THE JACKSON LABORATORY
Bar Harbor, Maine 04609

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FINAL REPORT

to

The National Foundation
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The Short Course in Medical Genetics for 1972, held at the Jackson Laboratory from 31 July through 11 August, was the largest and by general consensus "the best yet." This was the 13th annual course in genetics at the Laboratory, the 10th in medical genetics. The course was conceived in 1959 and first conducted in 1960. During the past year an account of the course was published in Science (19 May 1972, p. 820-821; see Appendix 6). On the last evening of this year's course, Dr. V. A. McKusick, course co-director, gave an illustrated survey of the history of the course.

The 1972 course was attended by 113 students, 35 faculty members, and 12 science writers. The background of the students was as diverse as ever. The group included pediatricians (Degnan, Duncan, Falletta, Glorieux, Sass-Kortsak, Tipton), dermatologists (Brodin, Muller, O'Keefe), pathologists (Ahern, Gill, Palutke, Spear), gastrointerologist (Binder), ophthalmologist (Macrae), a radiologist (Dorst), an obstetrician-gynecologist (Dunn), a neurologist (Harlan), and an immunologist (Levy). The students ranged from medical students (Bieber, Keene, Stokes) to department chairmen (Dunn, Gill, Tallalay). Many of the "students" teach human genetics at the university level: e.g., Bailin, Darlington, Daniel, Friedlander, Newell, Tegenkamp, Champlin. A considerable number of students came from Canada, and one each came from Peru and Germany; all these persons came to the United States expressedly to attend the course.

The faculty from Johns Hopkins and from the Jackson Laboratory had somewhat the same composition as in recent years. The guest lecturers (i.e., non-Johns Hopkins or non-Jackson Laboratory faculty) included Dr. Park Gerald who has the unique distinction of having been a faculty member for each of the 10 years of the medical genetics course. The others included Drs. Howell, Littlefield, Renwick, Ruddle, Miller, Scriver, and Sutton. This was the first year for the last three, although Scriver was a student in the course in an earlier year.

A particularly exciting new aspect of the course in 1972 was the presentation of information on the new chromosome technology, i.e., fluorescent staining, Giemsa banding, and heterochromatin staining. Their application to identifying chromosomes and parts of chromosomes of mouse and man for analysis of rearrangements and for assignment of linkage groups to specific chromosomes was described. The methods in the analysis of inversions in mice and men was discussed by Dr. Roderick; Dr. Eicher discussed translocations. Assignment of genes to specific chromosomes in the mouse was discussed by Dr. Miller, and in man by Dr. Ruddle.

Dr. Renwick discussed linkage by pedigree study. The present state of the map of human chromosomes was assembled, based on the combined approaches of pedigree study and cell hybridization (see Appendix 4). The progress in the mapping of Chromosome 1 is noteworthy. Several of the chromosome assignments achieved by cell

hybridization need classical pedigree studies in order to determine the interval separating loci on the same chromosome. For example, adenine phosphoribosyltransferase, which has been assigned to Chromosome 16, occurs in a polymorphism of heat-resistant and heat-sensitive forms, and mapping of its position relative to that of the haptoglobin locus should be feasible.

Afternoon workshops in the new cytogenetic techniques supplemented the lectures. Two other workshops, one on biomedical screening and one on statistical methods, were offered. Drs. Howell, Scriver, and Thomas were in charge of the screening workshop, at which Dr. Holtzman gave a valuable discussion. Part of Dr. Abbey's discussion of probability dealt with the Bayesian question: "What is the likelihood that disease A is present given a positive test?" One of the student papers (R. Gold) dealt with tests for recognizing the heterozygote by making use of two tests.

One of the student papers (H. Golomb) dealt with electron microscopy and cytogenetics and therefore filled a gap which had been left earlier between the Watson-Crick molecule and the chromosomes as seen with the light microscope.

Dr. Abbey's presentation was organized into consideration of four laws of probability. Dr. Murphy's discussion of population genetics concerned itself with three laws: (1) the Hardy-Weinburg Law, (2) the Dahlberg Law, and (3) the Haldane Law. Dr. Murphy played a recording of a statistical operetta with words composed by him and sung by Dr. Chase to the music of Gilbert and Sullivan's, "He is the very model of a modern major general." The 18 or so stanzas covered the whole range of population genetics and statistical genetics, including linkage analysis. It will probably become a minor classic.

Immunogenetics was represented by the H-2 story in the mouse told by Drs. Snell and Bailey of the Jackson Laboratory, the parallel HL-A story in man told by Dr. Bias, and the genetics of the immunoglobulin reviewed in a particularly lucid manner by Dr. Dintzis. Cutting through the jargon with which the field has become encrusted, he compared the immunoglobulin molecule to a lobster (appropriate for a course in Bar Harbor).

