The Bar Harbor Course in Medical Genetics

The tenth session of the Short Course in Medical Genetics (the "Bar Harbor course") is scheduled to be held in Bar Harbor, Maine, 30 July to 11 August 1972. Since its initiation in 1960 (*1*) the course has been a joint effort of the Johns Hopkins University and the Jackson Laboratory; it has been supported by the National Foundation–March of Dimes as part of its program on birth defects.

The 1972 session will actually be the 13th annual course. Since 1967 a course in mammalian genetics has been substituted for the medical genetics course in alternate years. The emphasis in the latter course is on the mouse, but man and, to a lesser extent, other mammals come in for attention.

Lecturers in the annual course usually include about ten from Johns Hopkins, ten from the staff of the Jackson Laboratory, and six or eight guest lecturers from other institutions. John L. Fuller of the Jackson Laboratory was codirector of the course for the first 7 years. In 1968 Seldon Bernstein served in this role and in 1970 Thomas Roderick of the Jackson Laboratory was codirector as he will be in the 1972 course. Elizabeth Russell of the Jackson Laboratory has been mainly responsible for the course in mammalian genetics. Earl Green, director of the Jackson Laboratory and host for the course, has been an enthusiastic supporter and a valuable lecturer.

The medical genetics course is intended for faculty members of medical and dental schools and schools of public health and for staff members of teaching hospitals and research institutions. However, the "students" have also included faculty members from veterinary schools, outstanding medical students, and some department chairmen and deans, as well as teachers of human genetics at universities. More than 800 students have taken the course, a few more than once. Most of the students are from the United States, but a significant number are from Canada, and each year five or more, usually completing a period of training or research work in this country, have come from overseas.

An objective of the course is to upgrade the teaching of genetics, and it aims at utilizing the different but complementary approaches taken by the physician geneticist and the experimental mammalian geneticist in studying comparable genetic abnormalities. While it is impossible for the course to create a professional in human genetics ("instant genetics" is a humorous title for the course), it tries to give pediatricians, endocrinologists, pathologists, biochemists, and many other specialists a background in genetics that they can incorporate in the teaching of their particular discipline. The student body of the mammalian genetics course is weighted toward those working with mouse models, but many who work in human genetics find it a valuable experience because of the differences and similarities in approach—the principles and problems are the same. As a medical student who attended the 1970 course remarked, genetics is the language of medical science just as mathematics is the language of science generally.

This is a course, not a conference. The intention is to cover the field systematically, beginning with first principles and developing the discussion in a way that can be followed by all members of the heterogeneous audience. Although at almost every lecture at least one of the students is an expert on the topic, most do not have the whole picture and it is useful for all to observe the lecturer's technique of presentation. Most of the lecturers attend every session, which is desirable for continuity and avoiding repetition, and all contribute to the discussions. The lecturers are active workers in the field they are discussing, so, although upgrading of teaching is the main objective of the Bar Harbor course, new results are introduced each year and research in human genetics is fostered.

The great progress in medical genetics since 1959 has been reflected in the curriculum of the course. In the first year or two lectures sometimes tended to be catalogs of genetic disorders of an organ system, such as the cardiovascular system. Lately, although detailed listings of particular categories of disorders are occasionally given, it is to illustrate principles—for example, genetic heterogeneity. In 1962 the Lyon hypothesis was an exciting new topic in relation to the genetics of both mouse and man. It has been interesting to observe the unfolding of the mouse H-2 locus story (as told by George Snell) and the more recent development of the parallel topic HL-A in man. Highlights of the 1970 course (medical genetics) included fluorescence microscopy of chromosomes after staining with fluorochromes, a demonstration that some normal males lack the fluorescence-staining part of the Y chromosome, chromosome mapping by in situ RNA-DNA hybridization, gene localization by linkage studies and by cell hybridization, the study of the early embryo in vitro, vitamin-dependent inborn errors of metabolism, chemical mutagenesis, genetic heterogeneity as illustrated in the hereditary hyperbilirubinemias, the genetic disorders of the adrenal cortex, prenatal diagnosis by amniocentesis, and a historical résumé of the development of genetics, particularly that of man (by Curt Stern, who introduced his characteristically superb lecture by saying that his objective was to bridge the genetic generation gap).

In general, the 2-week course consists of lectures for 3½ hours in the morning and 2 hours in the evening. Laboratory exercises are not feasible, but techniques are often demonstrated —dermatoglyphics was, for example, featured in the 1970 course. During the first week a "mouse clinic" is conducted to illustrate mutant states that are demonstratedly or potentially useful models of human disease. For example, these have included "Jimpy," an X-linked disorder with parallels to the Pelizaeus-Merzbacher disease; several anemia, chondrodystrophy, and osteosclerosis mutants; the mouse homolog of Chediak-Higashi disease, and so on. In the second week, in recent years, Morris Lambdin has conducted a medical genetics clinic. This involves the presentation and discussion of patients and their families from eastern Maine; most of them are drawn from the Maine Genetic Counseling Center at the Maine Coast Medical Center in Ellsworth. The medical genetics clinic is potentially a valuable clinical service as well as an important instructional feature of the course.

