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Visit to China: Part 1

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The following report, by Wendell W. Weber, of the University of Michigan, is being published in two parts. The second part will be published in the July issue of BioEssays.

In the Fall of 1987 a delegation of American professionals specializing in human genetics visited the People's Republic of China at the invitation of the Chinese Medical Association under the auspices of the Citizen Ambassador Program of the People to People Organization. The American team visited universities, medical colleges, institutes and research facilities in three cities to discuss topics of mutual interest with Chinese colleagues, to get to know them better, to observe their techniques and to discover similarities and differences between our approaches to human genetics problems.

The People to People (PTP) Human Genetics Delegation* to the People's Republic of China left Seattle, Washington, on 25 October 1987, stopping overnight in Narita, Japan, *en route* to Beijing. We also visited Kunming, in inland Southern China, and Shanghai. We left China at Shanghai and returned to the United States via Hong Kong and Narita two weeks later on 8 November.

Beijing – 28–29 October 1987: The Chinese Academy of Medical Sciences and the Institute of Genetics, Chinese Academy of Sciences (Acadmia Sinica). The PTP delegation spent two days visiting scientists in their laboratories at the Chinese Academy of Medical Sciences and the Institute of Genetics. On the first day, Dr Luo Hui-yuan (Wilson H. Y. Lo), Associate Director of the Institute of Basic Medical Sciences, greeted us and introduced the delegation to Dr Chen Shae-xian, Director of the Institute. The Institute is situated in the inner city adjacent to the Peking Union Medical College a few blocks from Tiananamen Square. Dr Chen told us the Institute houses 16 departments staffed by 30 Professors, 75 Associate Professors and several hundred technicians, and trains approximately 30 undergraduate and 50 graduate students per year. Completion of the medical curriculum takes 8 years, including 2·5, 2·5 and 3 years of preclinical, undergraduate and medical training, respectively, and leads to the Master of Science degree. The M.D. degree is not awarded, but approval of that program is pending. We learned that Chinese medical students trained in Beijing are expected to keep abreast of their field by reading Western journals and thus must be proficient in English.

During the morning of the first day in Beijing we toured the Department of Biochemistry and the Department of Medical Genetics. The Biochemistry Department, headed by Professor Wang Linfang, has 96 staff, including 12 Professors and 10 Associate Professors conducting five major areas of research: atherosclerosis and the study of serum lipoproteins, prenatal diagnosis of genetic disorders, cancer, control of gene expression, and the development and production of an antimalarial vaccine. Professor Wang Linfang spoke about the use of recombinant DNA techniques and the use of monoclonal antibodies in her studies of atherosclerosis and serum lipoproteins. Her group is currently preparing some 20 types of restriction enzymes for this purpose because of limited foreign currency to purchase supplies abroad. In some cases, according to Dr Luo, a year's delay in procurement of supplies is not unusual for chemicals which are available in the United States within a week. Professor Wang Shen-Wu, Associate Professor of Molecular Genetics, described their molecular biology studies of the hemoglobinopathies and thalassemias. He explained the techniques of cloning, synthesis and sequencing of new β-globin gene alleles and their recent attempts to apply site-directed mutagenesis to this problem. Prenatal diagnosis of these maladies is accomplished through oligonucleotide probes, analyses of restriction fragment length polymorphisms (RFLP's), or direct restriction endonuclease gene mapping. Among their achievements they have found a 4-base deletion in codons 41 and 42 of the β-globin gene, a mutation that accounts for about 40% of the β-thalassemias native to South China. A 19-mer oligonucleotide probe has been synthesized for the detection of beta thalassemias and probes have been developed in this laboratory for prenatal diagnosis of hemophilia A and B by RFLP analyses. Collaborations between Dr Liu J. Z of this laboratory and Dr Titus H. J. Huisman of the Medical College of Georgia on gene amplification have led to highly sensitive diagnostic techniques requiring extremely minute quantities of DNA.

