Department of International Community Health

Outline and Research Objectives

The mission of our department is to seek equity and equality in health and health care, and social justice within and across the nations with caring, sharing and compassionate spirit, by the people, with the people and for the people, by means of comprehensive and integrated scientific research and education on health and health care, and social development in collaboration with other related institutes of various disciplines including universities, governmental and non-governmental organizations and private sectors.

Our aim is to bring together the clinical, public health and social science research to address the broad issues of health and health care.

The goals are: 1) to investigate how to change the *status quo* by improving health status of the most vulnerable, the most underprivileged and the poorest of the poor; 2) to undertake research on the influences of 'globalization' and 'free market' system on health and social development; 3) to investigate the mechanisms to reduce inequalities between and within nations on health and development and 4) to develop the mechanisms to link the above three goals with individual research activities described below.

Focusing on the followings:

1. Target diseases or topics: 1) HIV/AIDS (prevention and health care services), 2) Tuberculosis control, 3) Leprosy control, 4) Appropriate treatment and prevention of common diseases and injuries including traffic accidents in Japan and developing countries, 5) Public health aspects of Stroke, 6) Health care services for international migrant workers in Japan, 7) Maternal and Child Health Care (issues on contraceptives excluded).
2. Site/Field: 1) Aral Sea area, 2) Cambodia, 3) Bangladesh, 4) Nepal, 5) Nicaragua and 5) Japan.
3. Research topics are related to Epidemiology, prevention and health care service delivery.

Faculties and Students

Professor and Chair	Susumu Wakai, MD, PhD (1999-)
Lecturer	Nasamine Jimba, MD, PhD
Associate	2
Graduate student	20
Research student	1
Secretary	2

Past Research and Major Accomplishments

Please refer to the Select Publications related to Research on International Health including Advocacy papers (number 1 to 31)

Current Research

1) Injury prevention in Japan and developing countries
2) HIV/AIDS prevention and care among migrant workers living in Japan
3) Leprosy and tuberculosis control in Asian countries
4) Environmental degradation and people's health: Aral Sea region and elsewhere
5) Epidemiology of Stroke and its prevention
6) Maternal and child health

In each six research field a concerted effort has been made with the Faculty members and Graduate students to contribute for improving people's health status in developing countries but in developed countries including Japan as well.

Future Prospects

We continue focusing our research efforts on the 6 major research fields described above. We utilize deferent tools such as Epidemiological, medical. Quantitative and Qualitative research methods. We also need human resource development for continuing such research efforts by mobilizing Graduate students.

Research Grants

Ministry of Education and Science

1. FY 1999 5.5 million Yen: S Wakai, K Pyo. Mechanisms of spondylotic changes of the spine.
2. FY 2001~2002: 3.4 million Yen: S Yanagisawa and S Wakai. Health reform in Cambodia and its effects on people's health seeking behavior
3. FY 2002-2003: 8 million Yen: J Okumura and S Wakai Ministry of Health and Welfare
4. FY 2000-2002: 21.5 million Yen: S Wakai. Health system building for supporting people with HIV/AIDS from overseas.

Select Publications

Research on International Health including Advocacy paper

1. Wakai S: Primary health care projects and social development. *Lancet* 345:1241, 1995
2. Wakai S: Sanctions against Iraq. *Lancet* 347: 200, 1996
3. Wakai S: Access to the Internet. *Science* 271: 1347, 1996
4. Kunii O, Wakai S, Honda T, Tsujimoto K: Role of external medical volunteers after disasters. *Lancet* 347: 1411, 1996
5. Wakai S. Role of neurosurgeons in Japan. *Lancet* 349: 140, 1997
6. Yoshimoto Y, Wakai S: Unruptured intracranial vertebral artery dissection: clinical course and serial radiographic imagings. *Stroke* 28:370-374, 1997
7. Wakai S: Global health care and neurosurgeons. *Neurol Med Chir* 37:483-490, 1997
8. Wakai S: Scourge of Japanese encephalitis in southwestern Nepal. *Lancet* 351:759, 1998
9. Wakai S: Health care in Burma. *Lancet* 352: 1230, 1998
10. Wakai S: Surgical treatment for incidentally discovered intracranial aneurysms. *Lancet* 1999; 353:1975-1976
11. Barua S, Wakai S, Shwe T, Umenai T: Leprosy elimination through integrated basic health services in Myanmar: the role of midwives in the pre- and post-elimination phases. *Leprosy Rev* 70:174-179, 1999
12. Yoshimoto Y, Wakai S: Cost-effectiveness analysis of screening for asymptomatic, unruptured intracranial aneurysms: A mathematical model. *Stroke* 30: 1621-1627 1999
13. Inaoka E, Wakai S, Nakamura Y, Babily YA, Saghayroun AAR. Correlate of visit regularity among family planning clients in urban Yemen. *Adv Contraception* 1999; 15: 257-274
14. Wakai S. Pysicians for peace. *Lancet* 2000; 355: 1365-1366
15. Wakai S. Life after sanctions: the fate of Iraq. *Lancet* 2000; 356: 685
16. Kuroiwa C, Vongphrachanh P, Chosa T, Murakami H, Hashizume M, Wakai S, Tanaka M. Risk of poliomyelitis importation and reemergence in Laos. *Lancet* 2000; 356: 1487-88.
17. Toyama N, Wakai S, Nakamura Y, Andryansyah Arifin. Mother's working status and nutritional status of children under the age of five in urban low-income community, Surabaya, Indonesia. *J Trop Pedatr* 2001; 47: 179-181
18. Jimba M, Wakai S. Is Gandhi's philosophy of non-violence dead in Nepal? *Lancet* 2001:358;1018- 2.
19. Nakahara S, Wakai S. Underreporting of traffic injuries involving children in Japan. *Injury Prevention* 2001;7: 242-244
20. Sase E, Wakai S. A world war against terrorism. *Lancet* 2001:358;1365
21. Ichikawa M, Nakahara S, Wakai S. Death with unbeled passengers. *Lancet* 2002:359;43-44
22. Ichikawa M, Okumura J, Wakai S. Two decisions of Japanese court on detaind Afghan asylum seekers. *Lancet* 2002:359;448
23. Saengdidtha B, Lapparat G, Torugsa K, Suppadit W, Wakai S. Sexual Behavior and HIVInfection Among Thai Army Conscripts between 1992 and 1998. *Military Med* 2002: 167(4):272-6
24. Nakahara S, Wakai S. Differences between Japanese pre-school and school-age pedestrian mortality and moridity trends. *Public Health* 2002:116;1-7
25. Kunii O, Nakamura S, Abdur R, Wakai S. The Impact on Health and Risk Factors of the Diarrhoea Epidemics in the 1998 Bangladesh Floods. *Public Health* 2002:116; 68-74
26. Okumura J, Wakai S, Umenai T. Drug utilisation practice at household focusing self-medication in rural communities in Vietnam. *Soc Sci Med* 2002:54;1875-1886
27. Md. Akramul Islam, Susumu Wakai, Nobukatsu Ishikawa, A.M.R. Chowdhury, J. Patrick Vaughan: Tuberculosis control by community health workers inBangladesh: are they more cost-effective? *Bull WHO* 2002:80;445-450
28. Phoxay C, Okumura J, Nakamura Y, Wakai S. Influence of Women's Knowledge and Health Seeking Behaviour on Maternal Health Care Utilization in Southern Laos. *Asia-Pacific J Public Health* 2001:13;13-18
29. Flores FP, Umenai T, Wakai S. Shoud community-managed drugstores be phased out? *Asia-Pacific J Public Health* 2001:13;9-12
30. Wakai S. Mobilization of Cuban doctors in developing countries. *Lancet* 2002: 360;92
31. Miura S, Kunii O, Wakai S. Home Gardening in Urban Poor Communities of the Philippines. *Int J Food Sci Nutrition* 2002 (in print)
32. M Hashizume,[1] O Kunii,[1] S Sasaki,[2] T Shimoda,[3] S Wakai[1] and M Chiba. Anemia and Anthropometrical Status of School-age Children in the Aral Sea Region, Kazakhstan. *J Trop Pediatr* (in press)

