Department of Molecular Preventive Medicine

Outlines and Research objectives

This department originates from The Department of Hygiene which was first established by Prof. Masanori Ogata in 1885. Prof. Ogata is the first Japanese bacteriologist who was trained by Prof. Pettenkofer in Munich. The Department of Microbiology was separated in 1920. I (K.M.) am the 8th professor of this department.

Main current research interests are as follows:

1. Molecular pathogenesis of inflammatory and immune diseases focusing on chemokines and dendritic cells, and development of novel therapeutics for inflammatory and immune diseases.
2. Molecular mechanism of leukocyte trafficking in vivo and chemotaxis in vitro.
3. Development of novel, effective ways of dendritic cells(DC)-based vaccination for infectious and inflammatory diseases as well as cancer.
4. Identification of novel targets for intervention therapy and prevention of inflammatory and immune diseases through completing comprehensive gene expression profiling of human leukocyte subsets.

Faculties and Students

Professor and Chair	Kouji Matsushima MD and PhD (1996 appointed)
Associated Professor	Sho Ishikawa MD and PhD
Associate	2
Assistant	1
Postdoctoral Fellows	2 (JSP) 1 (SORST, JST)
Graduate Students	9
Graduate Students from outside	8
Visiting Scientists	5
Technical Assistants	1+1 (SORST, JST)
Secretary	1 (SORST, JST)

Past Major Accomplishments

Chemokine, chemotactic cytokine family now consists of over 40 and is subdivided into four subfamilies based on the location of the very conserved first two cysteine residues. Interleukin 8 (IL 8), which was purified based on in vitro neutrophil chemotactic activity and molecularly cloned by me in collaboration with Teizo Yoshimura in 1987, is a prototype of CXC chemokines. On the other hand, MCAF/MCP-1, which was purified based on monocyte chemotactic activity and molecularly cloned by me and Teizo Yoshimura independently in 1989, is a prototype of CC chemokines.

From the beginning of the 1990's we and several other groups initiated the studies to establish the pathophysiological roles of chemokines in various animal inflammation models using specific blocking antibodies against chemokines. We reported the essential involvement of IL 8 in recruiting neutrophils in acute inflammation models such as LPS/IL-1 induced dermatitis, immune-complex induced acute glomerulonephritis, lung reperfusion injury, acute respiratory distress syndrome and brain infarct; and that intervention of IL 8 leads to the prevention of neutrophil infiltration-associated tissue injury. We also revealed the pivotal role of MCAF/MCP-1 in recruiting monocytes/macrophages in chronic inflammatory diseases through working on chronic glomerulonephritis caused by anti-glomerular basement membrane antibody, thickening of endothelium after carotid artery injury as an atherosclerosis model, and monocrotaline-induced pulmonary hypertension model in rats. Later, the pivotal role of IL 8 and MCAF/MCP-1 in recruiting neutrophils and monocytes, respectively was essentially confirmed by other groups analyzing gene targeted mice for IL 8 receptor homologue, and JE (murine homologue of MCAF/MCP-1) and its receptor CCR2.

Recent discovery of numerous novel chemokines by others through signal sequence trap method and EST data base, most of which are chemoattractants for immune cells such as subclasses of T lymphocytes, B lymphocytes and DC, has changed our understanding of the role of chemokines in host defense responses. For example, CD4+CD45RA+naive T lymphocytes express CCR7. CD4+CD45RO+memory T lymphocytes express CXCR3 and CCR5 on Th1 subset and CCR4 on Th2 subset. We generated a monoclonal antibody against human CCR4 and established that about 20% of CD4+ memory T lymphocytes in the circulation of normal individuals express CCR4 and

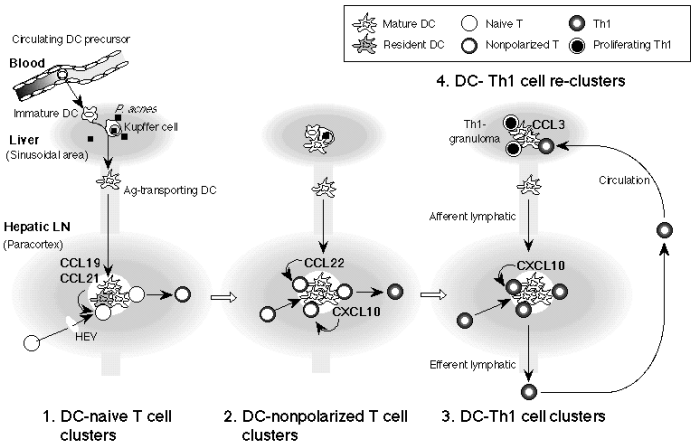

Figure 1: Peripheral and regional DC-Th cell clusters as the sites of Th1 cell generation regulated by DC-derived chemokines

these cells are committed Th2 population producing preferentially Th2 cytokines without any cultures to polarize into Th2 cells in vitro and the percentage of this population is much increased in atopic diseases such as atopic dermatitis and asthma. We also reported a pivotal role of the ligands for CCR4, TARC and MDC in causing and regulating atopic diseases in murine models.