Professor Qiang Boqing was a recent visitor to the New England Biolabs in the United Sates and participated in the discovery of three restriction endonucleases, including SfiI, which recognizes the base sequence GGCC-GGCC, and NotI, another 8-base cutter. In return for his achievements there, Dr Qiang was given plasmids containing DNA coding for 21 restriction endonucleases, and his laboratory now supplies these enzymes for much of the molecular biology research in the People's Republic of China. In joint studies with the Department of Parasitology, Professor Qiang has prepared monoclonal antibodies against sporozooite surface proteins of *P. falciparum malariae* that provide protection *in vitro* against various *P. falciparum* strains. A cDNA library prepared from malarial parasite messenger RNA has been used to clone genes for numerous malarial antigenic proteins. Professor Qiang believes their studies hold promise of yielding an effective antimalarial vaccine within three years.

Professor Huang Bing-ren, whose researches concern DNA structure and

* The roster of delegates consisted of Ernest H. Y. Chu (Leader), Junius G. Adams III, Arlene G. Adams, Mary L. Alexander, Richard L. Borowsky, Elof A. Carlson, Elizabeth M. Center, W. Scott Champney, Nien-Si L. Chu, Sisir K. Dutta, Walton L. Fangman, Nancy L. Fisher, Phillips M. Frossard, Gary N. Gussin, Joy Hochstadt, Jan P. Kraus, Bert N. La Du, Jr., Dale McCall, Ann Miller, Veronica A. Miller, Ronald L. Niece, Harriet H. Parker, Donald F. Poulson, Thomas H. Roderick, Hilda K. Roderick, George T. Rudkin, Kathleen A. Schmidt, Sophia Vinogradov, Robert P. Wagner, Wendell W. Weber and Joan L. Williams-Thomas.

function, is attempting to define more precisely the evolutionary tree at the molecular level. He is also studying the expression of human epidermal growth factor. He is splicing the gene for this factor, cloned in his laboratory, to various promoters to determine the effect of the latter on expression of the growth factor.

We toured the Department of Medical Genetics with its Director, Dr Luo. This Department is located in the Peking Union Medical College adjacent to the Institute. It was established during the 1960s but ceased to exist during the Cultural Revolution (approx. 1966–76) and was only started again in 1979. The Department has four divisions: Pediatrics, Cytogenetics, Biochemistry and Molecular Genetics, and will be the mainstay of the new National Genetics Center. This unit provides a number of genetic services, including genetic counselling and the teaching of human genetics (mainly through their twice-weekly Pediatrics Clinic) as well as conducting research in the field. In general, affected offspring and family members are examined for markers of genetic disease and affected fetuses are identified. Parents are counselled about expected risks to the unborn fetus and abortion. In the past they have relied on amniocentesis for diagnosis but a shift toward transvaginal sampling of the chorionic villi for diagnosis is under way. The Molecular Genetics Laboratory works in close collaboration with other laboratories of the Department and with departments of the Institute to develop appropriate DNA oligonucleotide probes for diagnosis. The integration of molecular techniques with more conventional diagnostic techniques for prenatal diagnosis is stressed, and the development of biotin-labeled probes rather than radio-labeled probes is emphasized in this work.

Medical Genetics investigators presented oral summaries of their current research on cytogenetics and several metabolic disorders, including the aminoacidopathies and lysosomal storage diseases. In cytogenetics, Dr Zhao Ying described their work on the fragile X syndrome in affected kindred. They are very concerned about this syndrome because it is a major cause of mental retardation in China, ranking second only to Down's syndrome (trisomy 21). A recent survey of 40 mentally retarded patients in Beijing has yielded 3–4 families with the fragile X syndrome. Studies of this disorder in lymphocytes in culture focus on attempts to find suitable oligonucleotide probes for detecting the fragile X chromosome. Some promising leads are forthcoming. They hardly ever observe the occurrence of Down's syndrome in women over 35 because the one-child policy practiced in China virtually assures that most women will have borne a child before that age. Even so, the occurrence of Down's syndrome is high because nondisjunction is not limited to older women.