Clinical Research and Epidemiology

33. Wakai S, Fukushima T, Furihata T, Sano K: Association of cerebral aneurysm with pituitary adenoma. *Surg Neurol* 12:503-507, 1979
34. Wakai S, Fukushima T, Teramoto A, Sano K: Pituitary apoplexy: its incidence and clinical significance. *J Neurosurg* 55:187-193, 1981
35. Sano K, Wakai S, Ochiai C, Takakura K: Characteristics of intracranial meningiomas in childhood. *Child' Brain* 8:98-106, 1981
36. Wakai S, Yamakawa K, Mananka S, Takakura K: Spontaneous intracranial hemorrhage caused by brain tumor: its incidence and clinical significance. *Neurosurgery* 10:437-444, 1982
37. Segawa H, Wakai S, Tamura K, Yoshimasu N, Kakamura O, Ohta M: Computed tomographic measurement of local cerebral blood flow by Xenon enhancement. *Stroke* 14:356-362, 1983
38. Wakai S, Narita J, Hashimoto K, Nagai M: Dermoid cyst communicating with the subarachnoid space and lateral ventricle: demonstration by metrizamide computed tomographic cisternography. *Neurosurgery* 13:696-698, 1983
39. Wakai S, Arai T, Nagai M: Congenital brain tumors. *Surg Neurol* 21:597-609, 1984
40. Wakai S, Nagai M: Ventricular diverticulum. *J Neurol Neurosurg Psychiatry* 47:514-517, 1984
41. Wakai S, Ueda Y, Inoh S, Nagai M: Angiographically occult angiomas: A report of thirteen cases with analysis of the cases documented in the literature. *Neurosurgery* 17:549-556, 1985
42. Wakai S, Nagai M: Histological verification of microaneurysms as a cause of cerebral haemorrhage in surgical specimens. *J Neurol Neurosurg Psychiatry* 52:595-599, 1989
43. Wakai S, Hashimoto K, Watanabe N, Inoh S, Ochiai C, Nagai M: Efficacy of closed-drainage system in treating chronic subdural hematoma: A prospective comparative study. *Neurosurgery* 26:771-773, 1990
44. Iwanaga H, Wakai S, Ochiai C, Narita J, Inoh S, Nagai M: Ruptured cerebral aneurysms missed by initial angiography. *Neurosurgery* 27:45-51, 1990
45. Wakai S, Kumakura N, Nagai M: Lobar intracerebral hemorrhage: A clinical, radiographic and pathologic study of 29 consecutive operated cases with negative angiography. *J Neurosurg* 76: 231-238, 1992

Biomedical Research

46. Wakai S, Hirokawa N: Development of the blood-brain barrier to horseradish peroxidase in the chick embryo. *Cell Tiss Res* 195:195-203, 1978
47. Wakai S, Matsutani M, Mizutani H, Sano K: Tight junctions in choroid plexus papillomas. *Acta Neuropathol* 45:159-160, 1979
48. Wakai S, Hirokawa N: Development of blood-cerebrospinal fluid barrier to horseradish peroxidase in the avian choroidal epithelium. *Cell Tiss Res* 214:271-278, 1981
49. Wakai S, Meiselman SE, Brightman MW: Muscle grafts as entries for blood-borne proteins into the extracellular space of the brain. *Neurosurgery* 18:548-554, 1986
50. Wakai S, Meiselman SE, Brightman MW: Focal circumvention of blood-brain barrier with grafts of muscle, skin and autonomic ganglia. *Brain Res* 386:209-222, 1986

Department of Human Genetics

Outline and Research Objectives

The Department of Human Genetics was established in April 1992 as one of the departments at the newly established School of International Health. The department educates students at the Graduate School of International Health with courses covering basic principles as well as clinical applications of human genetics. A series of lectures on human genetics are also provided to the first year students at the School of Medicine (compulsory). In addition, for undergraduate students at the School of Health Sciences, a series of lectures are given to each of the sophomore (Human Genetics I, compulsory) and junior (Human Genetics II, elective) classes.

The major research projects in the department are: (1) Search for susceptibility genes to rheumatic diseases and other autoimmune diseases, (2) Search for susceptibility genes to clinical subsets of malaria, (3) Genome diversity of Asia-Pacific populations, (4) Search for susceptibility genes to behavioral disorders, and (5) Analysis of gene expression profiles in inflammatory tissues and cell differentiation.

Faculties and Students

Professor and Chair	Katsushi TOKUNAGA, DSc
Associate Professors	Naoyuki TSUCHIYA, MD, DMSc
Associate	Jun OHASHI, DHSc
Postdoctoral Fellow	2
Graduate student	12
Research student	3
Research Technician	7
Secretary	2

Past Research and Major Accomplishments

(1) By means of extensive variation screening of a number of candidate genes followed by association analyses with complex diseases including rheumatic diseases, malaria and narcolepsy, several disease-gene associations have been newly found as follows.
- Rheumatoid arthritis (RA): *LIR1(ILT2), BLYS/BAFF-R, TNFR2, FCGR3A/HLA-DRB1*
- Systemic lupus erythematosus (SLE): *TNFR2, CD19, FCGR2B, FCGR3A*

Cerebral malaria (in Thailand): *HLA-B, TNFA, CD36*
Severe malaria (in Thailand): *HLA-DRB1, iNOS*
Narcolepsy: *TNFA, TNFR2*
ANCA-associated vasculitis: *HLA-DRB1*

(2) Studies on HLA gene and haplotype distribution in East Asian and Pacific populations have demonstrated genetic affinities and clustering of the populations, multiple migration and dispersal routes of ancestral populations, and the genetic link between Asians and Native Americans.

(3) Gene expression profiling in synovia from RA patients demonstrated several up-regulated genes including *ID* family genes. Also a number of up-regulated and down-regulated genes including *TNF-TNFR* family were identified in the differentiation of monocytes into dendritic cells.

Current Research

(1) Establishment of Human SNP (single nucleotide polymorphism) Typing Center for large scale SNP typing (goal: 1,000,000 typing/year).
(2) Continue the search for susceptibility genes to rheumatic diseases, malaria subsets, and narcolepsy mainly by means of candidate gene approach.
(3) Screening of novel candidate regions for susceptibility genes to SLE and narcolepsy by means of whole genome association studies.
(4) Analyses of linkage disequilibrium blocks on chromosome 1 for the determination of primary genes.
(5) Functional analyses of disease-associated SNPs and ID family genes.

Future Prospects

(1) High-throughput SNP typing in the Human SNP Typing Center will contribute to the identification of susceptibility genes to various complex diseases including allergy, diabetes, hypertension, and infectious diseases.
(2) Using the new strategy of the whole genome association analyses, several candidate regions for SLE and narcolepsy will be newly found.

(3) Extensive studies on linkage disequilibrium blocks will contribute to effective search of disease associated genes.
(4) Further development of new high-throughput SNP typing technologies.

Research Grants

<Only the grants of more than 10,000,000 yen/year are listed below>

1. "Medical Genome Science", Grant-in-Aid for Scientific Research on Priority Areas, Grant-in-Aid for Scientific Research by The Ministry of Education, Culture, Sports, Science and Technology: Human SNP Typing Center. 2001-2004.
2. "Medical Genome Science", Grant-in Aid for Scientific Research on Priority Areas, Grant-in Aid for Scientific Research by The Ministry of Education, Culture, Sports, Science and Technology: Susceptibility genes to rheumatic diseases. 28,000,000 yen/year. 2000-2004.
3. "Genome Informatics Research and Technology Development", by the New Energy and Industrial Technology Development Organization (NEDO): Development of DNA capillary array. 10,000,000 yen/year. 1999-2002.
4. "Genome Diversity Project", by the New Energy and Industrial Technology Development Organization (NEDO): Genome-wide association studies on rheumatoid arthritis. 10,000,000 yen/year. 2001-2004.

