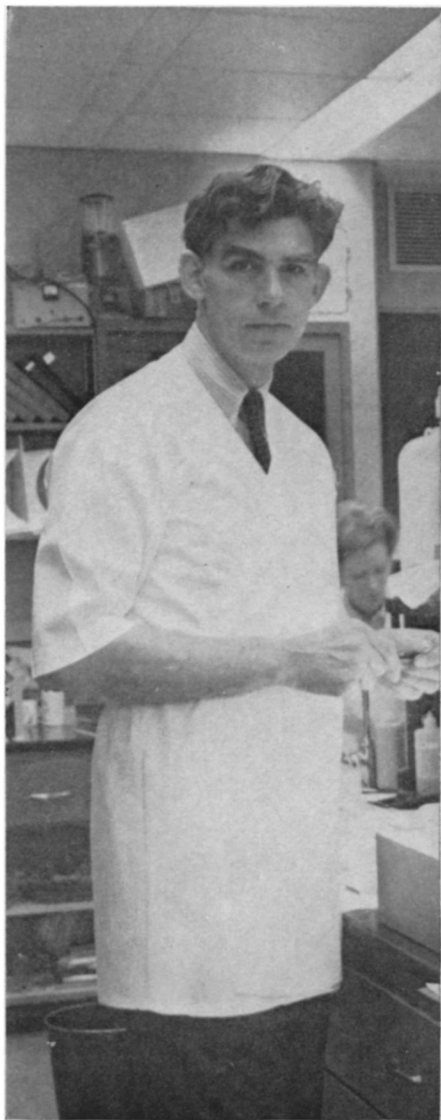


Human gene maps: A first step toward genetic engineering

The work of compiling an atlas of human genes is showing progress

by Barbara J. Culliton



Yale Univ.

Ruddle: The tools are now in hand.

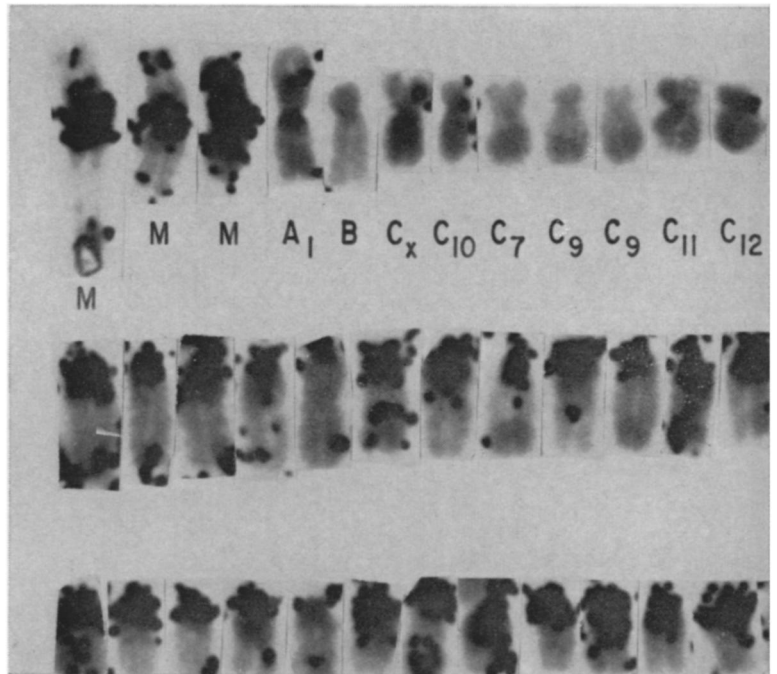
During the 21st century, man will almost surely achieve some measure of control of his own genetic inheritance. Although the advent of genetic engineering is not imminent, its scientific foundations are already being laid.

Before genetic engineering becomes a reality, before scientists can predictably and precisely repair or replace a faulty gene, they must know which genes reside on which of man's 46 chromosomes, and beyond that, specific locations of individual genes on those chromosomes. To this end, investigators have launched a monumental task of compiling an atlas of human genes (SN: 10/11, p. 323).

"The tools," says Dr. Frank Ruddle of Yale University, "are now in hand." Optimistically, he predicts that within as few as five years the broad outlines of human gene maps may be drawn. But the work is tedious, and even if it can be completed, gene mapping is not the only obstacle to genetic engineering. "I'm not at all prepared at this point," he comments, "to even hazard a guess about the details of techniques that will have to evolve to permit us to repair genes once we know their location."

Nevertheless, as the necessary first step toward genetic engineering, the mapping process is going on, and progress is being made.