Dr Yuan Lifang presented work on tyrosinemia, phenylketonuria, histidinemia, maple syrup urine disease and related diseases that are diagnosed with the aid of high-voltage and two-dimensional electrophoresis, or by means of gas chromatography. Among the aminoacidopathies, phenylketonuria is most prevalent, but a strong effort to screen for this disorder is not made in Beijing because equipment for diagnosis is lacking and the low phenylalanine diet is unavailable. It is interesting to note that this is untrue in Shanghai, where the diet is available. A number of lysosomal diseases are also diagnosed prenatally. Through amniocentesis they have detected carrier fetuses and several cases of these disorders, including four cases of Tay Sachs (hexosaminidase A), four varieties of the mucopolysaccharidoses (MPS I-Hurler; MPS II-Hunter; MPS-III-San Fillipo; MPSIV-Morquoi) and one case of mucolipodystrophy (Type III-Pseudo-Hurler).

Dr Luo touched on their goals and priorities for prenatal diagnosis of the β-thalassemia in China. These studies are aimed at finding new β-thalassemia genes in a concerted attempt to reduce the incidence of this disease among Chinese. In addition to the 4-nucleotide deletion already mentioned by Dr Wang Shen-Wu, studies of the haplotype of twenty-three affected families have revealed an A→G mutation in position 29 of the TATA box, a new mutation in the Chinese. Dr Luo acknowledged the contributions of Dr Haig Kazazian and others at the Johns Hopkins University Medical Center with whom Dr Luo had studied while on sabbatical in the United States. Dr Zhang Jon Wu described the use of chromosome RLFPs HD14 and HD18 that has led to identification of hemophilia cases from carrier females. Dr Luo mentioned that RFLP-haplotype analysis permits prenatal diagnosis of α-thalassemia and hemoglobin E, and that at least seven different β-thalassemias have now been identified in Chinese individuals that are similar to those found in Thailand and Laos, but dissimilar from those of Mediterranean peoples. To avoid duplication of effort, only new haplotypes are being sequenced.

During the afternoon session the PTP delegation reconvened with the Chinese researchers and students at the Institute Building for research talks by delegation members. Dr Ernest Chu, leader of the delegation, talked on the 'Determination of Human Mutation Rates', followed by Dr Sophia Vinogradov on 'Molecular Biology in Psychiatric Disorders', by Dr Robert Wagner on 'The Anatomy of the Human Genome: Structure and Conservation of Domains', by Dr Gary Gussin on 'DNA–Protein and Protein–Protein Interactions in Control of Gene Expression', by Dr Sisir Dutta on 'Electropollution, Brain Tumors and Experimental Models', and by Dr Richard Borowsky on 'The Logic of Genetic Relatedness: The Probability of Paternity'.

Beijing – Day 2: The Genetics Institute and the Cancer Institute. On the morning of the second day approximately half of our PTP delegation was bussed to the Genetics Institute on the outskirts of Beijing while the rest of the delegation was bussed to the Cancer Institute Chinese Academy of Medical Sciences in another part of the city. We were greeted at the Genetics Institute by Dr Wang and Dr Du Ruofu. The Institute, a 7- to 8-story building, houses facilities for laboratories, classrooms, a library and animals and has 250 scientists, including 71 senior staff and an equal number of technicians. Institute scientists are working on bacterial, plant, animal and human genetics, emphasizing molecular and population approaches to their research. They are assisted by 70 doctoral and master's graduate students, of whom 26 are working toward their Ph.D.

Professor Du and his staff presented an extensive poster display describing their initial studies of the population genetics of the Han people, who comprise more than 90% of the Chinese. They also described 16 of the 55 ethnic Chinese minorities. Field studies of these populations were illustrated with slides and scrapbooks of photographs describing genetic polymorphisms and the physiognomy of the minority groups. They have accumulated a vast amount of data on consanguineous marriages, sex ratios, blood group, phenylthiocarbamide (PTC) taste testing, red cell and serum protein polymorphisms, and lactase deficiency, but analysis of these data is incomplete. Dr Du called our attention to the re-

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markable decline occurring in consanguineous marriages in Beijing over the past several years from 1·66% to 1·2% to 0·8% to 0·3%. He drew attention to the prevalence of lactase deficiency among Chinese that varies from 83% to 94% in the Han and from 76% to 96% in the national minorities, and the correlation of M blood groups with latitude (high in the north and low in the south). The large tribal variation in PTC taste testing and the high prevalence of color blindness were also mentioned. An interesting comprehensive population study of Chinese surnames has been carried out that explores the relationship of the surname to ancestry, name of state, residential place, official position, occupation, life style, etc., and which describes the maternal transmission of the surname from generation to generation and also the implications of a 'mutation' in the surname of individuals. Reprints of these investigations and of other research publications were available to the delegates.