Select Publications

1. Tokunaga K, Araki C, Juji T, and Omoto K: Genetic polymorphism of the complement C2 in Japanese. Hum. Genet. 58: 213-216, 1981.
2. Tokunaga K, Omoto K, Juji T, and Itoh T: Polymorphism of BF, C2 and GLO in Japanese patients with insulin-dependent diabetes mellitus: Confirmation of an increase of BF*FT. Hum. Genet. 62: 86-88, 1982.
3. Tokunaga K, Yukiyama Y, and Omoto K: Polymorphism of the complement C6 in Japanese. J. Immunogenet. 10: 419-424, 1983.
4. Tokunaga K, Omoto K, Yukiyama Y, Sakurai M, Saji H, and Maruya E: Further study on a BF silent allele. Hum. Genet. 67: 449-451, 1984.
5. Matsuki K, Juji T, Tokunaga K, Naohara T, Satake M, and Honda Y: Human histocompatibility leukocyte antigen (HLA) haplotype frequencies estimated from the data on HLA class I, II, and III antigens in 111 Japanese narcoleptics. J. Clin. Invest. 76: 2078-2083, 1985.
6. Tokunaga K, Dewald G, Omoto K, and Juji T: Family study on the polymorphisms of the sixth and seventh components (C6 and C7) of human complement: Linkage and haplotype analyses. Am. J. Hum. Genet. 39: 414-419, 1986.
7. Matsuki k, Juji T, Tokunaga K, Mochizuki M, Hayashi K, Fujino Y, Numaga J, and Yamashita H: HLA antigens in Behcet's disease with refractory attacks. Tissue Antigens 29: 208-213, 1987.
8. Tokunaga K, Sauerecker G, Kay P, Christiansen F, Anand R, and Dawkins RL: Extensive deletions and insertions in different MHC supratypes detected by pulsed field gel electrophoresis. J. Exp. Med. 168: 933-940, 1988.
9. Watanabe Y, Tokunaga K, Matsuki K, Takeuchi F, Matsuta K, Maeda H, Omoto K, and Juji T: Putative amino acid sequence of HLA-DRB chain contributing to rheumatoid arthritis susceptibility. J. Exp. Med. 169: 2263-2268, 1989.
10. Matsuki K, Juji T, Tokunaga K, Takamizawa M, Maeda H, Soda M, Nomura Y, and Segawa M: HLA antigens in Japanese patients with myasthenia gravis. J. Clin. Invest. 86: 392-399, 1990.
11. Tokunaga K, Jin F, Mauff G, Nishimukai H, Simeoni E, Suzuki K, Weber W: C6 reference typing report. Complement Inflamm. 7: 234-239, 1990.
12. Kuwata S, Tokunaga K, Jin F, Juji T, Sasaki T, and Honda Y: Analysis of HLA-DRB gene in narcolepsy. N. Engl. J. Med. 324: 271-272, 1991.
13. Tokunaga K, Zhang WJ, Christiansen FT, and Dawkins RL: The genomic structure of two ancestral haplotypes carrying C4A duplications. Immunogenet. 34: 247-251, 1991.
14. Uchigata Y, Kuwata S, Tokunaga K, Eguchi Y, Takayama-Hasumi S, Miyamoto M, Omori Y, Juji T, and Hirata Y: Strong association of insulin autoimmune syndrome with HLA-DR4. Lancet 339: 393-394, 1992.
15. Mitsunaga S, Kuwata S, Tokunaga K, Uchikawa C, Takahashi K, Akaza T, Mitomi Y, and Juji T: Family study on HLA-DPB1 polymorphism: Linkage analysis with HLA-DR/DQ and two "new" alleles. Hum. Immunol. 34: 203-211, 1992.
16. Bannai M, Mazda T, Tokunaga K, and Juji T: DNA single-strand conformation polymorphism method to distinguish DR4 alleles. Lancet 341: 769, 1993.
17. Lin L, Tokunaga K, Ogawa A, Ishikawa Y, Kashiwase K, Akaza T, Tadokoro K, and Juji T: Genotyping and association analysis of HLA-B61 in Japanese. Hum. Immunol. 37: 95-100, 1993.
18. Wang L, Juji T, Tokunaga K, Takahashi K, Kuwata S, Uchida S, Tadokoro K, and Takai K: Polymorphic microsatellite markers for the diagnosis of graft-versus-host disease. N. Engl. J. Med. 330: 398-401, 1994.
19. Oka T, Matsunaga H, Tokunaga K, Mitsunaga S, Juji T, and Yamane A: A simple method for detecting single base substitutions and its application to HLA-DPB1 typing. Nucleic Acid Research 22: 1541-1547, 1994.
20. Tokunaga K, Sideltseva EW, Tanaka H, Uchikawa C, Nieda M, Sideltsev VV, Zhuravleva E, Imanishi T, Itoh K, Akaza T, Takahashi K, Khalturin V, Alexeev LP, and Juji T: Distribution of HLA antigens and haplotypes in the Buryat population in Siberia. Tissue Antigens 45: 98-102, 1995.

21. Yoshida M, Ohtsuka R, Nakazawa M, Juji T, and Tokunaga K: HLA-DRB1 frequencies of non-Austronesian-speaking Gidra in South New Guinea and their genetic affinities with Oceanian populations. Am. J. Phys. Anthrop. 96: 177-181, 1995.
22. Uchigata Y, Tokunaga K, Nepom G, Bannai M, Kuwata S, Dozio N, Benson EA, Ronningen KS, Spinas GA, Tadokoro K, Hirata Y, Juji T, and Omori Y: Differential immunogenetic determinants of polyclonal insulin autoimmune syndrome (Hirata's Disease) and monoclonal insulin autoimmune syndrome. Diabetes 44: 1227-1232, 1995.
23. Suto Y, Tokunaga K, Watanabe Y, and Hirai M: Visual demonstration of the organization of the human complement C4 and 21-hydroxylase genes by high-resolution fluorescence in situ hybridization. Genomics 33: 321-324, 1996.
24. Lin L, Tokunaga K, Tanaka H, Nakajima F, Imanishi T, Kashiwase K, Bannai M, Mizuno S, Akaza T, Tadokoro K, Shibata Y, and Juji T: Further molecular diversity in the HLA-B15 group. Tissue Antigens 47: 265-274, 1996.
25. Ogasawara K, Yabe R, Uchikawa M, Saitou N, Bannai M, Nakata K, Takenaka M, Fujisawa K, Ishikawa Y, Juji T and Tokunaga K: Molecular genetic analysis of variant phenotypes of the ABO blood group system. Blood 88: 2732-2737, 1996.
26. Fujiwara K, Isa K, Oka T, Maekawajiri S, Yamase A, Akaza T, Tadokoro K, Juji T, Shibata Y, and Tokunaga K: Large-scale DNA typing for human platelet alloantigens by PCR-PHFA (preferential homoduplex formation assay). Brit. J.Haematol. 95: 198-203, 1996.
27. Bannai M, Tokunaga K, Tanaka H, Lin L, Kashiwase K, Tokunaga K, and Juji T: Five HLA-B22 group alleles in Japanese. Tissue Antigens 49: 376-382, 1997.
28. Miyake M, Nakahori Y, Matsushita I, Kobayashi K, Mizuno K, Hirai M, Kanazawa I, Nakagome Y, Tokunaga K, and Toda T: YAC and cosmid contigs encompassing the Fukuyama-type congenital muscular dystrophy (FCMD) candidate region on 9q31. Genomics 40: 284-293, 1997.
29. Watanabe Y, Tokunaga K, Geraghty DE, Tadokoro K, and Juji T: Large scale comparative mapping of MHC class I region of predominant haplotypes in Japanese. Immunogenet. 46: 135-141, 1997.
30. Tokunaga K, Ishikawa Y, Ogawa A, Wang H, Mitsunaga S, Moriyama S, Lin L, Bannai M, Watanabe Y, Kashiwase K, Tanaka H, Akaza T, Tadokoro K, and Juji T: Sequence-based association analysis of HLA class I and II alleles in Japanese supports conservation of common haplotypes. Immunogenet. 46: 199-205, 1997.
31. Tsuchiya N, Shiota M, Moriyama S, Ogawa A, Komatsu-Wakui M, Mitsui H, Geraghty ED, and Tokunaga K: MICA allele typing of HLA-B27 positive Japanese patients with seronegative spondylarthropathies and healthy individuals: Differential linkage disequilibrium with HLA-B27 subtypes. Arthritis Rheum. 41: 68-73, 1998.
32. Ogawa A, Tokunaga K, Lin L, Kashiwase K, Tanaka H, Herrero MJ, Vilches C,Park MH, Jia GJ, Chimge N-O, Sideltseva EW, Ishikawa Y, Akaza T, Tadokoro K, and Juji T: Diversity of HLA-B61 alleles and haplotypes in East Asians and Spanish Gypsies. Tissue Antigens 51:356-366, 1998.
33. Kobayashi K, Nakahori Y, Miyake M, Matsumura K, Kondo-lida E, Nomura Y, Segawa M, Yoshioka M, Saito K, Osawa M, Hamano K, Sakakibara Y, Nonaka I, Nakagome Y, Kanazawa I, Nakamura Y, Tokunaga K, and Toda T: An ancient retrotransposal insertion causes Fukuyama-type congenital muscular dystrophy. Nature 394: 388-392, 1998.
34. Wuerzer R, Witzel-Schloemp K, Tokunaga K, Fernie BA, Hobart MJ, and Orren A: Reference typing report for complement components C6, C7, and C9 including mutations leading to deficiencies. Exp. Clin. Immunogenet. 15: 268-285, 1998.
35. Komata T, Tsuchiya N, Matsushita M, Hagiwara K, and Tokunaga K: Association of tumor necrosis factor receptor 2 (TNFR2) polymorphism with susceptibility to systemic lupus erythematosus. Tissue Antigens 53(6): 527-533, 1999.
36. Komatsu-Wakui M, Tokunaga K, Ishikawa Y, Kashiwase K, Moriyama S, Tsuchiya N, Ando H, Shiina T, Geraghty DE, Inoko H, and Juji T: MIC-A polymorphism in Japanese and a MIC-A-MIC-B null haplotype. Immunogenet. 49(7/8): 620-628, 1999.
37. Hatta Y, Ohashi J, Imanishi T, Kamiyama H, Iha M, Shimabukuro T, Ogawa A, Tanaka H, Akaza T, Gojobori T, Juji T, and Tokunaga K: HLA genes and haplotypes in Ryukyuan suggest a recent gene flow to the Okinawa islands. Hum. Biol. 71(3): 353-365, 1999.
38. Chida S, Hohjoh H, and Tokunaga K: Molecular analyses of the possible RNA-binding protein gene located in the human leukocyte antigen (HLA)-DR subregion. Gene 240: 125-132 1999.
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40. Keicho N, Ohashi J, Tamiya G, Nakata K, Taguchi Y, Azuma A, Ohishi N, Emi M, Park MH, Inoko H, Tokunaga K, and Kudoh S: Fine localization of a major disease-susceptibility locus for diffuse panbronchiolitis. Am. J. Hum. Genet. 66 (2): 501-507, 2000.
41. Shibue T, Tsuchiya N, Komata T, Matsushita M, Shiota M, Ohashi J, Wakui M, Matsuta K, and Tokunaga K: Tumor necrosis factor α 5'-flanking region, TNF receptor ll, and HLA-DRB1 polymorphisms in the Japanese patients with rheumatoid arthritis. Arthritis Rheum. 43 (4): 753-757, 2000.
42. Ohashi J, Yamamoto S, Tsuchiya N, Hatta Y, Komata T, Matsushita M, and Tokunaga K: Comparison of statistical power between 2×2 allele frequency and allele positivity tables in case-control studies of com-