Molecular pathogenesis of inflammatory and immune diseases

Chemokines in a murine model of bacteria-induced fulminant heapatitis

Propionibacterium acnes (P.acnes) is the most probable causing bacterium of sarcoidosis. In this model, administration of P.acnes causes numerous granuloma formation in the sinusoidal area of the liver, and subsequent challenge of the mice with low dose of LPS induces massive hepatic injury around granuloma. We first revealed that Th1 type immune response dominates in granuloma formation in terms of chemokine/chemokine receptor expression as well as cytokine production, whereas dramatic shift to Th2 response occurs immediately after LPS administration. Administration of the antibody against TARC (a ligand of CCR4, Th2 chemokine receptor) significantly inhibited liver injury. This is the first presentation that the rapid local shift from Th1 to Th2 by chemokines leads to severe tissue injury. We next identified TARC producing cells at the granuloma sites to be DC. We, then extensively analyzed the mechanism of granuloma formation, and revealed that numerous CCR1/5+DC-precursors appear shortly after P.acnes administration in the circulation and rapidly migrate into sub-sinusoidal area (Disse's space) in response to MIP1a produced by Kupffer cells to participate in the initial granuloma formation. Antigen-laden DC matured at the granuloma sites start to express CCR7, and subsequently migrate to portal area and the draining lymph nodes (hepatic/celiac lymph nodes) in response to SLC produced by lymphatic endothelium. We revealed that the first immune response occurs at the portal area and inflammation-associated lymphoid tissue appears at the portal area which we termed "portal tract-associated lymphoid tissue, PALT. We also showed directly that Th1 polarization occurrs at the draining lymphnodes by visualizing IFN-gamma producing CD4+T cells clustered with DC in the paracortex of lymph nodes. We provided evidence that IP-10 produced by migrated mature DC in the hepatic lymph nodes regulates DC-Th1 cluster formation and controls the exit of memory/effector T cells from the lymph nodes to home to the liver to complete granuloma formation (Figure 1). This is the first report describing the existence of DC at the granuloma sites and the identification of inflammation-associated DC precursors in the circulation. This implies that even the exit/release of memory/effector T cells from the peripheral lymph nodes is regulated by chemokines. This study has provided a new concept that chemokine-recruited DC tightly link inflammation (innate immunity) and acquired immunity. Inflammation and immunity should not be conceptually separated any more, and granuloma formation is not a mere end-point of chronic inflammation, rather a very active immune site.

1; Initiation and induction of DC-naive T cell clusters by ELC(CCL19) or SLC(CCL21). **2;** Amplification of DC-nonpolarized T cell clusters by MDC(CCL22). **3;** Promotion and retention of DC-Th1 cell clusters (this study). These clusters may develop in the given spaces of the paracortex called "cytokine fields". DC-derived chemokines may regulate T cell traffic depending on their state of activation between these given spaces to magnify the effective immune responses. After leaving the LNs, Th1 cells migrate into the liver through the circulation and **4.** re-form clusters with peripheral tissue-resided inflammatory DCs (granuloma formation) possibly by MIP1a(CCL3) or Mig(CXCL9). Th1 cells can further proliferate and produce higher amount of IFN-γ at the periphery of the granulomas to complete polarization. HEV, high endothelial venule.

Current Research

DC migration pathway so far described is limited

to the idea that tissue immature DC such as Langerhans cells mature after antigen capturing and start to express CCR7 to be recruited to draining lymph nodes through afferent lymphatics. There is neither direct presentation of DC precursor migration into any organs nor evidence of the entry of DC into secondary lymph nodes through HEV (high endothelial venule) directly from the circulation. We have now identified DC precursors which rapidly appear in the circulation in inflammation. We are currently studying the following issues:

Mechanism of rapid release of DC precursors from bone marrow---identification of chemokine(s) involved.

Heterogeneity of the identified DC precursors and fate of DC precursors after administering into normal and inflamed mice. Most of cells are CD11c+CD11b+myeloid type DC, but some of the cells express L-selectin and B220. Therefore, some of these cells may directly enter peripheral lymph nodes through HEV to act as tolerance-inducing DC.

Identification of homing molecules to the lymph nodes.

Examination of the possible usefulness of the identified DC precursors for vaccination and antigen-specific tolerance induction.

Future Prospective: Investigation of "lymph node-homing" circulating DC precursors may provide a clue to the mechanism of systemic tolerance induction and an approach to establish effective way of DC-based vaccination to cancer and microbes. We will further examine the role of chemokines in Th2 polarization, CTL generation and the recruitment and maintainance of memory state of CD4/8 T lymphocytes. We will also establish the critical role of TARC/MDC to recruit CCR4+CD4+CD25+ so called regulatory T cells in cancer and chronic infection models. The clinical development of humanaized monoclonal antibody against human CCR4 will be tried in a collaboration with a pharmaceutical. This antibody is expected to eliminate by ADCC CCR4+cells such as Th2, regulatory T cells and adult leukemia cells in a few hours in vivo. Therefore, this antibody treatment may be useful for the treatment of various atopic diseases. This antibody may also be useful to recover patients from immune-suppression to respond more to DC-based vaccination. This antibody may also become an effective drug for curing ATL patients.

Research Grants

Research Grants from JSP
1996 27,600,000 JPY
1997 11,100,000 JPY
2001 7,000,000 JPY
2002 20,300,000 JPY
Core Research of Evolutional Science and Technology (CREST, JST)
1996-2001 Total 600,000,000 JPY (about 5 million USD)
Solution Oriented Research for Science and Technology (SORST, JST)
15,000,000 JPY (about 120,000 USD)
70,000,000 JPY (about 500,000 USD)

50 Select Publications

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Department of Public Health

Outline and Research Objectives

Public health departments in medical schools in Japan were introduced after the World War II, following the model of the U.S. system of medical education. The Department of Public Health was established in 1948, in the Faculty of Medicine, University of Tokyo. In 1995, the Department became a part of the Division of Social Medicine, Graduate School of Medicine, as the result of the shift to a graduate school system in University of Tokyo.

