Meetings

Genetic Control Mechanisms in Man and Other Mammals

Forty West Coast human geneticists, basic geneticists, and molecular biologists met in La Jolla on February 13 and 14 for a workshop and symposium dealing with problems of genetic control in mammalian systems. It was hoped that informal contact among these groups might lead to new investigative approaches and stimulate the development of regional collaboration in the study of human genetic disorders. The meeting was supported by the National Foundation for Genetics and Neuromuscular Diseases.

R. Dulbecco (Salk Institute, San Diego) contrasted mammalian and bacterial regulation. He cited the redundancy of DNA, the complexity of cellular organelles, the differentiation of chromosomal structure, and the constraints of nuclear and plasma membranes in mammalian cells. Histones, acidic proteins, chromosomal RNA, and RNA polymerase were considered as possible regulatory molecules for transcriptional control in mammals. Histones seem to lack the specificity required for recognition of base sequences in DNA, but probably are involved in the inactivation of large portions of the genome. Replication of DNA precedes steps of cellular differentiation and may release histones so that certain parts of DNA become accessible for transcription by RNA polymerase. Nonidentical RNA polymerases may provide sites for differential regulation of transcription by hormones or growth factors. In contrast to bacterial systems, mammalian messenger RNA is long-lived. Polycistronic messengers have not been demonstrated, and there is no evidence for the existence of operons in mammalian systems. Modulation of the differentiated state in mammalian cells, as exemplified by enzyme induction, is probably controlled at a posttranscriptional level. Continuing control mechanisms are essential in mammalian systems, because DNA of differentiated cells is totipotential, as has been demonstrated in imaginal disk transdetermination in *Drosophila*, in nuclear transplantation of frog intestinal cell nuclei, and in ectopic production of polypeptide hormones by certain human tumors.

Dulbecco viewed the aging of somatic cells in culture as a stochastic process of accumulated mutations. Cell culture lines that have high cloning efficiency are characterized by loss of contact inhibition and by loss of aging and may represent an accumulation of mutations in control mechanisms, such as damage to amino acid–activating enzymes for protein synthesis or in important structural proteins.

Production of hybrid cells by the technique of cell fusion and studies of transformation of specific properties provide powerful new tools for study. Transformation has recently been reported in the mouse pigmentary cell system using embryonic material, and transduction has great promise but has not been achieved so far. Progress in somatic cell genetics is limited at present by the absence of somatic recombination, as well as by the lack of regulatory gene mutations, the tendency of these cells to become aneuploid, and the frequency of chromosomal rearrangements.

Discussion revolved about the regulatory role of cyclic adenosine monophosphate (AMP). G. Tomkins (University of California, San Francisco) suggested that "God uses cyclic AMP to make sugar," acting through a variety of mechanisms in cells. Cyclic AMP seems to affect transcription in bacteria, translational processes in adrenal steroidogenesis, and protein conformation in its effect on liver phosphorylase activation. It was thought that cyclic AMP may exert a generalized action in enhancing phosphorylation of proteins.

Tomkins discussed the hormonal induction of tyrosine aminotransferase in hepatoma cells in tissue culture. He presented evidence for a model in which inducing glucocorticoids have a single action—to antagonize a labile, posttranscriptional repressor which both inhibits transaminase messenger translation and promotes messenger degradation. The evidence that the inducer acts at a posttranscriptional level emphasizes that regulation of specific gene expression in higher organisms need not operate at the genetic or transcriptional level, as is usually the case in prokaryotic organisms. J. Monod (Institut Pasteur, Paris) raised again the possibility that this mammalian repressor may be an RNA species, whereas the repressor of the lac operon in *Escherichia coli* has been shown to be a protein.

R. Shimke (Stanford University, Palo Alto) has utilized inbred mouse strains to study the roles of enzyme synthesis and degradation in the quantitative regulation of enzyme concentration in animal cells. He has shown that a genetic locus affecting the degradation of hepatic catalase maps separately from the structural locus affecting the specific enzyme activity of catalase. A. Yoshida (University of Washington, Seattle) pointed out that immunoprecipitation techniques which depend upon a multimeric protein structure for enzyme activity must be modified to measure also the subunits, so that association and dissociation of monomers can be evaluated. Furthermore, specific activity measured in vitro for enzyme proteins may miss an alteration in affinity for substrate or in availability of ligands crucial to the in vivo activity.