In the July 18 NATURE, Dr. Ruddle and his colleagues report successful experiments showing that the genes carrying the information for production of the subunits of two enzymes are linked or located on the same chromosome, speculatively a C group chromosome. In the same issue, Dr. Walter F. Bodmer and his colleagues at the Stan-



Man-mouse hybrid cells share enzymes that function alike

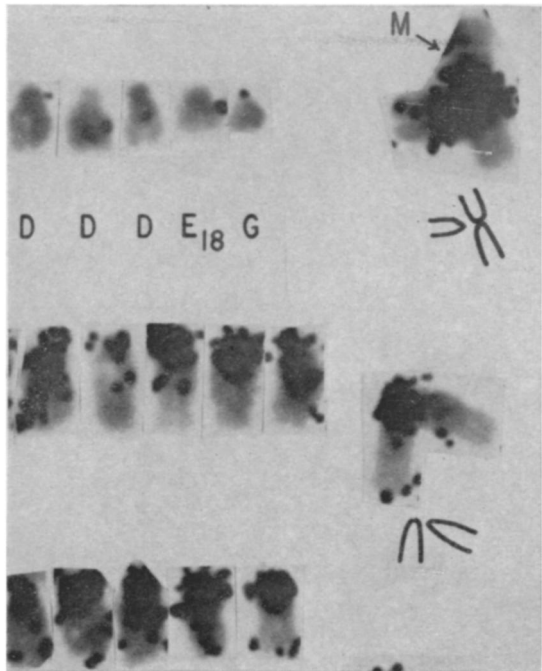
ford University School of Medicine report the same finding. Dr. Ruddle elaborated on his research this month at a seminar on medical genetics held at the Jackson Laboratory in Bar Harbor, Me. The seminar, sponsored by the laboratory and Johns Hopkins University, was supported by the National Foundation—March of Dimes.

The two genes whose linkage has been demonstrated are those coding for part of human lactate dehydrogenase, essential for the metabolic breakdown of lactic acid, and of peptidase B, a specific enzyme that breaks dietary proteins into small amino acid peptides. Each enzyme, in this case, is built of two subunits or chains of amino acids simply designated A and B. Each subunit is fully constructed before being joined to form a total enzyme and each is under the control of separate genes. The genes located in the experiment code for the B subunit. The location of the A genes remains unknown.

Human genes are mapped from information derived from studies of man-mouse hybrid cells. Using inactivated Sendai viruses as tools for fusing cells, researchers force the merger of carefully preselected cells from mice and man, creating a hybrid containing some genes from each. The first such hybrids were produced in 1967 by Dr. Howard Green of New York University.

The hybrids possess three special attributes which make them useful for map making:

- They share certain human and mouse enzymes that function alike biologically but differ biochemically in their physical properties. Thus, human and mouse peptidase B can be easily



Ruddle

but can be easily distinguished by geneticists.

distinguished by laboratory analysis.

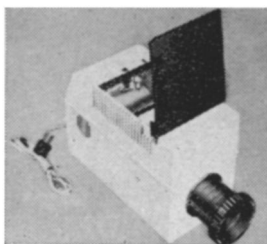
Human and mouse chromosomes differ in size, shape and biophysical properties, allowing investigators to look at a hybrid cell and identify which human chromosomes are present.

For reasons not fully understood, hybrid cells preferentially lose human chromosomes during the course of replication. Thus, after several generations, a hybrid cell will contain all of the mouse chromosomes originally present but only some of the original human chromosomes, seldom more than 12 and not necessarily the same ones from hybrid to hybrid. Again, the existence of easily determined differences among chromosomes in a hybrid offers geneticists a tool to use in their investigations.

Once hybrid cell lines have been established and analyzed for broad characteristics, scientists begin looking for gene linkages by studying enzymes present in those cells. Individual genes are not seen themselves but their presence is known by the presence of their products—enzymes. What the two teams of scientists discovered with regard to the B subunits of LDH and peptidase is that whenever one is present, the other is too. By contrast, LDH A may or may not also be there. From this they conclude that the genes for LDH B and peptidase B are linked on the same chromosome and LDH A is not linked to either.

This highly specific and admittedly limited information constitutes but one small dot on the maps scientists are striving to compile. But it is a beginning, one that validates the research effort to date and is encouraging to further exploration. □

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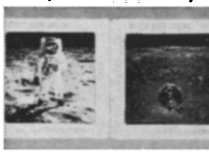
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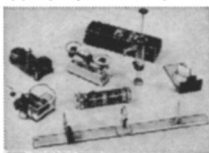
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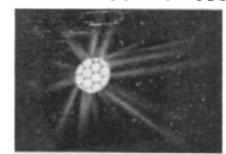


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