On the day of our visit the temperature of the breeze outside was decidedly cool and conditions inside the Institute were almost the same as those outside. The quantity and the quality of the research were impressive but all the more so for having been accomplished under such adverse circumstances.

PTP delegates visiting the Cancer Institute were greeted by Dr Wu Min and the morning was devoted to talks by PTP delegates to the research scientists at the Cancer Institute. Dr Elizabeth Center discussed specific chromosomal rearrangements known to accompany certain cancers in relation to the origin of the disease. Dr Nancy Fisher noted that there are about 35,000 Southeast Asians now living in the State of Washington. She discussed the influence of the social mores of these people on their health problems and the public health programs that have been devised in the USA to assist in their management. Dr Joy Hochstadt discussed the application of DNA probes to her studies of the regulatory genetics of the crystalline protein specific to the bovine lens cells, and Dr Ronald Niece discussed his experience with the economics, techniques, analyses and syntheses of protein and nucleic acid sequences and their cost of this work. Drs Chu and Gussin also repeated their talks of the previous day (see Beijing, Day 1).

During the afternoon the delegates toured the clinical and research facilities of the Cancer Institute and the Cancer Hospital, a 10-story building devoted to the care of cancer patients. Dr Wu Min told the delegates the Cancer Hospital was about 30 years old whereas the Cancer Institute was founded only about 12 years ago, as the Cultural Revolution wound down, with staff drawn from many regions of China. In 1983, when the Institute was transferred to the hospital, research facilities where inadequate.

Prior to the consolidation of the research and clinical units within the hospital, cancer research stressed field studies because they were relatively inexpensive. Dr Wu's studies have focussed on the epidemiology of esophageal cancer. His epidemiological studies of 360,000 persons, including 81,400 families of the Central region south of Beijing, and of certain other regions scattered far and wide throughout China, showed that esophageal cancer cases were distributed into high- and low-risk groups, suggesting that this disorder was determined by genetic and environmental components. The group at high risk featured two or more familial occurrences of cancer in persons 35–64 years old and comprised 25% of the population studied. No definitive causes of esophageal cancer have been identified but Dr Wu suspects that pickling of vegetables which are high in nitrosamine and the production of fungal carcinogens are implicated. Two of Dr Wu's associates and former students, Dr Su Xuan and Dr Wu De Feng, continued the discussion. Dr Su discussed cigarette smoking and lung cancer. She is concentrating on patterns of chromosomal rearrangement that are associated with cancer in smokers. Her data suggest that 32% of lung-cancer patients, mainly heavy smokers (22%), show damaged chromosomes compared to only 2–6% of non-smokers. Rearrangements of chromosomes 10, 14, 11 and 12 predominate. Dr Wu is investigating the effectiveness of DNA repair in cancer families compared to non-cancer families for esophageal, lung and gastric cancer. Patterns of fragile sites, rearrangement and repair capacity (induced by ultraviolet light) are categorized and compared. His results show, for example, that cancer patients have an average of 9·6 fragile sites/cell, compared to 2·3 and 0·02 fragile sites for unaffected relatives and non-cancer persons, respectively. Dr Wu concludes that cancer patients and their family members have diminished DNA repair capacity. These studies and those of Dr Wu's co-investigators are all aimed at identifying genes for susceptibility to cancer through studies of informative cancer families and, if successful, isolating and applying them to the development of inexpensive screening tests.

Just before we departed for Kunming, the next city on our agenda, we saw some of the sites in and close to Beijing, including the Imperial Palace (Forbidden City), the Ming Tombs and the Great Wall. Our host in Kunming, Dr Zeng Lingcai, flew to Beijing to accompany us on our trip to Kunming more than 1000 miles away in southwest China.

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