S. Ohno (City of Hope Medical Center, Duarte, California) reported new studies which suggest a regulatory gene locus in the mouse. In a search for such a locus, he selected the alcohol dehydrogenase system, in which electrophoretic variants are known to be inherited as autosomal traits. A regulatory mutation might be expected to affect only the kidney, where enzyme production is inducible by testosterone, and not the liver, where production is constitutive. A mutant tobacco male mouse was found with normal liver alcohol dehydrogenase activity and no kidney activity, even after stimulation with testosterone. Crosses with normal female mice gave F_1 progeny in which males were normal and females had the mutant phenotype, indicating X-linked, dominant transmission of a regulatory mutation. These results further require that the product of the regulatory gene affect all cells in the female kidney and therefore either be diffusible between cells or have a gene locus on the X chromosome which is not inactivated. This approach may be applicable to other mammalian systems, especially those in which hormone induction is known.

T. Puck (University of Colorado, Denver) discussed studies on the genetic analysis of somatic mammalian cells in vitro. He described techniques for inducing and selecting auxotrophic mutants in stable lines of monosomic hamster cells. Puck stressed that these techniques could be applied now to the testing of mutagenic and oncogenic agents and to the testing of food additives and drugs and other potential environmental pathogens. Using the techniques of cell fusion, he was able to perform complementation analysis on several mutations involving auxotrophy for the amino acid glycine. He discussed the application of these techniques to the study of linkage, to assignment of genes to human chromosomes, and to the investigation of dominant and recessive gene effects.

W. Nyhan (University of California, San Diego) reported studies on a family with hypoxanthine-guanine-phosphoribosyl transferase (HGPRT) deficiency, and X-linked disorder, characterized by choreoathetosis and self-mutilation with hyperuricemia and gout at an early age. Female heterozygotes, carriers for the disease, have normal red blood cell HGPRT enzyme activity. In this particular kindred, glucose-6-phosphate dehydrogenase (G6PD), another X-linked biochemical marker, was present in heterozygous A/B form. Both electrophoretic types were expressed in fibroblasts, but in the red blood cells only G6PD B was expressed. Cloning of fibroblasts showed that the G6PD A and the HGPRT-deficiency genes were on one X chromosome and that G6PD B and normal HGPRT genes were on the other X chromosome. The most probable explanation for the finding of G6PD B and normal HGPRT activity in red blood cells is that selection occurs against the HGPRT-deficient red blood cells.

J. Seegmiller (University of California, San Diego) described several basic biological processes that have been studied with HGPRT-deficient cells in tissue culture. At high cell density, mutant cells had some enzyme activity, which was due to a process called metabolic cooperation, mediated through physical contact between mutant and normal cells. Cell fusion of a G6PD-deficient fibroblast with an HGPRT-deficient fibroblast yielded clones having both activities, demonstrating that both X chromosomes remained active in the tetraploid hybrid cells. In attempts to transform HGPRT-deficient cells with DNA from normal cells, HGPRT-positive cells were detectable at a low frequency, but no HGPRT-positive cells could be cloned. These results are interpreted to indicate abortive transformation.

At the close of the meeting, some problems of intrauterine diagnosis by amniocentesis were discussed. It was pointed out that some enzymes in early pregnancy have not reached postnatal or adult levels of activity. It will be necessary to study the ontogenesis of enzyme activity for all enzymes involved in inborn errors of metabolism so that accurate diagnosis at different stages of fetal development will be possible. The need for standardized, well-controlled techniques and for reference laboratories was emphasized.

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Forthcoming Events

September

21–24. International Conf. on **Engineering in the Ocean Environment,** Panama City, Fla. (W. E. Burt, U.S. Naval Ship Research and Development Lab., Panama City 32401)

21–25. Intersociety **Energy Conversion Engineering** Soc., Las Vegas, Nev. (A. Smith, Kirkland Air Force Base, Albuquerque, N.M. 87117)

22–24. **Physics and Nondestructive Testing** Symp., 10th annual, Chicago, Ill. (W. J. McGonnagle, P.O. Box 554, Elmhurst, Ill. 60126)

22–1. Symposium on the Development and Utilization of **Geothermal Resources,** Pisa, Italy. (G. R. Robson, United Nations Geothermal Symp., United Nations, New York 10017)

23–24. **Electron Device** Techniques Conf., New York, N.Y. (M. Gallagher, Hughes Research Labs., 3011 Malibu Canyon Rd., Malibu, Calif. 92265)

23–25. International Symp. on **Sporopollenin,** London, England. (J. Brooks, c/o Dept. of Geology, Royal School of Mines, Imperial College, London S.W.7)