The objectives of the Department are both education and research of public health. The Department trains graduate and undergraduate students through lectures, seminars, field practice, and laboratory work in public health and occupational medicine, for the degrees of Medical Doctor (MD), Master of Medical Sciences (MSc), and Doctor of Medical Sciences (DMSc). The Department also provides those lectures related to public health and occupational medicine for undergraduate students in the School of Health Sciences and Nursing.

The Department has conducted research on a wide variety of public health issues, including health policy and economics, occupational medicine, environmental health, community and clinical epidemiology, behavioral medicine, and so on. In addition, the staff members of the Department have offered public and occupational health services to the central and local governments, industries, and local communities.

Currently, the Department comprises a professor and chair, an associate professor, a lecturer, an associate, a research resident, several part-time lecturers, and several visiting research fellows, all of who take part in the education and/or the research of the Department.

Faculties and Students;

Professor and Chair	Yasuki Kobayashi, MD, DMSc (since April 2001)
Associate Professor	Kazuhito Yokoyama, MD, DMSc
Lecturer	Hajime Sato, MD, MPH, DMSc, DPH
Associate	1
Research Resident	1
Postdoctoral Fellow	1
Graduate Students	10 (including 3 entrusted students)
Research Students	4
Secretary	2

Past Research and Major Accomplishments

1) Health policy and economics

We are interested in the topics of health care system and economics in general. We have performed and published those studies related to supply and demand sides of health services in Japan; such as supply and distribution of physicians, the separation of pharmaceutical dispensing and prescribing in medical practice, cost studies of outpatient and inpatient services, and the efficiency and equity of the Japan's health insurance system.

For the issues of physician supply, we examined and analyzed the impact of physician manpower policy in the 1970s and 1980s in Japan, through both economic and statistical methods, and showed that geographic mal-distribution of physicians did not improve despite the growing number of physician during the period. Also, we projected future demand of physicians by specialty in Japan, since this issue brought a constant debate among the government, medical schools, medical providers, and patients. Our projections could facilitate these arguments.

For Japan's insurance system, we first showed that it would be cost-beneficial if an electronic claiming system were introduced to the system. On the other hand, the financing system for the elderly health care is really a global issue worldwide, and we also have tackled the issue. Since the late 1980s, we have shown the effectiveness and efficiency of home care for the elderly in terms of their quality of life. In the late 1990s, there have been wide and continuous debates on the matter nationwide, and finally the new insurance system, namely the Long-term Care Insurance for the Elderly has been introduced to Japan since the year 2000. Our study results have definitely facilitated these discussions.

We have examined what factors are relevant to early discharge of elderly patients. We did a follow-up survey of hospitalized patients with cerebrovascular

diseases (CVD) in almost all the hospitals in a prefecture. The study showed that the caregiver's conditions, including economic ones, as well as the patient's conditions, were closely related to earlier home discharge of the CVD patients.

We have carried on several policy studies in the health and environmental fields, especially those from international comparative perspectives, such as tobacco smoking control, and patient isolation policy for Hansen's disease. These studies have been published in some international policy journals.

Overall, we have contributed to the evidence based health policy in Japan, through numerous empirical studies using the methods of epidemiology and health economics.

2) Occupational medicine and environmental health

We have tackled the issues of neurotoxicologic effects of lead and other heavy metals and solvents, sarin poisoning, particulate matter monitoring, and health effects of pesticides in developing countries as part of the Alliance for Global Sustainability project. We have been also interested in the issues of behavioral medicine, such as socioeconomic and psychological aspects of drinking and traffic accidents. For the above purposes, the Department conducted international collaborative studies in the Faeroes islands of Denmark (methyl-mercury), Seoul of Korea (lead, chromium and mercury poisonings) and Kota Bahr of Malaysia (pesticide poisoning). Also, the former chairman of the Department (Araki), as Chairman of the Scientific Committee on Neurotoxicology and Psychophysiology of the International Commission on Occupational Health (ICOH), promoted symposia at the ICOH 2000 Congress in Singapore. The Department also held the 48th Annual Meeting of the Japanese Society of Occupational Medicine and Traumatology in Tokyo in November 2000.

3) Community and clinical epidemiology

We have done several epidemiological studies in community, occupational, or clinical settings, such as active life expectancy for the elderly, quality of life assessment in RA patients, work-related diseases, and outcome studies for various kinds of treatments. Most of these studies have been carried on in collaboration with local communities, industries, or clinical departments, and published in various journals.

Current Research

Most of the above mentioned research topics are tackled at present, with new perspectives and methodologies. For the insurance system, recently the separation of prescribing and dispensing of pharmaceuticals has progressed, however, our study has suggested that the separation itself would not necessarily lead to the cost containment of pharmaceuticals because physicians tend to prescribe bland-name pharmaceuticals. Therefore, we suggest that such a separation policy should be combined with a policy encouraging the use of generics.

In addition, we study the methods and guidelines by which health insurance claim data will be used for research with securing the patients' privacy. Such a study would facilitate expanding the volume of and improving the quality of health services research in Japan, consequently lead to the improvement of quality of health services in Japan.