plex diseases genes. Ann. Hum. Genet. 65(2): 197-206, 2001.
43. Ogasawara K, Yabe R, Uchikawa M, Nakata K, Watanabe J, Takahashi Y, and Tokunaga K: Recombination and gene conversion-like events may contribute to ABO gene diversity causing various phenotypes. Immunogenet. 53(3): 190-199, 2001.
44. Sakurai D, Yamaguchi A, Tsuchiya N, Yamamoto K, and Tokunaga K: Expression of ID family genes in the synovia from patients with rheumatoid arthritis. Biochem. Biophys. Res. Commun. 284(2): 436-442, 2001.
45. Lapteva N, Ando Y, Nieda M, Hohjoh H, Okai M, Kikuchi A, Dymshits G, Ishikawa Y, Juji T, and Tokunaga K. Profiling of genes expressed in human monocytes and monocyte-derived dendritic cells using cDNA expression array. Br. J. Haematol. 114(1): 191-197, 2001.
46. Tokunaga K, Ohashi J, Bannai M, and Juji T: Genetic link between Asians and Native Americans: Evidence from HLA genes and haplotypes. Hum. Immunol. 62(9): 1001-1008, 2001.
47. Sirikong M, Tsuchiya N, Chandanayingyong D, Bejrachandra S, Suthipinittharm S, Luangtrakool K, Srinak D, Thongpradit R, Siriboonrit U, and Tokunaga K: Association of HLA-DRB1*1502-DQB1*0501 haplotype with susceptibility to systemic lupus erythematosus in Thais. Tissue Antigens 59 (2): 113-117, 2002.
48. Kyogoku C, Dijstelboem M.H, Tsuchiya N, Hatta Y, Kato H, Yamaguchi A, Fukazawa T, Jansen D.M, Hashimoto H, Winkel G.J. J, Kallenberg G.M. C, and Tokunaga K: Fcg receptor gene polymorphisms in Japanese patients with systemic lupus erythematosus: Contribution of FCGR2B to genetic susceptibility. Arthritis Rheum. 46(5): 1242-1254, 2002.
49. Ohashi J, Naka I, Patarapotikul J, Hananantachai H, Looareesuwan S, and Tokunaga K: Significant association of longer forms of CCTTT microsatellite repeat in inducible nitric oxide synthase (iNOS) promoter with severe malaria in Thailand. J. Infect. Dis.186: 578-581, 2002.
50. Kuroki K, Tsuchiya N, Tsao B, Grossman J, Fukazawa T, Hagiwara T, Kano H, Takazoe M, Iwata T, Hashimoto H, and Tokunaga K: Polymorphisms of human CD19 gene: Possible association with susceptibility to systemic lupus erythematosus in Japanese. Genes. Immun. (in press)
(Number of the other original papers in English: 229)

Department of Developmental Medical Sciences

Outline and Research Objectives

In 1996, the Department of Mother and Child Health was formed at the University of Tokyo. In Japan, it was the first division in International Health, which specifically focused on maternal and child health issues. Maternal and child health involves all activities to maintain and promote psychological and physiological health of mothers and children. The field of maternal and child health covers (1) countermeasure for infectious diseases, (2) maternal and child nutrition, (3) prevention of diseases, and (4) protection of mothers and children from environmental unhealthy factors.

The study of maternal and child health not only covers research areas where clinical intervention is possible but also it is beneficial for studying diseases where intervention is difficult and abnormalities cannot be prevented. Maternal and child health research helps administration and health policy makers to develop policies and to take decisions that are in accordance with the current problems and are in the best interest of the communities. Since 1998, in order to broaden its vision in research, scope of work and teaching activities the division changed its name to "Developmental Medical Sciences". Aging, human and environment, and their related items are newly added to our theme. This comes under International Biomedical Sciences, which is a division of Institute of International Health. Since then, our research scope and work have expanded to foreign countries, mainly in Asia

Faculties and Students

Professor	Hiroshi Ushijima, M.D., Ph.D. (1995 - to date)
Associate Professor	Hideoki Fukuoka, M.D., Ph.D.
Associate	2
Postdoctoral Fellow	3
Graduate student	20
Research student	4
Secretary	2

Past Research and Major Accomplishments

Background

After graduation from medical university and obtaining license of medical doctor, I first worked at Tokyo University Hospital and related hospitals as a pediatrician. At the same time, I studied clinical research regarding pediatric infection, pediatric immunology, and pediatric neurology. My research produced results, which were related to clinical medicine. Following that I had an opportunity to study in the United States as a virologist (Research fellow) at State University of Alabama for about 2 years. My major was molecular study of Bunyaviruses, which infect humans as well as animals. Some of the viral strains caused emerging diseases. During my research, I discovered reassortant viruses and non-structure proteins in the family. After returning to Japan, in addition to being a pediatrician I also worked as a researcher on molecular epidemiology, diagnosis and development of medicine for diarrhea caused by viruses and HIV at National Institute of Infectious Diseases (NIID) and National Institute of Public Health (NIPH) as a chief and director, respectively. After that, I moved to the University of Tokyo in 1995. Since then, I have been engaged in various researches in topics ranging from infection, nutrition, maternal and child health in the world, with a special focus in Asia.

Followings are few researches, which I had carried out and supervised in the University of Tokyo. The researches include basic and field studies.

Diarrheal viruses

Rotavirus disease is an important diarrheal disease especially in children. More than 500,000 children die every year especially in developing countries. In the developed countries, almost all infants have viral disease within 2 years after birth. My experience in working on molecular epidemiology of rotavirus in Japan expands over a period of a little more than 20 years. Besides, in the past four years, extensive collaboration has been done with researchers, microbiolo-

gists and pediatricians in countries like Korea, China, Vietnam and Thailand. It has been done with similar themes of epidemiological studies of diarrheal viruses. These studies are important to develop vaccines because serotypes and genotypes sometimes change and the most appropriate vaccines are needed.

Major diarrheal viruses are rotavirus, astrovirus, adenovirus, Norwalk virus and Sapporo virus. Currently, we study all of them up to molecular level. Immunodeficient persons discharge the viruses for long time. Through research we have highlighted complications of encephalopathy, hepatitis and others, which were caused by these viruses. Stool samples, slightly over 10,000 were collected for more than 20 years in five areas in Japan. Besides Japan, stool samples were also collected in Asian countries. In complicated cases, cerebrospinal fluids, bloods and liver tissues are also examined at times.

I have the honor of pioneering the concept and developing molecular epidemiology of diarrheal viruses in Japan. During the process, I established particulars about diarrheal viruses causing encephalopathy and other complications in humans. Due to seasonal changes and serotype distribution, detail analyses of all the viruses were done during the past 20 years. Reassortment and recombination were also discovered. The changes in serotypes or genotypes were affected principally by time and also by geographic distributions across the countries. We established the facts about Norwalk virus spreading in early winter and rotavirus spreading in late winter in Japan. However the detail of mode of spread of viruses is still largely unknown, except for outbreaks of food poisoning and outbreaks at institutes. We also brought forward the fact that rotavirus infection starts at the same time all over Japan. We have established a research system in Japan and nowadays we are examining the shellfishes and sewerages regularly. The results of the research will contribute to the health policy and decision-making in Japan.