In the 1970 course afternoons were used for optional 1-hour sessions for discussion of statistical problems in human genetics [testing a new study guide (*2*) for use with courses in human genetics], sessions for practice in the techniques and interpretation of dermatoglyphics, and, during the second week, the medical genetics clinic. Workshops in new cytogenetic tech-

niques and in biochemical screening techniques are planned for the 1972 course. Also, some of the free time is used by conscientious students for visits to investigators, to the library at the Jackson Laboratory, or to the neighboring Mount Desert Island Biological Laboratory, which specializes in marine biology. The final session of the course is customarily either a summing up by one of the lecturers or a panel discussion by several of the senior faculty, representing both human and mouse aspects of the problems.

Through the 12 years of its existence the course has encountered most of the problems that were pointed out by Francis Crick (*3*) in his perceptive essay "On running a summer school"—for example, too many lectures, inadequate briefing of lecturers on the level appropriate to the audience, and so on. However, most of the defects have been remedied in recent years. Achievement of the proper level has presented no serious problems because a number of the guest lecturers are alumni of the course and the group of lecturers from Hopkins and the Jackson Laboratory has undergone little change. Some of Crick's considerations—legible name tags, distributed lists of home addresses, opportunities to get together in a social setting for informal discussions—have from the beginning been standard operating procedure at Bar Harbor. For example, at a party each night after the evening lecture all the lecturers of that day and usually many of the others are available for discussions.

It is likely that the Bar Harbor course has had a significant and beneficial influence on the progress of research and teaching in human genetics in this country and elsewhere. There is no sign of decline in the usefulness of or demand for the Bar Harbor course—either the medical genetics or the mammalian genetics course.

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References

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2. V. A. McKusick, *Study Guide in Human Genetics* (Prentice-Hall, Englewood Cliffs, N.J., 1972).
3. F. Crick, *Nature* **220**, 1275 (1968).

Order in an Anarchic Field

Problems in cellular and multicellular differentiation and morphogenesis in a wide range of organisms including *Saccharomyces, Paramecium, Naegleria, Neurospora, Blastocladiella, Physarum, Polysphondylium,* and *Dictyostelium* were discussed at a workshop meeting on Differentiation in Eukaryotic Microorganisms held on 18 to 21 February 1972 at La Jolla, California.

These discussions proved useful, not because of new factual information presented, but because all participants made very strong efforts to define real questions that must be answered to understand cell differentiation, whether in one-cell or multicellular organisms. Two central problems emerged. (i) How are the hundreds of enzymes that change during development coordinated in a temporally and quantitatively regulated sequence? This is the problem of complexity. (ii) How are the products of enzymatic reactions laid down so as to form a structure of definite shape and size? This is the morphogenetic problem. Many of the presentations were approaches to one or the other of these questions.

The meeting was opened by T. Sonneborn (Indiana) who talked on morphogenesis in ciliates. A major question concerns the source of information for controlling the developmental behavior of the unit territory which belongs to each kinety on the cortex of *Paramecium.* Evidence from natural "microsurgical" experiments in which rows of cilia are inverted suggests that certain aspects are controlled by the pattern of the surrounding cortex, while others are determined by information from within the unit. Sonneborn concluded that further analysis would probably have to utilize specific conditional mutants, which he is now attempting to isolate.

S. Brody (La Jolla) reported on a series of mutants that affect the pattern of mycelial branching in *Neurospora* and his efforts to identify the responsible biochemical lesions. The difficulties encountered are instructive. One set of mutants is deficient in reduced nicotinamide adenine dinucleotide phosphate, but it is not clear how this compound affects cell wall biosynthesis. Second, genetically distinct mutants were found which affect the same enzyme (glucose-6-phosphate dehydrogenase), but all have visibly different patterns of mycelial branching. Although biochemical events must determine the branching pattern, it is clear that the relation is not one-to-one.

Somewhat related is work on *Blastocladiella* presented by D. Sonneborn (Wisconsin). His starting point is the hypothesis that some of the changes that occur in cell development may occur by rearrangement of structural material already present in the cell, without new gene activity or synthesis of new enzymes. One specific instance is the sudden increase in cell wall glucosamine compounds and the simultaneous sudden decrease in stored glycogen which occurs over a 20-minute period when germinating zoospores form hyphal outgrowths.

In contrast with these biochemical or genetic analyses, P. Green (Stanford) presented a physical interpretation of morphogenesis in the growing cell of the alga *Nitella.* The attempt was to express the shape changes in terms of a distribution of rates of expansion of the cell wall, and to determine the physical factors (like orientation of microfibrils) which modulate the rate. Green suggested that the gap between morphogenesis and biochemical genetics must be bridged from the phenotypic end.

G. Gerisch (Max-Planck-Institut, Tübingen) reported on his studies of the mechanism of aggregation and adhesion in the cellular slime mold *Dictyostelium.* He has been able to distinguish two adhesive components, one inhibited by ethylenediaminetetraacetate (EDTA) and another that is present only in developing cells and is insensitive to EDTA. Studies with univalent antibodies suggest that the second adhesive site is distinct from the first and may be involved in end-to-end cellular adhesion seen in aggregating cells. H. Aldrich (Gainesville) presented electron microscopic evidence from freeze-etched preparations for an increase in intramembrane 153-Å diameter particles during aggregation. These particles may be involved in morphogenetic adhesions.

Other offerings dealt in one way or another with the problem of the biochemical complexity of cell differentiation. B. Wright (Boston Biomedical Research Institute) reviewed her position that control of formation of the end product, such as cell wall, is in