For the issues of the financing system worldwide, we have recently began to study a system for providing the effective treatment for people with HIV/AIDS in developing countries, since the issue is a global and urgent one both in terms of health and economics. We have conducted a cost study of providing highly active antiretroviral therapy (HAART) to AIDS patients in Khon Kaen Province, Thailand. As a result, we indicate that a substantial increase of resources would be necessary to provide HAART to all the adult AIDS patients under the current universal coverage system in Khon Kaen province, and we suggest possible solutions for this financial obstacle. This type of analysis would be also useful to assess the financial implications of providing HAART for public health systems worldwide.

For the issues of environmental pollution and health effects of chemicals, we have recently started an international collaborative study on pesticide problem in Malaysia. In the study, the health effects of pesticide in relation to occupational safety behavior are studied among tobacco-growing farmers in Kelantan, Malaysia. So far, the following results are obtained; (i) Organophosphate and dithiocarbamate pesticides affect peripheral nerve conduction, whereas pyrethroid affects postural balance system. (ii) Nonsmoking while spraying, good-sprayer condition, and changing clothes immediately after spraying prevents occurrence of acute symptoms just after pesticide spray in male farmers; in female farmers, wearing a hat while spraying significantly prevents the symptoms. These results suggest that sub-clinical health effects are caused by pesticide use; the effects could be prevented by safety handling of pesticides so that health education would be effective.

Future Prospects

Our empirical studies on the health insurance system and health manpower policy in Japan are unique, and our strength. Therefore, we should continue to expand these kinds of studies and to train profession-

als in such fields, and hope to facilitate and contribute to improving our health care system. Furthermore, international collaborative studies for pubic health are also a tradition of the Department as well as its strength in terms of research. We would also like to continue such collaborative studies on health of and health care for disadvantaged people, such as the poor, the frail elderly, people with HIV/AIDS, and underprivileged workers. In addition, since there are growing needs for epidemiological studies in occupational and clinical settings, we should expand outcome studies and clinical epidemiology, in collaboration with clinical departments. In order to maintain and promote health for all the people in Japan and in the world, it is essential to promote both theoretical and empirical studies in public health. The Department is making every effort for this purpose through domestic, international and interdisciplinary collaborative researches.

Research Grants

1. 2001-03 Research Grants from Ministry of Education, Culture, and Sports. Study on payment system for the checking functions preventing adverse events of pharmaceuticals in the separation of prescribing and dispensing. (Kobayashi Y)
2. 2001-03 Health Sciences Research Grants (Research on Policy Planning and Evaluation) from the Ministry of Health, Labor and Welfare of Japan. Study on use and security of insurance claim data in Japan's health insurance system. (Kobayashi Y)
3. 2001-04 Grant for Health Cooperation Research from the Ministry of Health, Labor and Welfare of Japan. Study on a financing system for providing the effective treatment for people with HIV/AIDS in developing countries. (Kobayashi Y)
4. 2001-03 Research Grants from Ministry of Education, Culture, and Sports. Study on risk assessment of subclinical neuro-behavioral effects of environmental pollutants. (Yokoyama K)
5. 2001-04 Research Grants from Ministry of Education, Culture, and Sports. International collaborative study on health effects of pesticides and their safe use. (Yokoyama K)

Select Publications

Health policy and economics

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Department of Forensic Medicine

Outline and Research Objectives

Since Professor Kunika Katayama founded our department first in Japan on 1888, we have performed10258 autopsies by September 30th, 2002. Our precursors have devoted to so many outstanding cases that were paid social attentions. Research objectives are blood-DNA typing, serology, toxicology, forensic pathology, etc. as described below.

Faculties and Students

Professor	Ken-ichi Yoshida, M.D (1999)
Associate Professor	Hirotaro Iwase, M.D. (2001)
Associate	2
Graduate students	6
Technical persons	4
Secretary	2

Past Research and Major Accomplishment

Besides the research on forensic pathology and determination of death cause, there have been outstanding accomplishments in basic medical field since Professor Mita, S., the founder of the Department of Immunology. Professor Furuhata, T. was outstanding in the study on the inheritance of ABO blood group. Professor Ueno, S. discovered complements, while he studied on medical law. Professor Miki was famous for blood typing. Professor Ishiyama introduced DNA typing in the forensic practice, while encouraged forensic pathology. Professor Takatori, T. was famous in the autopsy and research on the Sarin murder cases, while his research on lipid has been inherited today.

Current Research

1) Reactive oxygen generation, and Lipid peroxidation and their implication in the pathogenesis:

We identified several lipid species that are generated in the presence of heme-proteins and associated with peroxidation. These lipids may be associated with the pathogenesis caused by oxidative stresses that are caused by ischemia-reperfusion (myocardial or brain infarction) or various drugs or toxins (amphetamines, carbon monoxide, agricultural medicines etc.). We undertake to clarify the molecular mechanism of the injury or the cell death due to these pathogens with reference to lipid peroxidation. Of these, 4-hydroxynonenal (HNE) is rapidly induced in the endothelium and sarcolemma of the infarcted myocardium.

Carbon monoxide (CO) is the most common cause of death due to intoxication, and is often supposed to aggravate fatality due to ischemic heart diseases (IHD) or cause delayed neuronal death. CO protects cardiomyogenic cells against ischemia and alleviates reactive oxygen (ROS) generation. By contrast, in the *in vivo* experiments in the rat, CO plus hypoxia induces necrotic cortical neuronal death, which is associated with the enhanced production of lipid peroxide. Hypothermia reduced the neuronal injury and lipid peroxide generation, suggesting the implication of lipid peroxidation in the neuronal death induced by CO.