What was not included in the 1972 course is also of interest. For example, blood groups were not discussed as such. The ABO, secretor, Lewis, and Bombay interrelationships were not reviewed.

The immunoglobulins were discussed by Dr. Dintzis as part of the developmental genetics program. Other parts were likewise exciting and included, as noted on the program, description of methods for culture and storage of the early embryo (Whittingham), genetic studies of the early embryo (Whitten), and differences in enzyme levels in the developing brain of different strains of mice (Kozak).

Boyer, McKusick, and others made the point that allelic genes can result in quite diverse phenotypes. Although inborn errors of diverse phenotype, but with the same enzyme deficit, may be allelic, the fact that many enzymes are now known to have more than one structurally different subunit means that non-allelism is possible in some such cases.

Somatic cell genetics has established itself in human genetics. The use of cell culture methods in prenatal diagnosis (Littlefield), in the study of inborn errors of metabolism (several speakers), in mapping the chromosome through cell hybridization (Ruddle), and in the study of mutation (Littlefield, Sutton) was described in appreciable detail.

Dr. Boyer weighed the relative importance of selection and non-adaptive factors in human evolution. Likewise, Dr. McKusick on the same evening considered the alternative possibilities of selective advantage and founder effect or drift in determining the high frequency of certain genes in certain populations, e.g., that of Tay-Sachs disease in Ashkenazim.

On Tuesday of the second week, mouse models were discussed and a mouse clinic was conducted at which mutant mice were presented. New ones included lethal milk, a syndrome probably comparable to breast-feeding hyperbilirubinemia of the infant discussed by Dr. Arias during the first week. These are genetic disorders based on the genotype of the mother, not on that of the affected individual. Thus this condition is like the damage of the offspring of mothers with phenylketonuria. A newly discovered X-linked dominant hypophosphatemia in the mouse was unveiled. This is probably precisely analogous to the condition in man. Dr. Glorieux discussed this gene-determined defect in the human disease in a student paper on the last day of the course. Ohno's Law of the evolutionary conversion of the X chromosome implies that the X-linked mutation may be among the most useful animal models of human genetic disease. The testicular feminization syndrome in mice is a good case in point. Although linkage, proportion of new mutation cases, and Lyonization in heterozygotes have not served to establish X-linked recessive inheritance as opposed to male-limited autosomal dominance in man, the mouse model is so close to that in man physiologically (Goldstein and Wilson. 1972. J. Clin. Invest. 51:1647), and Ohno's Law is now supported by so many examples, that X-linked recessive inheritance seems almost certain. Isolated growth hormone deficiency is another newly recognized mouse mutation. Previous pituitary dwarfism in the mouse has been panhypopituitarism.

Dr. Lambdin again arranged the medical genetics clinic which was held on Thursday afternoon of the second week. Of the 15 cases prepared for presentation and discussion, 10 appeared. The cases were presented by students of the course from Johns Hopkins who had had an opportunity to examine the patients prior to the clinic. A diagnosis of pseudo-pseudo-hypoparathyroidism was made in the case of a 5-year-old

girl with short stature, full-moon facies, eceopic calcification, and short metacarpals and milatarsals. Two "new" syndromes were manifested by two sisters in one family and a single case with kinky hair as a leading feature in the second. Dr. Lambdin suggested that these may represent the same disorders as those reported, respectively, in Am. J. Diseases of Children 124:11, 1972 and Pediatrics 49:6, 1972. The 12-year-old sister of an 18-year-old girl with cerebellar ataxia, seen at Johns Hopkins several times in the past, has begun to show signs of the disorder. This suggests a recessive form.

Dr. Renwick on Tuesday night of the second week, introduced a discussion of environmentally induced birth defects, namely data bearing on the potato blight as a cause of anencephaly, spina bifida, and meningoencephalocele. This provided a good balance to the genetic discussions. It reminded us that genetics is the science of variation and that the geneticist must keep non-heritable causes of variation in view.

Excellent use was made of handouts: reference lists, techniques for new chromosome study, preprints of the Paris Chromosome Standardization Conference, etc. The library of the course has, unfortunately, become obsolete, but students and staff made specific proposals for bringing it up to date.

APPENDICES

1. List of Participants
2. Schedule
3. Medical Genetics Clinic
4. Linkages, including specific autosomal assignments where known
5. Student Papers
6. The Bar Harbor Course in Medical Genetics (Reprint of Science article)