We newly developed RT-PCR, enzyme immunoassay, immunochromatography and latex agglutination tests for rapid, easy and sensitive diagnosis. Anti-diarrheal virus agents are examined by *in vitro* assay. We found that tea extracts, pine seed extracts and poly IC were effective on rotavirus infection. This method is useful to find anti-viral agents *in vitro. In vivo* assays by using mouse model are also used. Mouse pups born to and nursed by dams fed *Bifidobacterium breve* and immunized orally with rotavirus were more strongly protected against rotavirus-induced diarrhea than those born to and nursed by dams immunized with rotavirus only.

HIV and hepatitis viruses

HIV and hepatitis infections have become important areas of research not only in Asia in general but also in Japan in particular. It is now an established fact that HIV, hepatitis B and C viruses cause mother to child infection. Transportation of such sample safely across different countries has always been a problem. To transport HIV samples safely from foreign counties, we introduced the use of filter paper method for blood and saliva. New primers were designed for subtyping of HIV subtype B and E. We succeeded to determine HIV from several countries. Now we are developing primers for all subtypes. The PCR was useful for the samples from blood, saliva and breast milk. Basic research of HIV infection was also done through collaboration with Prof. Muller in Germany; it was found that exposure to gp120 of HIV induces apoptosis in neuronal cell culture. Moreover, I am still a member of National research group to find anti-HIV candidate drugs. For the said purpose we screen anti-HIV drugs distributed from pharmaceutical companies. We have found some effective chemicals *in vitro.* Molecular Epidemiology of hepatitis B has been done through the collaboration with Dr. Abe, NIH Japan. Our results revealed that there was high prevalence of HBV pre-S mutant in Asia, where there are high endemic regions of HBV, except for Japan. The appearance of HBV mutation seemed to be correlated to duration of persistent infection and genotypes of HBV. In fact, we found higher prevalence of HBV mutation in hepatocellular carcinoma patients and genotypes B and C. Mode of transmission of hepatitis C infection in Japan is different to that in Asia. The patients in most countries in Asia are due to co-infection with HIV but the majority of the patients in Japan are due to misuse of syringes.

Field studies

The field study of maternal and child health is also integral part of our department. One project is "maternal and child health in minority groups in Asian countries". Dr. Li Y, a researcher from Yunnan, China, has conducted a project in rural minority area of Yunnan. An interview of 2019 rural mother was conducted. We found that maternal child-rearing behaviors differed significantly among ethnic groups as well as between urban and rural areas. The behaviors were significantly associated with maternal education level, family type, family income, maternal age at delivery, and number of children in the family. We continued this project and found the malnutrition was especially due to vitamin B_1 deficiency. The main reason was eating too much polished rice, deficiency of vegetables and longer time for cooking.

Current Research

Viruses

We have continued epidemiological studies of diarrheal viruses, HIV and hepatitis, especially in children. It will help achieve the final goal of decreasing mortality and morbidity caused by these diseases. Enzyme immunoassay, (RT-) PCR, sequence analysis and other methods are used for the diagnosis. Immunochromatographic method is useful for diagnosis in outpatient clinics because of simplicity and rapidity.

We are trying to develop;

(1) Diarrheal virus detection kit for rotavirus, enteric adenovirus, astrovirus and Norwalk virus,
(2) Hepatitis virus detection kit for hepatitis A, B, C and E, and TTV.

To make antibodies for immunochromatograph, we culture the viruses that grow *in vitro*, make synthetic peptides and make virus like particles with genetic engineering. Rapid detection kit using gene amplification is also proceeding.

Field research

Asia: As further activity in Yunnan, we conducted training course of maternal and child health for about 60 health workers and physicians who belong to minority areas. Education session focused on proper cooking methodology, general physical examination, knowledge about HIV and other diseases. We made pamphlets and CD. Then, the health workers and physicians teach the caregivers by using them. Vitamin B1 is used in the area as a treatment. In addition, we used rapid methods of detecting viruses in the areas.

A student from Vietnam, who worked before at NGO GROUP, is studying in minority group in rural mountain areas in north part of Vietnam. Physical conditions of infants and attitudes of caregivers are examined every 3 months after birth for 2 years. In 2003, a student will come from Laos. She will also conduct similar research in Laos. Maternal and child health in minority groups in the border areas in China, Thailand, Laos and Vietnam are examined and intervention is planned.

Japan: We are conducting a project of maternal and child health in ethnic minority in Japan. This project started in 2001. Due to globalization, children of ethnic minority group have increased in Japan in the last 10 years. However health check system, medical care and health insurance system are not enough for them. In addition, education of mother and child, communication among health workers and residents are sometimes not sufficient for them. We have multipronged approach for the research. It includes (a)Ask 3000 local health workers about their activities on mother and child health in ethnic minority groups, (b)Interview health workers, physicians, NGO members and administrators deeply at two local areas how they succeeded in high quality of health care for minority groups. (c)Some families stay in Japan over the time than officially allowed. They do not receive enough medical care. To improve the situation, we examine it and make proposals for their better living. (d)Lack of communication among themselves and with health workers causes anxiety among them. Proper and efficient communication system and health service system will be suggested. (e)In addition to health care, education of mother and child is also needed. Both are related and necessary for their better health. All minorities in high class, middle class and lower class should be improved irrespective of ethnicity, religion or country of origin.

Others

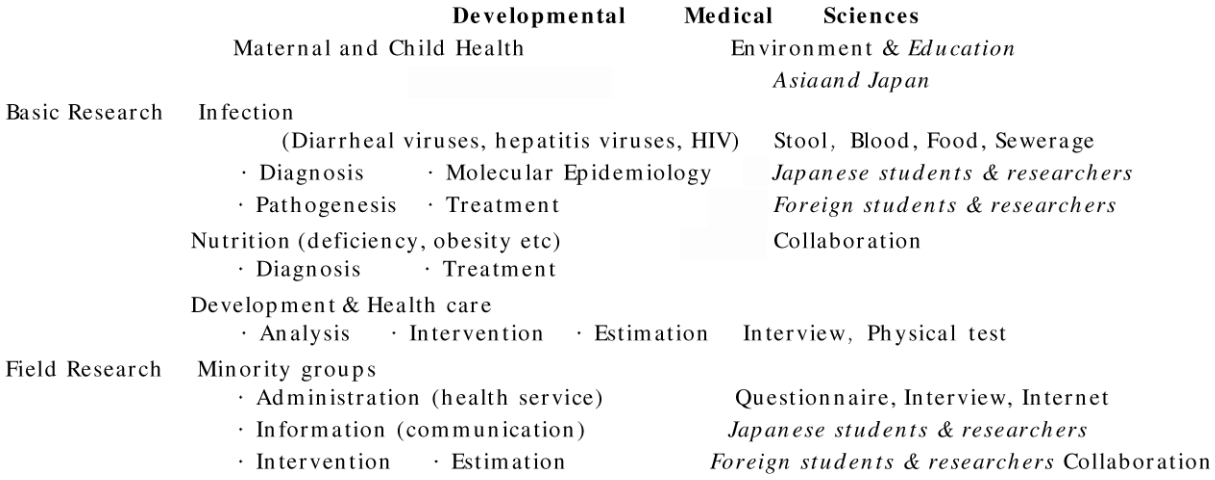
Other activities are concurrently carried out in my department are such as relation between development of voice / sucking and growth, mother's relaxation/infant development and touch care, maternal mortality and obesity in developed and developing countries. Moreover, other staffs in the division have their own projects. We regularly communicate, help and discuss together on our research agendas.

Future Prospects

21st century has started in the wake of social chaos. World has become a global village and emerging and reemerging infectious diseases are gaining importance. While, exchanges of people and information are rapidly increasing via various modes of transportation and internet service. Under these circumstances, the health of mother, child, and elderly is especially important. Our research of health in children among ethnic minority groups will become highly valuable. The results will contribute in making evidence based decision as regards maternal and child health.

In order to keep environment safe, a decrease in infection diseases and malnutrition are equally important. Our diagnostic methods are useful to for the above said cause and thus help fight against diseases. Further development of vaccine, medicine and molecular epidemiological survey of infection is the need of the time, to make the future safe for our generations in the times to come.

Followings are schema of our research of past, present and future.



Research Grants

a: Health-welfare and labor science research

(1) Maternal and child heath in multi-racial cultural society, a project of "general research on child and family" (2001-2004) 11,000,000 yen/3years

(2) Research of survey of microorganism contamination in foods and evaluation of safety, a project of "general research on safety of food and chemicals" (2001-2004) 1,000,000 yen/year

b: Basic research supported by the ministry of education and science

(1) Diagnosis, molecular epidemiology, pathology, prevention and treatment of diarrheal viruses. (2002-2005) 18,891,000 yen(2002)

(2) Molecular epidemiological study of maternal and child infection in Asia. (2001-2004) 4,200,000 yen(2002)

c: Others

(1) Research for gravity and infection supported by space development project. 520,000 yen(2002)

(2) Research for Nano-technology supported by human science foundation. Other small grants are not shown. 7,500,000 yen/year

Select Publications

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infection in Tokyo and Saitama in late 1995. J. Jap. Assoc. Infect. Dis. 70: 840-841, 1996.
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10 majors are No.1, No.3, No.22, No.26, No..28, No.32, No.38, No.40, No.41, No.48 and No.49.