2) The molecular mechanism of the injury and cell death of myocardium or brain after ischemia-reperfusion or toxic substances.

More than two thirds of the causes of unusual death are ischemic heart or brain diseases. Most of such death occurs within an hour of the onset of the symptoms. Because it takes more than several hours from the onset of symptoms for the myocardium to show distinct histological changes (coagulation necrosis), it is mandatory to establish a diagnostic method for the early ischemia. To this end, we have to understand the molecular basis of the evolution of the ischemic heart or brain disease. We have clarified on the roles of proteases or intracellular signaling molecules in the pathogenesis of ischemic diseases and toxic cell injuries. 1) Brief ischemic (e.g. 10min) followed by reperfusion induces proteolysis of cytoskeletal proteins fodrin and ankyrin by Ca^{2+}-dependent protease calpain, which causes contractile dysfunction in the isolated heart. This is the earliest irreversible change so far documented. 2) Protein Kinase C (PKC) isoforms translocate to membrane or nucleus during ischemia. Nitric oxide (NO) mediates the translocation of PKC-α, δ, and ε, which protects myocardium against reperfusion injury. 3) Ischemia-reperfusion causes sequential activation of PI3 kinase-PKC-ζ-MEK-MAP kinase- *c-fos*, thereby preventing apoptotic death. This study disclosed that MAP kinase translo-

cates to the nucleus independent of phosphorylation, but is activated by phosphorylation through MEK activation during postischemic reperfusion in the nucleus, in contrast with the paradigm. 4) Hypoxia under normoglycemia causes autophagic cell death through acidosis through PI3 kinase-mediated activation of glycolysis, explaining the myocardial death under pulmonary hypoventilation or hypoxic hypoxia. 5) Angina attacks often attenuate the injury due to subsequent myocardial infarction (MI). This phenomenon, ischemic preconditioning (IP), is reproduced in rat coronary occlusion model of acute MI. IP induces endothelial NO synthase (eNOS) and collateral vasodilation in the early MI, whereas IP induces angiogenesis in late MI through PKC- ε activation and Vascular Endothelium Growth Factor (VEGF) up-regulation. The both salvage myocardium in MI. 6) Connexin (Cx)-43 undergoes proteolysis during early MI through lysosomal and proteasomal proteases independently of calcineurin-mediated proteolysis. IP attenuates the Cx43 proteolysis in early MI. These finding explain the arrhythmias in early MI and its prevention by IP. 7) Emotional stress evoked by immobilization of rat causes activation of MAP kinase-*c-fos* pathway. 8) Methamphetamine (MAH) induces hyperthermia through symphathetico-adrenal activation and enhanced skeletal muscle metabolism, which is blocked by a sarcoplasmic reticulum Ca^{2+}-release blocker dantrolene. Repeated intermittent administration of MAH causes enhanced cardiovascular, thermal, and behavioral responses to MAH or emotional stress. We are willing to apply the findings of the experimental studies to exploit a new method for the diagnosis of ischemic or other disease states.

3) The study on the legal aspects of forensic medicine.

Forensic practices are associated with various legal or social problems that ought to be solved, though there have been research on such issues. On the other hand, those who provide expert opinion in the civil or legal litigation were far less than those required. There is dissociation in the thought-ways between medical doctors and lawyers, which can seriously violate the human right of persons concerned as well as causes the shortage of the expert witnesses. The courts have made effort to increase the numbers of expert witnesses for the litigation, though no adequate. On the other hand, the expression or the way of the expert witness may affect the judgment in the litigation or prosecution, as suggested by the questionnaire study.

The "reportable unusual deaths" in the guideline proposed by Japanese Society of Legal Medicine includes the unexpected death during or shortly after any medical practice. According to the Doctor¬s Act in Japan, doctors must report unusual death cases to the police. The police (prosecutors) demand autopsy under the guidance of superintendents. In England, coroners request autopsy after inquiry with the police, relatives and forensic pathologists. Medical accidents are largely autopsied in England whereas, in Japan, medical accidents are rarely reported nor. In Tokyo and few other districts, medical examiners decide autopsy of 1/4~1/3 of unusual deaths, but autopsies in other districts are mostly conducted by police judgment in search for a possible crime. It should be reminded that death cause tells criminality and the responsibility only if the cause is diagnosed exactly by autopsy performed under proper judgment and that autopsy is often effective to clarify the cause of unexpected deaths. Recently in Japan, unexpected deaths in hospitals have come to be increasingly suspected as caused by malpractice. For lack of a proper system to answer for complaints from patients¬ side, the relatives sometimes go to the police. Though most cases are asked only for civil liability, the police investigate the hospital in question and this makes doctors hesitate to report. Prosecutors judge criminality on autopsy operator¬s expert opinion, whereas they insist that autopsy results should not be disclosed to protect privacy of investigation. Thus, an insufficient information on patient¬s side explains to a great extent why nearly 700 relatives sue doctors every year in Japan. In 2001, Japan Surgical Society announced to the public and Society of Legal Medicine that patients¬ death during or shortly after operations should not be accounted as an unusual death reportable to the police, but to the independent authority, if required. Though many cases are unavoidable and not problematic, doctors sometimes neither inform the patient¬s side enough to get satisfactory consent for the practice nor explain the necessity of autopsy to clarify death cause. As accepted in U.K., there should only be reasonable cause to suspect for "unusual death". Accordingly, although deaths in medical accident may be sometimes inevitable or unrelated to the malpractice, the doctor¬s explanation as such for an unexpected death can be hardly accepted by patient¬s side. Therefore, independent investigation and autopsy are required in medical accidents in order to determine and explain the cause of death to patient¬s side and to disclose and improve the medical practice by doctors. We are willing to devote to set up valid system for the death investigation in the medical accident cases.