23–26. Academy of **Psychosomatic Medicine,** San Francisco, Calif. (E. Dunlop, 150 Emory St., Attleboro, Mass. 02703)

24–26. Federation-Unified **Science Education** Conf., Portland, Ore. (M. Fiasca, General Sciences Dept., Portland State Univ., P.O. Box 751, Portland 97207)

24–27. American **Medical Writers'** Assoc., New York, N.Y. (W. W. Curtis, AMWA, 420 Lexington Ave., New York 10017)

26–31. American **Fracture** Assoc., New York, N.Y. (H. W. Wellmerling, 610 Griesheim Bldg., Bloomington, Ill. 61701)

27–28. Society for **Pediatric Radiology,** Miami Beach, Fla. (J. L. Quinn, Children's Hospital, 4650 Sunset Blvd., Los Angeles, Calif. 94305)

27–30. American **Mining** Congr., Denver, Colo. (R. W. Van Evera, Ring Bldg., Washington, D.C. 20036)

27–1. International Soc. of **Fat Research,** 10th congr., Chicago, Ill. (F. Bradley, 135 Sharps Lane, Ruislip, Middlesex, England)

27–1. American **Oil Chemists'** Soc., Chicago, Ill. (C. H. Hauber, AOCS, 35 E. Wacker Dr., Chicago 60601)

27–1. National **Therapeutic Recreation** Soc., Philadelphia, Pa. (D. C. Park, NTRS, 1700 Pennsylvania Ave., NW, Washington, D.C.)

28–30. **Fast Reactor Fuel and Fuel Elements,** Karlsruhe, Germany. (K. Wirtz, Univ. of Karlsruhe, Kaiserstrasse 12, 75 Karlsruhe)

28–30. Conference on **Immunological Tolerance to Microbial Antigens,** New York, N.Y. (H. Friedman, Albert Einstein Medical Center, Philadelphia, Pa.)

28–30. **Plastic Papers,** 25th conf., Technical Assoc. of the Pulp and Paper Industry, Syracuse, N.Y. (M. A. Burnston, 360 Lexington Ave., New York 10017)

28–30. **Thermal Conductivity** Conf., 10th annual, Boston, Mass. (R. P. Tye, Dynatech R/D Co., 17 Tudor St., Cambridge, Mass. 02139)

28–1. **Iron and Steel** Annual Conv., Cleveland, Ohio. (W. C. Friesel, 1010 Empire Bldg., Pittsburgh, Pa. 15222)

28–2. **Gas Chromatography,** 8th intern. symp., Dublin, Ireland. (C. H. Maynard, Inst. of Petroleum, 61 New Cavendish St., London W1M 8AR, England)

29–2. National **Environmental Pollution** Conf. and Exposition, Washington, D.C. (Natl. Environmental Pollution Conf., 1040 Shoreham Bldg., Washington, D.C. 20005)

29–2. **Optical** Soc. of America, Hollywood, Fla. (M. E. Warga, OSA, 2100 Pennsylvania Ave., NW, Washington, D.C.)

29–2. American **Roentgen Ray** Soc., Miami Beach, Fla. (T. F. Leigh, Emory Univ. Clinic, Atlanta, Ga. 30322)

30–2. **Entomological** Soc. of America, Eastern Branch, 42nd annual, Washington, D.C. (S. G. Gesell, Dept. of Entomology and Economic Zoology, Rutgers Univ., New Brunswick, N.J. 08903)

October

2–3. **Wood Industry** Show, West Plains, Mo. (J. P. Slusher, West Plains Chamber of Commerce, West Plains 65775)

2–4. National Conf. on **Marine Sciences in Education,** 3rd annual, Avalon, Santa Catalina Island, Calif. (R. B. Linsky, Coordinator, Orange County Dept. of Education, 1104 Civic Center Dr. West, Santa Ana, Calif. 92701)

4–8. **Prestressed Concrete** Inst., Minneapolis, Minn. (W. B. Bennett, 205 W. Wacker Dr., Chicago, Ill. 60606)

4–9. International Union of **Biological Sciences,** 17th conf., Washington, D.C. (F. A. Stafleu, Dept. of Botany, 106 Lange Nieuwstraat, Utrecht, Netherlands)

4–9. **Electrochemical Soc.,** Atlantic City, N.J. (E. G. Enck, ES, 30 E. 42 St., New York 10017)

4–9. Society of **Motion Picture and Television Engineers,** 108th semiannual,