Department of Human Ecology

Outline and Research Objectives

In 1965, our department was established in the School of Health Sciences. From 1966 to 1972, however, there was no full-time professor in our department and thus its scientific activities were limited. Between 1972 and 1976, Professor Akira Koizumi took the office and made efforts for founding the bases in this new field, focusing on environmental health and population analysis. For three years from 1976 when Professor Koizumi transferred to Department of Public Health in our university, however, there was no professor again. In 1979, Professor Tsuguyoshi Suzuki transferred from Tohoku University, and since then research activities of our department have flourished; in this period, particularly in the later half, I fully assisted Professor Suzuki as an associate professor. In 1992, when I took his place, our department was reorganized as one of six departments in the newly established School of International Health.

Regarding the research objectives, human ecology is unique in elucidating health and survival of humans at the individual and population levels, particularly from the relations or interactions with their environment (not only the natural components but also the sociocultural components). Thus, the research of human ecology aims to integrate various aspects, i.e. biomedical, environmental and sociocultural, as far as possible.

Since 1972 and particularly since 1979, the staff and students in our department have conducted fieldworks and experimental works, with special interest in the linkage between them. For the former, various populations in the Asia-Oceania region have been investigated, focusing on food-producing and consuming activities, nutritional and health status, population dynamics including births, deaths and migrations, and infectious and chronic degenerative (lifestyle-related) diseases; my own major contributions were related to the fieldworks. For the latter, toxicological and nutritional examinations have been conducted for biological specimens (i.e. urine, blood and hair) and environmental samples (i.e. water and foods), most of which were collected in our fieldworks; in addition, the associated animal experiments have also been carried out.

Faculties and Students (in October 2002)

Professor and Chair	Ryutaro Ohtsuka, D.Sc., since 1992.
Associate Professor	Chiho Watanabe, Ph.D.
Associates	2
Postdoctoral Fellow	1 (foreigner).
Graduate Students	13 (including 3 foreigners).
Research Students	5 (including 3 foreigners).
Secretaries	3 (1 full-time and 2 part-time).

Past Research and Major Accomplishments

It is reasonable to review the whole research activities of our department from the 1980s to the recent past since I, as an associate professor from 1981 to 1992, actively participated in most of them, while assisting, and collaborating with, the then Professor T. Suzuki. For convenience, the major research foci are shown in Table 1, separately for the 1st period (up to 1992, when I became a professor) and the 2nd period (up to the late 1990s); in the same table, those in the current and future periods are also mentioned. It is noted that this table does not include the common themes, such as nutritional adaptation, behavioral adaptation and population dynamics, which have always been pursued.

The most important goal of my research (with Professor T. Suzuki and other staff) in the 1980s was to establish the research framework of human ecology, focusing on human population ecology. Briefly, the significance of human population ecology or human population biology, which aims to elucidate human adaptation at the population level not only in the short term, e.g. within a year, but also in the long term, e.g. through generations, had long been pointed out by many human ecologists and human biologists worldwide, but its systematic studies had been lacked. For this purpose, my efforts were devoted to the collaborative research in the Gidra-speaking popu-

Table 1. The major research items, broken down into four periods

	1st (-1992)	2nd (1990s)	3rd (current)	4th (future)
Establishment of research framework	++			
Developments/Innovations of methodologies*				
Human activity	+		+	(?)
Nutritional/health status	++	+	+	(?)
Energy expenditure	+	++	+	(?)
Microdemography	++			(?)
Specific themes**				
Infectious diseases	+	++	+	+
Toxic elements		+	++	+
Lifestyle-related diseases		+	+	++
Harmonized development			+	++

* Including only fieldwork-based methodologies.

** The common themes are not included.
Infectious diseases: mostly, malaria in the earlier stages and schistosomiasis in the later stages.
Toxic elements: mostly, mercury in the 2nd period and arsenic in the 3rd and 4th periods.
Lifestyle-related diseases: mostly, obesity, hypertension and cardiovascular disorders.

lation in Papua New Guinea. The Gidra people are suited to this purpose since they have maintained the basic characteristics of a population, forming a unit of marriages and thus a unit of gene pool, despite the small number, i.e. about 2,000 in total, but their microenvironmental conditions differ from village to village, e.g. inland, riverine and coastal terrains from the natural settings and in the degree of modernization from the sociocultural settings.

Our Gidra studies were characterized by the following two points. First, long-term field investigations were repeatedly conducted, based on observation, measurements and interviews, for the people's daily activity pattern, especially food procurements and intakes, nutritional and health status and population dynamics. Second, biological specimens (blood, urine and hair) and environmental samples (foods and water) were systematically collected for laboratory analyses.

In tandem with the establishment of the research framework, my efforts were directed to the developments and innovations of various biological, behavioral and microdemographic methods applicable to field investigations. The major achievements included 1) genealogical-demographic analysis which has been useful for reconstruction of long-term change in fertility, mortality and increase rates, 2) heart rate-monitoring method for estimation of energy expenditure which has now become popular in human ecological fieldworks and 3) determination of sodium, potassium and urea nitrogen concentrations from urine samples, using filter papers, which has also been widely used.

Following the findings from the Gidra studies, most of which were based on the combined efforts of fieldwork and laboratory analysis, more than 40 original papers were published in international journals. In addition, I, with Professor T. Suzuki, collected the important papers to edit a book in English, titled *Population Ecology of Human Survival: Bioecological Studies of the Gidra in Papua New Guinea* (No. 15 in Select Publications), which has been distributed worldwide to not only human ecologists but also scientists in the related fields. The 20 chapters of this book are categorized into four parts: "The ecology of food production," "The ecology of food consumption," "Nutrition and health" and "Population structure and dynamics." Among various findings, some contributed to the health promotion plans of the national and provincial governments of Papua New Guinea: for instance, disadvantageous effects of dietary modernization due to reduced intakes of essential micronutrients (e.g. zinc and potassium) and less effects of iron supplementation to the anemia patients in malaria endemic areas because their anemic states were caused not by inadequate iron intake but by malaria-induced haemolysis and dyserythropoiesis.

Since the late 1980s, I have increased the study populations for more generalized understanding of the people's health and survival, based on the research framework which was established. For instance, our studies revealed an extraordinarily high mercury levels (in hair) among the Lake Murry population under artificially nonpolluted environment due to large consumed amounts of fish in which mercury was accumulated through biological concentration. For another instance, our studies in the most modernized rural population, called Balopa, disclosed that their prevalence rates of obesity and hypertension were higher than those in many other populations even in developed countries, mostly due to their less energy-consuming activity pattern and large amounts of intake of fat-rich purchased foods.

Aside from the studies in Papua New Guinea, both field research and toxicological and nutritional experiments were conducted for various Japanese popula-

tions, though only a few of them are listed in the Select Publications.

Current Research

Since the late 1990s, my research foci have extended to clarify the effects of modernization on human health and survival on the one hand, and on the other, the effects of some specific harmful environmental factors on human health and their mitigations.

In Papua New Guinea, our major efforts have been devoted to the comparative analysis of rural (homeland) dwellers and rural-urban migrants of the same populations, particularly the Huli and the Balopa, whose genetic backgrounds markedly differ. For this purpose, we have conducted research in both environments, the homelands and Port Moresby, i.e. the capital city, focusing on energy and nutrient intakes, energy expenditure and the prevalence of obesity, hypertension and other cardiovascular diseases and have disclosed the significance of lifestyle change on them; protein status has been improved while obesity, hypertension and many other cardiovascular risks have been worsened. Furthermore, the comparison between the two rural-urban migrant populations in Port Moresby revealed difference in the trigger factor, obesity for the Balopa (an Austronesian group) and high lipoprotein-a level for the Huli (a Non-Austronesian group).

Concurrently, I began research projects in several Asian countries. Of them, the study for Bangladeshi populations under arsenic hazards has been the major target in the last several years. Despite that 35-50 million Bangladeshi people are recognized as a risk population of arsenic poisoning, systematic analyses, the dose-response relationships in particular, have seldom been conducted. Our research contributed to concrete elucidation for the interrelations among arsenic concentration of drinking water, urinary arsenic concentration and the extents of skin lesions (i.e. keratosis and melanosis as the major symptoms of arsenic poisoning), in collaboration with dermatologists in our University Hospital. Furthermore, in this research project headed by me, many colleagues of different disciplines, such as water chemists and public health engineers from Switzerland and Japan and hydrologists from USA, have collaborated to seek integrated ways for mitigation of arsenic hazards and sustainable water supply systems in arsenic affected areas.