4) Forensic pathology.

Because each case is unique and diversity is a important determinant of the death, we try to perform microscopic analyses in as many cases as possible. We undertake to take the advantage of the above-

mentioned studies in the immunohistochemical method for the diagnosis of our autopsy cases.

Future Prospective

The correct and fair determination of death cause in the medico-legal autopsy cases has been the most important mission of us. We must accept very difficult and socially notable victims and requirements of expert opinion. We must play this important role carefully and impatiently, and train young forensic pathologists.

There has been not so much evolution in the forensic practice except for the DNA identification technology. This may be the cause of the low overall activity in the forensic medicine. To open the window to the future of forensic medicine, we must do every effort to find new directions of forensic medicine and let them known to the public as well as medical field. Actually, there are many medico-legal issues in the clinical medicine, which have manifested as the growing criticisms from the society on the medical malpractice, inadequate risk management of the medical accidents, etc. In Japan, the death investigation system for the medical accidents and the unexpected death in hospitals is quite immature, so that it is very important and urgent to set up an independent organization for the death investigation for such cases. As forensic pathologists, we have autopsied such cases and recognize the problems to be addressed. We are going to take part in such activity in cooperation with clinicians and civil servants to find and build up the good system. Additionally, the education on these issues to the clinicians, citizens, as well as medical and law students are very important.

The legal systems for death investigation of "unusual death", prosecution and litigation have inherent drawbacks, which require improvement. We have taken effort to inform on the problems to persons concerned, but it is far from what is ought to be.

The 15~20% of total deaths are "unusual deaths", which requires death investigation. The misdiagnoses of the "unusual deaths" by clinicians, and police surgeons, are police officers have been manifested due to the inherent inadequacy of the system and poor education of those who investigate. Because there are some typical patterns of misdiagnoses and poor management of those cases, we must educate on these issues to students, medical service personnel, and the society.

Research Grant

Grant-in-aid from Monbusho (B) for Yoshida et al.

1) A survey for the myocardial proteins and genes induced by ischemia or psychological stress and its application to the forensic practices (1998~1999) 10,200,000 yen
2) Identification and path-physiological study of novel peroxidized fatty acids formed in the tissue after ischemia or various intoxication and the exploitation of the new diagnostic method (2000~2001) 14,800,000 yen
3) Research on the mechanism of cellular injury due to nitric oxide or carbon monoxide in tissues undergoing ischemia or shock (2002) 14,000,000 yen

Grant-in-aid from Monbusho (C) for Uemura, Yoshida et al.

4) Research on the intracellular stress response in the amphetamine-induced neuro-degeneration (1999~2000) 2,500,000 yen
5) Research on the molecular mechanism of promotion and protection of cell death by carbon monoxide (2002) 2,700,000 yen

Select Publications

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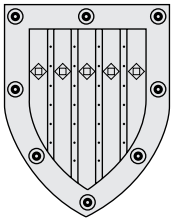

Department of Medical Informatics and Economics

Outline and Research Objectives

In 1983, the Department of Hospital Information Management(Hospital Computer Center) was established as one of central facilities in the University of Tokyo Hospital. The major roles have been designing, implementing, and maintaining the hospital information management system based on up-to-date information technology and improving functions of clinical information management required in the university hospital. The University Medical Information Network Center(UMIN Center) was opened in the department as a cooperate organization for national medical schools in Japan. The purposes of the UMIN Center are to provide up-to-date communication environment to healthcare professionals via the Internet. In 1997, according to the reconstruction of Graduate School, the Department of Medical Informatics and Economics was established in the Division of Social Medicine, Graduate School of Medicine, and the functions of research and education and the staffs were formally moved from the hospital to the department in the Graduate School of Medicine. However, all the administrative works for providing various services of hospital information management have been conducted by the same staffs as before.

From the responsibilities of the hospital described as above, most of the researches have been based on practical development, integration, and implementation of hospital information systems using an innovative information technology. The scope covers standardization of medical information exchange, evaluation of new technologies for distributed hospital information systems, development of electronic medical record systems(EMRS) and medical decision support systems(MDSS), application of the Internet technology in healthcare fields, and method of knowledge discovery from clinical database. The goal is to contribute to improvement of quality of care using information technology

Faculties and Students

Professor and Chair	Kazuhiko Ohe, M.D., Ph.D. (1997-)
Associate Professors	Takahiro Kiuchi, M.D., Ph.D. (for UMIN Center)

Graduate student 9
Research student.....2

Past Research and Major Accomplishments

1) Development and evaluation of a hospital information system using open standard and HL7 (1993-Current)

