

## Department of Public Health and Environmental Medicine

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### General Summary

Our major research project in the 2006 academic year focused on 1) the comet assay for detection of DNA damage; 2) genotoxic effects of micronucleus induction of vitamin E and its 2 derivatives, and magnetic fields; 3) induction of micronuclei by ketamine, 3, 4-methylenedioxymethamphetamine (MDMA), and its nitroso compounds; 4) metabolites of opium and heroin in human urine; 5) the epidemiology of studies of type 1 diabetes in Japan; 6) methods of medical informatics education and evidence-based medicine (EBM); 7) the health effects of electromagnetic fields (EMFs); 8) the urinary concentration of 8-hydroxydeoxyguanine (8-OHdG) as an indicator of oxidative DNA damage in workers exposed to intense EMFs.

### Research Activities

#### *In vitro* micronucleus test

1. A possible mechanism for the enhancement by co-exposure to static magnetic fields of micronucleus formation by mutagens

We reported that micronuclei induced by chemicals that produce active oxygen radicals increased after co-exposure to strong static magnetic fields (SMFs) but that these increases were blocked by pretreatment with ascorbic acid. These results suggest that exposure to SMFs triggers the induction of mutagen-related radicals. The present study examined the optimal timing of ascorbic acid pretreatment to block this increase and the duration of the effect. The frequency of micronuclei induced by co-exposure to mitomycin C (MMC) and SMFs decreased strongly when the interval of ascorbic acid pretreatment was 20 minutes. The effects of ascorbic acid on the micronucleus frequency were maintained for at least 72 hours. These results suggest that active oxygen radicals may be related to micronucleus induction by SMFs.

2. Chromosomal aberration of astrocytes exposed to EMFs

We studied the effect of EMF exposure on chromosomal aberrations by means of an *in vivo* micronucleus assay of newborn rat astrocytes. Micronuclei were not increased by exposure to EMFs (50 Hz, 10 mT, 72 hours). On the other hand, micronuclei induced by vincristine were increased by co-exposure to EMFs (50 Hz, 10 mT, 48 hours).

3. DNA damage by exposure to EMFs

We studied the effect of EMF exposure on DNA damage using the comet assay. We found that damage to DNA was not increased by exposure to EMFs (50 Hz, 10 mT, 1, 3, and 6 hours).

#### 4. Urine 8-OHdG in researchers exposed to intense magnetic fields

The urinary concentration of 8-OHdG, which is an indicator of oxidative DNA damage, was measured in 38 volunteers who worked in intense magnetic fields. The mean concentrations of urinary 8-OHdG did not differ significantly between the beginning and end of the workers' shift.

#### 5. *In vitro* genotoxicity study

A genotoxicity study of 2 derivatives of vitamin E that react as antioxidants (a collaborative study with Kyoritsu Pharmaceutical University)

A genotoxicity study of 2 derivatives (6-hydroxy-2,2-dimethylchroman and 2,2,5,7,8-pentamethyl-6-chromanol) of vitamin E was performed. Chinese hamster lung CHL/IU cells were exposed separately to both derivatives and MMC. The number of chromosomal aberrations and the micronucleus frequencies were lower with exposure to both the derivatives and MMC than with exposure to MMC alone.

#### *Physiological affects of drug abuse*

##### 1. Genotoxicity of MDMA as an illegal drug of abuse

Illegal use of MDMA has recently become a social problem. MDMA ingested orally reacts with nitrites in the stomach and is synthesized into *N*-nitroso-MDMA. We synthesized *N*-nitroso-MDMA and studied its genotoxicity using the micronucleus and chromosomal aberration tests. The genotoxicity of *N*-nitroso-MDMA was observed in both the micronucleus and chromosomal aberration tests.

##### 2. Genotoxic effects of ketamine

Ketamine have recently begun to be abused in Japan. The Japanese government has proposed new studies of the toxicity of abused drugs as part of a plan to eliminate drug abuse. Orally administered ketamine may be metabolized to nitrites; therefore, we have synthesized their nitroso compounds and studied them with the micronucleus and chromosome aberration tests using Chinese hamster lung cells. *N*-nitrosoketamine showed positive results on both tests.

##### 3. Inference of opium or heroin from analysis of metabolites in urine samples

Metabolites of opium and heroin were analyzed in human urine. After drug administration, the metabolites of both morphine and codeine were detected in urine by using the chromatography pattern analysis of gas chromatography/mass spectrometry.

#### *Epidemiology, EBM, community health and medical informatics*

##### 1. EBM

A systematized body of epidemiologic principles with which studies can be designed and judged has been established only in the last two decades. These principles have evolved in tandem with an explosion of epidemiologic activity covering a wide range of health problems. Our greatest concern is to clarify risk factors for adult disease and intractable diseases. We also studied the methodology of medical informatics education and EBM.

##### 2. Is changing from neutral protamine hagedon insulin to insulin glargine as the basal insulin in a basal bolus regimen effective in Japanese patients with diabetes?

We studied the clinical efficacy of changing from neutral protamine hagedon (NPH) insulin to insulin glargine as the basal insulin in a basal bolus regimen. The subjects

of this study were patients with type 1 and type 2 diabetes who had started to use glargine for a basal bolus regimen from 2004 through 2006. Twelve months after changing from NPH to glargine, the patients were able to decrease their required daily dosages and the numbers of insulin injections per day without changes in hemoglobin A1c or weight gain.

### 3. Epidemiological study of the effects of EMFs on health

To clarify the effects of EMFs on health, we performed an epidemiological study of workers exposed to strong EMFs and of control subjects. We also examined the effects of cellular telephones on health. The full epidemiological study, included health examinations, biochemical tests of blood, monitoring of personal exposure to EMFs, and measurement of the magnetic environment.

### Publications

**Suzuki Y, Toyama Y, Miyakoshi Y, Ikehata M (Railway Tech Res Inst), Yoshioka H, Shimizu H.** Effects of static magnetic fields on the induction of micronuclei by some mutagens. *Environ Health Prev Med* 2006; **11**: 228-32.

**Miyakoshi Y, Yoshioka H, Matsudaira T, Toyama Y, Suzuki Y, Shimizu H.** Fifty-Hertz electromagnetic fields decrease the frequencies of the micronuclei induced by Mitomycin C in newborn rat astrocytes. *Genes Environm* 2006; **28**: 123-6.

**Asanuma K, Agata T, Nakamura Y, Naruse S, Suzuki Y, Shimizu H.** A study of health influence of magnetic field (in Japanese). *Tokyo Jikeikai Ikadaigaku Zasshi (Tokyo Jikeikai Med J)* 2006; **121**: 119-32.

**Shimada M, Sugimoto M, Agata T, Nitta N.** A

nation-wide study of mother's troubles, needs about infant care support and nursing environment for 1 month after childbirth: 'healthy mother and children in 21 century'. *Comparison in 5 years* 2006; **65**: 752-62.

### Reviews and Books

**Agata T.** The usefulness of global health network and preventive Tele-medicine. *Jpn J Health Human Ecol* 2006; **72**: 49-50.

**Agata T.** How to read medical statistics and clinical trials. *Jpn Med J* 2007; **4326**: 94-5.

**Agata T.** Health statistics made simple 4th ed. Tokyo: Nankodo; 2007.