Energetics, i.e. the balance between energy intake and energy expenditure, has been one of the important research themes in our department. The recent studies have clarified its particularly significant roles on degradation of health status in modernization process among populations in Papua New Guinea, Thailand and Bangladesh.

Finally, I began a biosocial research, which seeks harmonized ways of community development and environmental conservation in the Asia-Oceania region. The major reason why I organized this project came from my judgment that the basic idea of human ecology is useful for this issue. In this project, I recruited not only biomedical scientists but rather sociocultural scientists from Japan and some other Asian and Oceanian countries. At the beginning stage, our findings have still been limited mostly due to difficulties in data collection by means of sociocultural methods, but I will continue this research in the future.

Future Prospects

My term of professor is not long, and thus I will concentrate in the three research projects: the arsenic hazards in Asian countries (not only Bangladesh but several countries) and the harmonized community development with environmental conservation in the Asia-Oceania region, both which have already commenced, and a new project which has begun in the year 2002 and will continue for three years. This new project aims to elucidate the causes of markedly different prevalence of lifestyle-related diseases among Asian, Melanesian and Polynesian populations. Based on my previous research findings and in collaboration with the staff in our school, particularly those from Department of Human Genetics (headed by Professor K. Tokunaga), the effects of both genetic factors and environmental (mostly lifestyle) factors will be simultaneously clarified.

My intentions for these three projects, with special interest in collaborations with scientists of other disciplines, are as follows. The arsenic project, which has been and will be sponsored by the Alliance for Global Sustainability (the joint programs of Massachusetts Institute of Technology in USA, Swiss Federal University of Technology and our university), is expected to contribute our human ecology research to the integrated efforts for solution/mitigation of this environmental issue, recognized very serious for human health and survival in several Asian countries. The genetico-ecological project for lifestyle-related diseases aims at development of collaborative works with many colleagues, particularly, those from Departments of Human Genetics, Biomedical Chemistry and Developmental Medical Sciences (all of which belong to a large Department called International Biomedical Sciences, together with our department). The harmonized development project is expected to broaden human ecology aspects through collaboration with scientists of social medicine and social ecology in our school, i.e. a large Department of International Social Medicine) and some others.

Research Grants

1. (as the Cluster Sub-leader, with many colleagues from many countries) "People, land management and environmental change" organized by the United Nations University and sponsored by the Global Environmental Facility through the United Nations Environmental Programme: 1998-99; 7,816,860 Yen (in total, for my own team).
2. (as the Leader, with 15 colleagues from Japan, USA, Switzerland, Bangladesh and Nepal) "Mitigation of groundwater-derived arsenic hazards and sustainable water supply system in Asian countries" sponsored by the Alliance for Global Sustainability Programs; 1999-2002; 29,420,518 Yen (in total).
3. (as the Leader, with 30 colleagues from Japan, China, Solomon Islands and Nepal) "Influences of development on local communities and their mitigations" sponsored by the Japan Society for Promotion of Science: 1999-2002; 184,000,000 Yen (in total).
4. (as the Leader, with 15 colleagues from Japan, Solomon Islands and Indonesia) "Genetico-ecological studies for high risks of lifestyle-related diseases in Oceanian populations" sponsored by the Monbukagaku-sho, Japan (Grant-in-Aid for Scientific Research); 2002- 2004; 29,300,000 Yen (in total).
5. (as the Leader, with 10 colleagues from Japan, Papua New Guinea, Malaysia and Nepal) "Application of high-quality satellite images to analyses of land use and environmental change" sponsored by the Monbukagaku-sho, Japan (Grant-in-Aid for Scientific Research); 2002-2005; 15,800,000 Yen (in total).

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Department of Biomedical Chemistry

Outline and Research Objectives

Aim of our department is to contribute to global health and welfare from basic research. Our department, formerly named Biochemistry and Nutrition was renamed on April 1st, 1996 to The Department of Biomedical Chemistry as newly affiliating with Biomedical Science Division of International Health, Graduate School of Medicine, The University of Tokyo. Prof. Kita has moved from The Institute of Medical Science, The University of Tokyo on March 1st, 1998. Therefore, we are quite new and all of our members are highly motivated.

Faculties and Students

Professor and Chair	KITA Kiyoshi, Dr. of Pharmacy (1998-)
Lecturer	WATANABE Yoh-ichi, Dr. of Technology

Associate.....3
Postdoctoral Fellow 2
Graduate student 12
Research student.....4
Secretary 1

Past Research and Major Accomplishments

Energy metabolism is essential for the survival, continued growth and reproduction of living organisms. From the standpoint of biological adaptation, we have been studying on the molecular mechanism of energy transducing systems such as mitochondrial and bacterial respiratory chain. Because energy metabolisms of pathogenic organisms such as bacteria and parasites are quite different from that of mammalian host and these unique aspects of pathogens would be promising targets for chemotherapy.

For the first step to understand a mechanism of adaptation to the change of oxygen availability, composition and its change during aerobic growth of *Escherichia coli* was studied. Finally, we found two different terminal oxidases, cytochrome *bo* and *bd* complexes. Cytochrome *bo* complex is expressed in early log phase and possesses proton-pumping activity, while cytochrome *bd* complex is expressed from late log phase to stationary phase with higher affinity to oxygen than cytochrome *bo* complex. Thus, we found that *E. coli* keep their energy supply by changing the respiratory chain during their growth.

Then, we have started our research on the biological strategy to adapt to different oxygen availability in eukaryotes. Purpose of this project is multiple. We would like to know the common strategy to maintain energy supply in different environments and also to understand unique feature of energy metabolism in pathogenic organisms. If we could understand the mechanism clearly, it would be quite important information to fight against infectious diseases caused by bacteria and parasites in addition to the basic knowledge on the molecular mechanism of biological adaptation. As a model system, we selected *Ascaris suum* which is a parasitic nematode resides in our small intestine where oxygen tension is quite limited, because 1) they are rather large in size allowing biochemical study, 2) their life cycle has been well characterized and 3) they are closely related to *Caenorhabditis elegans* which is well known free-living nematode, of which whole genome sequence has been reported.

Current Research

I. Human mitochondria

1) succinate dehydrogenase
2) mitochondrial myopathy

Succinate-ubiqinone oxidoreductase (complex II and/or SQR) is an important enzyme complex in both the tricarboxylic acid cycle and the aerobic respiratory chains of eukaryotic mitochondria and prokaryotic cells. Complex II catalyzes the oxidation of succinate to fumarate (succinate dehydrogenase: SDH) and transfers its reducing equivalent to ubiquinone. To elucidate the molecular basis of a mitochondrial disease caused by a deficiency in the SDH activity of complex II, we cloned the cDNAs for all four subunits of human liver complex II. During this study, we found two isoforms of complex II containing Fp subunits of liver type and heart type.

Then we have mapped large (CybL) and small (CybS) subunits of cytochrome *b* in complex II of

human mitochondria to chromosome 1q21 and 11q23, respectively. Recently, the human *SDHD* gene encoding CybS was cloned and characterized. The gene comprises four exons and three introns extending over 19 kb. Sequence analysis of the 5' promoter region showed several motifs for the binding of transcription factors including nuclear respiratory factors NRF-1 and NRF-2 at positions -137 and -104, respectively. In addition to this gene, six pseudogenes of CybS were isolated and mapped on the chromosome.

II. *Ascaris suum* and *Caenorhabditis elegans*

1) molecular mechanism of adaptation to low oxygen tension (regulation of gene expression of mitochondrial proteins)
2) mitochondrial quinol-fumarate reductase (structure-function relationship, enzyme evolution)
3) *C. elegans* as a model system of parasitic nematodes and ageing (expression of foreign genes, gene knockout, oxygen stress)

Parasites have developed a variety of physiological functions necessary for existence within the specialized environment of the host. Regarding energy metabolism, which is an essential factor for survival, parasites adapt to low oxygen tension in host mammals using metabolic systems that are very different from that of the host. The majority of parasites does not use the oxygen available within the host, but employ systems other than oxidative phosphorylation for ATP synthesis.

In addition, all parasites have a life cycle. In many cases, the parasite employs aerobic metabolism during their free-living stage outside the host. In such systems, parasite mitochondria play diverse roles. In particular, marked changes in the morphology and components of the mitochondria during the life cycle are very interesting elements of biological processes such as developmental control and environmental adaptation. Recent our research on adult *A. suum* has shown that the stage-specific mitochondrial complex II plays an important role in the anaerobic energy metabolism of parasites inhabiting hosts, by acting as quinol-fumarate reductase (QFR). Sequence analysis of the subunits in the enzyme revealed that mitochondrial QFR is new enzyme evolved by "reverse evolution" of SQR rather than direct evolution from bacterial QFR.