Although the Health Level Seven(HL7) Version 2.1 was the only proposal for connecting distributed information systems in a hospital around 1993, it was no so-called "standard" protocol. Because it was essential for developers of develop large-scale hospital information systems(HISs) to introduce a standard communication protocol that could be generally used in different departmental computer systems and their terminals, an experience and evaluation of real implementation of HL7 in a large-scale HIS were needed in the field of medical informatics in the early '90s. Ohe designed a new architecture of client-server-type HIS using HL7-based messaging protocol between client terminals and the server over TCP/IP network, which had never been used in Japan. The innovative HIS was successfully implemented based on this new architecture in the University of Tokyo Hospital in 1995 and the good performance was proved in this implementation[7]. This first experience of implementing the standard communication protocol or HL7 contributed to move most HISs in Japan from the vender proprietary systems into multi-vender distributed systems using open standard. Subsequent activities related to the open standard brought about foundation of the Association of HL7 Japan(Ohe is the vice-chair of the technical committee), foundation of Japan Health Information and Communication Standards Board (HELICS Board; Ohe is the Chair of the Board),

2) Modeling a semantic structure of clinical information using object-oriented approach and development of HIS using OODB and CORBA(1996-Current)

Analyzing and Modeling a semantic structure of clinical information in terms of information science

are essential tasks to develop both multi-purpose EMR systems and future intelligent decision support systems. Object-oriented analysis(OOA) and modeling(OOM) were proposed in the '90s as powerful methods to model a semantic relationship among information objects in a target domain and they were gradually applied in various fields as well as medical information. We recognized the importance of the OOA/OOM at the early stage, and focused on applying the approach to developing a future intelligent clinical information systems. At first we analyzed and made a model of data of ECG, and implemented a retrieval system using Object-Oriented Database(OODB)[5,6,10]. The research proved the feasibility and realization of OOA/OOM and OODB system to develop multi-media clinical information systems.

Based on this result, we proposed a new architecture for managing distributed medical information using OODB and CORBA(Common Objects Request Broker Architecture). This approach aimed to share inter-hospital distributed clinical information for improvement of quality of care and quality of multi-institutional large-scale clinical researches. In this research, we have been developing CORBA-based EMR systems in the University of Tokyo Hospitals[12,18,21].

3) Standardization of medical information exchange and terminology (1997-Current)

Ohe and the collaborative researchers in other institutes have been concurrently developing a new standard protocol for exchanging medical information electronically among hospitals in collaboration with the Association of HL7-USA /Japan and related working group of ISO/TC215, in which Ohe is the delegate of Japan of WG3; concept representation). We proposed a protocol named "MML(Medical Markup Language)" based on XML(eXtensible Markup Language) in the early stage of the work[8], and later we proposed a new protocol named "MERIT-9" based on integration of XML, HL7, DICOM, and other de-facto standard through our experiences of implementing the previous protocol[14,16]. This new protocol is in the stage of evaluation in several hospitals in Japan.

In the domain of medical terminology, Japan had double standards of Japanese clinical disease terminology and all of hospitals in Japan have not decided to use which of them for a long time. Ohe and Kaihara, who was a former professor of this department, proposed a method of integrating these two Japanese standard into one unified standard terminology that is available for general-purpose clinical information systems and EDI(Electronic Data Interchange) system of health insurance claim reimbursement. Each term in the unified disease terminology is linked to an ICD-10 code and semantic relations among the terms. Further a new standard methods to access to a database of the terminology was developed and published as a open software in 2001 by Ohe and the colleagues. Most large-scale university hospitals has been moving to introduce the standard disease terminology since 2002 and Japan Ministry of Health, Labor, and Welfare announced that all of the hospitals must use this terminology including the codes in EDI.

4) Application of the Internet technology to medical field by the UMIN

Application of the Internet technology to medical field by the UMIN has been the major topic of the researches[13,15,17,]. Associate Professor Kiuchi is the director of the UMIN Center and he has been developing and managing the nation-wide medical information network sponsored by the Ministry of Education, Culture, Science, Sports and Technology (MEXT). Using this infrastructure, Kiuchi and his colleagues proposed a standard method of on-line abstract and paper entry and developed a system for Japanese academic medical societies. Hundreds of the societies have been adopting this system and as a result this methods and the system has become the de-facto standard in Japan. Kiuchi and his colleagues also developed Internet-based data collection system for nation-wide clinical and epidemiological research. The system have been enhancing the scale and the efficiency of such research[22].

Current Research

Most of the researches described above is continuing and currently expanded toward the next stage.

1) Enhancing Standardization of electronic representation of medical information:

Revising and evaluating the "MERIT-9" standard protocol in harmonization with HL7 ver.3 that is proposed to cover comprehensive clinical information systems.

2) Implementing large-scale EMR system integrated with order entry system using distributed object technology:

Based on the evaluation study of CORBA-based HIS, we are preparing and developing large-scale EMR system that will be operated from Apr. 2003 in the University of Tokyo Hospital.

3) Trial of knowledge discovery from large-scale medical database created by HIS for future Intelligent decision support system:

We are investigating a method of data mining and

knowledge discovery from large-scale medical database[23].

Future Prospects

We will shift to develop an intelligent decision support system that uses both large-scale clinical database and real-time knowledge discovering process, and for the purpose a new method of data mining including both natural language processing and temporal data processing should be created. Further, we want to focus on a method of creating an practical ontology that is specific to healthcare domain. In other words, integration of management of clinical data and handling of electronic medical knowledge is the next objectives for our goals.