We have been studying free-living nematode, *C. elegans* as a control nematode living in an aerobic condition. In addition, we also have been studying ageing by using *C. elegans*. Our study on long-lived *clk-1* mutants of *C. elegans* demonstrated that biosynthesis of UQ is dramatically altered in mutant mitochondria. Demethoxy ubiquinone (DMQ), that accumulates in *clk-1* mutants in place of UQ, may contribute to the extension of life span. We proposed the possible mechanisms of life span extension in *clk-1* mutants, with particular emphasis on the electrochemical property of DMQ. On the other hand, in the short-lived *mev-1* mutant, a point of mutation glycine 71 of CybL in SQR results in hypersensitivity to oxidative stress. We demonstrated the production of reactive oxygen species (ROS) was higher in the mutant complex II than wild type, indicating ROS is responsible for the short life span of *mev-1* mutant.

III. Malaria and Trypanosome (Plasmodium falciparum, Trypanosoma brucei,Trypanosoma cruzi)

1) characterization of mitochondria as a target for the chemotherapy
2) molecular biology of mitochondrial DNA
3) structure based drug design (SBDD)

The mitochondria of parasitic protozoa that have been most studied are those of *Trypanosoma brucei*, which is the causative agents of African trypanosomiasis in human and nagana in cattle. Parasitic protozoa living within a mammalian host do not generally use oxygen, and instead synthesize ATP via the glycolytic pathway. In comparison to research on helminthes, research on mitochondrial electron transfer of protozoa during the developmental stage within the host is lacking. However, mitochondria have become a focus of chemotherapy, and researches, particularly on mitochondria of the malaria parasite and trypanosomes are currently progressing.

To study the unique properties of *Plasmodium* complex II, we have cloned and characterized the genes for the flavoprotein subunit (Fp) and the iron-sulfur protein subunit (Ip) subunits of complex II. This is the first report of the primary structure of protozoan complex II. Interestingly, a *P. falciparum*-specific insertion and a unicellular organism-specific deletion were found in the amino acid sequence of Fp. Despite the fact that Fp and Ip are generally well-conserved subunits, the structure of both subunits in the malaria parasite clearly differs considerably from that of the host.

Cyanide-insensitive trypanosome alternative oxidase (TAO) is the terminal oxidase of the respiratory chain of long slender bloodstream forms of the African trypanosome. TAO is a cytochrome-independent, cyanide-insensitive quinol oxidase. These characteristics are distinct from those of the bacterial quinol oxidase, a protein that belongs to the heme-copper terminal oxidase superfamily. TAO has been targeted for the development of anti-trypanosomal drugs because it does not exist in the host. We found the most potent inhibitor of TAO to date, ascofuranone, a compound isolated from phytopathogenic fungus, *Ascochyta visiae*. The inability to purify stable TAO has severely hampered biochemical studies of the

alternative oxidase family. Recently, we were able to purify recombinant TAO to homogeneity from *E. coli* membranes using the detergent digitonin. Kinetic analysis of the purified TAO revealed that ascofuranone is a competitive inhibitor of ubiquinol oxidase activity.

IV. *Escherichia coli*

1) succinate dehydrogenase complex (mechanism of molecular assembly, electron transport mechanism in the complex)
2) regulation of energy supply

E. coli is one of the useful model systems to investigate biological reactions common to living organisms. In order to investigate the role of the heme in the assembly of complex II, we used a *hemH* (encodes ferrochelatase) mutant of *E. coli* lacking the ability to insert iron into the porphyrin ring. The *hemH* mutant failed to synthesize functional complex II in the cytoplasmic membrane and the catalytic portion of complex II, Fp and Ip, was localized in the cytoplasm of the cell. In contrast, complex II was assembled in the membrane of a heme-permeable and *hemH* double mutant when hemin was present in the culture. Only a small amount of succinate-ubiquinone reductase (SQR) activity was found in the membrane when hemin was replaced by non-iron metalloporphyrins; Mn-, Co-, Ni-, Zn-, Cu-protoporphyrin IX or protoporphyrin IX. These results indicate the indispensability of iron of heme for the functional assembly of complex II in the cytoplasmic membrane of *E. coli*, and add a new aspect to the biological role of heme in the molecular assembly of the multi-subunit enzyme complex.

Future Prospects

Dynamic rearrangement of the respiratory chain during parasite life cycle that we found is a key element of their adaptation to different environments. In the case of mammals, cells are able to sense decreased oxygen and activate response systems, including hypoxia-inducible factor-1 (HIF-1)–mediated transcriptional activation of several genes. Quite recently, HIF-β and a homologue of HIF-1α were found in the free-living nematode *C. elegans.* Although it is not known whether such a pathway exists in the parasites, *A. suum* shows a very clear transition between larval and adult metabolic systems. Thus, *A. suum* is an excellent model system for studying the regulation of transcription by the oxygen level in the environment.

Current research on *C. elegans* including our result has revealed that oxygen concentration, its availability, and oxidative stress can produce a variety of interesting phenotypes such as modified life spans. As described above, in the long-lived *C. elegans* mutant *clk-1*, UQ biosynthesis is altered so that mitochondria do not possess detectable levels of UQ-9 but instead contain the UQ biosynthesis intermediate DMQ-9. On the other hand, in the short-lived *mev-1* mutant, a point of mutation glycine 71 of CybL in SQR results in hypersensitivity to oxidative stress. These findings indicate that the respiratory chain plays an important role in sensing and responding to the oxygen level in the environment. Consistent with this, recent reports suggest that complex II functions as an oxygen sensor in human. We would like to understand a molecular mechanism of biological adaptation to the change of oxygen availability by using these nematodes and human systems. Diversity of complex II was also found in human complex II. Studies on the human respiratory chain will be achieved from the viewpoint of physiological role of energy supply and related diseases.

It remains unclear which critical factor determines the catalytic direction of electron transfer in complex II. Biochemical and molecular biological studies showed that both the properties and the primary structures of mitochondrial and bacterial quinol-fumarate reductase (QFR) differ significantly. Identification of the amino acid residues of mitochondrial QFR responsible for the directional specificity of its catalysis should help to clarify the molecular mechanism of this "new" parasite enzyme. Furthermore, investigations of the molecular pathways of parasite survival may provide insight into general mechanisms of biological adaptation.

Finally, we would like to develop anti-parasitic drugs which should be used in endemic areas. As described in "Current Research", the parasite metabolic system is an attractive target for chemotherapy because it is different than the host metabolic system and because it is essential for parasite survival. TAO in trypanosome mitochondria and its specific inhibitor, ascofuranone are excellent examples in this regard. As pointed out by Dr. Opperdoes, ascofuranone is the most potent TAO inhibitor to date. Because of its high selectivity and low toxicity, ascofuranone is a potential candidate for the next generation of anti-trypanosomal agents. Indeed, current studies are examining the molecular mechanism of ascofuranone and ways of improving its efficacy *in vivo.* We already have started a trial by using goat in Africa. One problem that must be solved is that glycerol must be administered along with ascofuranone, to inhibit the reverse reaction of glycerol kinase. Although glycerol is not toxic, it is not practical to give the large dose (3g /kg) required, and an inhibitor of the reverse reaction of glycerol kinase is expected to be more useful. Fortunately, glycerol kinase has

been cloned and the recombinant enzyme can be over-expressed. We are now trying to screen and find a specific inhibitor of glycerol kinase.

Thus, we would like to contribute to global health and welfare from basic research and train young scientists to be thoughtful and powerful colleagues.

Research Grants

1. "Molecular and biochemical studies on *Plasmodium* mitochondria" from a Grant-in-aid for scientific research on priority areas from the Ministry of Education, Science, Culture and Sport, Japan
   40,000,000 yen (2001-)
2. "Crystalization of parasite proteins and molecular design of anti-parasitic drugs" from Pilot Applied Research Project for the Industrial Use of Space" of the National Space Development Agency of Japan (NASDA) and Japan Space Utilization Promotion Center (JSUP).
   30,000,000 yen (2000-)
3. "New anti-trypanosome drug, ascofuranone" from a Grant for research on emerging and re-emerging infectious diseases from the Ministry of Health and Welfare
   120,000,000 yen (1999-2001)
4. "Molecular structure and role of mitochondrial fumarate reductase from *Ascaris suum*" from a Grant-in-aid for scientific research on priority areas from the Ministry of Education, Science, Culture and Sport, Japan
   13,200,000 yen (1999-2000)
5. "Molecular properties of *Plasmodium* mitochondria in the erythrocytic stages" from a Grant-in-aid for scientific research on priority areas from the Ministry of Education, Science, Culture and Sport, Japan
   28,000,000 yen (1997-2000)

Select Publications

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