Research Grants

five recent grants selected:

1) 2000F.Y.-2001F.Y. Health and Labor Sciences Research Grants of MHLW, Research on Health Technology Assessment, Research on development of formal electronic representation of logics of Japan medical fee payment system and a standard software of source-code generator for calculating medical fee. Head Researcher.
2) 2002F.Y Health and Labor Sciences Research Grants of MHLW, Research on Policy Planning and Evaluation, Investigation of DRG for inpatients with acute diseases. Co-researcher.
3) 2001F.Y.-2002F.Y. Grants-in-Aid for Scientific Research of MEXT, Scientific Research-C, Development of a method to discover similar cases from clinical database using semantic relationship among medical terms, Head researcher.
4) 2001F.Y-2002F.Y. Health and Labor Sciences Research Grants of MHLW, Research on Policy Planning and Evaluation, A study on roles of Health Insurance Agency, Head researcher.
5) 1999F.Y.-2001F.Y. Health and Labor Sciences Research Grants of MHLW, Research on Health Technology Assessment, A study on modeling healthcare information domain. Head Researcher.

Select Publications

1) Ohe,K., Kaihara,S.: An Object -Oriented Model of Physicians' Strategy at First Encounters - An Approach to sharing Distributed Knowledge-bases. K.C.Lun et al.(eds), Elsevier Science Publishers, B.V.(North-Holland), MEDINFO92: 434-439, 1992.
2) Kaihara S., Ohe K., Sakurai T. and Kiuchi T.: HIS and Research. Hospital Information Systems: Scope-Design-Architecture, A.R. Bakker et al. (eds), Elsevier Science Publishers B.V.(North-Holland), 97-101, 1992.
3) T. Koyama, K. Ohe: Building a Common Knowledge Base for Internal Medicine. Proceedings of Korea/Japan Joint Conference on Expert Systems: 876-888,Seoul (Korea), 1993.
4) K.Ohe, S.Kaihara, K.B.Ishikawa, T.Hishiki, T.Nagase, T.Sakurai: Hospital Information system and the Internet. K.Chon (ed), Proceedings of the International Networking Conference INET'95, 1033-1036, Internet Society, 1995.
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9) Hishiki T.,Ohe K., Kaihara S.: Extraction of Clinical Information from Narrative Medical Records Using Natural Language Processing Journal of Japan Medical Informatics, 17(3)Suppl.,1997.
10) Wang C, Ohe K, Kaihara S: Dynamic link between ECG and clinical data by a CORBA-based query engine and temporal mapping. Proceedings of AMIA Annual Fall Symposium,27-31,1997.
11) K.Miyo, K.Ohe: SGML-based Construction and Automatic Organization of Comprehensive Medical textbook on the Internet. Proceedings of MEDINFO98, B.Cesnik etal.(Eds), Amsterdam:IOS press,145-149,1998.
12) K.Ohe: A Hospital Information System based on Common Object Request Broker Architecture (CORBA) for Exchanging Distributed Medical Objects - an approach to future environment of sharing healthcare information. Proceedings of MEDINFO98, B.Cesnik etal.(Eds), Amsterdam:IOS press,962-964,1998.
13) T. Kiuchi, T. Sakurai, K. Ohe, Y. Ohashi, S. Kaihara: University Medical Information Network - Past, Present, and Future. Proceedings of MEDINFO98, B.Cesnik etal.(Eds), Amsterdam:IOS press,420-424,1998.
14) M. Kimura, K.Ohe, H. Yoshihara, Y. Ando, F. Kawamata, T. HIshiki, et.al.: Patient Information Exchange Guideline MERIT-9 using Medical Markup Language MML. Proceedings of MEDINFO98, B.Cesnik etal.(Eds), Amsterdam:IOS press,433-437,1998.
15) H. Yamakami, T.Kiuchi, T.Nagase, K.Ohe, S.Kaihara, T.Sakurai: Development and Trial operation of a World Wide Web-based data entry system

for the collection of statistical data on the management of the national university hospitals in Japan. Medical Informatics,23(1),19-29,1998.
16) M. Kimura, K. Ohe, H. Yoshihara, Y. Ando, F. Kawamata, T. Hishiki, et.al.: MERIT-9; a patient information exchange guideline using MML, HL7, and DICOM. International Journal of Medical Informatics, 59-68,51(1),1998.
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20) E.Hanada, Y.Antoku, S.Tani, M.Kimura, A.Hasegawa, S.Urano, K Ohe, Member, IEEE, M.Ymaki, Y.Nose: Electromagnetic interference on medical equipment by low-power mobile telecommunication systems. IEEE TRANSACTIONS ON ELECTROMAGNETIC COMPATIBILITY, 42(4),470-476, 2000.
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22) T.Kiuchi,K. Ohe,T.Sakurai: UMIN-Key information infrastructure for the Japanese Medical Community. Proceedings of MEDINFO2001, V.Patel etal.(Eds), Amsterdam:IOS press,1359-1363,2001.
23) D.Koide,K. Ohe: Applying data mining to detection of adverse drug reactions. Proceedings of MEDINFO2001, V.Patel etal.(Eds), Amsterdam:IOS press,1421,2001.
24) S.Kataoka, K. Ohe, M.Mochizuki, S.Ueda: Developing and integrating an adverse drug reaction reporting system with the hospital information system. YAKUGAKU ZASSHI,122(1),113-116, 2002.
25) Y.Ohyama, K.Funao, E.Kawabe, D.Hayashi, T.Yamazaki, T.Iga, D.Koide, K. Ohe, K.Kubota : Calcium channel blockers and myocardial infarction: A case-control study in a Japanese hospital. PHARMACOEPIDEMIOLOGY AND DRUG SAFETY, 2002, 11, 487-492, 2002.